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RESEARCH

Neonatal septicaemia: prevalence and antimicrobial susceptibility patterns of common pathogens at Princess Marina Hospital, Botswana

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Background: Septicaemia is the third most common cause of neonatal death after prematurity and birth asphyxia. The prevalence of neonatal sepsis and the spectrum of causative microorganisms fluctuates over time, thus facility-specific surveillance of neonatal bloodstream infections is important. Increasing levels of antimicrobial resistance documented worldwide, necessitate regular monitoring of institutional resistance patterns to ensure appropriate and effective empirical antimicrobial therapy.
Method: The laboratory blood culture reports and patient records from a neonatal unit at a Botswana referral hospital were retrospectively reviewed to determine the one-year prevalence of neonatal sepsis and the antimicrobial susceptibility patterns of common pathogens.
Results: Of 909 neonates investigated for suspected sepsis using 1 119 blood cultures, 89 (9.8%) had laboratory-confirmed episodes of bloodstream infection (septicaemia). The most prevalent pathogens included *Klebsiella pneumoniae* (29.4%), group B streptococcus (16.3%) and *Escherichia coli* (11.9%). Blood culture contamination rates were high at 18.6% (208/1 119). Gram-negative pathogens showed low susceptibility to gentamicin (40%) and cefotaxime (47%), but high susceptibility to amikacin (86%). Streptococci and enterococci were moderately sensitive to ampicillin (79%), and fully susceptible to vancomycin. Methicillin-resistant *Staphylococcus aureus* was not isolated. Exposure to maternal syphilis and previous antibiotic exposure were significantly associated with neonatal septicaemia.
Conclusion: Neonatal sepsis is common, with a predominance of Gram-negative pathogens. The high rate of blood culture contamination should be addressed. Emerging antibiotic resistance may require clinicians to review currently used antibiotics for the empirical treatment of late-onset neonatal septicaemia.

Keywords: antimicrobial susceptibility, blood culture, neonates, septicaemia

Introduction

Septicaemia is the third most prevalent cause of death in the first 28 days of life, after prematurity and birth asphyxia.[1] Sub-Saharan Africa has the highest neonatal mortality rate worldwide with 32 deaths per 1 000 live births in 2012, representing 38% of global neonatal deaths.[2] Neonatal septicaemia can be categorised as early-onset neonatal sepsis, representing maternally derived infections; and late-onset neonatal sepsis, representing hospital-acquired infection.[3,4] Knowledge of the local epidemiology of neonatal sepsis assists clinicians and infection control programmes to prioritise interventions for prevention of neonatal sepsis-related morbidity and mortality.

The spectrum of microorganisms and burden of neonatal infection fluctuates within neonatal units over time.[5,6] A predominance of Gram-positive bacteria is reported in most high-income settings, while Gram-negative bacteria are reportedly responsible for most early- and late-onset neonatal sepsis in low- to middle-income countries.[7–10] Regular institutional-level surveillance is needed because of the constant shift in regional and institutional neonatal sepsis pathogen profiles and antimicrobial susceptibility patterns.[7,11,12] Ampicillin and gentamicin are the World Health Organization's recommended first-line antibiotics for the empirical treatment of early-onset neonatal sepsis.[13] Periodic validation of this empirical antibiotic treatment regimen against the institution's pathogen profile is required.

Data from sub-Saharan African countries on the prevalence, spectrum and antimicrobial susceptibility of laboratory-confirmed neonatal sepsis are limited. The objective of this study was to determine the period prevalence of neonatal sepsis, and the spectrum of bloodstream pathogens and their antimicrobial susceptibility patterns at Princess Marina Hospital, Botswana. Additionally, an association between the demographic and clinical characteristics of the study population and culture-confirmed neonatal bloodstream sepsis was investigated.

Method

Study design, population and setting

An analytical cross-sectional, laboratory-based study of culture-confirmed, neonatal bloodstream sepsis was conducted. All neonates (0–28 days) admitted to the Princess Marina Hospital's neonatal unit with blood culture submitted during the study period from 1 January 2012 to 31 December 2012 were included. Infants in the neonatal ward with blood culture collected after the first 28 days of life were excluded. Princess Marina Hospital is a public (government) tertiary hospital in the capital city of Botswana. The neonatal unit has 40 beds, and receives neonates from the onsite labour ward and referrals from the surrounding clinics and district hospitals. There are approximately 1 400 neonatal admissions per year. Ampicillin and gentamicin were the first-line empirical treatment regimen for early-onset neonatal sepsis; and cefotaxime and vancomycin, or cefotaxime and amikacin, were used to treat late-onset neonatal sepsis during the study period.

Laboratory methods

An onsite clinical microbiology laboratory processed the blood culture requests using the Oxoid® Signal Blood Culture System

(Oxoid, Hampshire, UK) which has an indicator device which detects microbial growth by a change in pressure. Blood cultures that exhibited any growth (bacterial colonies) were subcultured onto sheep blood agar, chocolate agar and MacConkey agar. Bacterial identification was performed manually with biochemical tests and antimicrobial susceptibility testing using the Kirby-Bauer disk diffusion method.[14]

Definitions

Neonatal septicaemia was defined as a laboratory-confirmed bloodstream infection (LCBI) where one or more blood culture specimens isolated a known pathogen. Isolation of the same pathogen within seven days of the original isolate was considered to represent a single episode of LCBI. Blood culture isolates known to be contaminants were excluded from the calculation of neonatal sepsis prevalence, except for coagulase-negative staphylococci (CONS) whose growth is potentially pathogenic in neonates.[15] Only a single CONS isolate was obtained from each neonate. Hence, CONS isolates were considered to be probable contaminants in this study. However, owing to this diagnostic limitation, yield and LCBI prevalence were reported, with the exclusion and inclusion of CONS. Polymicrobial infection was defined as a single, positive blood culture which isolated two or more recognised pathogens.

Data sources

The following data sources were used:

- Neonates from whom blood cultures had been taken during the study period were identified from the laboratory reception register.
- An electronic request form and/or the hospital's data management system for age on blood culture, date of birth, gender, date of admission, date of discharge, previous antibiotic exposure, the blood culture result and the antimicrobial susceptibility result for positive blood culture.
- Neonatal unit and labour ward admission registers for gestational age at birth, birthweight, mode of delivery, place of birth, and maternal human immunodeficiency virus (HIV) and syphilis status.
- Hospital files where information was missing from the other source documents. A file was considered to be missing after two searches.

Statistical method

Blood culture yield (the culture positivity rate) and the period prevalence of LCBI were calculated by dividing the number of positive cultures by the total number of blood cultures collected in one year, and the total number of neonates who had blood culture collected, respectively. Categorical variables were compared using chi-square analysis or Fisher's exact test if the size of a cell was < 5. Binary logistic regression analysis was performed to determine the factors associated with LCBI. A *p*-value of less than 0.05 was considered to be statistically significant. Stata® version 12.0 was used for analysis.

Ethical considerations

Ethical approval and waiver of informed consent was obtained from the Human Health Research Ethics Committee of the University of Stellenbosch (S13/05/106), Health Research Development Committee Botswana [PPME1318/1 PSV (255)], and Princess Marina Hospital, Research and Ethics Committee [PMH5/79(42a)].

Results

A total of 1 399 neonates were admitted to the ward during the study period. Eighty-nine neonates were excluded from the study because their date of birth could not be established. The demographics and birth history of 909 neonates investigated for neonatal sepsis is shown in Table 1. The mean birthweight was 2 103 g [standard deviation (SD) 901 g], gestational age 33.6 weeks (SD 5.0 weeks) and median length of hospital stay 15 days (interquartile range 8-29 days). A total of 1 119 blood cultures were submitted from 909 neonates during the 12-month study period (a mean of 1.2 blood cultures per neonate). Of the 909 neonates investigated for sepsis, 89 had LCBI, representing a period prevalence of 9.8% [95% confidence interval (CI): 7.9–11.7].

The prevalence of LCBI if CONS were classified as possible pathogens increased to 27% (245/909) (95% CI: 24.3– 29.7). The prevalence of LCBI per 100 neonatal admissions was 6.4 (89/1 399) (95% CI: 5.1–7.7). Eighty-seven neonates had a single episode of LCBI, whereas two neonates had 2 LCBI episodes, i.e. a total of 91 LCBI episodes, in which 92 pathogens were isolated.

The results of the univariate logistic regression analysis are shown in Table 1. A significant association between LCBI and exposure to syphilis [odds ratio (OR) 4.8, *p* 0.024) and previous antibiotic exposure (OR 2.6, *p* 0.002) was shown. A significant relationship between LCBI and gender, HIV exposure, birthplace, mode of delivery, gestational age, birthweight and length of hospital stay was not established (Table 1). Only exposure to syphilis and previous antibiotic exposure were entered into the multivariate logistic regression model using the forward stepwise regression method, and both factors emerged as independent predictors of LCBI, i.e. OR 5.6, 95% CI: 1.4–22.0, *p* 0.015, and OR 2.7, 95% CI: 1.5–5.0, *p* 0.001, respectively.

Table 2 shows the blood culture yield and contamination rates. The culture positivity rate was 8.1% (91/1 119) (95% CI: 6.5–9.7), and 22.3% (249/1 119) (95% CI: 19.9–24.7), inclusive of CONS. The blood culture contamination rate was 4.5% (50/1 119) (95% CI: 3.3–5.7), excluding CONS; and 18.6% (208/1 119) (95% CI: 16.3–20.9), when CONS were classified as probable contaminants.

The spectrum of neonatal pathogens is shown in Table 3. The predominant isolate type was Gram-negative bacteria (67.4%) as opposed to Gram-positive bacteria (32.6%). The most commonly isolated pathogen was *Klebsiella pneumoniae,* followed by group B streptococcus. All *Klebsiella* spp. combined accounted for 46.7% (42/92) of the total isolated pathogens. Of all the LCBI episodes excluding CONS (n = 91), 34.1% (31) comprised early-onset neonatal sepis and 65.9% (60) late-onset neonatal sepsis. Gram-positive pathogens predominated in early-onset neonatal sepis (53.1%, 17/32) whereas Gram-negative pathogens were predominant in late-onset neonatal sepsis (78%, 47/60).

The antimicrobial susceptibility pattern of the isolated pathogens, excluding CONS, is shown in Table 4.

Gram-negative pathogens were highly susceptible to amikacin (80%, 20/25) and ciprofloxacin (75%, 18/24) and moderately susceptible to piperacillin tazobactam (62%, 15/24) and amoxicillin clavulanate (58%, 19/33) in late-onset neonatal sepsis. The Gram-negative pathogens in late-onset neonatal sepsis showed low susceptibility to gentamicin (32%, 12/37) and cefotaxime (40%, 17/42), respectively. Early-onset neonatal sepis pathogens were 58% (7/12) susceptible to gentamicin and 52% (11/21) susceptible to ampicillin, the institution's current empirical treatment regimen for early onset neonatal sepsis. The susceptibility of early-onset neonatal sepis pathogens to other antibiotics was as follows: penicillin 75% (6/8), amoxicillin clavulanate 67% (8/12), vancomycin 100% (13/13), piperacillin tazobactam 43% (3/7), ciprofloxacin 88%

Table 1: Factors investigated* for any associations with laboratory confirmed-bloodstream infection episodes at Princess Marina Hospital from 1 January 2012 to 31 December 2012

Characteristics	*n*	LCBI, *n* (%)	OR (95% CI)	*p*-value
Gender				
Male	491	48 (9.8)	1	
Female	381	38 (10.0)	1.0 (0.7–1.6)	0.923
Unknown	37	3 (8.1)	0.8 (0.2–2.8)	0.741
Mode of delivery				
Normal vertex	342	33 (8.1)	1	
Caesarean section	180	11 (6.1)	0.6 (0.3–1.2)	0.170
Forceps	5	0 (0.0)	-	-
Unknown	382	45 (11.8)	1.3 (0.8–2.0)	0.357
Place of delivery				
Princess Marina Hospital	418	34 (8.1)	1	
Other (health facility)	81	9 (11.1)	1.4 (0.6–3.1)	0.384
Other (born before arrival)	20	1 (5.0)	0.6 (0.1–4.6)	0.617
Unknown	390	45 (11.5)	1.5 (0.9–2.4)	0.105
HIV exposure				
No	331	27 (8.2)	1	
Yes	162	16 (9.9)	1.2 (0.6–2.4)	0.526
Unknown	416	46 (11.1)	1.4 (0.9–2.3)	0.186
Syphilis exposure				
No	372	24 (6.5)	1	
Yes	12	3 (25.0)	4.8 (1.2–19.0)	0.024
Unknown	525	62 (11.8)	1.9 (1.2–3.2)	0.008
Previous antibiotic exposure				
No	643	56 (8.7)	1	
Yes	85	17 (20.0)	2.6 (1.4–4.8)	0.002
Unknown	181	16 (8.8)	1.0 (0.6–1.8)	0.956
Gestational age				
0–37 weeks	305	27 (8.9)	1	
37–43 weeks	130	6 (4.6)	0.5 (0.2–1.2)	0.133
Unknown	474	56 (11.8)	1.4 (0.9–2.2)	0.192
Birthweight (g)				
0–2 500	343	32 (9.3)	1	
2 500–5 000	184	10 (5.43)	0.6 (0.3–1.2)	0.120
Unknown	382	47 (12.3)	1.4 (0.8–2.2)	0.201
Length of hospital stay				
0–7 days	179	16 (8.9)	1	
7–14 days	189	10 (5.3)	0.6 (0.3–1.3)	0.177
14–28 days	183	19 (10.4)	1.2 (0.6–2.4)	0.642
28–170 days	189	27 (14.3)	1.7 (0.9–3.3)	0.113
Unknown**	169	17 (10.1)	1.1 (0.6–2.3)	0.722

Note: CI: confidence interval, HIV: human immunodeficiency virus, LCBI: laboratory confirmed-bloodstream infection, OR: odds ratio.
*: Using univariate logistic regression analysis.
**: The information was not recorded in the patient file or admission register, or the admission register or patient file could not be found.

(7/8) and cefotaxime 69% (9/13).Owing to laboratory constraints, limited testing for extended-spectrum beta-lactamase (ESBL) production was performed. Six of the 10 *Klebsiella* isolates tested and 1 of 11 *E. coli* isolates tested were ESBL producers. Methicillin resistance was not encountered in the *Staphylococcus aureus* isolates.

Discussion

Prevalence of neonatal septicaemia

The period prevalence of neonatal LCBI determined in our study (9.8%) was similar to that reported from a neonatal intensive care unit within the region.[16] Much higher rates of neonatal LCBI (33.1%) were reported from a Nigerian special care infant unit.[17] Many studies report on blood culture yield, rather than

Table 2: Yield and contamination rate of blood cultures for the investigation of neonatal sepsis

Blood culture yield	n (%), *n* = 1 119
Pathogens	91 (8.1)
Probable contaminant*	158 (14.1)
Contaminants**	50 (4.5)
No growth (negative)	831 (74.3)
Number of positive blood culture with polymicrobial infection	5 (0.4)

*: All isolated coagulase-negative staphylococci
**: Contaminants included 2 *Micrococcus* spp., 7 diptheroids, 4 *Bacillus* spp., 1 *Candida* (grown at day 7), 2 *Streptococcus viridians,* 34 non-*Enterococcus* group D

Table 3: Spectrum of neonatal bloodstream infection pathogens (*n* = 92)

Neonatal bloodstream pathogens	Early-onset neonatal sepis pathogens *n* = 32	Late-onset neonatal sepsis pathogens *n* = 60	Total	%
Gram-positive organisms				
Group B streptococcus	10	5	15	16.3
Streptococcus pneumoniae	2	0	2	2.2
Group C streptococcus	1	0	1	1.1
Staphylococcus aureus	3	5	8	8.7
Enterococcus species	1	3	4	4.3
Total Gram-positive organisms	**17**	**13**	**30**	**32.6**
Gram-negative organisms				
Klebsiella pneumoniae	6	21	27	29.3
Klebsiella oxytoca	1	7	8	8.7
Klebsiella species	1	7	8	8.7
Escherichia coli	5	6	11	11.9
Enterobacter species	0	4	4	4.4
Other Gram-negative bacteria*	2	2	4	4.4
Total Gram-negative organisms	**15**	**47**	**62**	**67.4**

*: Only a single isolate of each of the following pathogens was obtained: *Pseudomonas aeruginosa*, *Serratia marcescens*, *Acinetobacter* species and lactose-fermenting coliform.

prevalence, with higher rates compared to our study culture positivity of 8.1%.[18–21]

Timing of neonatal septicaemia

Early-onset neonatal sepis predominates[18,19,22] in some low- to middle-income countries. Our study and others from Africa report a higher prevalence of late-onset neonatal sepsis.[12,17,23,24] This pattern represents horizontal infection transmission, i.e. hospital-acquired infections, which are largely preventable by good infection control practices. The median hospital stay reported in our study was lengthy at 15 days, increasing the exposure time of neonates to the hospital environment and pathogens.

Demographic and clinical characteristics

LCBI was not associated with gender, birthweight, gestational age and mode of delivery in our study, and this has been reported previously.[9] An association between gestational age and LCBI was not reported in another study, and neither was one reported between place of delivery and LCBI, in agreement with our study.[25] Our study reported a statistically significant association between exposure to syphilis and LCBI the reason for this association was uncertain. Prior antibiotic exposure, as a risk factor for LCBI, was also identified in our study. This could be a result of the predominance of late-onset neonatal sepsis. Most neonates were given empirical antibiotics at birth for prematurity, or had experienced an earlier episode of suspected sepsis.[26] It is well-documented that antibiotic exposure in neonates alters the host's flora and may predispose to colonisation, and later to invasion with pathogens acquired from the environment, i.e. hospital-acquired infections.[27]

Blood culture yield

CONS were the most commonly isolated bacteria in our cohort, in keeping with the findings of other studies.[16] CONS are potential neonatal pathogens. However, we could not establish their significance in this cohort as only a single blood culture was obtained for each infant.[15] It is most likely that the high yield of CONS in our setting was due to blood culture contamination at the time of specimen collection through inadequate hand washing and/or skin decontamination. However, it is possible that some CONS isolates represented true episodes of neonatal bloodstream infection. Therefore, we have reported the LCBI prevalence rates, including and excluding CONS. A prospective study is needed to verify whether the CONS isolates in this setting represent true pathogens or are merely contaminants.

Table 4: Antibiotic susceptibility patterns of common neonatal bloodstream pathogens, *n* = 92

Number of isolates tested (% susceptible)	Gentamicin	Amoxicillin clavulanate	Vancomycin	Cefoxitin	Penicillin	Ampicillin	Amikacin	Ciprofloxacin	Piperacillin tazobactam	Cefotaxime
Gram-positive organisms *(n)*										
Staphylococcus aureus (8)	4 (25)	4 (100)	NT	8 (100)	NT	NT	NT	NT	1 (100)	NT
Group B streptococcus (15)	NT	NT	13 (100)	NT	9 (100)	9 (100)	NT	NT	NT	NT
Enterococcus species (4)	NT	NT	4 (100)	NT	2 (50)	4 (25)	NT	NT	NT	NT
Group C streptococcus (1)	NT	NT	1 (100)	NT	1 (00)	NT	NT	NT	NT	NT
Streptococcus pneumoniae (2)	NT	NT	2 (100)	NT	1 (100)	1 (100)	NT	NT	NT	NT
Gram-negative organisms *(n)*										
Klebsiella pneumoniae (27)	19 (32)	20 (55)	NT	NT	NT	23 (0)	16 (81)	17 (82)	13 (62)	23 (35)
Escherichia coli (11)	8 (63)	7 (86)	NT	NT	NT	9 (22)	7 (100)	3 (67)	4 (75)	10 (80)
Klebsiella oxytoca (8)	7 (0)	6 (50)	NT	NT	NT	7 (0)	6 (83)	5 (40)	5 (20)	7 (0)
Klebsiella species (8)	8 (38)	7 (43)	NT	NT	NT	8 (13)	5 (80)	4 (100)	4 (50)	8 (38)
Enterobacter species (4)	2 (50)	1 (0)	NT	NT	NT	2 (0)	NT	3 (100)	3 (100)	4 (100)
Other Gram-negative organisms (4)	4 (100)	3 (100)	NT	NT	NT	3 (0)	2 (100)	1 (100)	1 (0)	3 (100)

Note: NT: not tested (antimicrobial susceptibility testing was not performed on all of the isolates, and some of them were not tested against each appropriate antibiotic disk, owing to intermittent shortages of antibiotic disks.

Pathogen spectrum

A predominance of Gram-negative bacteria as neonatal pathogens has been reported elsewhere.[7,19,24] *K. pneumoniae* was the predominant pathogen, as has been reported in other studies.[9,16,21,23] Group B streptococcus was the most prevalent Gram-positive pathogen in our study, which contrasts with the findings in other published literature from low- to middle-income settings, in which the total absence of this pathogen was reported.[19,22,24] Pregnant women are not routinely screened for group B streptococcus in our setting and the isolation of group B streptococcus in our study is an indication of missed opportunities for antenatal screening. Notably, fungal pathogens, i.e. *Candida* spp., were not isolated from our neonatal cohort, in contrast to the findings of other studies.[7,12,19] Variation in the neonatal population, rate of central line use, use of fluconazole prophylaxis and laboratory blood culture incubation periods may account for this difference.

Antibiotic susceptibility patterns of pathogens

The susceptibility of *Klebsiella* isolates to gentamicin and cefotaxime was very low (< 50%) in our study, and although few isolates were tested, a 60% ESBL rate was documented, in keeping with other reports of *Klebsiella* ESBL rates from the region.[5,16] Our Gram-negative isolates had high susceptibility to amikacin, in contrast to one study which reported 95% resistance of Gram-negative isolates to amikacin.[7] Given this finding, local empirical late-onset neonatal sepsis antibiotic regimens would not be effective in treating many cases of *Klebsiella* sepsis, unless amikacin was included in the empirical sepsis regimen. Methicillin-resistant *S. aureus* (MRSA) was not isolated in this study, suggesting that the use of vancomycin in the late-onset neonatal sepsis empirical treatment regimen for empirical coverage of MRSA is unwarranted. The absence of MRSA was surprising, given the high rates reported by other neonatal units in southern Africa.[5,16,19] Only three enterococci were isolated from late-onset neonatal sepsis cases, and two of the three were ampicillin susceptible. Ampicillin and gentamicin susceptibility rates for early-onset neonatal sepis pathogens in this cohort were lower than expected. However, a larger current sample of blood culture isolates, as well as clinical outcome data, are needed to establish whether or not the institutional empirical early-onset neonatal sepis regimen should be amended.

Limitations

Some infants remained in the unit for longer than 28 days. Blood cultures collected after day 28 were excluded in our study. This may have resulted in bias towards underestimation of the prevalence of late-onset neonatal sepsis. The use of adult blood culture bottles, which require a larger blood inoculum, discourages doctors from collecting two neonatal blood cultures within 24 hours, leading to difficulty in classifying CONS as a contaminant versus a pathogen. Suboptimal blood inoculum volumes, leading to lower culture yields in the neonatal population, may be another important factor in the use of adult blood culture bottles. Antibiotic disk shortages resulted in some pathogens not being tested against certain antibiotics in our study, particularly limiting testing for ESBL production. This was a limitation with regard to the analysis of susceptibility patterns. In addition, a small number of isolates from each bacterial species isolated during the study period limited the usefulness of the antibiogram data.

Recommendations for changes in practice

Microbiology laboratories, particularly those in resource-limited settings, should restrict the use of antibiotic disks to those which are

appropriate for the susceptibility testing of blood culture isolates in neonates. Conversely, laboratories should ensure appropriate testing of all Enterobacteriaceae for beta lactamases as the rate of ESBL carriage appears to be high, and this has implications for the empirical and definitive antibiotic management of neonatal sepsis.

The need for periodical review of institutional empirical antibiotic treatment regimens for neonatal sepsis is clear. With these data, neonatal units can establish or amend site-specific treatment regimens, based on their institution's variance in prevalence, pathogen spectrum and antibiotic susceptibility patterns over time. In addition, retraining medical staff to improve their blood culture technique, i.e. hand hygiene, skin antisepsis and the inoculation of optimal blood volume, is recommended in order to reduce the very high rates of blood culture contamination and to increase potential blood culture yield.

Conclusion

The prevalence, spectrum of pathogens and antibiotic susceptibility rates in Batswana neonates with LCBI is comparable to those reported in other low- to middle-income settings. Previous antibiotic exposure and maternal syphilis were identified as independent risk factors for neonatal septicaemia in this study. Late-onset neonatal sepsis predominated, indicating a need for improved infection prevention and control practices. The ongoing local surveillance of antimicrobial susceptibility patterns in neonatal units in low- to middle-income countries is warranted to ensure appropriate selection of empirical antibiotic regimens.

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