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The importance of knowing the local epidemiology of neonatal sepsis

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Neonatal sepsis is a disease with a high associated morbidity and mortality. In a systematic review and meta-analysis, the estimated pooled incidence of neonatal sepsis was 22‰ of live births, with an associated mortality rate of 11–19% and an overall incidence of 3 000 000 cases of neonatal sepsis per year.[1] The diagnosis of sepsis is based on the isolation of a microorganism in a culture, but only 0.8% of assessed newborn infants (NBIs) have culture-proven sepsis and 1.4% have a diagnosis of clinical sepsis with negative culture.[2]

Available data were obtained mainly from middle- and high-income countries. Early-onset neonatal sepsis (EONS) refers to infections that develop in the first 72 hours of life and are transmitted vertically at birth; the most commonly associated microorganisms are *Streptococcus agalactiae* (GBS) and *Escherichia coli* (EC). The rate of EONS reported in the US was 0.98‰ of live births; of these, 43% were due to GBS (0.41‰ of live births) and 29% were due to EC (0.28‰ of live births), with rates inversely related to birth weight (10.6‰ for a birth weight of 401–1500 g, 1.38‰ for a birth weight of 1501–2500 g, and 0.57‰ for a birth weight > 2500 g).[3,4] The incidence of EONS has decreased in relation to improvements in health care and antenatal prophylaxis for GBS. The rate of EONS at the Yale-New Haven Hospital, which has been recording neonatal sepsis since 1928, decreased from 3.2‰ of live births in 1979 to 1‰ of live births in 2003, following the universal implementation of prophylaxis in GBS carriers in 1990, and remained stable from 2004 to 2013.[5,6] GBS remains the most frequent microorganism in EONS, but there has been a shift from GBS to EC as the most important microorganism associated with EONS among preterm and very low birth weight NBIs.[3,4] *Listeria monocytogenes*, non-typeable *Haemophilus influenzae* and other enteric negative bacilli have been involved in EONS.[4] EONS due to *Listeria monocytogenes* reduced in the US from 4.78 cases per 10 000 admissions (1992–1995) to 2.24 (1996–2002) and 1.31 (2003–2013) ($p < 0.0001$).[7]

Late-onset neonatal sepsis (LONS) develops after 3 to 5 days of life and up to 3 months of age. LONS most frequently affects low birth weight NBIs, may be hospital- or community-acquired and, in some situations, may be acquired at birth, but manifest after the 72 hours of life. In the neonatal intensive care unit, coagulase-negative *Staphylococcus* (CoNS) is the most commonly isolated microorganism, and *Staphylococcus aureus* (SA) is also associated with LONS, most

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commonly in NBIs with central vascular access.[4,8,9] Other causes of LONS include GBS, EC, other gram-negative bacilli, *Listeria monocytogenes*, and *Candida* spp.[4] The incidence rate of LONS in the general population may range from 1 in 1800 live births to 1 in 3000 live births,[10] and its incidence has increased in parallel with the increased survival of preterm NBIs associated with hospitalization and medical devices in the pathogenesis of LONS.[6]

The prevalence of microorganisms varies among countries, with a higher burden of gram-negative infections in low-resource areas.[2] The epidemiology of EONS and LONS is not as clearly delineated in low- and middle-resource countries, where the disease burden and mortality from neonatal sepsis is higher.[10]

An adequate antibiotic treatment of neonatal sepsis improves prognosis, mortality, and morbidity; but an inadequate and excessive antibiotic use is associated with a higher incidence of antibiotic resistance, necrotizing enteritis, and neonatal mortality. A thorough knowledge of the local epidemiology is key to the appropriate selection of empirical treatment and the reduction of side effects. Recently, Zarate et al. published the study *Prevalence of microbiologically confirmed neonatal sepsis at a maternity center in the City of Buenos Aires*, which accounted for one-third of the population born at public hospitals in that city. They reported an overall prevalence of EONS of 0.86‰ (CI: 0.52–1.20‰) and a prevalence of EONS by birth weight of 0.48‰ among those with a birth weight > 2500 g; 0.96‰ (OR: 2, CI: 0.44–9.02) among those with a birth weight of 1500–2499 g; 16.08‰ (OR: 33.91, CI: 10.56–96.79) among those with a birth weight of 1000–1499 g; and 31.39‰ (OR: 67.21, CI: 24.33–175.84) among those with a birth weight < 1000 g, similar to what has been published in the international bibliography.[11] Compared to historical data from this maternity hospital published by Sarubbi et al., the prevalence of neonatal sepsis due to GBS was 0.8‰ and 1.2‰ in 1985 and 1997, respectively;[12] however, they currently report a prevalence of EONS due to GBS of 0.1‰, evidencing a decrease in the prevalence of EONS due to GBS as described in other facilities. As reported in the bibliography, NBIs with EONS and isolation of GBS were term NBIs. In contrast to what was reported in the US, the most frequent microorganism found in EONS was EC, but, as reported in other facilities, it affected LBW NBIs.

In the case of LONS, as described in the bibliography, the hospital-acquired infection affected significantly more LBW NBIs with an OR of 725.17 (CI: 444.06–1197.11) for a birth weight < 1000 g, an OR of 273.32 (CI: 167.65–458.93) for a birth weight of 1000–1500 g, and an OR of 21.98 (CI: 12.79–36.02) for a birth weight > 1500 g. The main isolated microorganisms were CoNS and SA, followed by EC and *Candida* spp. In the case of community-acquired infection, the most frequent microorganisms were EC and SA, and bacteremia, urinary tract infections, and soft tissue infections predominated.

In conclusion, knowledge of the local epidemiology and its variation over time allows for a better empirical treatment, and improve morbidity and mortality associated with this very frequent infection. ■

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