Late-onset Neonatal Infections 1997 to 2017 Within a Cohort in Western Sweden—The Last 21 Years of a 43-Year Surveillance

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Background: The objective of the study was to assess the epidemiology of late-onset (LO) neonatal invasive infections with surveillance covering 43 years, starting from 1975.

Methods: Observational epidemiologic, retrospective study including a cohort of infants born in western Sweden in 1997–2017, who had a positive blood and cerebral spinal fluid culture between 3 and 120 days of age. A comparison was made of the incidence between 1997–2007 and 2008–2017. Data on LO infections during 3–27 days of life were assessed from 1975.

Results: A total of 473 cases of LO infections were registered in 437 patients. The incidence increased from 2.0 to 3.1/1000 live births (LB) between 1997–2007 and 2008–2017 (P < 0.001). The increase in incidence was most pronounced among infants born <28 weeks gestation (from 255 to 398/1000 LB, P < 0.001). The most frequent pathogens were Staphylococcus aureus (25%), coagulase-negative staphylococci (17%), and Escherichia coli (13%). Infections due to group B Streptococci rose from 0.16/1000 LB to 0.33 (P = 0.03). During the whole surveillance period from 1975 to 2017, there were 579 cases between 3 and 27 days of life. Although the incidence increased in 2008–2017 to 1.9/1000 LB after first declining in 1997–2007, the case-fatality rate continued to decline from 27/284 (9.5%) between 1975 and 1996 to 6/182 (3.3%) in 2008 and 2017 (P = 0.01).

Conclusions: The incidence of LO neonatal invasive infections increased during the study period (1997–2017), but the case-fatality rate remained lower than in the previous surveillance period (1975–1996). Further surveillance and interventions with focus on prevention is critical to counteract the increasing incidence among high-risk infants.

Key Words: neonatal sepsis, meningitis, late-onset, epidemiology

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The study was approved by the regional ethics committee.

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blood should have been drawn for culture but this was not controlled or measured. Bacteria and fungi were cultured, isolated and identified at the microbiology laboratory using methods validated for clinical routine diagnostics.8

The occurrence of recognized pathogens was regarded as the cause of infection but cultures having questionable clinical significance had to meet criteria that are listed in Text (Supplemental Digital Content 1, http://links.lww.com/INF/E210). Cultures not fulfilling the criteria were excluded from the study. We chose not to follow the criteria stated by Centers for Disease Control that a minimum of 2 positive blood cultures are required for a commensal-related sepsis since these criteria changed in year 2008, and it is not a routine at our unit to draw more than 1 blood culture.9 Multiple positive cultures from a single infant yielding the same pathogen and the same antibiotic susceptibility profile within 7 days were considered to represent the same infectious episode. Death related to infection was defined as death occurring within 7 days of culturing and the infection documented as the direct cause of death. Possible changes in incidence and etiology were assessed by comparing the last 10 years (2008–2017) with the prior 11 years (1997–2007).

Findings on incidence and fatality of LO infections occurring at 3–27 days of age were compared with 22 years of preexisting data from the same population.

The Ethics Committee of Gothenburg, Ö 020-03, approved the study with waiver of consent, given the minimal risk. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection reporting guideline.10

Statistical Analysis
Incidence rates were estimated as the number of infected infants overall or by subgroup, divided by the total number of LB within the population or by the total number of LB reported for the same subgroup. Cases with missing or wrongly registered gestational age were included in calculations on overall incidence data but otherwise excluded. Demographic data were presented as mean or median after being tested for normality with Kolmogorov-Smirnov test. Proportions were compared with Fisher’s exact test (2-tailed), and correlations between continuous outcomes were analyzed using the Spearman test. Analyses were conducted in SPSS version 26.0 (IBM Corp). A 2-sided P < 0.05 was considered significant.

RESULTS
Participants
The total number of LB within the study area during 1997–2017 was 181 928, which were missing registration on gestational age in 53 cases. A total of 1296 cases between 1997 and 2017 were evaluated, and 757 did not fulfill the inclusion criteria and were excluded (see Figure, Supplemental Digital Content 2, http://links.lww.com/INF/E212). Thus, 473 confirmed cases of LO infections were identified at the microbiology laboratory using methods validated for clinical routine diagnostics.8

Among all cases with infection in the age of 3–120 days, 65% (306/469) were preterm (gestational age ≤36 weeks). The proportion of infants born <28 weeks gestation rose from 30% in 1997–2007 to 42% in 2008–2017 (P = 0.01). The highest rise in incidence was among those born at gestational age 24–25 weeks (see Table, Supplemental Digital Content 3, http://links.lww.com/INF/E212).

All 4 with missing data on gestational age belonged to the group of 117 patients admitted from home. The mean birthweight within this group was 3459g [95% confidence interval (CI): 3327–3590] and mean gestational age was 39 weeks (95% CI: 38.7–39.5). The most common pathogens were E. coli (41/117), GBS (26/117), and Staphylococcus aureus (19/117). Sixteen of these patients had a birth defect or preexisting condition [urogenital defects (9), choanal atresia (1), Pfeiffer syndrome (1), Down syndrome (1), asplenia (1), hepatitis (1), arthrogryposis (1), and maple syrup disease (1)].

Meningitis
Among 102 LP, the CSF culture was positive in 32 cases. Of those, 31% (19/32) yielded GBS and 22% (7/32) yielded E. coli. Half of the cases with meningitis had the same pathogen cultured in blood. The median gestational age was 37.5 weeks (IQR, 28–39) and the case-fatality rate was 6% (2/32). The majority (20/32) of meningitis cases were diagnosed in the first 28 days of life, but the highest proportion of positive CSF cultures among infants with LO infection was observed at >60 days of age (7/58). The meningitis incidence of 0.2/1000 LB did not change between 1997–2007 and 2008–2017.

Fatal Cases
There was no difference in birthweight or gestational age between the 29 fatal cases [mean birthweight 1852g (95% CI: 1472–2232), median gestational age 30 weeks (IQR: 26–39)] and the ones that survived (1934g (95% CI: 1811–2057), median gestational age 34 weeks (IQR: 26–37), P = 0.7, respectively, P = 0.9).
In 1997–2007, infections at 28–120 days of age were diagnosed in 178 infants with median gestational age of 30 weeks (IQR: 26–38) and birthweight 1500 g (IQR: 810–3180). The total incidence was 1.0/1000 LB and increased from 0.7 to 1.2/1000 LB, \( P = 0.001 \), between 1997–2007 and 2008–2017, but the case-fatality rate remained unchanged at 8.4% (15/178).

In 1987–1996, which was the first surveillance period on LO infections between 28 and 120 days of age, the incidence was 1.0/1000 LB.\(^6\)

### DISCUSSION

Our study shows that LO infections increased during the last decade, which agreed with our main hypothesis. LO infections among infants born extremely preterm increased as well from 25% (53/208) to 40% (126/317). The increase within the same gestational age group does not correlate with the hypothesis that a higher survival of infants born extremely preterm would explain the rising incidence. Yet, infants born at gestational age 24–25 weeks had the highest rise in incidence rate, and they often require prolonged intensive care with invasive procedures to be able to survive which can explain the increase. Among the extremely preterm compared with other studies, which have reported proportions of 21%–27% among surviving VLBW infants,\(^12–14,17\) this might be the reason for the increased incidence in our study although we did not see a rise in central catheters and respiratory support at the time of infection (Table 1).

Previous studies have reported median age for occurrence of LO infections between the 10th and 22nd day of life, and this is in agreement with our study.\(^12,15,16\)

This study showed a higher proportion of LO infections among the extremely preterm compared with other studies, which have reported proportions of 21%–27% among surviving VLBW infants.\(^12–14,17\) These studies only counted the first LO episode in each infant, but nonetheless our rate was higher, 32% (159/525) agreement with our study.\(^12,15,16\)
TABLE 2. The Incidence—Per 1000 Live Births Within the Same Gestational Age Group—of Organisms Cultivated From Blood and Cerebrospinal Fluid Among 473 Cases at 3–120 Days of Age Between 1997 and 2017: Comparison Between 1997–2007 and 2008–2017

| Type of Organism          | Gestational Age (wks) | Median Age—d (IQR) |
|---------------------------|-----------------------|--------------------|
|                           | <28                   | 28–36              | ≥37    | Missing | Total |
| **Gram-positive bacteria**|                       |                    |        |         |       |
| *Staphylococcus aureus*   | 101.0                 | 3.2                | 0.20   | 0.66    | 20    |
| Nr cases 1997–2007        | 14                    | 16                 | 16 (25) | 1       | 47 (27) |
| Nr cases 2008–2017        | 39                    | 15                 | 19 (19) | 73 (25) |
| P                         | 0.04                  | ns                 | ns     | ns      |       |
| Coagulase-negative Staphylococci* | 85.7                | 2.6                | 0.06   | 0.45    | 12 (7–27) |
| Nr cases 1997–2007        | 13                    | 8                  | 4      | 25      |       |
| Nr cases 2008–2017        | 32                    | 17                 | 7      | 56      |       |
| P                         | ns                    | ns                 | ns     | 0.004   |       |
| **Gram-negative bacteria**|                       |                    |        |         |       |
| *Escherichia coli*        | 15.2                  | 1.0                | 0.24   | 0.33    | 18 (12–30) |
| Nr cases 1997–2007        | 3                     | 7                  | 17     | 10      |       |
| Nr cases 2008–2017        | 5                     | 3                  | 24     | 1       | 33     |
| P                         | ns                    | ns                 | ns     | ns      |       |
| *Klebsiella pneumoniae*   | 13.3                  | 0.7                | 0.05   | 0.13    | 36 (14–48) |
| Nr cases 1997–2007        | 2                     | 5                  | 2      | 8       |       |
| Nr cases 2008–2017        | 5                     | 5                  | 5      | 15      |       |
| P                         | ns                    | ns                 | ns     | ns      |       |
| Other Enterobacter spp    | 13.3                  | 0.4                | 0.06   | 0.12    | 41 (16–55) |
| Incidence/1000 live births| 1                     | 0                  | 0      | 5       |       |
| Nr cases 1997–2007        | 6                     | 4                  | 4      | 17      |       |
| Nr cases 2008–2017        | 7                     | 0                  | 0.01   | 8       |       |
| P                         | ns                    | ns                 | ns     | ns      |       |
| *Serratia marcescens*     | 19.1                  | 0.2                | 0.01   | 0.07    | 22 (7–48) |
| Incidence/1000 live births| 3                     | 2                  | 0      | 5       |       |
| Nr cases 1997–2007        | 7                     | 0                  | 0.01   | 8       |       |
| Nr cases 2008–2017        | 1                     | 3                  | 1      | 5       |       |
| P                         | ns                    | ns                 | ns     | ns      |       |
| *Klebsiella oxytoca*      | 3.8                   | 0.5                | 0.01   | 0.05    | 10 (7–27) |
| Incidence/1000 live births| 1                     | 2                  | 1      | 4       |       |
| Nr cases 1997–2007        | 1                     | 3                  | 1      | 5       |       |
| P                         | ns                    | ns                 | ns     | ns      |       |
| *Pseudomonas spp.*        | 1.9                   | 0.3                | 0.01   | 0.03    | 47 (19–90) |
| Incidence/1000 live births| 0                     | 0                  | 0.01   | 0.01    | 55 (37–55) |
| Nr cases 1997–2007        | 0                     | 0                  | 0      | 2       |       |
| Nr cases 2008–2017        | 0                     | 0                  | 0      | 0       |       |
| P                         | ns                    | ns                 | ns     | ns      |       |
| *Haemophilus influenzae*  |                       |                    |        |         |       |
| Incidence/1000 live births| 0                     | 0                  | 0.01   | 0.01    | 63 (41–73) |
| Nr cases 1997–2007        | 0                     | 0                  | 1      | 1       |       |
| Nr cases 2008–2017        | 2                     | 1                  | 0      | 3       |       |
| P                         | ns                    | ns                 | ns     | ns      |       |

(Continued)
among 51.2% in infants with birth weight between 501 and 750 grams. Many studies group infants according to birthweight instead of gestational age. However, immune competence and risk for infection are more in line with gestational age than with birth weight.4,8

In the present study, we had a higher incidence of *Staphylococcus aureus* than CoNS within all gestational age groups. CoNS accounted for 25% (45/179) of all infections among infants born extremely preterm but many other studies have reported that CoNS accounts for more than half of all pathogens on LO infections among VLBW infants.11,13,19 It is challenging to compare incidence of LO infections especially regarding commensal species like CoNS. Many units recommend that at least 2 cultures should yield the same organism before stating that it is an infection.9 One study showed that including 2 positive blood cultures does not change the outcome.20

The higher incidence of LO-GBS infections in the latter period (2008–2017) is in agreement with other studies showing an incidence rate of 0.3/1000 LB among infants 7–89 days of age.21,22 European studies, reporting data from 1997 to 2003, showed a lower incidence, at the range of 0.14–0.24/1000 LB,23–25 which is consistent with our results from 1997 to 2007. A study from Australia also showed an increasing trend but since the study was not population-based they could not rule out that the increasing trend was due to a higher rate of transfer from peripheral hospitals.26 A study from Iceland showed a rising number of LO-GBS cases as the period (2008–2017) is in agreement with other studies showing an incidence rate of 0.3/1000 LB among infants 7–89 days of age.21,22

### TABLE 2. (Continued.)

| Type of Organism | <28 | 28–36 | ≥37 | Missing | Total | Median Age—d (IQR) |
|------------------|-----|------|-----|--------|-------|-------------------|
| **Mixed infections** |     |      |     |        |       | 56 (29–62) |
| Incidence/1000 live births |     |      |     |        |       | 0.04 |
| Nr cases 1997–2007 | 9.5 | 0.1  | 0.01| 0.04   |       |       |
| Nr cases 2008–2017 | 5   | 1    | 0   | 1      |       |       |
| P | ns | ns | ns | ns |       |       |
| **Fungi** |     |      |     |        |       | 21 (12–45) |
| *Candida albicans* |     |      |     |        |       |       |
| Incidence/1000 live births | 22.9| 0.8  | 0.02| 0.13   |       |       |
| Nr cases 1997–2007 | 7   | 4    | 1   | 12     |       |       |
| Nr cases 2008–2017 | 5   | 4    | 2   | 11     |       |       |
| P | ns | ns | ns | ns |       |       |
| **Total** |     |      |     |        |       | 21 (11–40) |
| Incidence/1000 live births | 341 | 13.1 | 0.95| 2.6    |       |       |
| Nr cases 1997–2007 | 53  | 55   | 65  | 2      | 175   |       |
| Nr cases 2008–2017 | 126 | 72   | 98  | 2      | 298   |       |
| P | <0.001 | ns | ns | ns |       | <0.001 |

*Staphylococcus epidermidis, S. hominis, S. capitis.*

†Streptococcus parasanguinis, *S. anginosus, S. Pneumoniae, Bacillus cereus, Rothia mucilaginosa, Beta-hemolytic streptococci group A.

‡Acinetobacter spp, Moraxella spp, Stenotrophomonas maltophilia.

§S. aureus and Enterococcus (3), S. aureus and Acinetobacter (1), Klebsiella pneumoniae and Enterococcus (1), *K. pneumoniae* and Pseudomonas aeruginosa (1), *K. pneumoniae* and *Escherichia coli* (1).

IQR indicates interquartile range (25%–75%); ns, not significant.

The main strength of this study is the long surveillance of LO infections within the same population for 43 years. The study is population-based and many previous studies focused only on infants within the NICU or selected risk groups of VLBW infants. There are several limitations to our study. The study is retrospective and diagnostic bias is always a concern, especially when comparing with preexisting data during a long follow-up. In the beginning of the surveillance (1975–1986), CoNS was considered a contaminant and therefore not treated and not fulfilling the criteria since 2008 for all infants born <28 weeks gestation. Infections with *Candida* spp. are often expected after the third week of admittance in the NICU and this is in correlation with our study.23 We cannot state if the empirical treatment has had an impact or not since the observed decline in rate after 2007 was not statistically significant. The proportion of meningitis among LO cases in the present study was 6.8%. Confirming the diagnosis of meningitis with culture can be challenging considering that an LP is often delayed until the patient is clinically stable enough, and the results of other tests relied upon to diagnose meningitis, like polymerase chain reaction, were not included in our analysis. A previous study showed a lower proportion of meningitis among LO infections at 5.7%.29 Our incidence of meningitis, 0.2/1000 LB, is likely an underestimation considering that only 22% (102/473) had an LP.

We found no evidence that our secondary hypothesis was true, since the overall case-fatality did not change. However, during the whole surveillance period of infants at age 3–27 days the case-fatality among LO infections declined despite the same incidence. We observed an increased case-fatality among recurrent cases. This can partly be explained by a higher incidence of Gram-negative bacterial infections in this group and therefore a higher mortality.13,30,31 The recurrence rate of 11% (20/179) among infants born extremely preterm was lower than in other studies, reporting rates of 21%–28% among VLBW infants.21,22,30,31 The reason for higher use of central catheters and continuous positive airway pressure among cases with recurrent infections is most likely a reflection of this group being more preterm compared with cases with a single episode of LO infection, and we cannot comment on any causation.

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for a causative agent. We included single blood cultures, although they showed commensal bacteria and this might have led to an overestimation of the incidence of infections caused by these bacteria. We only included culture positive infections, and low sample volume might be a problem, especially in infants born extremely preterm, thereby underestimating the true incidence of neonatal infections. We did not exclude infants that died within 3 days of life from the analysis and thereby we might have overestimated the true incidence of LO infections. As the study was population-based it makes the study population heterogeneous and since the population only included infants within western Sweden the results cannot be generalized.

We do not believe that changes in culture techniques have had any impact on the incidence since the vast majority of the episodes were caused by bacteria easily cultured and identified at the clinical laboratory.

In summary, this study shows that the epidemiology of LO neonatal infections continues to change. Ongoing surveillance is critical and prevention needs to be optimized, especially among the high-risk infants born extremely preterm.

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