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Risk factors for death in suspected severe bacterial infection in infants aged <90 days in Luanda, Angola

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ABSTRACT

Background: Yearly, about two million infants die during the first 28 days of life. Most of these deaths occur in sub-Saharan Africa and a third of those are caused by severe infections. The early identification of infants at risk of death is important when trying to prevent poor outcomes.
Objective: The aim of this study was to identify risk factors for death among young infants with possible serious bacterial infection (pSBI) at hospital admission.
Methods: This prospective, observational, single-site, descriptive study forms part of a larger study on bacterial meningitis in infants <90 days of age admitted to the Pediatric Hospital of Luanda, the capital of Angola, from February 1, 2016 to October 23, 2017. Infants with pSBI, a known outcome, and a final diagnosis were included.
Results: Of 574 young infants with pSBI, 115 (20%) died in hospital. An altered level of consciousness, absence of spontaneous movements, dyspnea, CSF that is not clear, low CSF glucose, high CSF protein, heart rate over the median, and seizures were identified as risk factors for death in the univariate analysis. In the multivariate analysis, only heart rate over the median and seizures were independent predictors of death.
Conclusions: Easily recognizable clinical signs – tachycardia and seizures – may guide clinicians to identify infants at high risk of death due to severe bacterial infections in sub-Saharan Africa.

Introduction

Globally, 5.2 million children under five die annually (UN Inter-agency Group for Child Mortality Estimation, 2020). Forty-seven percent of those deaths are in neonates within the first 28 days of life (UN Inter-agency Group for Child Mortality Estimation, 2020). The majority of all under five and neonatal deaths occur in sub-Saharan Africa. Furthermore, of all neonatal deaths, 15% are sepsis-related (UN Inter-agency Group for Child Mortality Estimation, 2019). Yet, in sub-Saharan Africa, severe neonatal infections drive 37% of all deaths in these critical first 28 days of life (Alliance for Maternal and Newborn Health Improvement mortality study group, 2018). During the neonatal period, mortality due to sepsis ranges from 11% to 19% (Fleischmann-Struzek et al., 2018), whereas mortality due to bacterial meningitis (hereafter meningitis) ranges from 10% to 58%. Severe bacterial infections (sepsis, meningitis, and pneumonia) account for 12% of all disability-adjusted life-years (DALYs) during the neonatal period (GBD DALYs and HALE Collaborators, 2018). One study estimated that annually 6.9 million neonates need treatment for possible severe bacterial infections (pSBI) (Young Infants Clinical Signs Study Group, 2008) in sub-Saharan Africa, Southeast Asia, and Latin America (Seale et al., 2014).

The early identification of children at risk of death is critical to guide effective treatment strategies and prevent poor outcomes.

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Only a few recent studies have reported prognostic factors for death in young infants at hospital admission (English et al., 2003; Tette et al., 2020), in invasive bacterial infections (Pruitt et al., 2019), or in meningitis (Okike et al., 2018; Mao et al., 2018). The aim of this study was to identify risk factors for death among young infants with pSBI at hospital admission.

Materials and methods

Setting

Sub-Saharan Africa continues to be the region with the greatest burden of childhood mortality. In Angola, a sub-Saharan country, the <5 years, infant, and neonatal mortality rates are 75, 50, and 28 per 1000 live births, respectively. In 2019, 35 000 Angolan infants died in the first 28 days of life (UN Inter-agency Group for Child Mortality Estimation, 2020).

The Pediatric Hospital of Luanda (Hospital Pediátrico David Bernardino, HPDB) is a tertiary teaching hospital in the capital of Angola. The city area has a population of 2.8 million. When ill, most newborn babies and small infants are taken to HPDB directly from home and only a few are transferred from other healthcare facilities. Most babies in Luanda are born in maternity hospitals. During the study, the 30-bed neonatal ward had no facilities for mechanical ventilation. Neonatal sepsis and pneumonia were treated with a combination of benzyl penicillin and gentamicin, and meningitis with ampicillin and cefotaxime.

Study design

This study formed part of a prospective, observational, single-site, descriptive study with the primary objective of assessing the etiology of meningitis in infants <90 days of age (Pelkonen et al., 2020). The records of 1287 infants from February 1, 2016 to October 23, 2017 were screened for eligibility. Infants with pSBI, a known outcome, and a final diagnosis were included in the present study. The definition of pSBI was based on a World Health Organization (WHO) multisite study in young infants, where any one of the following signs and symptoms predicted severe illness requiring hospitalization: history of difficulty in feeding, history of convulsions, movement only when stimulated, respiratory rate of ≥60 breaths per minute, severe chest indrawing, temperature of ≥37.5 °C or <35.5 °C (Young Infants Clinical Signs Study Group, 2008; Seale et al., 2014).

Meningitis was considered confirmed when bacteria were identified in the cerebrospinal fluid (CSF) by culture, Gram stain, antigen detection, or PCR. Meningitis was 'probable' when CSF was turbid or showed leukocytes $>100 \times 10^6$/l or with milder leukocytosis ($10–100 \times 10^6$ cells/l) if the protein concentration was >100 mg/dl or glucose <40 mg/dl. Due to a lack of resources, blood cultures were not performed for the infants at the time of the study. The final diagnosis of sepsis was based on physician judgment and took into account obstetric risk factors, prematurity, low birth weight, perinatal hypoxia, and several clinical manifestations: fever, hypothermia, lethargy, inability to feed, vomiting, convulsions, dyspnea, icterus, pallor, and prolonged capillary refill (≥3 s) (McGovern et al., 2020). Infants with this clinical diagnosis of sepsis were treated with at least 5 days of antibiotics. The main outcome measure was in-hospital death.

Premature birth was defined as birth before the completion of 37 weeks of pregnancy. Weight ≥2500 g was considered appropriate for a newborn. Dyspnea was defined as increased work of breathing in an infant presenting with at least one of the following signs: sub-costal, intercostal, or supra-sternal indrawing, nasal flaring, grunting, and head nodding. Impaired consciousness referred to any abnormal status of consciousness, a Glasgow coma scale (GCS) score (Kirkham et al., 2008) below 15, or a Blantyre coma scale (BCS) score (Molyneux et al., 1989) below 5. Deep coma was defined as a BCS below 3.

The study was approved by the Ethics Committee of HPDB. Once information had been given by the attending physician, the legal guardians of enrolled infants provided consent by signing or fingerprinting a specific form.

Data collection

Six specially trained study nurses in collaboration with the attending doctors registered clinical information on specially designed paper forms. This data extraction form included questions on demographics, history of acute illness, findings on admission, laboratory test results, admission and discharge diagnoses, and the outcome (Supplementary material Appendix). The study staff trained the study nurses, two laboratory technicians, and three local pediatricians before the study start, and a follow-up meeting was held every 3 months. The hospital records and database of the laboratory of microbiology were also checked (TP) for available data concerning the study infants. The data were then transferred from the forms into an electronic database (SU), following which the information was double-checked (TP).

Statistical analysis

All data were computed and analyzed with JMP Pro 14.1.0 (SAS Institute Inc., Cary, NC, USA). Contingency analysis was used to examine relationships between two categorical variables and Pearson's Chi-square test was used to calculate the *P*-value. Associations with continuous characteristics were assessed using one-way analysis of variance (ANOVA).

Clinical variables available at hospital admission with a *P*-value <0.05 in the univariate analyses were submitted to a multivariate model. Those laboratory test results that are not immediately available and perhaps not available at all in resource-poor settings were not included in the analysis. Altered status of consciousness and the BCS score both measure the same thing; the BCS score performed better in the univariate analysis and so was chosen for the multivariate analysis. The first multivariate model included five variables. The model was then reduced to include the three best performing variables. The results are presented as odds ratios (OR) with 95% confidence intervals (CI). The area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated for the models.

Results

Of 1287 infants, 574 (45%) fulfilled the study inclusion criteria. Table 1 describes the background data and characteristics of the patients. Of the 574 infants, 49% were female and 51% were male. The age distribution of the entire cohort was as follows: 87% age ≤30 days, 10% age 31–60 days, and 3% age 61–89 days. Thirty percent of infants weighed <2500 g. Eleven percent were classified as premature, 22% small-for-date, and 67% were born at term with an appropriate weight. The median duration of illness prior to admission was 2 days (interquartile range (IQR) 1–3 days); 19% were ill for >3 days and 5% for >7 days before admission. Potential previous treatment was rarely recorded, but when this information was available, 25% had received some medication like paracetamol or malaria treatment and 9% had received antibiotics. Three percent were born to HIV-positive mothers.

Infant symptoms present at the time of admission were reviewed. Overall, 82% had fever (axillary temperature ≥37.5 °C)

Table 1
Background data and characteristics of the study patients (*N* = 574).

Characteristics	Median or number	IQR or %
Demographics		
Sex		
Female	282/574	49%
Male	292/574	51%
Age >30 days	76/574	13%
Weight, kg	2.9	2.3–3.3
Premature	59/523	11%
History of acute illness		
Ill before admission, days	2	1–3
Difficulty feeding	285/451	63%
Previous fever and/or malaria treatment	55/221	25%
Previous antibiotics	18/196	9%
Findings on admission		
Weight <2500 g	139/514	27%
Axillary temperature, °C	37.8	36.9–38.5
Seizures	129/404	32%
No spontaneous movements	164/416	39%
Altered level of consciousness	155/411	38%
Blantyre coma score	5	4–5
Heart rate, beats/min	138	120–145
Respiratory rate, breaths/min	50	40–60
Dyspnea	126/427	34%
Laboratory test results		
Hemoglobin, g/dl	10.7	9.0–12.6
Blood glucose, mg/dl	83	54–104
CSF clear	233/557	42%
CSF xanthochromic	195/557	35%
CSF hemorrhagic	100/557	18%
CSF turbid	29/557	5%
CSF leukocytes $\times 10^6$/l	0	0–2
CSF glucose, mg/dl	50	30–72
CSF protein, mg/dl	80.0	50.6–133.8
Final diagnosis and outcome		
Bacterial meningitis as final diagnosis	139/574	24%
Sepsis as final diagnosis	356/574	62%
Other final diagnosis	79/574	14%
Death	115/574	20%

IQR, interquartile range; CSF, cerebrospinal fluid.

and 1.5% had a low temperature (≤35.5 °C). Other presenting symptoms or signs were difficulty feeding (63%), gastrointestinal symptoms such as vomiting or diarrhea (7%), irritability (3%), bulging fontanelle (2%), and neck stiffness (1%).

At presentation, 32% had seizures, 38% showed an altered level of consciousness, 34% had dyspnea, 13% were dehydrated, and 31% appeared undernourished based on the attending pediatrician's judgment. The median heart rate was 138 beats/min (IQR 120–145 beats/min) and capillary refill time was 1 s (IQR 1–2 s). Of the 103 infants with hemoglobin measured, the median value was 10.7 g/dl (IQR 9.1–12.6 g/dl). The median blood glucose level of 110 infants was 83 mg/dl (IQR 54–103 mg/dl).

Twelve percent of the infants had hyperbilirubinemia, 7% were hypoxic, 5% had congenital or chromosomal abnormalities, and 3% had hemorrhage. Malaria parasites were found in 12 (11%) of the 108 tested infants. Focal infections were diagnosed in 15% of infants, the most common of which were pneumonia (in 6%), omphalitis (3%), cellulitis (1%), gastroenteritis (1%), and septic arthritis (1%).

Sepsis was the final diagnosis in 63% of infants and their inpatient mortality was 18% (65/360). Of the infants, 24% met the criteria for meningitis. Bacteria were found in the CSF of 96 infants and meningitis was considered probable in 39 infants, as suggested by other CSF characteristics. The most common agents were *Streptococcus pneumoniae* in 12 infants (two deaths), *Streptococcus agalactiae* in 11 (four deaths), *Klebsiella* spp. in 11 (one death), *Escherichia coli* in eight (one death), and *Staphylococcus aureus* in six (one death). Overall inpatient mortality due to meningitis was 24%. There were no significant differences in mortality according to infant age, either in sepsis or in meningitis.

The overall inpatient mortality rate was 20%. Forty-two percent died at <3 days of hospital admission, 46% at 3 to 7 days, and 12% at >7 days. On univariate analysis, the risk factors for death were seizures, altered level of consciousness, absence of spontaneous movements, dyspnea, tachycardia, CSF that is not clear, low CSF glucose, and high CSF protein (Table 2). All three infants in a deep coma at admission died.

Table 2
Univariate analysis of factors predicting death in young infants with suspected sepsis and meningitis in Luanda.

Characteristics	Fatal outcome *n* (%) or median (IQR)	Survived *n* (%) or median (IQR)	OR for death (95% CI)	*P*-value
Demographics				
Age >30 days	17/115 (15)	59/459 (13)	1.18 (0.66–2.11)	0.58
Female sex	59/115 (51)	226/459 (49)	1.09 (0.72–1.63)	0.69
Premature	16/104 (15)	43/416 (10)	1.58 (0.85–2.93)	0.15
History of acute illness				
Illness >7 days	7/76 (9)	15/330 (5)	2.13 (0.84–5.42)	0.11
No fever	22/86 (26)	60/363 (17)	1.74 (0.99–3.03)	0.051
Findings on admission				
Seizures	34/76 (45)	91/324 (28)	2.07 (1.24–3.46)	0.005
No spontaneous movements	40/79 (51)	124/337 (37)	1.76 (1.08–2.89)	0.024
Altered level of consciousness	39/78 (50)	114/330 (35)	1.89 (1.15–3.12)	0.011
Blantyre coma score <4	20/56 (36)	46/272 (17)	2.73 (1.45–5.13)	0.001
Heart rate >138 beats (median)/min	23/37 (62)	86/193 (45)	2.04 (0.99–4.21)	0.0495
Dyspnea	38/83 (46)	108/341 (32)	1.82 (1.12–2.97)	0.015
Congenital malformations, chromosomal abnormality	9/112 (8)	19/451 (4)	1.99 (0.87–4.52)	0.096
Laboratory test results				
CSF not clear	76/110 (69)	248/447 (55)	1.79 (1.15–2.80)	0.010
CSF turbid	8/110 (7)	21/447 (5)	1.59 (0.69–3.69)	0.28
CSF leukocytes >10 $\times$ 10^6/l	15/114 (13)	39/448 (9)	1.59 (0.84–3.00)	0.15
CSF glucose <25 mg/dl	28/110 (25)	78/441 (18)	1.59 (0.97–2.60)	0.0065
CSF protein >120 mg/dl	41/91 (45)	111/416 (27)	2.25 (1.41–3.59)	0.0005
Final diagnosis				
Bacterial meningitis as final diagnosis	34/115 (30)	105/459 (23)	1.42 (0.90–2.23)	0.13
Sepsis as final diagnosis	64/115 (56)	292/459 (64)	0.72 (0.47–1.09)	0.12
Other final diagnosis	17/115 (15)	62/459 (14)	1.11 (0.62–1.98)	0.72

IQR, interquartile range; OR, odds ratio; CI, confidence interval; CSF, cerebrospinal fluid.

Table 3
Multivariate analysis of factors predicting death in young infants with suspected sepsis and meningitis in Luanda (n = 177).

Characteristics	Model with AUC = 0.704		Model with AUC = 0.709	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
No fever	1.50 (0.47–4.81)	0.51		
Seizures	2.73 (1.14–6.52)	0.026	2.83 (1.19–6.70)	0.019
Blantyre coma score <4	2.21 (0.76–6.46)	0.15	2.29 (0.88–5.93)	0.088
Heart rate over median (>138 beats/min)	2.84 (1.17–6.87)	0.016	2.85 (1.18–6.89)	0.020
Dyspnea	1.17 (0.46–2.97)	0.74		

AUC, area under the curve; OR, odds ratio; CI, confidence interval.

On multivariate analysis, only seizures and a heart rate >138 beats/min (the median) were independent predictors of death (Table 3). The first model with all five clinical predictors of death from the univariate analysis gave an AUC of 0.704. The second model with the three strongest predictors had an AUC of 0.709. This second model had a sensitivity of 90%, specificity of 35%, PPV of 22%, and NPV of 94%.

Discussion

The prognosis of infants with suspected severe bacterial infection in Luanda, Angola was poor; 20% of them died in the hospital. Neonatal sepsis was diagnosed in most cases (63%), followed by bacterial meningitis (24%). Only a slightly higher inpatient mortality rate was observed in meningitis (24%) when compared to sepsis (18%). In a recent review of the global burden of sepsis, fatality among neonates was estimated to be 11% to 19% (Fleischmann-Struzek et al., 2018). In Kenya, 17% of 4467 young infants born outside the hospital but admitted with suspected invasive bacterial infection died (Talbert et al., 2010). The figures from Luanda are in the same range, albeit somewhat higher. In Kenya, among those with confirmed invasive bacterial infection, the fatality rate was 33% (Talbert et al., 2010). In contrast, only 1.4% of infants aged ≤60 days with invasive bacterial infections in the USA died (Pruitt et al., 2019). In Ghana, 9% of newborns admitted to hospital due to any cause died (Tette et al., 2020). Similar to Ghana (Tette et al., 2020), about 40% of deaths in the present study also occurred within 48 h of hospital admission, suggesting that the infants arrived already very severely ill.

Among young infants admitted to hospital in Kenya, severe infection accounted for approximately 30% of deaths; hypoxemia and inability to feed were associated with a fatal outcome (English et al., 2003). In Ghana, suspected infections accounted for approximately half of the deaths of admitted neonates and mortality was associated with prematurity and age <3 days (Tette et al., 2020). In the USA, adverse outcomes (death or neurological sequelae) of young infants with invasive bacterial infection have been associated with prematurity, poor appearance (such as unresponsiveness, lethargy, irritability, apnea, poor perfusion), and bacterial meningitis (Pruitt et al., 2019). Specifically for neonatal meningitis, the reported risk factors for death are prematurity, low birth weight, coma, pneumococcal etiology, positive CSF culture, and early-onset disease (<7 days after birth) (Okike et al., 2018; Mao et al., 2018).

The cause of death from severe bacterial infections is diverse. In the present multivariate analysis, tachycardia and seizures were found to be independent predictors of death. Although seizures are mostly observed in the acute phase of meningitis or are associated with sequelae (Mao et al., 2018), several studies have also found seizures to be associated with death. This was the case in our previous study on childhood bacterial meningitis in Luanda, in which impaired consciousness and severe dyspnea were also associated with a fatal outcome (Pelkonen et al., 2009). Here, in the univariate analysis, an altered level of consciousness, absence of spontaneous movements, dyspnea, CSF that is not clear, low CSF glucose concentration, and high CSF protein concentration also predicted death. Interestingly, age, prematurity, low birth weight, and meningitis did not predict death in this particular investigation.

This study has certain limitations. In the very busy emergency department, data were not always complete and limited resources prevented blood cultures. While these shortcomings are unfortunate, they also reflect the conditions in which most severe neonatal infections are treated. The study data did not cover outcomes following hospital discharge.

Some easily recognizable clinical symptoms and signs, such as tachycardia and seizures, may guide clinicians to suspect and identify infants at high risk of death due to severe bacterial infections in sub-Saharan Africa.

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Ethical approval

The study was approved by the Ethics Committee of HPDB and the Hospital Director on January 6, 2016. Once provided with information by the attending physician, the guardians of enrolled infants gave consent by signing or fingerprinting a specific form.

Conflict of interest

MHK was an employee of Sanofi Pasteur when this study was conducted. SU and TP report grants from the Pediatric Research Foundation, and TP from the Päivikki and Sakari Sohlberg Foundation, Helsinki, Finland. All other authors declare no competing interests.

Author contributions

TP and MHK conceived and designed the study. TP, SU, and OC conducted the study. TP analyzed the data. TP, SU, OC, MHK, IR, and HP interpreted the data. TP and MHK are accountable for the accuracy and integrity of the contents of the manuscript. All authors provided critical revisions of the manuscript for the intellectual content. All authors provided approval of the final draft of the manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.03.070.

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