Neonatal Sepsis of Early Onset, and Hospital-Acquired and Community-Acquired Late Onset: A Prospective Population-Based Cohort Study

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Objective To assess the epidemiology of blood culture-proven early- (EOS) and late-onset neonatal sepsis (LOS).

Study design All newborn infants admitted to tertiary care neonatal intensive care units in Switzerland and presenting with blood culture-proven sepsis between September 2011 and December 2015 were included in the study. We defined EOS as infection occurring <3 days after birth, and LOS as infection ≥3 days after birth. Infants with LOS were classified as having community-acquired LOS if onset of infection was ≤48 hours after admission, and hospital-acquired LOS, if onset was >48 hours after admission. Incidence was estimated based on the number of livebirths in Switzerland and adjusted for the proportion of admissions at centers participating in the study.

Results We identified 444 episodes of blood culture-proven sepsis in 429 infants; 20% of cases were EOS, 62% hospital-acquired LOS, and 18% community-acquired LOS. The estimated national incidence of EOS, hospital-acquired LOS, and community-acquired LOS was 0.28 (95% CI 0.23-0.35), 0.86 (0.76-0.97), and 0.28 (0.23-0.34) per 1000 livebirths. Compared with EOS, hospital-acquired LOS occurred in infants of lower gestational age and was more frequently associated with comorbidities. Community-acquired LOS was more common in term infants and in male infants. Mortality was 18%, 12%, and 0% in EOS, hospital-acquired LOS, and community-acquired LOS, and was higher in preterm infants, in infants with septic shock, and in those requiring mechanical ventilation.

Conclusions We report a high burden of sepsis in neonates with considerable mortality and morbidity. EOS, hospital-acquired LOS, and community-acquired LOS affect specific patient subgroups and have distinct clinical presentation, pathogens and outcomes. *(J Pediatr 2018;■■:■■-■■).*

Despite advances in perinatal care, neonatal sepsis remains a major cause of mortality, with an estimated toll of over 400 000 annual deaths worldwide.[1] Considering the importance of sepsis as a leading cause of neonatal death, the World Health Organization has recently defined the need to reduce the burden of maternal and neonatal sepsis as one of the Sustainable Development Goals and has accepted a resolution to improve prevention, recognition, and management of sepsis across all age groups.[2,3] Survivors of neonatal sepsis often require prolonged hospitalization and are at risk of long-term sequelae including chronic lung disease and adverse neurodevelopmental outcomes.[4-6] The incidence of neonatal sepsis varies in different geographic regions, reflecting differences in resources, maternal and infant risk factors, and prevention strategies, but sepsis represents one of the most common neonatal diseases even in high-income countries.[7] Neonatal sepsis is classified into early- (EOS) and late-onset sepsis (LOS). EOS presents within 72 hours after birth, affecting 0.5-1 out of 1000 infants in high-income countries, with a case fatality rate of 10%-15%.[8-12] LOS is

BSI	Bloodstream infection
CLABSI	Central line-associated bloodstream infection
CoNS	Coagulase-negative staphylococci
E coli	*Escherichia coli*
EOS	Early-onset neonatal sepsis
GBS	Group B *Streptococcus*
HR	Hazard ratio
LOS	Late-onset neonatal sepsis
UTI	Urinary tract infection

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characterized by onset beyond 72 hours after birth in infants exposed to microorganisms from the postnatal environment. Most vulnerable are preterm infants, with reported rates of hospital-acquired LOS as high as 40% in extremely preterm newborns.[13,14] In contrast, community-acquired LOS has been reported predominantly in late-preterm and term infants.[15-17]

Previous studies have focused on EOS or LOS,[12,18] without distinguishing between community-acquired and hospital-acquired LOS,[10,19] and were limited to specific gestational age groups and pathogens.[20-26] There are few recent population-based studies on neonatal sepsis.[11,12,16,22,24] Most of them were retrospective and none encompassed the full spectrum of neonatal sepsis. It is essential to monitor the epidemiology of neonatal sepsis for benchmarking and quality improvement, in particular considering that hospital-acquired LOS represents a disease that is at least partially preventable. In addition, contemporary population-based data are key to continuously update policies and clinical practices based on the most prevalent pathogens and their susceptibility to antibiotics, and to identify the patients at highest risk of developing infection and infection-related complications.

We hypothesized that EOS, hospital-acquired LOS, and community-acquired LOS represent distinct entities characterized by different host and pathogen characteristics and resulting in different outcomes. The present study prospectively assessed the incidence, clinical features, microbiology, and outcomes of blood culture-proven sepsis in neonates, distinguishing between EOS, hospital-acquired LOS, and community-acquired LOS, and covering the entire neonatal population in a national population-based cohort.

Methods

The Swiss Pediatric Sepsis Study prospectively investigated the epidemiology of blood culture-proven sepsis in the 10 main pediatric centers of Switzerland, including all 10 tertiary care neonatal intensive care units, and the 9 high risk maternities of the country.[27-30] Details of the study and the study protocol have been reported elsewhere.[28] Children were eligible if they developed bacteremia between September 1, 2011, and December 31, 2015, in the presence of a systemic inflammatory response syndrome.[31-33] Contaminated blood cultures were excluded based on the following criteria: (1) pathogens usually considered as contaminants (eg, *Micrococcus* species); (2) coagulase-negative staphylococci (CoNS) in the absence of a peripheral or central catheter at the time the blood culture was taken; (3) blood cultures growing a mixed flora of CoNS; (4) blood cultures considered as contaminants by the responsible physician, implying that antimicrobial therapy was discontinued in <5 days. For this study, we included infants born ≥37 weeks of gestation with sepsis onset before 28 days of life, and infants born <37 weeks of gestation with sepsis onset before 44 weeks corrected age.[33] We defined the onset of sepsis by the date of blood culture collection.

The ethics committees of all participating centers approved the study, and procedures were in accordance with the Helsinki Declaration of the World Medical Association. Data on demographics, perinatal risk factors, infection focus, severity, and outcome were recorded prospectively. We defined EOS by onset in the first 3 days of life and LOS by onset >3 days of life. Among infants with LOS, patients with sepsis onset ≤48 hours after admission were classified as having community-acquired LOS, and those with onset >48 hours after admission were classified as having hospital-acquired LOS.[34] Primary bloodstream infection (BSI) and central line-associated bloodstream infection (CLABSI) were defined according to Centers for Disease Control and Prevention criteria.[34] Septic shock was defined as hypotension requiring catecholamine treatment. We estimated the annual incidence of neonatal sepsis in Switzerland by including only sepsis episodes recorded during full study years (2012-2015). The number of livebirths in Switzerland according to sex and gestational age was obtained from the Swiss Federal Statistical Office as previously reported.[28,35] We used the following correction factors to adjust the denominator according to the proportion of newborn infants that were treated at the hospitals participating in the study: for infants born <32 weeks, 98% were born at or transferred postnatally to a study center (Mark Adams, written communication, March 2017); and for infants born ≥32 weeks, a model based on mandatory hospital statistics allowed to estimate that 80% of cases were treated at study centers.[28]

Statistical Analyses

We compared episodes of EOS, hospital-acquired LOS, and community-acquired LOS with respect to following characteristics: sex, gestational age, birthweight, ethnicity, presence of chorioamnionitis, maternal group B *Streptococcus* (GBS) status, maternal intrapartum antibiotic treatment, comorbidity, insertion of central venous catheter before sepsis onset, length of hospital stay, site of infection, pathogen, respiratory and hemodynamic support, and case fatality. We normalized the birthweight using the tables by Voigt et al.[36]

We used the Fisher exact test for differences in categorical variables, and the Kruskal-Wallis test for differences in continuous variables. We fitted a multinomial logistic regression model,[37] with timing of sepsis onset (EOS, hospital-acquired LOS, and community-acquired LOS; using EOS as reference group) as outcome variable, to examine which factors were independently associated with these groups. We selected variables for regression analysis if they were applicable to all 3 groups and had a P value of <0.2 in the Fisher exact or Kruskall-Wallis test. We first fitted univariable models to the selected predictors separately then used all selected predictors simultaneously in a multivariable model.

We estimated Kaplan-Meier curves for time to death within 30 days of onset stratified by timing of sepsis onset. Analysis time began at time of blood culture sampling and was right-censored at 30 days if children survived. We separately fitted univariable Cox proportional hazard regression models[38] on the same predictors used in multinomial regression to investigate the effects of timing of sepsis onset on case fatality. We then fitted a multivariable model containing all predictors simultaneously.

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