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# Presumed and definite bacteremia in extremely low gestational age newborns

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## Abstract

**Aim—**To explore risk patterns for presumed and definite, early and late neonatal bacteremia.

**Methods—**We studied 1106 ELGANs who survived until postnatal day 28. We defined early definite bacteremia as a positive bacterial culture in the first week and definite late bacteremia as a positive bacterial culture in week 2, 3 or 4. Bacteremia was presumed if antibiotics were given for more than 72 hours despite negative blood cultures.

**Results—**Risk patterns did not differ much for presumed and definite bacteremia in the first postnatal month. While maternal and pregnancy characteristics were associated with early bacteremia, neonatal co-morbidities, especially NEC, were the main antecedents/correlates of late bacteremia. All four categories of bacteremia were associated with younger gestational age and lower birth weight. Infants with presumed and definite bacteremia had similar distributions of days of ventilation and oxygenation.

**Conclusion—**Definite and presumed late bacteremia have rather similar risk patterns, while those of early and late bacteremia differ appreciably.

### Keywords

Infant; risk; sepsis

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## Introduction

Neonatal bacteremia is defined as bacteria in the blood stream (1,2). The host's immune response to infection (termed “sepsis”) can result in a systemic inflammatory state with hemodynamic consequences, damage to organs (1,3), and increased mortality risk (4). Many preterm newborns are treated empirically with antibiotics since failure to treat undiagnosed bacteremia can be fatal (1,3,5).

Neonatologists divide bacteremia into early and late onset. The assumption is that early-onset bacteremia is acquired during labor and delivery, and late-onset is acquired in the neonatal intensive care unit (NICU) (1-3,5,6). Known antecedents of early onset bacteremia include prelabor rupture of membranes (PROM) > 18 hours, low Apgar scores, chorioamnionitis/maternal fever, maternal vaginal or rectal colonization with group B Streptococcus (GBS), maternal GBS bacteruria, foul smelling amniotic fluid, maternal anemia, gestational hypertension, and a previous history of preterm labor (1,7-9).

The antecedents of late onset bacteremia are less well delineated. Because late bacteremia is regarded as nosocomial, maternal clinical history and demographics do not appear to be as important as for early-onset bacteremia (2). Nevertheless, antepartum hemorrhage, rupture of membranes > 6 hours, and chorioamnionitis appear to be potentially important antecedents (10). Neonatal co-morbidities also contribute to late-onset bacteremia (2,10). In both early and late-onset bacteremia, low birthweight and prematurity are associated with increased risk (2,7,8,10).

While previous reports have studied low birthweight infants, we focused on extremely low gestational age newborns (ELGANs) (i.e., < 28 weeks). We explored differences and similarities in risk patterns for presumed and definite bacteremia, both with early and late onset in a sample of 1098 newborns whose placenta was cultured and examined histologically.

## Subjects and Methods

The ELGAN (Extremely Low Gestational Age Newborn) study recruited women who were delivered before 28 weeks gestation at one of 14 participating institutions in 11 cities in 5 states during the years 2002-2004. The study was approved by all institutional review boards.

1249 mothers of 1506 infants consented (Table S1). Approximately 260 women were either missed or did not consent to participate. The sample for the analyses presented in this paper consists of the 1106 ELGANs who survived until postnatal day 28 and for whom we had information about early and late bacteremia, placenta bacteriology and placental histology.

### Demographic, pregnancy, and neonatal variables

After delivery, a trained research nurse interviewed each mother in her native language using a structured data collection form and following procedures defined in a manual. The mother's report of her own characteristics and exposures, as well as the sequence of events leading to preterm delivery, was taken as truth, even when her medical record provided discrepant information. Some mothers did not provide answers to every item in the questionnaire. After the mother's discharge, the research nurse reviewed the maternal chart using a second structured data collection form. We relied on the medical record for events following admission. The definitions of maternal and pregnancy (11-15), and neonatal variables (16-19) are documented in previous ELGAN publications.

### Bacteremia

Bacterial cultures were reported on the forms for days 7, 14, 21, and 28. As a result, we do not know on which day blood harbored an organism, but we do know during which week. Consequently, we define early bacteremia as evident in the first week and late bacteremia as evident in weeks 2, 3 or 4. Infants with multiple episodes of bacteremia were combined with children who had only a single episode.

Bacteremia was considered definite when bacteria were recovered from blood. Presumed bacteremia was culture-negative, but the infant received antibiotics for more than 72 hours, the usual timepoint when antibiotic treatment is discontinued in 'rule-out-sepsis' given that cultures remain negative and the infant is clinically stable.

### Data analysis

We evaluated the generalized null hypothesis that the risks of presumed and documented early and late bacteremia are NOT associated with maternal demographic characteristics, pregnancy exposures and characteristics, characteristics of the newborn, recovery of organisms from placenta parenchyma, or any histologic lesion in the placenta.

In the ELGAN Study sample, recovery of an organism from the placenta and some histologic features of the placenta are associated with gestational age (13,15), as is documented late bacteremia. Therefore, we adjusted for gestational age (by groups of weeks: 23-24, 25-26, 27) when creating all logistic regression models. Because presumed and definite bacteremias are mutually exclusive and each is appropriately compared to the same referent group, we used multinomial (also known as polytomous or polychotomous) logistic regression for the models of early bacteremia and of late bacteremia. We used a step down procedure seeking a parsimonious solution without interaction terms. The contributions of antecedents/correlates to early and late bacteremia are presented as risk ratios with 95% confidence intervals.

## Results

### Maternal illness and medication (Table S2)

Vaginitis is the only maternal, pre-delivery characteristic associated with a small increased risk of presumed and documented early bacteremia. Maternal aspirin consumption was associated with almost a doubling of the risk of early definite bacteremia.

### Delivery characteristics (Table S3)

A complete course of antenatal corticosteroids has no discernable effect on the risk of any of the four forms of bacteremia. Long durations of labor and of membrane rupture were associated with an increased risk of documented early bacteremia, as were cervical insufficiency and fetal indication for delivery. None of these delivery characteristics was associated with presumed or documented late bacteremia.

### Newborns' characteristics (Table 1)

A birthweight Z-score <-2 was the only physical characteristic of the newborn associated with a small increased risk of documented early bacteremia. While the rates of definite bacteremia tended to rise with decreasing gestational age, no such trend was observed for presumed bacteremia.

### Placenta bacteriology (Table S4)

Recovery of an organism from the placenta did not appear to substantially increase the risk of early or late bacteremia. The only association with documented early bacteremia that approached, but did not achieve, statistical significance was the recovery of a single bacterial species.

### Placenta histology (Table S5)

Umbilical cord vasculitis is the one histologic characteristic that was prominently associated with an increased risk of documented early bacteremia. Placental infarct was associated with an increased risk of presumed late bacteremia, but not with an increased risk of documented late bacteremia.

### Postnatal exposures (Table 2)

We did not collect information on the length of time the baby had a central line. Instead, we collected information about insertion of a new line each week. The later a new line was inserted, the higher the risk of documented early bacteremia, but not documented late bacteremia. The presence of an arterial or venous umbilical line was associated with an increased incidence for presumed or definite bacteremia, both early and late.

A central nervous system infection was associated with presumed and documented early bacteremia, as well as presumed late bacteremia. Infants who had documented trachea colonization were at increased risk of documented late bacteremia. The presence of necrotizing enterocolitis (NEC) was associated with an increased risk of late presumed and definite bacteremia. An isolated perforation was associated with a doubling of the risk of early and late definite bacteremia, while advanced necrotizing enterocolitis was associated with a significant increased risk for late definite bacteremia. Other postnatal characteristics associated with an increased risk of documented late bacteremia were pulmonary hemorrhage, patent ductus arteriosus, and oxygen dependency at 36 weeks post-menstrual age (chronic lung disease/bronchopulmonary dysplasia).

### Multivariable analyses (Table 3)

Four of the participating NICUs had much higher rates of early and late definite bacteremia than the other NICUs. To make sure that this difference did not obscure our perception of the contribution of other risk factors to bacteremia, we included this “high-risk hospital” variable in all multivariable models with candidates selected from the univariable tables. Four characteristics were significantly associated with an increased risk of culture-documented (definite) early bacteremia. These were low gestational age, umbilical cord vasculitis, deposition of hemosiderin and fibrin in the placenta decidua, and birth at a “high risk” hospital. This risk profile did not apply to early presumed bacteremia.

The seven characteristics associated with a significantly increased risk of late definite bacteremia were gestational age between 23 and 26 weeks (two variables, one for 23-24 weeks and one for 25-26 weeks), a birthweight Z score <-1, umbilical cord vasculitis, birth at a “high risk” hospital, PDA treatment, necrotizing enterocolitis (Bell stage III), and isolated intestinal perforation. Besides low gestational age, the only variables also associated with late presumed bacteremia were a placenta infarct and a central line.

### Duration of ventilation and oxygen exposure (S-Figure)

Infants with documented bacteremia had distributions of days of ventilation and oxygenation that were very similar to those of infants with presumed bacteremia, whether the bacteremia was early or late (S-Figure). All four bacteremia groups had distributions that invariably

differed from those of infants who were not thought to have bacteremia. The most prominent differences in the distributions of days of ventilation were seen between no bacteremia and presumed or definite late bacteremia (panel B).

## Discussion

Our first main finding is that that the major antecedents of early bacteremia are maternal and pregnancy characteristics, while neonatal characteristics are closely associated with late bacteremia. A second important finding is that multiple risk factors appear to be present in both presumed and definite bacteremia. Third, probably the most important postnatal correlates of late bacteremia are necrotizing enterocolitis and isolated intestinal perforation.

The major advantages of our analysis are the wealth of antenatal, perinatal, and postnatal information we had available, the large size of our data set, and the associated benefit of multivariable adjustment for confounders. With regard to bacteremia, however, one major limitation is that no detailed information was available about the species of bacteria isolated from cultures. Another drawback is that clinicians, as well as investigators, are sometimes unable to distinguish between pathogens and contaminants.

In a previous report based on our ELGAN sample, women with cervical insufficiency as the proximate cause of delivery were the most likely to have had vaginitis during pregnancy (11). Maternal vaginitis was a risk factor for early bacteremia, presumed and definite, while cervical insufficiency was a risk factor for early definite bacteremia.

Fetal indication was also an antecedent of early definite bacteremia. In this sample, ELGANs delivered for fetal indications tended to have the lowest birthweights, but not necessarily the lowest gestational age. Thus, it seems as if, among ELGANs, fetal indications define a group of preterm newborns who are growth restricted and at high risk of neonatal bacteremia. ELGANs born to women with preeclampsia, the only maternal indication for preterm delivery in this sample, also tended to be growth restricted. Yet, neither preeclampsia, nor an increased number of syncytial knots, one of the main histologic characteristics of preeclampsia, was associated with bacteremia. On the other hand, infarcts, another histologic characteristic of preeclampsia were associated with increased risk of presumed late bacteremia, but not documented late bacteremia. Since many of our findings for presumed late bacteremia are concordant with our findings for definite late bacteremia, we place a good deal of credence on the concordance between presumed and definite late bacteremia. Therefore, our failure to find such concordance with regard to placenta histology prompts us to be cautious about inferences that can be drawn from the histologic findings.

Pure (single species) cultures of the placenta, but not multi-species cultures, identified children at increased risk for bacteremia. The polymicrobial cultures were more likely than pure cultures to contain lower virulence organisms. Thus, the virulence of placenta organisms, rather than their diversity, might be more important in identifying a heightened risk of early bacteremia.

Umbilical cord vasculitis was associated with a significantly increased risk for early definite bacteremia. A prominent histologic expression of the fetal inflammatory response (20), umbilical vasculitis is often accompanied by microorganisms in the placenta (11). Umbilical vasculitis is also slightly more common among growth restricted infants (70%) than among infants with a birthweight Z-score >-1 (58%) (20). In light of these findings, umbilical vasculitis, recovery of organisms from the placenta, and growth restriction share information about the increased risk of early bacteremia.

By and large, the antecedents of late onset bacteremia are neonatal morbidities encountered in the NICU, such as extended duration of intubation, tracheal colonization, CSF infection, patent ductus arterious, pulmonary hemorrhage, and chronic lung disease.

NEC, an inflammatory bowel disease largely confined to the preterm population, was also prominently associated with documented late bacteremia. Others have also found that newborns with NEC are more likely than their peers to have bacteremia (2,10). At least part of the association we observed between presumed bacteremia and NEC might be due to the fact that prescription of antibiotic is standard treatment for NEC and also part of our definition of presumed bacteremia. In addition, the increased risk of late definite bacteremia among infants with a patent ductus arteriosus might reflect the increased risk of NEC that has been associated with PDA (21).

Characterized by a disruption of intestinal mucosal integrity, NEC is often accompanied by bacteria and other pro-inflammatory stimuli in the blood, including endotoxin, cytokines, chemokines and nitric acid (22-25). This suggests that late bacteremia might be a consequence of NEC and related phenomena.

Compared to their peers, children who developed an isolated perforation were at twice the risk for early and late definite bacteremia. Unfortunately, we do not know which came first.

In light of the many parallels and links between late bacteremia and NEC, as well as between late bacteremia and isolated intestinal perforation, we suggest that these bowel disorders be considered in studies of late bacteremia. This is especially important until the contribution of each to the occurrence of the other is clarified.

## Conclusion

In summary, we found that definite and presumed late sepsis have similar risk patterns, while those of early and late bacteremia differ appreciably. Growth restricted infants might be at a particularly high risk for developing bacteremia. Further research is needed to characterize these relationships, in order to improve clinical practice, identify newborns at highest risk, and avoid unnecessary antibiotic exposure.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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26. Previous Tables 1-3, 5, and 6 are now S1-S5 in the online Supporting Information

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**Table 1**

Risk of bacteremia associated with the newborn's characteristics at birth. These are row percents.

| Characteristics of the infant | | Early bacteremia | | Late bacteremia | | Row N |
|---|---|---|---|---|---|---|
| | | Presumed | Definite | Presumed | Definite | |
| Sex | Male | 37 | 6 | 16 | 25 | 594 |
| | Female | 34 | 8 | 14 | 27 | 512 |
| Type of gestation | Multiple | 35 | 7 | 14 | 25 | 351 |
| | Singleton | 35 | 7 | 16 | 26 | 755 |
| Gestational age (weeks) | 23-24 | 40 | 8 | 19 | 33 | 242 |
| | 25-26 | 34 | 8 | 16 | 27 | 503 |
| | 27 | 34 | 4 | 11 | 20 | 361 |
| Birthweight (grams) | ≤ 750 | 39 | 7 | 18 | 31 | 427 |
| | >750, ≤ 1000 | 33 | 7 | 15 | 26 | 460 |
| | >1000 | 31 | 6 | 10 | 16 | 219 |
| Birthweight Z-score* | < -2 | 43 | 9 | 20 | 34 | 70 |
| | ≥ −2,< −1 | 39 | 6 | 17 | 32 | 145 |
| | ≥ −1 | 34 | 6 | 14 | 24 | 981 |
| Maximum number of infants | | 390 | 72 | 165 | 286 | 1106 |

*Based on standard values from Yudkin et al. (27)

**Table 2**

Risk of bacteremia in relation to postnatal characteristics, events and exposures. These are row percents.

| Characteristics of the infant | | Early bacteremia | | Late bacteremia | | Row N |
|---|---|---|---|---|---|---|
| | | Presumed | Definite | Presumed | Definite | |
| Central line (week first placed) | Never | 35 | 7 | 14 | 26 | 1018 |
| | 1 | 22 | 0 | 23 | 18 | 40 |
| | 2 | 44 | 9 | 24 | 29 | 34 |
| | 3 | 50 | 13 | 38 | 25 | 8 |
| | 4 | 33 | 17 | 33 | 33 | 6 |
| Umbilical line (arterial or venous) | Yes | 36 | 7 | 15 | 26 | 1034 |
| | No | 23 | 4 | 9 | 21 | 71 |
| Days intubated | ≤ 7 | 29 | 5 | 9 | 14 | 331 |
| | 8 – 14 | 31 | 9 | 17 | 34 | 121 |
| | 15 - 21 | 34 | 5 | 14 | 28 | 109 |
| | 22 - 28 | 40 | 7 | 19 | 31 | 545 |
| Trachea colonization (definite) | Yes | 36 | 9 | 16 | 40 | 248 |
| | No | 35 | 6 | 15 | 22 | 849 |
| CSF infection (presumed/definite) | Yes | 53 | 18 | 31 | 33 | 85 |
| | No | 34 | 6 | 15 | 25 | 1000 |
| Necrotizing | None-Stage II | 35 | 7 | 14 | 25 | 1018 |
| enterocolitis | Stage III | 35 | 2 | 20 | 38 | 52 |
| | Isolated perf | 47 | 14 | 25 | 42 | 40 |
| Retinopathy of prematurity | None | 27 | 6 | 10 | 23 | 285 |
| | Stage 1-2 | 37 | 5 | 14 | 24 | 476 |
| | Stage 3-5 | 41 | 9 | 23 | 32 | 301 |
| Pneumothorax | Yes | 44 | 7 | 15 | 30 | 84 |
| | No | 35 | 6 | 15 | 26 | 1022 |
| PIE | Yes | 39 | 8 | 21 | 27 | 179 |
| | No | 35 | 6 | 14 | 26 | 927 |
| Pulmonary hemorrhage | Yes | 40 | 8 | 18 | 40 | 40 |

| Characteristics of the infant | | Early bacteremia | | Late bacteremia | | Row N |
|---|---|---|---|---|---|---|
| | | Presumed | Definite | Presumed | Definite | |
| | No | 35 | 6 | 15 | 25 | 1060 |
| PDA | No | 36 | 5 | 13 | 18 | 356 |
| | Clinical | 45 | 6 | 19 | 24 | 155 |
| | Echo confirmed | 33 | 8 | 15 | 31 | 595 |
| CLD | Yes | 39 | 7 | 19 | 29 | 542 |
| | No | 32 | 6 | 12 | 22 | 513 |
| Respiratory group classification | EPPD* | 41 | 7 | 19 | 27 | 458 |
| | PD** | 35 | 6 | 14 | 26 | 401 |
| | Low $FiO_2$ | 25 | 5 | 9 | 22 | 218 |
| Maximum number of babies | | 390 | 72 | 165 | 286 | 1106 |

*Early and persistent pulmonary dysfunction

**Pulmonary deterioration

## Table 3

Risk ratios (and 95% confidence intervals) for the form of bacteremia listed at the top of each column associated with the antecedents listed on the left. These have been adjusted for the other variables listed on the left that remain in the model.

| | Early bacteremia | | Late bacteremia | |
|---|---|---|---|---|
| | **Presumed** | **Definite** | **Presumed** | **Definite** |
| Gestational age 23-24 wks | 1.3 (0.96, 1.7) | 2.1 (1.3, 3.4) | 2.4 (1.5, 3.9) | 2.5 (1.7, 3.6) |
| Gestational age 25-26 wks | | | 1.7 (1.1, 2.5) | 1.6 (1.1, 2.2) |
| Birthweight Z-score <-1 | | | 1.2 (0.8, 1.8) | 1.5 (1.05, 2.1) |
| Umbilical cord vasculitis | 1.2 (0.8, 1.6) | 2.4 (1.4, 4.1) | | |
| Placenta infarct | | | 1.8 (1.2, 2.8) | 1.0 (0.6, 1.4) |
| Decidual hemosiderin/fibrin | 0.7 (0.5, 0.9) | 2.4 (1.4, 4.1) | | |
| High risk hospital[§] | 0.8 (0.6, 1.02) | 2.8 (1.7, 4.6) | 1.1 (0.7, 1.6) | 2.3 (1.7, 3.0) |
| Central line placed (wk 1-4) | | | 2.2 (1.3, 3.6) | 1.3 (0.8, 2.1) |
| PDA (treated) | | | 1.3 (0.9, 1.8) | 1.5 (1.1, 2.1) |
| NEC stage III | | | 1.5 (0.8, 2.9) | 1.8 (1.02, 3.1) |
| Isolated intestinal perforation | | | 2.0 (0.9, 4.8) | 2.1 (1.02, 4.4) |

[§]Four hospitals that had higher early or late bacteremia rates than the other 10 hospitals.