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Risk of community- and hospital-acquired bacteremia and profile of antibiotic resistance in children hospitalized with severe acute malnutrition in Niger

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Abstract

Objective: To estimate the prevalence and antibiotic resistance profile of community- and hospital-acquired bacteremia among hospitalized children with severe acute malnutrition in Niger.

Methods: A descriptive, longitudinal study was conducted in an intensive nutritional rehabilitation center in Madarounfa, Niger. Children aged 6 to 59 months admitted for inpatient treatment of complicated severe acute malnutrition (n=2187) had blood specimens drawn at admission to assess prevalence of community-acquired bacteremia. Subsequent specimens were drawn per physician discretion to assess incidence of hospital-acquired bacteremia. Antibiotic susceptibility testing was performed on positive blood cultures.

Results: The prevalence of community-acquired bacteremia at admission was at least 9.1% (95% CI: 8.1, 10.4%), with non-typhoid *Salmonella* identified in over half (57.8%) of cases. The cumulative incidence of hospital-acquired bacteremia was estimated at 1.2% (95% CI: 0.8, 1.7%), among which the most common organisms were *Klebsiella pneumoniae* (19.4%), *Acinetobacter baumannii* (16.1%), *Enterococcus faecalis* (12.9%), and *Escherichia coli* (12.9%).

Among community-acquired bacteremia, 58% were resistant to amoxicillin-clavulanate; 100% of hospital-acquired bacteremia were resistant to amoxicillin and amoxicillin-clavulanate. Mortality risk was elevated among children with hospital-acquired bacteremia (RR=9.32) and community-acquired bacteremia (RR=2.67).

Conclusion: Bacteremia was a significant contributor to mortality. Antibiotic resistance poses a challenge to effective clinical management of SAM.

Keywords

severe acute malnutrition, bacteremia, community-acquired, hospital-acquired, nosocomial, antimicrobial resistance, Niger

Background

Severe acute malnutrition (SAM) poses a significant risk of mortality to children under the age of 5 years. Although the majority of SAM cases are non-complicated and can be treated in an outpatient setting, approximately one in ten children with SAM require inpatient management during treatment due to clinical complications.(Murray and Manary, 2014) These complications are often due to bacterial infections, including bloodstream infections (bacteremia) than can lead to systemic inflammatory response syndrome, septic shock, multiple organ dysfunction syndrome and death.(Jones and Berkley, 2014, Smith D.A. and Nehring, 2020)

To reduce the risk of death, children receiving inpatient treatment for complicated SAM should be monitored closely for any signs or symptoms suggestive of systemic infections, and infections should be treated in a timely manner with the correct antibiotic regimen. Third generation cephalosporins – particularly ceftriaxone – is the main empirical treatment for

bacteremia in low and middle countries. However, the emergence of multidrug-resistant strains of Enterobacterales to third generation cephalosporins may affect clinical treatment outcomes in countries where it used as first line empirical antibiotics. (Le Doare et al., 2015)

Bacteremia among hospitalized patients may be community-acquired or hospital-acquired. There is some data available on the prevalence, etiology and antibiotic resistance profile of community-acquired bacteremia among children in sub-Saharan Africa, but a paucity of data among children with SAM.(World Health Organization, 2018) In a meta-analysis of 11 studies from 1992 to 2010, the prevalence of community-acquired bacteremia was 15.5% among 51,197 children from African countries.(Droz et al., 2019) Since only a few studies have described bacteremia among SAM children, the association between SAM and bloodstream infections is yet to be established. Some studies have shown an increased risk of bloodstream infection associated with SAM,(Berkley et al., 2005, Meremikwu et al., 2005) while others have not.(Hill et al., 2007, Nathoo et al., 1996)

The prevalence of hospital-acquired infection in developing countries (15%) is estimated to be much higher than what is reported in high-income countries (7.6%).(World Health Organization, 2011) There are few studies on hospital-acquired infections among pediatric populations in sub-Saharan Africa, and none focused on hospitalized malnourished children.(Allegranzi et al., 2011, Irek et al., 2018, World Health Organization, 2011) This is a considerable gap in knowledge, since inpatient facilities for the treatment of SAM can face overcrowding and

suboptimal hygiene conditions, which presumably places them at high risk for transmission of hospital-acquired infections.

The present study aimed to describe the risk of both community- and hospital-acquired bacteremia in a Médecins Sans Frontières (MSF)-supported nutritional treatment center for children affected by SAM in rural Niger. Furthermore, the profile of antibiotic resistance was assessed among bacteremia cases. Finally, risk factors at admission for bacteremia and the association of bacteremia with clinical outcomes were examined. Results are intended to inform the development of updated guidelines for improved clinical management, with the aim of reducing the risk of mortality and the emergence of antibiotic resistance associated with hospital care.

Materials and methods

Study setting

The study took place in Madarounfa, Niger, at the Madarounfa Intensive Nutritional Rehabilitation Center (Centre de Récupération Nutritionnelle Intensive, CRENI) managed by the Niger Ministry of Public Health with support from MSF. The facility provided inpatient treatment for children suffering from complicated SAM. All children presenting to the study site were assessed by program staff for clinical and anthropometric status. The MSF triage classification, an adapted version of the World Health Organization (WHO) Emergency Triage Assessment and Treatment system, was used to determine whether children required emergency (red), priority (yellow), or non-priority (green) attention and care.(World Health Organization, 2016) Care was provided in three separate units, according to clinical severity. Children with urgent and serious clinical complications were treated in the intensive care unit, where clinical surveillance was conducted every hour, and therapeutic milk was provided as clinically indicated. After clinical stabilization in the intensive care unit (usually 1-3 days) or immediately followingly admission if already stable, children were treated in the Phase 1 unit, where clinical surveillance and meals of therapeutic milk were given every 3 hours. Once clinically and nutritionally stable (including restored appetite, usually 2-3 days following admission), children were transferred to the Transition Phase unit, where ready-to-use therapeutic food (RUTF, Plumpy'Nut) was introduced and clinical surveillance was conducted every 6 hours until discharge (usually 1 day). At the time of discharge, children were provided a

one-week ration of RUTF for use at home and referral to the nearest outpatient treatment program center for continued management.

The CRENI facility included a collective bathing and laundry area, where materials and supplies for daily bathing of children were provided. Children too ill to be moved to the bathing area were washed at bedside. Therapeutic milk was prepared by trained health staff at the time of each meal. Children with nasal gastric tubes were fed by a program nurse. Meals (therapeutic milk or RUTF) were otherwise brought to the bedside for the caregiver to feed the child. Feeding and clinical surveillance by a program nurse was generally conducted at the same time to allow clinical staff to monitor how children were eating and being fed. Hygiene within the units was assured by program hygienists. Caregiver educational sessions were provided in each unit three times per week, covering a range of topics such as hygiene, infant and young child feeding practices, malaria prevention, and routine vaccination.

Study design and data collection

This was a descriptive, longitudinal cohort study of children admitted to the CRENI from October 2016 to November 2017. Study inclusion criteria were:

(i) Children aged 6-59 months

(ii) Children admitted during study team's working hours

(iii) Children not requiring emergency care at admission (due to the need for specimen collection at admission)

Caregivers of eligible children were invited to participate in the study and provided informed consent at time of admission. At admission, data on demographics, anthropometry, clinical symptoms, and diagnoses was collected. During follow-up, routine clinical data was collected on standardized forms (in conjunction with routine clinical monitoring visits) and included information on clinical status, medical procedures, pharmaceutical prescriptions and therapeutic feeding. Evaluation of clinical status included use of a pediatric early warning score (PEWS), a system used to monitor pediatric inpatients through close surveillance of specific clinical signs, with a total score indicating severity. It is meant to alert when children are at particular risk of deterioration, and increased medical attention is indicated. While the MSF triage classification was used only at time of admission, the PEWS was collected and used throughout the course of hospitalization, with the admission score serving as baseline. The PEWS used in this study was an early version of scoring adapted and implemented by MSF for specific use in low resource settings (see Supplementary Table 1).(Médecins sans frontières, 2017) In case of death, the cause of death was determined by study staff according to available clinical records.

Sample collection and laboratory testing

Half of children admitted during the study team's working hours and not requiring emergency care were randomly selected to provide a blood sample for hemoculture at time of admission, regardless of clinical indication of bacteremia. Blood samples (2-3mL) were taken by trained study nurses, transferred to a blood culture bottle (BACT/ALERT® PF Pediatric FAN®, bioMérieux, Marcy L'Etoile, France) and incubated at +25°C in the hospital until transport to the

Epicentre Maradi laboratory within an average of 8 hours after inoculation for incubation in BACT/ALERT® 3D instrument at +35°C. In case preincubation lasted > 12h, the bottles were subcultured prior to loading into the instrument.(Lee et al., 2013, Sautter et al., 2006, Seegmüller et al., 2004) Blood cultures were declared negative if there was no evidence of bacterial growth after 7 days of incubation. If positive before 7 days, program staff were informed immediately of Gram stain results. Antibiotic susceptibility testing (AST) was carried out using the Kirby-Bauer's disk diffusion technique and E-test as per the EUCAST recommendations.(The European Committee on Antimicrobial Susceptibility Testing, 2020) Pathogen identification was done using metabolic method with API strips (bioMérieux). Pathogen and AST results were communicated to program staff within 1-2 days after positivity to inform appropriate management. Community-acquired bacteremia was defined as a positive hemoculture with significant pathogen resulting from blood sampled at admission.

Blood culture to assess hospital-acquired bacteremia was requested at the discretion of the program doctor in the case of a clinical deterioration (defined as an increase of at least one point in the child's PEWS). For analysis, hospital-acquired bacteremia was defined as a clinical deterioration (i.e. ≥1 point increase in PEWS) and positive hemoculture with significant pathogen more than 48 hours after admission, and no evidence of bacteremia with the same pathogen at admission. In order to account for the possibility of infections at the hospital through exogenous (e.g. introduced through medical procedures) or endogenous (e.g. infection via mucosal translocation or broken skin barriers) mechanisms, the WHO's definition of a health-care associated infection was used (i.e. "health care-associated infections … affect

patients in a hospital or other health-care facility, and are not present or incubating at the time of admission").(World Health Organization, 2002)

Statistical analysis

Descriptive statistics (medians, interquartile ranges, frequencies, and percentages) were calculated for baseline characteristics, antibiotic resistance, and treatment outcomes. Weight-for-height Z scores (WHZ) were calculated according to WHO recommendations.(World Health Organization and UNICEF, 2009) Bivariate risk ratios for the association of risk factors at admission with bacteremia were calculated using Poisson regressions models with robust standard errors.(Zou, 2004) Diagnoses on admission were included in the set of risk factors for bacteremia if they were reported in more than 5% of the study population. For AST, intermediate results were considered as resistant.

Results

Characteristics on admission

A flowchart of children included in the analysis is presented in Supplementary Figure 1. Among the children admitted to the CRENI in Madarounfa from October 2016 to November 2017 (n=4974), a total of 4824 (97%) were aged 6 to 59 months. After excluding children who required emergency care or arrived outside the study team's working hours, 2187 children were randomly selected for blood sampling and analysis of bacteremia. Supplementary Table 2 compares the characteristics at admission between children selected for blood sampling compared to those who were not selected. Children selected for blood sampling had statistically significantly better clinical condition at admission (as per MSF triage classification and PEWS) and were less likely to experience a deterioration or a PEWS ≥3 points more than 48 hours after admission; the absolute magnitude of the differences was approximately four to six percentage points.

Baseline characteristics of the study population are provided in Table 1. Nearly half (46.4%) of children had a WHZ < -4, and about two thirds (67.7%) had a mid-upper arm circumference (MUAC) <115 mm. The most frequent symptoms and diagnoses on admission were gastroenteritis/dysentery (50.4%), malaria (44.5%), severe acute respiratory infection (23.2%), pallor (11.1%), edema (8.6%), and anorexia (5.7%). Nearly three-quarters of children had a PEWS score of 2 points or less at admission (73.1%). The MSF triage classification placed almost

half of children in the lowest risk group, green (46.6%). Around one third of included children (31.2%) received antibiotics in the 48h prior admission.

Bacteremia prevalence and risk factors

Community-acquired bacteremia was identified among 9.1% (198 out of 2187; 95% CI: 8.1, 10.4%) of children; prevalence was 5.0% among children who received antibiotics in the 48 hours prior to admission (34/683; 95% CI: 3.5, 6.9%) whereas it was 10.8% among children who did not receive antibiotics (162/1504; 95% CI: 9.2, 12.4%, p<0.001). Community-acquired bacteremia was most common from October to December; malaria positivity was also highest during these months (72% in Oct-Dec 2016 and 65% in Oct-Dec 2017). Increasing levels of MSF triage classification were predictive of community-acquired bacteremia, while no linear predictive increase was seen for the PEWS taken at time of admission. Among cases of community-acquired bacteremia, non-typhoid Salmonella (NTS) predominated (57.8%), followed by other Enterobacterales (*Escherichia coli*, *Salmonella* Typhi; Table 3). *Haemophilus influenzae*, *Pneumococcus*, and *Staphyloccocus aureus* were rarely isolated among cases of community-acquired bacteremia.

Among enrolled children who experienced a clinical deterioration (n=845, 38.6%), a blood specimen was ordered by a physician for 253 children (29.9%). Hospital-acquired bacteremia was identified among 1.2% of all children (26 out of 2187; 95% CI: 0.8, 1.7%; Table 2). Other than the month of admission, no other risk factors recorded at admission were predictive of

hospital-acquired bacteremia. Hospital-acquired bacteremia involved *Klebsiella pneumoniae* (19.4%), *Acinetobacter sp.* (22.6%), *Enterococcus faecalis* (12.9%), and *Escherichia coli* (12.9%).

Antibiotic resistance

Among the 230 pathogens identified among cases of bacteremia, 223 underwent antibiotic susceptibility testing (Supplementary Figure 1). The majority of Enterobacterales isolated in community-acquired bacteremia were resistant to ampicillin (92%) and amoxicillin-clavulanate (65%) (Table 4). Approximately two thirds of *E. coli* and *K. pneumoniae* (16/26, 61.5%) and 1/128 NTS expressed extended-spectrum beta-lactamase (ESBL), rendering them resistant to all beta-lactam antibiotics except carbapenems. No strains were resistant to carbapenems. Almost all Staphylococci were resistant to benzylpenicillin but none were resistant to cloxacillin (no Methicillin resistance). Pneumococci had decreased sensitivity to penicillins (27% were resistant) but all were sensitive to ampicillin, as well as Enterococci. *Haemophilus spp.* were sensitive to ampicillin and amoxicillin-clavulanate. Among hospital-acquired bacteremia, nearly all Enterobacterales (93%) were resistant to third-generation cephalosporins (86% expressed ESBL) and 3 (21%) were resistant to carbapenems (Table 5). A high proportion of non-fermentative Gram-negative bacilli (82%) were resistant to ceftazidime, 36% were resistant to carbapenems and 27% to ciprofloxacin.

Bacteremia co-infection with malaria

On admission, 54% (n=106) community-acquired bacteremia were associated with malaria confirmed by rapid diagnostic test. The risk of community-acquired bacteremia was significantly

higher in children with malaria (risk ratio [RR] = 1.47; 95%CI 1.13,1.93). A co-occurring malaria infection was significantly more common among cases of NTS bacteremia (63.7%) than among non-NTS bacteremia (41.7%, p=0.001).

Clinical and program outcomes

During hospitalization, 42% of children had at least one clinical deterioration after 48 hours (Table 6). Clinical deteriorations were more common among children with community-acquired bacteremia (RR = 1.34; 95% CI: 1.17, 1.54; p<0.001) and with hospital-acquired bacteremia (RR=2.20; 95% CI: 1.94, 2.50; p<0.001). Children with community-acquired bacteremia had significantly lower weight gain (median of 4.0 g/kg/d versus 7.2 g/kg/d among those without community-acquired bacteremia; p<0.001) and longer lengths of stay (median of 4.9 days versus 3.9 days; p=0.001), and children with hospital-acquired bacteremia had an average length of stay over twice that of children without bacteremia (median of 8.4 days versus 3.9 days among those without hospital-acquired bacteremia; p<0.001). Overall, outcomes at discharge were favorable, with low rates of default (<1%) and 92% of children stabilized and referred to outpatient care. Mortality (n=119, 5.4%) was below the international SPHERE standard of <10%.(Association, 2018) Children with community-acquired bacteremia had a risk of death 2.67 times higher than children without community-acquired bacteremia (95% CI: 1.76, 4.05; p<0.001), and children with hospital-acquired bacteremia had a risk of death 9.32 times higher than children without hospital-acquired bacteremia (95% CI: 5.92, 14.69; p<0.001). The two most common clinical diagnoses at the time of death were sepsis (36.5%) and severe malaria (29.2%). Among children who died of sepsis, 89% (n=98) received Ceftriaxone.

Discussion

Summary of key findings

This study is the first to report the risk of hospital-acquired bacteremia and antibiotic resistance of hospital-acquired bacteremia among children receiving inpatient treatment for SAM. The prevalence of community-acquired bacteremia at admission was found to be at least 9.1%, and 1.2% of children had a hospital-acquired bacteremia detected during hospital stay. Malaria was associated with an increased risk of community-acquired bacteremia; month of admission into treatment was associated with both community- and hospital-acquired bacteremia. High levels of antibiotic resistance were detected, particularly in hospital-acquired bacteremia in which most pathogens were resistant to first-line empirical treatments for the inpatient treatment of SAM and showed emergent resistance to last resort antibiotics like carbapenems. The risk of death was greatly elevated among children with hospital-acquired bacteremia (RR=9.32), and among children with community-acquired bacteremia (RR=2.67).

Prevalence of community- and hospital-acquired bacteremia

At admission, the estimated prevalence of community-acquired bacteremia (9.1%) was similar to other studies in the region.(Reddy et al., 2010) A study in a rural hospital in Kenya found community-acquired bacteremia among 10.9% of severely malnourished children.(Berkley et al., 2005) In a study among severely malnourished children in Niger, the prevalence of community-acquired bacteremia was estimated at 17%.(Page et al., 2013) We note that in our study blood samples were not collected from the most severely ill children requiring emergency care at admission in order to ensure appropriate management; statistically significant (though

clinically modest) differences were observed between children selected for blood sampling versus those who were not. In addition, blood culture positivity rate was lower among children having received antibiotics of any type within 48h prior to blood collection (often before transfer to hospital) than among children without. Therefore, it is likely that our study underestimated the burden of community-acquired bacteremia, and it is perhaps most accurate to indicate that the prevalence of community-acquired bacteremia is “at least” 9.1%.

This study estimated a low risk of nosocomial bacteremia (n=26 or 1.2%). Limited published literature is available to which we can compare our results. In a recent study in an Ethiopian teaching hospital, 1.6% of pediatric patients (only some of whom had SAM) had hospital-acquired bloodstream infections. In the same study, children with SAM had risk of developing hospital-acquired infections 2.83 times higher than non-SAM children.(Sahiledengle et al., 2020) In a pediatric hospital in Kilifi, Kenya, the risk of developing a hospital-acquired bacteremia during hospitalisation was 0.6%, with the risk for SAM children being approximately twice as high.(Aiken et al., 2011) Potential sources of hospital-acquired infection in this study include catheterization procedures, low hand hygiene compliance, and a contaminated hospital environment (as shown in a sub-study of the study facility). (Tang et al., 2019) It is important to note that the risk of hospital-acquired bacteremia in our study may be under-estimated. Request for a blood specimen and culture was at the discretion of the study physician in cases where a deterioration was observed. Since the definition used to define clinical deterioration in this study was an increase in PEWS by a minimum of one point, this threshold may have been

too inclusive and physicians may not have considered it appropriate to take hemocultures in all cases.

Pathogens identified and antibiotic resistance

The main pathogens found to be involved in community-acquired bacteremia were NTS, mainly associated with malaria, followed by other Enterobacterales. These results are consistent with other studies in sub-Saharan Africa. Several studies in this region show that invasive strains of NTS have emerged and are currently a major cause of septicemia, especially in malaria endemic settings.(Feasey and Molyneux, 2011, Lunguya et al., 2013, Mtove et al., 2010, Park et al., 2016) However, in a recent meta-analysis including 11 studies on community-acquired pediatric bloodstream infection in Africa from 1992 to 2010, the most frequent pathogens were *S. aureus* (17.8%) and *S. pneumoniae* (16.8%) and NTS accounted only for 9.8% of pathogens.(Droz et al., 2019) On the contrary, according to another meta-analysis from 1966 to 2014,(Uche et al., 2017) NTS were responsible for nearly 39% of community-invasive infections in sub-Saharan Africa, with an average lethality of 19%. This review also confirmed that invasive NTS was more prevalent in young children with malaria, anemia and malnutrition. Thus, although *S. aureus* and Pneumococci are commonly considered to be the most predominant pathogens in pediatric bloodstream infection in Africa as opposed to Asia, additional studies in specific and vulnerable populations (like SAM children in malaria endemic areas and increasing coverage of Pneumococcal vaccine) are necessary to adapt treatment and clinical management.

The main organisms causing hospital-acquired bacteremia were notably different from community-acquired bacteremia, mainly *Klebsiella spp*., *E.coli* and *Acinetobacter spp.*, which is consistent with the few other studies in sub-Saharan Africa on hospital-acquired bloodstream infections.(Aiken et al., 2011, Allegranzi et al., 2011) In terms of Gram-positive organisms, we isolated *E. faecalis*, but no *S. aureus* as opposed to other studies in low-income countries.(Aiken et al., 2011, Allegranzi et al., 2011)

As has been reported elsewhere in Africa regarding community-acquired bacteremia,(Droz et al., 2019, Page et al., 2013) a large majority of Enterobacterales were resistant to ampicillin, amoxicillin-clavulanate and cotrimoxazole. We showed that approximately 10% expressed an ESBL that made them resistant to ceftriaxone, a common empirical treatment for severe infections in MSF programs. The proportion of ESBL among Enterobacterales was even much higher (82%) in hospital-acquired bacteremia. Although no strain was resistant to carbapenems in community-acquired bacteremia, the emergence of such resistance was observed in hospital-acquired bacteremia (21%) would imply the failure of all antibiotic alternative treatments available locally. These results confirm that enhanced microbiological surveillance in Niger is crucial to adapt empiric and targeted antibiotic therapies for treating and preventing pediatric bacteremia and reducing child mortality. Subregional and national recommendations should be adapted to local antimicrobial resistance patterns and causative pathogens for both community- and hospital-acquired bloodstream infections. For this purpose, laboratory-based antimicrobial resistance surveillance is crucial to implement in many African countries (O'Neill,

2016, World Health Organization, 2013) and was developed as a major action in the WHO global action plan on antimicrobial resistance (World Health Organization, 2015).

Bacteremia and treatment outcomes

Hospital-acquired bacteremia was associated with very high mortality. Although other morbidity co-factors may have contributed to the risk of both bacteremia and death, the case-fatality rate for hospital-acquired bacteremia was more than 8 times higher compared to children without hospital-acquired bacteremia. Despite high levels of ceftriaxone use among children with sepsis, resistance among nearly all hospital-acquired bacteremia to this drug indicates that this is a considerable challenge for empirical treatment and clinical management.

Conclusions and recommendations

Our findings show that although the proportion of SAM children affected by hospital-acquired bacteremia is low, the effect on mortality is very high. Antibiotic resistance to commonly used antibiotics for sepsis as well as the appearance of multi-drug resistant bacteria such as ESBLs and carbapenemases is of particular concern for treatment of both inpatients and outpatients. Microbiological surveillance should be reinforced in Niger to adapt pediatric therapeutic guidelines for severely malnourished children to local pathogens and antimicrobial resistance pattern in order to increase care effectiveness and limit development of further resistance.

Conflicts of interest: The authors declare no competing interests.

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Table 1 Baseline characteristics of the study population [a,b]

Characteristics	All participants	No bacteremia	Community-acquired bacteremia	Hospital-acquired bacteremia
n	2187	1967	198	26

Age, months	19 (11, 24)	19 (11, 24)	20.5 (12, 24)	18 (12, 24)
6-11	547 (25.0)	504 (25.7)	39 (19.7)	5 (19.2)
12-23	875 (40.1)	776 (39.5)	88 (44.4)	12 (46.2)
24-59	763 (34.9)	685 (34.9)	71 (35.9)	9 (34.6)
Female sex	978 (44.7)	860 (43.7)	89 (45.0)	13 (50.0)
Weight-for-Height z-score (WHZ)				
WHZ ≥ -2	128 (6.1)	111 (5.8)	17 (9.0)	1 (3.9)
-3 ≤ WHZ < -2	292 (13.8)	267 (14.1)	25 (13.2)	1 (3.9)
-4 ≤ WHZ < -3	712 (33.7)	645 (33.9)	60 (31.8)	7 (26.9)
WHZ < -4	980 (46.4)	878 (46.2)	87 (46.0)	17 (65.4)
Mid-upper arm circumference (MUAC), mm	110 (102, 116)	110 (102, 116)	112 (103, 117)	107 (98, 113)
<115	1313 (67.7)	1187 (68.0)	108 (62.4)	19 (82.6)
Signs, symptoms, and diagnoses at admission				
Gastroenteritis/dysentery	1103 (50.4)	990 (50.3)	99 (50.0)	15 (57.7)
Malaria	973 (44.5)	855 (43.5)	111 (56.1)	11 (42.3)
Severe acute respiratory infection	507 (23.2)	458 (23.3)	45 (22.7)	4 (15.4)
Edema	368 (16.8)	329 (16.7)	37 (18.7)	4 (15.4)
Pallor	242 (11.1)	212 (10.8)	27 (13.6)	3 (11.5)
Lack of appetite	125 (5.7)	112 (5.7)	12 (6.1)	1 (3.9)
Severe dehydration	72 (3.3)	66 (3.4)	5 (2.5)	1 (3.9)
Fever	76 (3.5)	66 (3.4)	9 (4.6)	1 (3.9)
Severe infection (undetermined origin)	58 (2.7)	49 (2.5)	8 (4.0)	1 (3.9)
Skin infection	38 (1.7)	33 (1.7)	5 (2.5)	0 (0.0)
Shock	27 (1.2)	26 (1.3)	1 (0.5)	0 (0.0)
Stagnant weight gain	14 (0.6)	14 (0.7)	0 (0.0)	0 (0.0)
Suspicion of tuberculosis	11 (0.5)	8 (0.4)	2 (1.0)	1 (3.9)
Urinary tract infection	7 (0.3)	7 (0.4)	0 (0.0)	0 (0.0)
Weight loss > 5 %	8 (0.4)	8 (0.4)	0 (0.0)	0 (0.0)
Trauma or injury	3 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)
Intoxication	4 (0.2)	3 (0.2)	1 (0.5)	0 (0.0)
Typhoid fever (suspected)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Pediatric Early Warning Score (PEWS)				
Green (0-2 points)	1553 (73.1)	1409 (73.7)	132 (68.8)	16 (64.0)
Yellow (3-4 points)	339 (16.0)	290 (15.2)	42 (21.9)	7 (28.0)
Orange (5-6 points)	142 (6.7)	132 (6.9)	10 (5.2)	0 (0.0)

Red (≥7 points)	92 (4.3)	82 (4.3)	8 (4.2)	2 (8.0)
Médecins sans Frontières triage classification				
Green	1020 (46.6)	933 (47.4)	77 (38.9)	13 (50.0)
Yellow	929 (42.5)	828 (42.1)	91 (46.0)	11 (42.3)
Red	238 (10.9)	206 (10.5)	30 (15.2)	2 (7.7)
Received antibiotics within 48h prior admission[c]	683 (31.2)	643 (33.4)	34 (17.2)	9 (33.3)
Ceftriaxone	594 (27.2)	564 (29.3)	24 (12.1)	8 (29.6)
Cloxacillin	46 (2.1)	43 (2.2)	2 (1.0)	2 (7.4)
Amoxicillin	77 (3.5)	68 (3.5)	10 (5.1)	2 (7.4)

[a]Values are median (25^{th}, 75^{th} percentile) or n (%).

[b]Categories may not sum to total due to missing data.

[c]Categories may not sum to total due to multiple antibiotics received.

Table 2 Risk factors at admission for community- and hospital-acquired bacteremia

	Community acquired bacteremia (n=198)		Hospital-acquired bacteremia (n=26)	
	RR (95% CI)	p-value (χ^2)	RR (95% CI)	p-value (χ^2)
Age		0.17		0.74
6-11	0.77 (0.53, 1.11)		0.77 (0.26, 2.30)	
12-23	1.08 (0.80, 1.45)		1.16 (0.49, 2.74)	
24-59	ref		ref	
Female sex	1.05 (0.80, 1.37)	0.74	1.28 (0.60, 2.75)	0.53
Month of admission		<0.001		0.02
October to December 2016	ref		ref	
January to March 2017	0.56 (0.37, 0.85)		0.37 (0.04, 3.57)	
April to June 2017	0.50 (0.34, 0.74)		2.15 (0.57, 8.07)	
July to September 2017	0.50 (0.34, 0.73)		1.35 (0.34, 5.36)	
October to November 2017	0.84 (0.56, 1.27)		4.08 (1.09, 15.26)	
WHZ		0.36		0.21
WHZ ≥ -2	ref		ref	
-3 ≤ WHZ < -2	0.64 (0.36, 1.15)		0.44 (0.03, 6.96)	
-4 ≤ WHZ < -3	0.63 (0.38, 1.05)		1.26 (0.16, 10.15)	
WHZ < -4	0.67 (0.41, 1.09)		2.22 (0.30, 16.55)	
MUAC <115 mm	0.79 (0.59, 1.06)	0.12	2.27 (0.77, 6.64)	0.14
MSF triage classification		0.03		0.86
Green	ref		ref	
Yellow	1.30 (0.97, 1.73)		0.93 (0.42, 2.06)	

Red	1.67 (1.12, 2.49)		0.66 (0.15, 2.90)	
PEWS		0.12		0.17
Green (0-2 points)	ref		ref	
Yellow (3-4 points)	1.46 (1.05, 2.02)		2.00 (0.83, 4.83)	
Orange (5-6 points)	0.83 (0.45, 1.54)		n/e	
Red (≥7 points)	1.02 (0.52, 2.02)		2.11 (0.49, 9.04)	
Signs, symptoms, and diagnosis at admission				
Gastroenteritis/dysentery	0.98 (0.75, 1.28)	0.90	1.34 (0.62, 2.91)	0.46
Malaria	1.47 (1.13, 1.93)	0.004	0.78 (0.36, 1.72)	0.54
Severe acute respiratory infection	0.97 (0.71, 1.34)	0.87	0.60 (0.21, 1.74)	0.35
Pallor	1.27 (0.86, 1.86)	0.22	1.05 (0.32, 3.47)	0.94
Edema	1.32 (0.87, 2.01)	0.19	0.42 (0.06, 3.10)	0.40
Lack of appetite	1.06 (0.61, 1.85)	0.83	0.66 (0.09, 4.83)	0.68

Abbreviations: CI, confidence interval; MSF, Médecins sans Frontières (Doctors without Borders); MUAC, mid-upper arm circumference; n/e, not estimable; PEWS, Pediatric Early Warning Score; ref, reference group; RR, risk ratio; WHZ, weight-for-height z score

Table 3 Organisms identified as the cause of community-acquired and hospital-acquired bacteremia

Species	Organisms identified among community-acquired bacteremia[a] n=199	Organisms identified among hospital-acquired bacteremia[b] n=31
Acinetobacter spp.	0 (0.0)	1 (3.2)
Acinetobacter baumannii	3 (1.5)	5 (16.1)
Acinetobacter lwoffi	0 (0.0)	2 (6.5)
Aeromonas salmonicida	1 (0.5)	0 (0.0)
Burkholderia cepacia	1 (0.5)	1 (3.2)
Campylobacter jejuni	3 (1.5)	0 (0.0)
Candida spp.	0 (0.0)	1 (3.2)
Enterobacter cloacae	0 (0.0)	2 (6.5)
Enterococcus faecalis	6 (3.0)	4 (12.9)
Escherichia coli	23 (11.6)	4 (12.9)
Haemophilus influenzae	1 (0.5)	0 (0.0)
Haemophilus parainfluenzae	1 (0.5)	0 (0.0)
Klebsiella oxytoca	0 (0.0)	1 (3.2)
Klebsiella pneumoniae	3 (1.5)	6 (19.4)
Mannheimia haemolytica	1 (0.5)	0 (0.0)
Pseudomonas aeruginosa	3 (1.5)	2 (6.1)
Pseudomonas oryzihabitans	1 (0.5)	0 (0.0)

Non-typhoid *Salmonella*	115 (57.8)	1 (3.2)
Salmonella Typhi	13 (6.5)	0 (0.0)
Sphingomonas paucimobilis	1 (0.5)	0 (0.0)
Staphylococcus aureus	7 (3.5)	0 (0.0)
Stenotrophomonas maltophilia	1 (0.5)	0 (0.0)
Streptococcus spp.	1 (0.5)	0 (0.0)
Streptococcus group D	0 (0.0)	1 (3.2)
Streptococcus pneumoniae	9 (4.5)	0 (0.0)
Streptococcus pyogenes	3 (1.5)	0 (0.0)
Gram-negative bacteria (no growth on subculture)	2 (1.0)	0 (0.0)

[a]1 community-acquired bacteremia had 2 distinct pathogens in the same blood culture.

[b]1 patient had 2 successive hospital-acquired bacteremia with different pathogens; 4 hospital-acquired bacteremia had two distinct pathogens in the same blood culture.

Table 4 Antibiotic resistance among community-acquired bacteremia caused by the most frequently identified groups of organisms[a]

	Group of organisms[b]					
	Salmonella spp.	Other Entero-bacterales	Non-fermentative GNB	*S. aureus*	*Pneumococcus/ Streptococcus*	*Enterococ*
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Total, *n*	128	26	9	7	11	6
Benzylpenicillin	n/a	n/a	n/a	6 (85.7)	3 (27.3)	n/a
Cefoxitine	n/a	n/a	n/a	0 (0.0)	n/a	n/a
Ampicillin	117 (91.4)	25 (96.2)	9 (100.0)	6 (85.7)	0 (0.0)	0 (0.0)
Amoxicillin + Clavulanate	80 (62.5)	20 (76.9)	9 (100.0)	0 (0.0)	0 (0.0)	n/a
Piperacillin + Tazobactam	n/a	n/a	6 (66.7)	n/a	n/a	n/a
Third-generation Cephalosporins (Ceftriaxone or ceftazidime)	1 (0.8)	16 (61.5)	6 (66.7)	0 (0.0)	0 (0.0)	n/a
Carbapenems	0 (0.0)	0 (0.0)	3 (33.3)	n/a	n/a	n/a
Gentamycin	4 (3.3)	7 (26.9)	3 (33.3)	0 (0.0)	n/a	2 (33.3)
Amikacin	2 (1.6)	4 (15.4)	3 (33.3)	0 (0.0)	n/a	n/a
Tobramycin	n/a	n/a	3 (33.3)	0 (0.0)	n/a	n/a
Ciprofloxacin	1 (7.7)	11 (7.7)	3 (33.3)	0 (0.0)	0 (0.0)	1 (16.7)
Erythromycin	n/a	n/a	n/a	3 (42.9)	2 (18.2)	n/a
Vancomycin	n/a	n/a	n/a	0 (0.0)	n/a	0 (0.0)

ESBL[c]	1 (7.7)	16 (61.5)	n/a	n/a	n/a	n/a

[a]Data not shown for groups of organisms ≤ 2 organisms: 2 GNB unidentified, 1 *Aeromonas*, 1 *Mannheimia*, 2 *Haemophilus*. AST was not done for 3 Campylobacter.

[b]The organisms belonging to each group are:

Enterobacterales: *Escherichia coli, Klebsiella pneumoniae, Salmonella* Typhi*, Salmonella spp*

Non-fermentative GNB: *Acinetobacter baumannii, Burkholderia cepacia, Pseudomonas spp, Sphingomonas paucimobilis.* AST for *Stenotrophomonas maltophilia* not done because no recommendations from EUCAST v6,

Pneumo/Strepto: *Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus spp.* AST not done for 2 *Streptococcus pneumoniae* because of sterile subculture.

Enterococcus: *Enterococcus faecalis*

[c]ESBL: Extended Spectrum Beta-Lactamase: 14 *E.coli* ; 2 *K.pneumoniae* ; 1 *Salmonella spp*.

Abbreviations: n/a, not applicable; GNB, Gram-negative bacilli

Table 5 Antibiotic resistance among hospital-acquired bacteremia

	Group of organisms		
	Enterobacterales *n (%)*	Non-fermentative GNB *n (%)*	*Enterococcus n (%)*
Total, *n*	14	11	5
Ampicillin	14 (100)	11 (100)	3 (60.0)
Amoxicillin + Clavulanate	14 (100)	11 (100)	n/a
Piperacillin + Tazobactam	n/a	9 (81.8)	n/a
Third generation cephalosporins	13 (92.9)	9 (81.8)	n/a
Carbapenems	3 (21.4)	4 (36.4)	n/a
Gentamycin	10 (71.4)	7 (63.6)	3 (60.0)
Amikacin	4 (28.6)	2 (18.2)	
Tobramycin	n/a	7 (63.6)	n/a
Ciprofloxacin	10 (71.4)	3 (27.3)	4 (80.0)
Vancomycin	n/a	n/a	0 (0.0)
ESBL[a]	12 (85.7)	0 (0)	n/a

Note: Antibiotic susceptibility testing not done for 1 Candida

[a]ESBL, Extended Spectrum Beta-Lactamase: 3 *E. coli,* 7 *Klebsiella spp.,* 2 *Enterobacter cloacae*

Abbreviations: n/a, not applicable; GNB, Gram-negative bacilli

Table 6 Treatment outcomes

	Children without bacteremia (n=1967)[a]	Community-acquired bacteremia (n=198)[a]	p-value[b]	Hospital-acquired bacteremia (n=26)[a]	p-value[c]
Clinical progression					
Clinical deterioration after 48	776	106 (55.2)	<0.00	23 (92.0)	<0.00

hours[d]	(40.6)		1		1
Weight gain (g/kg/day)	7.2 (0, 16.4)	4.0 (0.7, 10.7)	<0.001	4.8 (-3.8, 9.4)	0.50
Length of stay (days)	3.9 (2.9, 5.9)	4.9 (2.9, 7.0)	0.002	8.4 (4.9, 12.9)	<0.001
Outcome at discharge					
Recovered	20 (1.0)	1 (0.5)	0.49	0 (0)	0.61
Stabilization/transfer to outpatient care	1835 (93.3)	171 (86.4)	0.001	13 (50.0)	<0.001
Default	12 (0.6)	1 (0.5)	0.80	1 (3.9)	0.04
Other	16 (0.8)	0 (0)	0.21	0 (0)	0.66
Death[e]	84 (4.3)	25 (12.6)	<0.001	12 (46.2)	<0.001
Sepsis	27 (32.1)	11 (44.0)		3 (25.0)	
Malaria	20 (23.8)	7 (28.0)		4 (33.3)	
Respiratory infection	11 (13.1)	1 (4.0)		0 (0)	
Intoxication	8 (9.5)	3 (12)		3 (25.0)	
Hypoglycemia	8 (9.5)	1 (0)		1 (8.3)	
Hypovolemic shock	7 (8.3)	0 (0)		0 (0)	
Other	6 (7.1)	2 (8.0)		0 (0)	
Gastroenteritis	6 (7.1)	0 (0)		0 (0)	
Dehydration	3 (3.6)	1 (0)		1 (8.3)	
Severe anemia	3 (3.6)	0 (0)		0 (0)	

[a]Values are n (%) or median (25^{th}, 75^{th} percentile)

[b]P-value for χ^2 or Kruskal Wallis test comparing children with community-acquired bacteremia to those without community-acquired bacteremia

[c]P-value for χ^2 or Kruskal Wallis test comparing children with hospital-acquired bacteremia to those without hospital-acquired bacteremia

[d]Defined as a 1 point increased in PEWS between assessment; denominator for children with data on deterioration available for n=2126 among the total cohort, n=192 for community-acquired bacteremia, and n=25 for nosocomial bacteremia

[e]Causes of death do not add up to 100% because a death can be classified with more than one cause