Original article

Arch Argent Pediatr 2023;121(3):e202202779

Prevalence of microbiologically confirmed neonatal sepsis at a maternity center in the City of Buenos Aires

Marcela Ortiz de Zárate[a], *Carolina Sáenz*[a], *Raúl Cimbaro Canella*[a], *Marcela Díaz*[a], *Josefina Mucci*[a], *Alejandro Dinerstein*[a], *Claudio Solana*[a]

ABSTRACT

Introduction. Neonatal sepsis is often suspected in hospitalized newborn infants, but only in 25–30% of cases it is confirmed via a positive culture. Selecting the antibiotics based on local epidemiology favors their rational use and minimizes their side effects.

Primary objective. To describe the prevalence of early- and late-onset sepsis with microorganism isolation and their clinical characteristics.

Population and method. Retrospective, cross-sectional study conducted between 01-01-2013 and 12-31-2017 in a public maternity center of Argentina in all hospitalized newborn infants with a diagnosis of early- and late-onset sepsis with microorganism isolation, and those re-admitted in their first month of life.

Results. A total of 3322 newborn infants were admitted; 1296 were assessed for suspected early-onset sepsis; 25 had a positive culture (1.9%; rate: 0.86‰). Of these, 52% were born before 33 weeks of gestation. Microorganisms: *Escherichia coli* 5, *Listeria monocytogenes* 4, *Streptococcus agalactiae* (SGB) 3*, Streptococcus pneumoniae* 3. Also, 68% of late-onset sepsis cases (rate: 8.73‰) occurred in infants born before 33 weeks of gestation. Hospital-acquired microorganisms: coagulase-negative *Staphylococcus* 115, *Staphylococcus aureus* 47, *Escherichia coli* 30, *Candida spp.* 16, *Enterococcus faecalis* 13, *Klebsiella pneumoniae* 11, and *Streptococcus agalactiae* 10. In re-admissions: *E. coli* 11, *S. aureus* 12*,* SGB 3, and *Haemophilus influenzae* 3*.*

Conclusions. During the study period, the frequency of early-onset sepsis was similar to international reports, with a predominance of *E. coli* and *L. monocytogenes*. The rate of late-onset sepsis showed a downward trend in the analyzed years, with a predominance of Gram-positive cocci.

Key words: *early-onset neonatal sepsis; late-onset neonatal sepsis; epidemiology.*

doi: http://dx.doi.org/10.5546/aap.2022-02779.eng

To cite: Ortiz de Zárate M, Sáenz C, Cimbaro Canella R, Díaz M, et al. Prevalence of microbiologically confirmed neonatal sepsis at a maternity center in the City of Buenos Aires. *Arch Argent Pediatr* 2023;121(3):e202202779.

[a] *Hospital Materno Infantil Ramón Sardá. City of Buenos Aires, Argentina.*

Correspondence to *Marcela Ortiz de Zárate: mlortizdezarate@gmail.com*

Funding*: None.*

Conflict of interest*: None.*

Received*: 7-17-2022*
Accepted*: 11-9-2022*

INTRODUCTION

Although neonatal survival has improved in recent years, sepsis remains one of the leading causes of morbidity and mortality among newborn infants (NBIs). The clinical manifestations of infection include a broad range of diseases (sepsis, bacteremia, pneumonia, meningitis, urinary tract infection, etc.). The microorganisms involved vary depending on the type of patient, type of facility, region, and study period.

Even so, the Consensus of the Ibero-American Society of Neonatology (Consenso de la Sociedad Iberoamericana de Neonatología, SIBEN) states that "neonatal sepsis is often assumed, but very few NBIs actually suffer from it (less than 25–30% of suspected cases)".[1]

When selecting an empirical antibiotic therapy, it is suggested that it should be adapted to the local epidemiology; however, few studies have been published in our region in the past few years.[2,3]

Another important aspect to take into account is the limited variety of antibiotics assessed and available in neonatology. Their rational use prevents harmful effects in the short and long term (selection of resistant strains, predisposition to fungal infections, necrotizing enteritis) and allows the selection of a spectrum dosage that is safe but limited to the prevalent flora in each facility and, obviously, an early discontinuation in the absence of diagnostic confirmation.

Early-onset neonatal sepsis (EONS) is defined as sepsis with symptoms beginning in the first 72 hours of life, whereas late-onset neonatal sepsis (LONS) is defined as that occurring after the 4th day of life and during hospitalization, mainly in very low birth weight preterm infants.[4] LONS is also caused by microorganisms found primarily in the hospital setting (hospital-acquired LONS [HALONS]) or in the community, in patients re-admitted after discharge (community-acquired LONS [CALONS]).[1,5]

The prevalence of EONS is very low (1‰ of live births) with a prevalence of Gram-negative bacilli (GNB) and *Streptococcus agalactiae* (SGB). The occurrence of SGB has been decreasing since the implementation of intrapartum antibiotic prophylaxis (IAP). Such prevalence is strongly influenced by gestational age (GA) and birth weight.[1,2,5–7]

LONS affects between 0.6% and 14.2% of hospitalized NBIs.[1] The etiologic agents vary between hospital-acquired (staphylococci) and community-acquired flora.

Primary objective

To describe the prevalence of early- and late-onset sepsis with microorganism isolation and to describe their clinical characteristics in a public maternity center of Argentina.

Secondary objective

To describe the microorganisms involved in the occurrence of early- and late-onset neonatal sepsis.

POPULATION AND METHOD

This was a cross-sectional study carried out at Hospital Materno Infantil Ramón Sardá (HMIRS), a tertiary care teaching hospital associated with Universidad de Buenos Aires, level 3B, between 01-01-2013 and 12-31-2017, where 28 965 infants were born, with an estimated overall prevalence of neonatal sepsis of 11.15‰.[8]

All NBIs diagnosed with suspected hospital-acquired early-onset or late-onset neonatal sepsis and re-admissions up to 30 days of life admitted to the Neonatal Intensive Care Unit (NICU), which has 26 beds, were included in this study. Clinical and laboratory data were collected from medical records. Bacteriological data were taken from microbiological records.

The statistical analysis of data was performed with the R Studio software, version 4.0.3. The variables and rates were expressed as absolute and relative values (prevalence rate = early- or late-onset neonatal sepsis per 1000 live births in the study period) and the χ^2 test was done to express the OR and its 95% confidence interval (CI); a p value < 0.05 was considered significant. The study was approved by the maternity center's Ethics and Research Committee.

Procedures

Once an early-onset infection is suspected, 2 blood culture (BC) samples were collected. With suggestive clinical manifestations or microorganism isolation in blood, cerebrospinal fluid (CSF) was cultured by inoculating the sample in thioglycollate broth, blood agar, chocolate agar, and Gram staining was performed. When LONS was suspected, 2 samples for BC, urine culture, CSF culture, cytological and physicochemical analysis and, eventually, aspiration puncture of abscessed lesions were collected. Any BC with growth of BGN or yeasts in 1 or more flasks was considered positive. For Gram-positive species, usually skin saprophytes, those isolates with

equal growth in 2 or more flasks were ranked; the patient was considered to be infected if they had clinical and/or laboratory data compatible with an infectious process. Urine cultures were obtained via aseptic technique, by suprapubic puncture (SPP) or bladder catheterization. In the samples collected by SPP, any growth of BGN or yeast count and > 10^3 CFU/mL of Gram-positive cocci (GPC) was considered positive. In the samples collected by bladder catheterization, a count > 10^4 CFU/mL, with growth of a single species, was considered positive. BCs were incubated for 5 days using the Bact-Alert automated system (Biomerieux, France). Positive flasks were sub-cultured on blood agar and chocolate agar, and Gram staining was performed.

RESULTS

Early-onset neonatal sepsis

Out of a total of 28 965 NBIs in the 2013–2017 period, 3322 were admitted to the NICU. A total of 1296 NBIs (39%) required assessment due to suspected EONS; diagnosis was confirmed in 25 by microorganism isolation (rate of EONS: 0.86‰).

Bacteriologically confirmed cases showed the following distribution by gestational age: 13 episodes in preterm infants with less than 33 weeks of gestation, 5 in preterm infants with 33–37 weeks of gestation, and 7 in term NBIs. Male sex predominated (76%).

The prevalence of the main microorganisms was *E. Coli* 0.17‰ (all NBIs with a birth weight of less than 1500 g), *Listeria monocytogenes* 0.13‰ (varied distribution of birth weight), and SGB and *Streptococcus pneumoniae* 0.1‰, respectively (all in term NBIs).

The annual rates and distribution by gestational age group, by birth weight, and by microorganism are shown in *Tables 1, 2, 3, and 4*, respectively.

CSF was collected in 18 of 25 patients (72%) and central nervous system involvement was ruled out.

Late-onset neonatal sepsis (LONS)

In the 5-year period, 738 NBIs required assessment for suspected LONS, and microbiological diagnosis was confirmed in 253 (overall LONS rate: 8.73‰) (*Table 1*). Of these, 32 cases were infants who were re-admitted to the NICU, following their rooming-in hospitalization at birth, and were therefore considered as having community-acquired sepsis.

Table 1. Annual rates of early- and late-onset neonatal sepsis with microorganism isolation. Years 2013-2017

Year	LBs	Early-onset sepsis (n)	Rate ‰ (95% CI)	Late-onset sepsis (n)	Rate ‰ (95% CI)
2013	6275	3	0.48‰ (0.00–1.02)	65	10.36‰ (7.85–12.86)
2014	5908	4	0.68‰ (0.01–1.34)	51	8.63‰ (6.27–10.99)
2015	5599	10	1.79‰ (0.68–2.89)	53	9.47‰ (6.93–12.00)
2016	5368	5	0.93‰ (0.12–1.75)	47	8.76‰ (6.26–11.25)
2017	5815	3	0.52‰ (0.00–1.10)	37	6.36‰ (4.32–8.41)
Overall	28 965	25	0.86‰ (0.52–1.20)	253	6.36‰ (4.32–8.41)

LBs: live births.

Table 2. Rate of neonatal sepsis specific for each gestational age group (22 to 42 weeks)

Gestational age	N	Early-one sepsis n (‰)	OR (95% CI)	Late -onset sepsis n (‰)	OR (95% CI)	Community--acquired late onset sepsis n (‰)	OR (95% CI)
> 37 w	23 981	7 (0.29)	1	18 (0.75)	1	20 (0.83)	1
33–37 w	4164	5 (1.20)	4.12 (1.31–12.98)*	33 (7.93)	10.57 (5.95–18.79)**	9 (2.16)	2.59 (1.18–5.70)*
< 33 w	806	13 (16.13)	55.39 (21.76–135.97)**	170 (210.92)	281.00 (172.00–459.08)**	3 (3.72)	4.46 (1.32–15.05)*

w: weeks.
** p = 0.01.*
*** p < 0.001.*

Table 3. Rate of neonatal sepsis specific for each birth weight group (N = 25 476)

Birth weight group	N	Early-onset sepsis n (‰)	OR (95% CI)	Late-onset sepsis n (‰)	OR (95% CI)	Community-acquired late-onset sepsis n (‰)	OR (95% CI)
>2500 g	22862	11 (0.48)	1	22 (0.96)	1	26 (1.14)	1
1500-2499 g	2080	2 (0.96)	2.00 (0.44-9.02)***	42 (20.19)	21.98 (12.79-36.02)**	6 (2.88)	2.54 (1.04-6.17)*
1000-1499 g	311	5 (16.08)	33.91 (10.56-96.79)**	65 (209.00)	273.32 (167.65-458.93)**	-	
<1000 g	223	7 (31.39)	67.21 (24.33-175.84)**	92 (729.56)	725.17 (444.06-1197.11)**	-	

** p = 0.03*
*** p < 0.001.*
**** p = 0.36.*

Hospital-acquired late-onset neonatal sepsis (HALONS)

Of the total number of NBIs admitted to the NICU at birth, who remained hospitalized and had suspected LONS, a microorganism was isolated in 221 (30%) (HALONS rate: 7.63‰). Sixty-eight percent (68%) occurred in NBIs born before 33 weeks of gestation and 28.84%, in NBIs with a birth weight of less than 1500 g. The annual rates and distribution by gestational age group, by birth weight, and by microorganism are shown in *Tables 1, 2, 3, and 4*, respectively.

Table 4. Distribution of absolute values and isolated microorganisms and specific sepsis rates between 2013 and 2017 (N = 28 965)

Microorganisms	N	Rate (‰)
Early-onset neonatal sepsis		
Escherichia coli	5	0.173
Listeria monocytogenes	4	0.138
Streptococcus agalactiae	3	0.104
Streptococcus pneumoniae	3	0.104
Coagulase-negative *staphylococcus*	2	0.069
Pseudomonas aeruginosa	2	0.069
Enterococcus faecalis	2	0.069
Corynebacterium spp.	2	0.069
Streptococcus viridans	1	0.035
Haemophilus influenzae	1	0.035
Late-onset neonatal sepsis		
Coagulase-negative *staphylococcus*	115	3.970
Staphylococcus aureus	48 (13)	1.657
Escherichia coli	30 (11)	1.036
Candida spp.	16	0.552
Enterococcus faecalis	13 (1)	0.449
Klebsiella pneumoniae	11 (1)	0.380
Streptococcus agalactiae	10 (3)	0.345
Enterobacter cloacae	8	0.276
Proteus mirabilis	5	0.173
Haemophilus influenzae	4 (2)	0.138
Polimicrobiana	3 (1)	0.104
Acinetobacter spp.	2	0.069
Citrobacter freundii	2	0.069
Pseudomonas auriginosa	2	0.069
Serratia marscesens	2	0.069
Chlamydia trachomatis	1	0.035
Streptococcus pyogenes	1	0.035

Note: The number of microorganism isolations in children with community-acquired late-onset sepsis is indicated between brackets.

Table 5. Distribution of clinical diagnosis based on microbiologically-confirmed neonatal sepsis

Diagnosis	Late-onset neonatal sepsis n: 221	Community-acquired late-onset neonatal sepsis n: 32
Bacteremia	144 (65%)	10 (32%)
UTI	26 (12%)	11 (34%)
Meningitis	8 (4%)	1 (3%)
Pneumonia	5 (2%)	2 (6%)
NEC	23 (10%)	0 (0%)
Skin and soft tissue	12 (5%)	8 (25%)
Endocarditis	2 (1%)	0 (0%)
Osteomyelitis	1 (0%)	0 (0%)
Total	221	32

UTI: urinary tract infections; NEC: necrotizing enterocolitis.

More than 1 infectious episode during hospitalization was observed in 60 NBIs.

A total of 193 NBIs (87%) had a positive BC, with or without an evident source. In the remaining 13%, microorganisms were isolated in other usually sterile sites, but with negative BCs. The distribution was as follows: bacteremia without apparent source 65%, urinary tract infections 12% (half with accompanying bacteremia), meningitis 4% (2/8 with negative BCs), pneumonia-bacteremia 2%, necrotizing enteritis 10% (21/23 with positive BCs and 2 with isolation in peritoneal fluid), skin infections 5% (5/12 with positive BCs), 1 case of osteomyelitis and 2 cases of endocarditis (*Table 5*).

Of the 221 cases of HALONS, CSF was collected in 65%; meningitis was confirmed in 5.6% of those assessed (4% of hospital-acquired sepsis), which corresponded to 0.28‰ of live births. In 2 of these cases, a microorganism was isolated only in CSF: *E. coli and Enterococcus faecalis.*

Among the HALONS-producing microorganisms, staphylococci prevailed: 115 coagulase-negative *Staphylococcus* (CoNS) and 47 *S. aureus* (SA), followed by *E. coli* in 30 patients. *Candida spp.* was isolated in 16 cases; *E. faecalis*, in 13; *Klebsiella pneumoniae*, in 11; and SGB, only in 10 (*Table 4*).

Community-acquired late-onset neonatal sepsis (CALONS)

Thirty-two (32) children were re-admitted after discharge due to suspected LONS in their first month of life. *Table 4* describes the microorganisms and *Table 5* shows the forms of clinical presentation.

The most common producing-microorganisms included *E. coli* (11) and *S. aureus* (12), followed by SGB (3) and *Haemophilus influenzae* (3).

The LONS rate for SGB in that period was 0.34‰ (hospital- and community-acquired).

DISCUSSION

Neonatal sepsis is responsible for prolonging the length of hospital stay, increasing mortality, and causing neurodevelopmental disorders, as well as increasing exposure to broad-spectrum antibiotics and their subsequent adverse effects.[1,9,10]

The distribution of etiological agents varies in each facility and across different regions of the same country due to demographic factors, bacterial colonization of the mother-child dyad, invasive procedures associated with health care, and policies adopted in the use of antibiotics.

The population seen in our facility accounts for one-third of the population born in public hospitals in the City of Buenos Aires. According to a 2018 report, the incidence of neonatal sepsis in these patients was 19% in those with a birth weight of less than 1500 g and 1% in those with a higher birth weight.[11]

In this study, we describe a downward trend in LONS, which may be due to the different health care policies that were adapted during that period, from the consolidation of teamwork between neonatologists and infectious disease specialists for the limited and rational use of antibiotics, to the continuous monitoring of a nurse specialized in infection control, the education and implementation of measures, such as hand-washing, hygiene, and preservation of the patient unit, isolation measures, etc. However, it is worth

noting that this study describes a reality from before the COVID-19 pandemic and that a new prospective, multicenter study would allow to corroborate current trends.

This was not the case with the rate of EONS (more than two-thirds of cases occurred in preterm infants), which varied over the years. However, there was a decrease in SGB in this period, as described after the introduction of IAP in other case series.

Historically, in our hospital, Sarubbi et al., have reported a prevalence of overall neonatal sepsis with microorganism isolation in 1994 of 8‰ of live births[12] and then, they published the incidence of neonatal bacteremia limited to SGB between 1985 and 1997, a rate of EONS and LONS of 0.8‰ and 0.11‰ of live births, respectively.[13]

Currently, we have observed that EONS due to SGB have fallen to 0.1‰. The prevalence of LONS due to SGB, however, rose to 0.34‰ of live births, which may be related to the greater survival among hospitalized NBIs.

Recently, Poppuolo has updated the 2015 USA frequency of EONS and LONS due to SGB to 0.23‰ and 0.31‰, respectively.[14]

Stoll, in their article on the burden of SGB and *E. coli* in early-onset sepsis in almost 400 000 live births between 2006 and 2009 in the USA (389 with EONS), reported an EONS rate of 0.98‰, with a marked decrease in early-onset infections mainly at the expense of SGB (0.41‰) and *E. coli* (0.28‰). Seventy-three percent (73%) of the infants with SGB were born at term and 81% of those with EONS due to *E. coli* were born preterm. In our hospital, we found a lower prevalence of SGB and *E. coli* (0.10‰ and 0.17‰, respectively), which is consistent with the gestational ages described; however, in our population, *L. monocytogenes* (0.13‰) has become relevant as the second most prevalent microorganism, together with *S. pneumoniae* (0.10‰), a microorganism that, according to the bibliography, is usually found in late-onset infections.[15,16]

Two bacteremias due to CoNS, occurring in the first 72 hours of life, were considered associated with health care interventions in extremely preterm infants with early-onset infection.

As in other series,[1–3] 67% of HALONS-producing microorganisms corresponded to *Staphylococcus*; however, 1/3 was *S. aureus*, a concerning event related to the outbreaks that occurred in that period.

In relation to gestational age, Dong reported an incidence of LONS inversely proportional to birth weight and GA: they reported that 36.3% of NBIs born before 28 weeks of gestation have at least 1 episode of LONS, compared to 29.6%, 17.5%, and 16.5% with a GA of 29–32 weeks, 33–36 weeks, and term NBIs.[3] Consistent with our population, 70% of late-onset infections occurred in infants born before 33 weeks of gestation; 17% and 15%, in those born after 33 and 37 weeks of gestation, respectively.

It is worth noting that a high percentage of patients had a lumbar puncture and there was a low prevalence of meningitis, probably influenced by the performance of the procedure after the initiation of antibiotics. However, microorganism isolation in 25% of the cases of positive CSF culture, despite the absence of isolation in the BC, denotes the need for the procedure.

Finally, in the sub-group of patients re-admitted in their first month of life due to an infectious process, with a predominance of bacteremia, urinary tract infections, and skin infections, it is not surprising that *S. aureus* and *E. coli* are the most common microorganisms, which should keep us alert when selecting the antibiotic therapy to be used.

CONCLUSIONS

The frequency of EONS in the study period was similar to that reported in the international bibliography and to our own historical data, although with a significant decrease in the presence of SGB and of *L. monocytogenes* as the second most frequent isolated microorganism. ■

REFERENCES

1. Sola A, Mir R, Lemus L, Fariña D, et al. Suspected Neonatal Sepsis: Tenth Clinical Consensus of the Ibero-American Society of Neonatology (SIBEN). *Neoreviews*. 2020; 21(8):e505-34.
2. Berberian G, Brizuela M, Rosanova MT, Travaglianti M, et al. Infecciones por bacilos Gramnegativos multirresistentes en neonatología. *Arch Argent Pediatr.* 2019; 117(1):6-11.
3. Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. *Arch Dis Child Fetal Neonatal Ed.* 2015; 100:F257-63.
4. National Institute for Health and Care Excellence. Neonatal infection: antibiotics for prevention and treatment: NICE guideline [NG195]. Royal College of Obstetrician and Gynaecologists; 2021. [Accessed on: September 13th, 2022]. Available at: https://www.nice.org.uk/guidance/ng195
5. Mukhopadhyay S, Puopolo KM. Neonatal Early-Onset Sepsis: Epidemiology and Risk Assessment. *Neoreviews*. 2015; 16(4):e221-30.
6. Stoll B, Hansen N, Sánchez P, Faix R, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and *E. coli* disease continues. *Pediatrics*. 2011; 127(5):817-26.

7. Weston E, Pondo T, Lewis M, Martell-Cleary P, et al. The Burden of Invasive Early-Onset Neonatal Sepsis in the United States, 2005–2008. *Pediatr Infect Dis J*. 2011; 30(11):937-41.
8. División Estadísticas, Sistema Informático Perinatal y Departamento Técnico. Estadísticas Sardá 2017: Comparación con años 2008 a 2016. *Rev Hosp Mat Inf Ramón Sardá.* 2018; 1(3):30-50.
9. Instituto Nacional de Epidemiología Dr. Juan H. Jara. Programa Nacional de Vigilancia de Infecciones Hospitalarias de Argentina (VIHDA). Reporte anual de vigilancia de infecciones asociadas al cuidado de la salud 2019. Ciudad Autónoma de Buenos Aires: ANLIS Dr. G. Malbrán; 2020. [Accessed on: August 7th, 2022]. Available at: http://sgc.anlis.gob.ar/handle/123456789/1626
10. Nizet V, Klein J. Bacterial sepsis and meningitis. In: Wilson C, Nizet V, Maldonado Y, Remington J, Klein J. Remington and Klein's Infectious Diseases of the Fetus and Newborn Infant. 8th ed. Philadelphia: Elsevier Saunders; 2016.- Pages 217-71.
11. Címbaro Canella R. Informe del registro colaborativo de recién nacidos menores de 1500 gramos. Años 2008-2017. *Rev Hosp Mat Inf Ramón Sardá*. 2018; 2(3):112-28.
12. Sarubbi MA. Bacteriemias Neonatales Experiencia en la Maternidad Sardá Recomendaciones para su manejo. *Rev Hosp Mat Inf Ramón Sardá*. 1995; 14(1):37-44.
13. Sarubbi MA, Dinerstein N, Paganini, H, Botto, L. Bacteriemias neonatales por estreptococo β hemolítico del grupo B: trece años de experiencia. *Rev Hosp Mat Inf Ramón Sardá*. 2000; 19(2):52-9.
14. Puopolo K, Lynfield R, Cummings J. Management of Infants at Risk for Group B Streptococcal Disease. *Pediatrics*. 2019; 144(2):e20191881.
15. Fernandez Rodriguez B, Rubio Mascaraque L, Ruiz Fraile L, Cuadrado Perez L, Kuder K. Streptococcus Pneumoniae: The Forgotten Microorganism in Neonatal Sepsis. *Fetal Pediatr Pathol*. 2015; 34(3):202-5.
16. Aldana-Valenzuela C, Rodriguez-López AM, Guillén-Blancas E. Fulminant early-onset neonatal sepsis due to *Streptococcus pneumoniae*: Case report and review of the literature. *Pediatr Rep*. 2019; 11(1):7953.