Clinical predictors of bacteraemia in neonates with suspected early-onset sepsis in Malawi: a prospective cohort study

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ABSTRACT

Objectives We studied neonates with suspected early-onset sepsis (EOS, sepsis developing in the first 72 hours after delivery) in Malawi to (1) describe clinical characteristics and microbiological findings, (2) identify which patient characteristics may be associated with pathogen positivity on blood culture, and (3) describe mortality and its potential determinants.

Design Prospective observational study (May 2018–June 2019).

Setting Neonatal ward in Queen Elizabeth Central Hospital, the largest government hospital in Malawi.

Patients All neonates with suspected EOS in whom a blood culture was obtained.

Results Out of 4308 neonatal admissions, 1244 (28.9%) had suspected EOS. We included 1149 neonates, of which 109 blood cultures had significant growth (9.5%). The most commonly isolated pathogens were *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Escherichia coli* and *Acinetobacter baumanii*. Many of the Gram negatives were extended-spectrum beta lactamase-producing Enterobacteriaceae, and these were 40–100% resistant to first-line and second-line antimicrobials. Gestational age (GA) of <32 weeks was associated with pathogen-positive blood cultures (<28 weeks: adjusted OR (AOR) 2.72, 95% CI 1.04 to 7.13; 28–32 weeks: AOR 2.26, 95% CI 1.21 to 4.21; p=0.005). Mortality was 17.6% (202/1149) and associated with low birth weight (<1000 g: AOR 47.57, 95% CI 12.59 to 179.81; 1000–1500 g: AOR 11.31, 95% CI 6.97 to 18.36; 1500–2500 g: AOR 2.20, 95% CI 1.42 to 3.39; p<0.001), low Apgar scores at 5 min (0–3: AOR 18.60, 95% CI 8.81 to 39.27; 4–6: AOR 4.41, 95% CI 2.81 to 6.93; p<0.001), positive maternal venereal disease research laboratory status (AOR 2.53, 95% CI 1.25 to 5.12; p=0.001) and congenital anomalies (AOR 7.37, 95% CI 3.61 to 15.05; p<0.001). Prolonged rupture of membranes was inversely associated with mortality (AOR 0.43, 95% CI 0.19 to 0.98; p 0.007).

Conclusion In Malawi, EOS was suspected in nearly a third of neonatal admissions and had a high mortality. Ten per cent were culture-confirmed and predicted by low GA. To reduce the impact of suspected neonatal sepsis in least developed countries, improved maternal and antenatal care and development of rapid point of care methods to more accurately guide antimicrobial use could simultaneously improve outcome and reduce antimicrobial resistance.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neonatal mortality has declined over the past decades; however, the decline is slower than the overall decrease in childhood mortality.
⇒ Neonatal sepsis is one of the three major contributors to neonatal mortality globally and the distribution among least developed countries (LDCs) is disproportionately large.
⇒ Timely treatment of early-onset sepsis (EOS) is important, but management approaches must be balanced by concerns with the rise in antimicrobial resistance (AMR), especially in LDCs. Correct diagnosis plays a crucial role in this balance.

WHAT THIS STUDY ADDS

⇒ To our knowledge, this is one of the largest and most comprehensive prospective African dataset describing suspected EOS.
⇒ The strongest predictor of pathogen-positive blood cultures is low gestational age.
⇒ Mortality in suspected EOS is associated with low birth weight, Apgar scores of <7 at 5 min, positive maternal venereal disease research laboratory status, prolonged rupture of membranes and congenital anomalies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Optimising the provision of maternal and antenatal care is critical to early neonatal outcomes.
⇒ Future research should evaluate the role of point of care diagnostics in EOS, both to improve clinical outcomes and to slow the rise of AMR.

INTRODUCTION

Under-5 mortality rates have substantially declined over the past decades globally, but neonatal mortality rates, especially in low-income and middle-income countries (LMICs), remain high. In 2019, 47% of under-5 deaths were among neonates, and infection was a leading cause.[1] An estimated 3 million cases of neonatal sepsis occur annually, with a mortality rate of 11%–19%.[2] However, limited clinical and microbiological data are available from least developed countries (LDCs).

In an LDC such as Malawi, resources needed for diagnosing sepsis are scarce, and even basic laboratory tests (eg, full blood count and C reactive protein) are not always available. Diagnosis of neonatal sepsis is therefore predominantly made on the basis of clinical assessment of risk factors, clinical signs and symptoms, supported by the result of a blood culture when available. Recognising true bacteraemia among cases of suspected neonatal sepsis could assist the clinician in the initiation, continuation and discontinuation of antimicrobial therapy, which is of particular importance in settings where both resources are limited and antimicrobial resistance (AMR) is rising.[3] As microbiological resources are scarce, very few studies have described the population of suspected early-onset neonatal sepsis (EOS, sepsis developing in the first 72 hours after delivery) in an LDC. Consequently, important questions concerning the magnitude of the problem, the chances and predictors of having a positive culture, and the outcome and its determinants are not well known, but highly needed to guide care in LDC settings.

Objectives

This study first describes clinical characteristics and microbiological findings in neonates with suspected EOS in a tertiary hospital in Malawi. Second, we evaluate whether clinical characteristics are associated with culture-confirmed sepsis. Third, we assess mortality and its potential determinants.

METHODS

Clinical setting

Queen Elizabeth Central Hospital (QECH) is a government hospital for Blantyre and the southern region of Malawi and the largest referral hospital for the country. There is an average of 30 deliveries per day (900 deliveries/month) at QECH. The neonatal ward is the largest neonatal unit in Malawi, which receives an average of 330 admissions per month (online supplemental table) and has a daily in-patient average of 70 neonates. On average, one nurse is caring for 12 patients, while the doctor–patient ratio is 1:20. The unit provides high-dependency care, and treatments like intravenous fluids, phototherapy and nasal continuous positive airway pressure (nCPAP) are available.

Gestational age (GA) of newborns admitted to the neonatal ward ranges from 24 weeks of gestation to term (37–42 weeks of gestation). In most cases, GA is estimated during pregnancy based on the last menstrual period or fundal height, but in some, the GA is unknown. Birth weight ranges from 500 g to over 5 kg. It is noteworthy that extremely low-birthweight (LBW) infants (<1000 g)[4] receive treatment but, given their low chance of survival, are not treated with nCPAP.

When a neonate has suspected sepsis, local clinical guidelines,[5] which follow WHO guidelines,[6] consist of taking a blood culture before starting first-line antimicrobial therapy (intravenous benzylpenicillin 50.000 IU/kg per dose every 12 hours and intravenous gentamicin 3–5 mg/kg once a day). Ceftriaxone is prescribed as second-line antimicrobial where a neonate fails to clinically improve on first-line therapy (intravenous dosage 100 mg/kg once a day). For neonates with major congenital malformations (eg, spina bifida and gastrointestinal malformation), those that have undergone surgery, or in cases of suspected necrotising enterocolitis, a combination of ceftriaxone and metronidazole is prescribed as first-line therapy. Third-line antimicrobial management is dependent on culture results, availability of specific antimicrobials and recent outbreaks. During the study period, amikacin monotherapy was often used as third-line therapy (intravenous dosage 15 mg/kg once a day).

Guidelines also recommend performance of a lumbar puncture in any unwell neonate that does not have a clear focus of infection. In this clinical setting, however, few cerebrospinal fluid data were available and only blood culture results were used. Other investigations like full blood count and inflammatory parameters were not available on a regular basis.

Study design, inclusion criteria and sepsis definition

We conducted a prospective observational study of all neonates with suspected EOS in whom a blood culture was obtained and were admitted to the neonatal ward between 1 May 2018 and 31 May 2019. Suspected EOS was defined as a case for where there was clinical suspicion of sepsis in the first 72 hours of life, based on risk factors, clinical signs and symptoms,[7] and blood culture was obtained; culture-confirmed EOS includes cases of suspected sepsis where a pathogen was isolated on blood culture; and pathogen-negative suspected EOS includes cases of suspected sepsis for which no pathogen was cultured.

During the 13 months of the study, a daily review was done of all neonatal cultures collected. Potential cases were approached by a study team member during office hours to obtain informed consent. After enrolment, the medical records of the neonate and mother were used to extract demographic features, antenatal, perinatal and postnatal factors, antimicrobial management, and outcomes onto an electronic case report form. In case data were missing, mothers were approached to complete the missing parameters. Pregnant women with prolonged rupture of membranes (PROM, rupture of membranes >18 hours before onset of labour) were treated according to WHO guidelines. Pregnant women were regularly screened for HIV and syphilis by venereal disease research laboratory (VDRL). When HIV-positive, they were started on antiretroviral therapy and the neonates were treated with nevirapine after birth. VDRL positivity in pregnancy led to immediate treatment with benzathine penicillin G to prevent adverse birth outcomes in neonates.

Microbiological surveillance

Since the late 1990s, the Malawi-Liverpool-Wellcome Programme has provided routine diagnostic microbiological services to patients admitted to QECH. Laboratory methods including antimicrobial susceptibility testing have been published elsewhere[3]; in brief, 1–2 mL of blood was obtained from neonates with suspected EOS for culture under aseptic conditions. In general, specimen bottles were transported immediately after collection to the laboratory, and samples were inoculated into a single aerobic bottle for automated culture (BacT/Alert; bioMérieux, Marcy-L'Etoile, France). Bottles that were flagged as positive were analysed using conventional phenotypical methods, and antimicrobial susceptibility followed the disc diffusion method using the European Committee on Antimicrobial Susceptibility Testing (eucast.org) breakpoints. When a culture still showed no growth after 7 days, it was deemed negative.

In the clinical setting, central venous catheters were not available, therefore coagulase-negative staphylococci (CoNS), *Bacillus* spp, *Micrococcus* spp and diphtheroids were considered to be contaminants.[8] Unless a neonate still showed clinical signs of infection, blood cultures were not recollected.

In case a blood culture was positive for a pathogen, it was standard practice to change antimicrobial regimen according to susceptibility of the cultured micro-organism, depending on the availability of antibiotics.

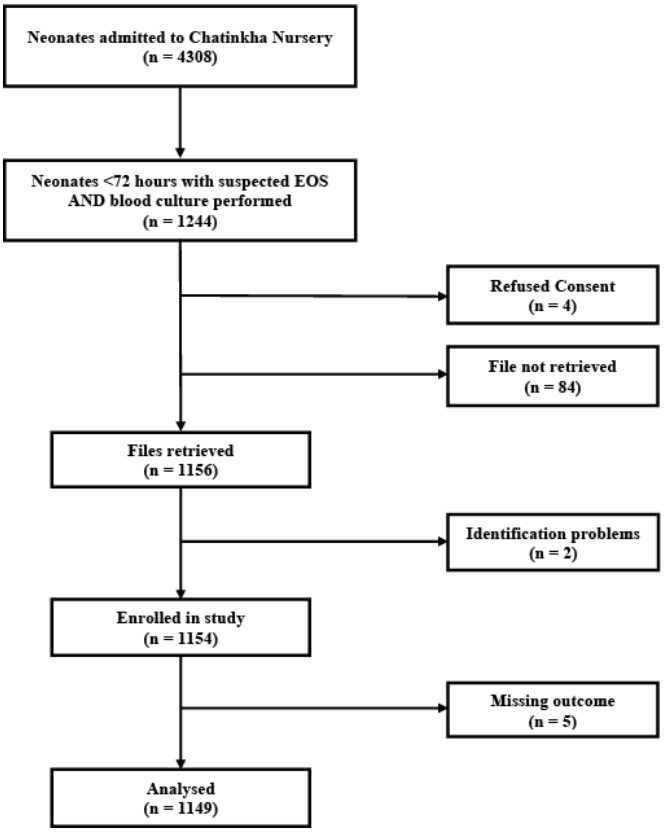

Figure 1 Flowchart of all neonates with suspected EOS at enrolment. EOS, early-onset sepsis.

Statistical analysis

Statistical analyses were performed using R V.4.0.0, 2020 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS V.25. Participant distribution was described using mean and SD or medians and IQRs for numerical data and proportions for categorical data. Distribution of variables was compared using unpaired t-tests for numerical data and χ^2 tests or Fisher's exact tests for categorical data. P values are two-sided and 0.05 was considered statistically significant.

A set of clinical characteristics and demographical features were predefined as candidate-independent covariates. First, univariable analysis was performed to identify associations between these characteristics and both culture-confirmed EOS and in-hospital mortality, with results presented as ORs and 95% CIs. Independent covariates that achieved a p value of <0.2 in univariable analysis were included in a stepwise backward multivariable logistic regression model to decrease the effect of confounding factors. Results of the multivariable analysis were depicted as adjusted ORs (AORs) and 95% CIs. Analyses were performed on complete data only.

RESULTS

During the study period, 4308 neonates were admitted to the neonatal ward. A blood culture was obtained for suspected EOS in 1244 neonates (28.9%), and of these, 1154 (92.7%) neonates were enrolled (figure 1). Outcome data were missing in 5 neonates, and therefore, 1149 were included in the analysis (92.4%). In our cohort (table 1), 635 (55.3%) were male; 469 (40.8%) had LBW (<2500 g)[4]; 275 (27.9%) were born preterm (<37 weeks of gestation)[4]; and 418 (36.4%) were born outside of QECH. The overall in-hospital mortality in our cohort was 202 (17.6%).

Table 1 Characteristics of all neonates with suspected early-onset sepsis at enrolment

Characteristics	All blood cultures 1149 (n/N)	%
Male sex	635/1149	55.3
Gestational age (weeks)		
<28	25/986	2.5
28–32	82/986	8.3
32–37	168/986	17.0
≥37	711/986	72.1
Birth weight (g)		
<1000	17/1136	1.5
1000–1500	137/1136	12.1
1500–2500	315/1136	27.7
≥2500	667/1136	58.7
Apgar score at 5 min		
0–3	39/953	4.1
4–6	184/953	19.3
7–10	730/953	76.6
Multiple gestation	89/1149	7.7
Positive maternal HIV status	155/1117	13.9
Positive maternal VDRL status**	57/842	6.8
PROM†	106/566	18.7
Maternal antimicrobials during labour	63/694	9.1
Mode of delivery		
Vaginal delivery‡	832/1149	72.4
Ceasarean section	317/1149	27.6
Place of delivery		
Outside health facility§	104/1147	9.1
Primary facility¶	298/1147	26.0
Secondary facility**	16/1147	1.4
QECH	729/1147	63.6
Congenital malformation	44/1149	3.8
In-hospital mortality	202/1149	17.6

*No data on congenital syphilis available
†>18 hours before onset of labour.
‡Including assisted vaginal delivery.
§Any delivery that did not take place in a health facility (ie, home birth).
¶Health centres.
**District hospitals, mission hospitals, private hospitals, central hospitals other than QECH.
PROM, prolonged rupture of membranes; QECH, Queen Elizabeth Central Hospital; VDRL, venereal disease research laboratory.

Microbiology

Among the blood cultures obtained, 109 (containing 118 micro-organisms) showed significant growth (9.5%); 321 grew contaminants (27.9%); and 719 had no growth (62.6%). The five most common organisms found in culture-confirmed EOS were *Staphylococcus aureus* (22, of which 4 (18%) were methicillin-resistant *S. aureus*), *Klebsiella pneumoniae* (20), *Enterobacter cloacae* (17), *Escherichia coli* (11) and *Acinetobacter baumanii* (5) (table 2). The highest number of neonatal deaths (eight) from culture-confirmed sepsis was attributable to *K. pneumoniae*, with a higher mortality in the lower GA categories (online supplemental figure). Among the five most common bacteria isolated, a large proportion of *K. pneumoniae*, *E. cloacae* and

Table 2 Antimicrobial resistance profiles to local first-line, second-line and third-line empirical regimens of the five most common bacterial isolates in culture-confirmed early-onset sepsis

		Penicillin		Gentamicin		Ceftriaxone		Amikacin	
Pathogen	Pathogens x/118(%)	n/N	%	n/N	%	n/N	%	n/N	%
*Staphylococcus aureus**	22 (19)	NT	–	4/22	18	NT		NT	–
Klebsiella pneumoniae	20 (17)	NT	–	15/19	78	16/20†	80	0/17	0
Enterobacte cloacae	17 (14)	NT	–	14/17	82	14/17†	82	0/16	0
Escherichia coli	11 (9)	NT	–	0/10	0	1/11†	9	0/1	0
Acinetobacter baumanii	5 (4)	NT	–	2/5	40	5/5†	100	NT	–

*Including methicillin-resistant *S. aureus*.
†Extended-spectrum beta lactamase-producing status was tested using a cefpodoxime disc.
NT, not tested.

A. baumanii isolates were extended-spectrum beta lactamase (ESBL)-producing Enterobacteriaceae and therefore exhibited resistance to ceftriaxone and, to a lesser extent, to gentamicin. In line with this, none of them demonstrated resistance to amikacin.

Pathogen positivity

In comparing neonates with pathogen-negative suspected EOS with pathogen-positive (culture-confirmed) EOS, we noted that GA of <32 weeks was significantly associated with culture-confirmed EOS (table 3). This was confirmed in multivariable analysis (<28 weeks: AOR 2.72, 95% CI 1.04 to 7.13; 28–32 weeks: AOR 2.26, 95% CI 1.21 to 4.21; data not shown). No other characteristics on multivariable analysis were found to be associated.

Mortality

The overall mortality in our cohort was 17.6%. In our cohort, mortality in neonates with suspected EOS was associated with LBW (<1000 g: AOR 47.57, 95% CI 12.59 to 179.81; 1000–1500 g: AOR 11.31, 95% CI 6.97 to 18.36; 1500–2500 g: AOR 2.20, 95% CI 1.42 to 3.39), low Apgar scores at 5 min (0–3: AOR 18.60, 95% CI 8.81 to 39.27; 4–6: AOR 4.41, 95% CI 2.81 to 6.93), positive maternal VDRL status (AOR 2.53, 95% CI 1.25 to 5.12) and having a congenital anomaly (AOR 7.37, 95% CI 3.61 to 15.05) (table 4). PROM was inversely associated with mortality (AOR 0.43, 95% CI 0.19 to 0.98).

DISCUSSION

This is the largest descriptive study specifically on suspected EOS performed in an LDC setting in sub-Saharan Africa and is distinct from other recent studies from LDCs that have focused on neonatal sepsis in the first 2 months of life.[9 10] In our study conducted at a tertiary hospital with robust bacteraemia surveillance, nearly a third of all admitted neonates had suspected EOS and received antimicrobial treatment. However, <10% of blood cultures obtained from these neonates were positive for a pathogen. Neonates born premature were more likely to have a pathogen-positive blood culture, but no other associated factors were identified. Mortality among neonates with suspected EOS was high (17.6%) and associated with maternal VDRL positivity and neonatal conditions like LBW, Apgar score of <7 at 5 min and congenital abnormalities. There was an inverse association with PROM.

Suspected EOS and blood culture positivity

Out of all neonatal admissions, 29.6% were suspected to have EOS and started on antibiotics. This is high but comparable to a recent systematic review on the prevalence of neonatal sepsis in East Africa that reported 29.7%.[11] Although this study included both early-onset and late-onset sepsis, these numbers indicate that neonatal sepsis and antimicrobial treatment are very common in this region.

The low pathogen positivity in cultures from neonates with suspected EOS illustrates the difficulty of accurate antimicrobial management, especially in settings with limited diagnostics. Our findings corroborate other studies in LMICs which have shown similar low proportions of positive cultures in neonates with suspected EOS,[12 13] though higher percentages have been reported.[10 14 15] Differences in prevalence might be explained by diversity in case definition of suspected EOS, or the use of small blood volumes sampled, which could have contributed to falsely negative results.[16] Another risk for false-negative results is blood culture collection after administration of antibiotics. In the current study, 21 subjects (1.8%) received antibiotics before the blood culture was taken. Of these 21 subjects, 6 still had a positive blood culture. While the prior receipt of antibiotics before the blood culture may have affected the results, the number of cultures involved was low and unlikely to impact the overall findings.

In this study, culture-confirmed bacteraemia was more common among neonates with low GA, with a quarter of neonates under 28 weeks of GA with suspected EOS having a pathogen-positive blood culture. This finding aligns with other studies demonstrating that the lower the GA, the higher the chance of developing EOS.[17] A possible explanation for this could be that preterm labour in the mothers of these neonates was caused by a chorioamnionitis, since this is a known risk factor for premature birth in our setting.[18] However, no clinical data on mothers nor placental histopathology were available.

We found no other associations between clinical characteristics and blood culture positivity. This indicates how difficult it is to judge which children may have an invasive bacterial infection. Furthermore, in our study, viral and fungal testing are not routinely available. Clinical features especially in neonates can be non-specific for illness; thus, clinicians tend to treat suspected infection proactively. It is therefore not surprising that the resultant antimicrobial use could contribute to the increasing levels of AMR.[19]

Microbiology

S. aureus was the most commonly isolated Gram-positive organism, while *K. pneumoniae* and *E. cloacae* were the most common Gram-negative bacteria, closely followed by *E. coli*. This corresponds to various reports from LMICs such as Nigeria, Tanzania, Ethiopia and Ghana.[13 15 20 21] In contrast to reports from high-income countries, very few group B *Streptococci* were

Table 3 Characteristics associated with a pathogen-positive blood culture in neonates with suspected early-onset sepsis

	Pathogen-negative blood culture, 1040 (n/N)	%	Pathogen-positive blood culture, 109 (n/N)	%	Univariable		
					P value*	OR	95% CI
Male sex	578/1040	55.6	57/109	52.3	0.512	0.88	0.59 to 1.30
Gestational age (weeks)					0.005		
<28	19/884	2.1	6/102	5.9		3.31	1.27 to 8.58
28–32	67/884	7.6	15/102	14.7		2.34	1.26 to 4.35
32–37	149/884	16.9	19/102	18.6		1.34	0.78 to 2.30
≥37†	669/884	73.4	62/102	60.8		1	
Birth weight (g)					0.063		
<1000	13/1027	1.3	4/109	3.7		3.49	1.10 to 11.08
1000–1500	120/1027	11.7	17/109	15.6		1.61	0.90 to 2.87
1500–2500	281/1027	27.4	34/109	31.2		1.37	0.87 to 2.16
≥2500†	613/1027	59.7	54/109	49.5		1	
Apgar score at 5 min					0.299		
0–3	33/860	3.8	6/93	6.5		1.64	0.66 to 4.04
4–6	170/860	19.8	14/93	15.1		0.74	0.41 to 1.35
7–10†	657/860	76.4	73/93	78.5		1	
Multiple gestation	81/1040	7.8	8/109	7.3	0.867	0.94	0.44 to 2.00
Positive maternal HIV status	141/1010	14.0	14/107	13.1	0.803	0.93	0.52 to 1.67
Positive maternal VDRL status‡	50/755	6.6	7/87	8.0	0.617	1.23	0.54 to 2.81
PROM§	97/504	19.2	9/62	14.5	0.368	0.71	0.34 to 1.49
Maternal antimicrobials during labour	59/612	9.6	4/82	4.9	0.159	0.48	0.17 to 1.36
Mode of delivery					0.809		
Vaginal delivery†¶	752/1040	72.3	80/109	73.4		1	
Ceasarean section	288/1040	27.7	29/109	26.6		0.95	0.61 to 1.48
Place of delivery					0.108		
Outside health facility**	92/1038	8.9	12/109	26.6		1.09	0.57 to 2.08
Primary facility††	280/1038	27.0	18/109	11.0		0.54	0.32 to 0.91
Secondary facility‡‡	15/1038	1.4	1/109	16.5		0.56	0.07 to 4.27
QECH†	651/1038	62.7	78/109	0.9		1.0	
Congenital malformation	40/1040	3.8	4/109	3.7	0.593	0.95	0.33 to 2.71
In-hospital mortality	177/1040	17.0	25/109	11.9	0.123	1.45	0.90 to 2.33

*P values calculated with χ^2 or Fisher's exact test.
†Default category.
‡No data on congenital syphilis available.
§>18 hours before onset of labour.
¶Including assisted vaginal delivery.
**Any delivery that did not take place in a health facility (ie, home birth).
††Health centres.
‡‡District hospitals, mission hospitals, private hospitals and central hospitals other than QECH.
PROM, prolonged rupture of membranes; QECH, Queen Elizabeth Central Hospital; VDRL, venereal disease research laboratory.

isolated in culture-confirmed EOS (4.5%), which is in line with low overall percentages of previous studies done in LMICs.[22]

One of the most striking findings is the high rates of ESBL-producing Gram negatives with corresponding resistance rates to both gentamicin (40%–82%) and ceftriaxone (80%–100%) among the most commonly isolated bacteria. This is in line with results from the BARNARDS cohort.[9] In Malawi, rates of AMR in neonatal bloodstream infections has showed a steep increase over two decades,[3] with a resultant impact on adequacy of available antimicrobial therapy for clinical care. Again this underlines that there is an urgent need for research in LMICs—and LDCs specifically—to evaluate the predictive ability of adjunctive point of care diagnostic tests in suspected EOS. Biomarkers and molecular diagnostics show promise in improved identification of neonatal sepsis and could guide targeted treatment with antimicrobials.[23]

Mortality

Among neonates with suspected EOS, the mortality was high but in line with data from a meta-analysis suggesting mortality rates in EOS of 6%–24%.[24] The finding that mortality in neonates with culture-confirmed EOS was lower could be explained by known fact that clinical symptoms in neonates are often non-specific for neonatal sepsis.[16] Critical illness in a neonate might be attributed to neonatal sepsis while there is actually another non-sepsis syndrome underlying. In this case, antimicrobials will not prevent clinical deterioration or even death.

Table 4 Characteristics associated with in-hospital mortality in neonates with suspected early-onset sepsis

Characteristics	Survived n=947		Died n=202		Univariable			Multivariable	
	947 (n/N)	%	(n/N)	%	P value*	OR	95% CI	AOR†	95% CI
Male sex	523/947	55.2	112/202	55.4	0.955	1.01	0.74 to 1.37	–	
Gestational age (weeks)					<0.001				
<28	10/824	1.2	15/162	9.3		12.00	5.21 to 27.62	1.84	0.53 to 6.38
28–32	51/824	6.2	31/162	19.1		4.86	2.94 to 8.05	1.95	0.85 to 4.46
32–37	131/824	15.9	37/162	22.8		2.26	1.47 to 3.49	1.46	0.71 to 2.99
≥37‡	632/824	76.7	79/162	48.8		1.0		1.0	
Birth weight (g)					<0.001				
<1000	3/934	0.3	14/202	6.9		37.97	10.66 to 135.27	47.57	12.59 to 179.81
1000–1500	76/934	8.1	61/202	30.2		6.53	4.31 to 9.90	11.31	6.97 to 18.36
1500–2500	261/934	27.9	54/202	26.7		1.68	1.15 to 2.46	2.20	1.42 to 3.39
≥2500‡	594/934	63.3	73/202	36.1		1		1	
Apgar score at 5 min					<0.001				
0–3	16/784	2.0	23/169	13.6		10.09	5.14 to 19.82	18.60	8.81 to 39.27
4–6	129/784	16.5	55/169	32.5		2.99	2.04 to 4.40	4.41	2.81 to 6.93
7–10‡	639/784	81.5	91/169	53.8		1		1	
Multiple gestation	70/947	7.4	19/202	9.4	0.331	1.30	0.77 to 2.21	–	
Positive maternal HIV status	117/925	12.6	38/192	19.8	0.009	1.70	1.14 to 2.55	1.24	0.76 to 2.03
Positive maternal VDRL status§	38/693	5.5	19/149	12.8	0.001	2.52	1.41 to 4.51	2.53	1.25 to 5.12
PROM¶	96/461	20.8	10/105	9.5	0.007	0.40	0.21 to 0.80	0.43	0.19 to 0.98
Maternal antimicrobials during labour	59/556	10.6	4/138	2.9	0.005	0.25	0.09 to 0.71	0.36	0.11 to 1.18
Mode of delivery					0.006				
Ceasarean section	277/947	29.3	40/202	19.8		0.60	0.41 to 0.87	0.73	0.46 to 1.13
Vaginal delivery‡**	670/947	70.7	162/202	80.2		1		1	
Place of delivery					0.020				
Outside health facility††	81/945	8.6	23/202	11.4		1.46	0.88 to 2.41	1.41	0.58 to 3.40
Primary facility‡‡	245/945	25.9	53/202	26.2		1.11	0.78 to 1.58	1.52	0.92 to 2.50
Secondary facility§§	9/945	1.0	7/202	3.5		3.99	1.46 to 10.91	2.92	0.74 to 11.62
QECH‡	610/945	64.6	119/202	58.9		1		1	
Congenital malformation	26/947	2.7	18/202	8.9	<0.001	3.47	1.86 to 6.45	7.37	3.61 to 15.05

*P values calculated with χ^2 or Fisher's exact test. Characteristics associated with in-hospital mortality (p<0.2) were included in the stepwise backward multivariate logistic regression model.
†ORs are shown only for characteristics with significant associations.
‡Default category.
§No data on congenital syphilis available.
¶>18 hours before onset of labour.
**Including assisted vaginal delivery.
††Any delivery that did not take place in a health facility (ie, home birth).
‡‡Health centres.
§§District hospitals, mission hospitals, private hospitals and central hospitals other than QECH.
PROM, prolonged rupture of membranes; QECH, Queen Elizabeth Central Hospital; VDRL, venereal disease research laboratory.

In our study, mortality was found to be associated with LBW, which has been previously described in other studies to be a predictor of mortality in neonatal sepsis.[25] The association between mortality and low Apgar scores, VDRL-positive mothers and neonates with a congenital anomaly all likely reflect increased risk of an unfavourable outcome even in the absence of an infection.

The finding that PROM was inversely associated with mortality (OR 0.43) was unexpected. One hypothesis is that neonates born to mothers with PROM are more likely to receive prompt antimicrobial therapy, as it is a known risk factor for EOS.[6] However, given the wide CI, the results should be interpreted with caution.

These findings on mortality were found in a selected population, namely, neonates with suspected sepsis, and might not be representative of the general population. Nevertheless, our findings support existing data[11] on the importance of targeting the antenatal period with an emphasis on preventing complications in pregnancy, such as LBW, to improve EOS outcomes.

Our study had limitations. We found a considerably higher number of isolates defined as contaminants in blood cultures obtained from patients with suspected EOS than has been reported in most other studies conducted in sub-Saharan Africa.[12 14 20] Although our staff received regular refresher training and feedback on phlebotomy practices, insufficiently aseptic conditions with blood culture sampling may be the cause. In neonates, especially those with LBW and low GA, contaminants such as CoNS can be a cause of EOS,[26] and therefore it is plausible that labelling all CoNS as contaminants could have resulted in undercounting of culture-confirmed bacteraemia cases. Another limitation is that we only recruited neonates into this study at the time the blood culture was collected. Therefore, although standard of care is to obtain a blood culture in all cases of suspected sepsis, patients with suspected EOS could have been missed if no blood culture was taken. In addition, while subjects entered the study after a blood culture sample was taken, it cannot be ruled out that inadequate amount of blood sampling may have affected our culture results.

If pregnant women tested VDRL-positive, treatment interval between receipt of benzathine penicillin G and birth was not always known. It is possible that if treatment took place within days before

delivery, this could have accounted for pathogen-negative suspected EOS. Finally, despite an exhaustive and comprehensive collation of patient and maternal records, we still had missing data. Nevertheless, we managed to retrieve >92% of records for inclusion in the analysis, which is remarkable for an LDC tertiary hospital setting with no established paediatric electronic medical record system.

CONCLUSION

The burden of suspected EOS in LDC settings like ours is high, and discriminating between suspected and culture-confirmed EOS and other neonatal conditions is difficult. Pathogen-positive blood cultures were identified in 10% and could only be predicted by low GA. Mortality in neonates with suspected EOS was significantly associated with LBW and maternal VDRL status. To reduce the impact of suspected neonatal sepsis in LDC, improved maternal and antenatal care and development of rapid point of care methods to more accurately guide antimicrobial use could simultaneously improve outcome and reduce AMR.

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Contributors TdB and P-YIT contributed to the concept and design of the work. RL, MN, SBG and NAF contributed to the concept. KK and QD oversaw the running of the ward. TdB and LG were involved in data acquisition. HHT and TdB were involved in data analysis and interpretation. TdB wrote the first draft, and P-YIT and MMvW critically reviewed and revised the manuscript. All authors reviewed and approved the manuscript. P-YIT was the guarantor of this study.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the University of Malawi College of Medicine Research Ethics Commission (P.08/17/2255) and Liverpool School of Tropical Medicine (17-069). The participants gave informed consent to participate in the study before taking part. Written consent was obtained by the parent or legal guardian of every participant. If for any reason consent was not feasible, only anonymised third party data were made available to the study team.

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