Epidemiology of community-onset bloodstream infections in Bouaké, central Côte d'Ivoire

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Abstract

Bacterial bloodstream infections (BSI) account for considerable morbidity worldwide, but epidemiological data from resource-constrained tropical settings are scarce. We analysed 293 blood cultures from patients presenting to a regional referral hospital in Bouaké, central Côte d'Ivoire, to determine the aetiology of community-onset BSI. The prevalence of bacteraemia was 22.5%, with children being most commonly affected. *Enterobacteriaceae* (predominantly *Klebsiella pneumoniae* and *Salmonella enterica*) accounted for 94% of BSI. *Staphylococcus aureus* was the only relevant Gram-positive pathogen. Clinical signs and symptoms were not significantly associated with blood culture positivity after controlling for malaria.

Keywords: Bacteraemia, Côte d'Ivoire, *Enterobacteriaceae*, *Klebsiella pneumoniae*, *Salmonella enterica*
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Bloodstream infections (BSI) are leading causes of morbidity and mortality worldwide [1]. Fever in the tropics is commonly interpreted as malaria, and empirical treatment is frequently administered without specific diagnostic testing [2]. However, recent research suggests that bacterial and viral infections are responsible for a large number of febrile illnesses in tropical settings [3]. For example, studies investigating the causes of fever in children in Tanzania and Kenya identified acute respiratory infections in 62% and 41% of symptomatic subjects, respectively [4,5]. Although viruses account for the majority of respiratory infections, bacterial BSI are important, yet underappreciated pathogens that commonly give rise to life-threatening systemic infections. Indeed, a recently published study from a referral hospital in Uganda showed that bacteraemia was detected in every fifth febrile child with a negative malaria test [6]. The diagnosis of invasive bacterial infections in resource-constrained settings is often limited by inadequate laboratory infrastructure, and culture-based evaluation of blood samples is not routinely available [7]. Hence, data on the aetiology of BSI in sub-Saharan Africa are scarce [8].

Access to basic healthcare and the quality of hospital and laboratory infrastructure might deteriorate during times of political unrest, armed conflict and war [9]. Côte d'Ivoire has gone through political crisis and armed conflict from 1999 to 2011 [10]. Bouaké, the second largest city, with a population of approximately 700 000 inhabitants, is located in the central part of the country, some 350 km north of Abidjan, the economic capital. Bouaké had been at the heart of the military and political crisis in Côte d'Ivoire. The University Teaching Hospital Bouaké (UTHB), the country's only academic hospital outside Abidjan, had to suspend all except the most basic medical services between 2002 and 2011. Here, we provide the first report on the aetiology of BSI in Bouaké, facilitated by blood cultures collected over a 27-month period after the political crisis ceased.

All venous blood cultures that were processed between June 2012 and September 2014 at UTHB were included for this study. Blood culture analysis was not feasible before mid-2012 in Bouaké, and the availability of blood culture reagents was scarce

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throughout the study period. Hence, blood cultures were only taken from severely ill patients, as judged by the attending physician, within 48 hours of presentation to the hospital, which led to the classification of detected bacteraemia cases as community-onset BSI [11]. Only a single blood culture was drawn per patient. Blood samples were taken by a phlebotomist and sent to the microbiology laboratory, where a conventional manual blood culture using brain–heart infusion (BHI) broth (reference no. 64014; Bio-Rad Laboratories; Hercules, CA, USA) was carried out. The inoculated blood volumes were 10 to 20 mL in 50 mL of BHI broth for adults, 2 to 5 mL in 35 mL of BHI broth for children and 1 to 2 mL in 35 mL of BHI broth for newborns. All cultures were aerobically incubated and examined daily for visible signs of bacterial growth (e.g. turbidity). In case of suspected growth, a Gram stain was performed and the sample was cultured on semisolid agar plates. Culture-grown colonies were identified using Kligler Iron agar and standard biochemical tests (e.g. β-galactosidase, indole production, lysine decarboxylase, oxidase and urease) [12]. All macroscopically negative blood culture broths were subcultured after 10 days of incubation to verify the absence of pathogens.

Clinical patient data were collected by chart review after sample receipt at the laboratory. Data were double-entered into Microsoft Excel 14.0 (edition 2010; Microsoft, Redmond, WA, USA), and statistical analysis was performed by Stata 12.0 (StataCorp, College Station, TX, USA). Self-reported clinical symptoms at admission to the hospital and findings obtained during medical examination were assessed for association with blood culture positivity. Differences in proportions between bacteraemic and non-bacteraemic individuals were described by the χ^2 test, and the partial correlation test was used to assess for significant correlations between clinical signs and bacteraemia while controlling for malaria [13].

Overall, 293 blood cultures were analysed at UTHB from June 2012 to September 2014. Slightly more than half of the blood cultures were taken from male patients (n = 155, 52.9%). The median age of the participants was 5 years (mean, 14.3 years; range, 1 day to 83 years). Relevant pathogens were detected in 66 of the blood samples, owing to a positivity rate of 22.5%. The prevalence of bacteraemia was 26.5% in male and 17.9% in female patients (p 0.090).

Table 1 summarises the aetiology of the 66 BSI. In brief, Gram-negative bacteria belonging to the family *Enterobacteriaceae* accounted for 93.9% (62/66) of all BSI. The most prevalent pathogens were *Klebsiella pneumoniae* (n = 25, 8.5%), *Salmonella enterica* (n = 17, 5.8%) and *Enterobacter* spp. (n = 11, 3.8%). *Staphylococcus aureus,* the only relevant Gram-positive pathogen, was found in four patients (1.4%). Neither fungi nor non-fermentative Gram-negative bacilli were detected.

Microscopic examination for *Plasmodium* parasitaemia was documented in 74 patients, and a positive malaria test result (based on microscopic examination of Giemsa-stained thick and thin blood films) was significantly more common in bacteraemic individuals (56.3% *vs.* 25.9%, p 0.022). BSI was significantly associated with documented febrile convulsions (24.6% *vs.* 13.7%; p 0.042) and showed a borderline significant association with self-reported fever (55.7% *vs.* 42.0%; p 0.057). However, after using a partial correlation test to control for malaria, no significant correlation between bacterial BSI and any clinical parameter was observed (Table 2). Fever had a sensitivity of 56% and a specificity of 58% for the diagnosis of BSI.

Anti-infective treatment information was available for 109 of 293 analysed individuals. The third-generation cephalosporin ceftriaxone was the most commonly administered antibiotic (53%, n = 58), followed by penicillin derivatives (42%, n = 46; ampicillin, n = 23; amoxicillin with or without clavulanic acid, n = 22; penicillin, n = 1). Combination therapy with the aminoglycoside gentamicin was administered to 42 patients (39%). In contrast, other antibiotics were used in less than 5% of the

TABLE 1. Aetiology of bloodstream infections in 293 patients presenting to the University Teaching Hospital Bouaké, central Côte d'Ivoire, between June 2012 and September 2014, stratified by medical department

	Total (n = 293)		General paediatrics (n = 174)		Internal medicine (n = 60)		Neonatology (n = 42)		Other department (n = 17)	
Pathogen	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Total positive blood cultures[a]	66	22.5	48	27.6	7	11.7	8	19.1	3	17.7
Klebsiella pneumoniae	25	8.5	19	10.9	1	1.7	3	7.1	2	11.1
Salmonella enterica	17	5.8	13	7.5	3	5.0	—	—	1	5.9
Enterobacter spp.	11	3.8	7	4.0	2	3.3	2	4.8	—	—
Escherichia coli	4	1.4	2	1.2	—	—	2	4.8	—	—
Other *Klebsiella* spp.	4	1.4	4	2.3	—	—	—	—	—	—
Staphylococcus aureus	4	1.4	3	1.7	1	1.7	—	—	—	—
Citrobacter spp.	1	0.3	—	—	—	—	1	2.4	—	—

[a]Additionally, 11 blood cultures grew coagulase-negative staphylococci and *Bacillus* spp., which were regarded as contaminants, and hence, were not considered for further analysis.

TABLE 2. Epidemiological, clinical and diagnostic characteristics of 293 bacteraemic and non-bacteraemic patients in Bouaké, central Côte d'Ivoire[a]

Characteristic	Data available[b]	Bacteraemia (n = 66)		No bacteraemia (n = 227)			
	n	n	%	n	%	p	p after controlling for malaria[c]
Sex	278	63		215			
Male	155	41	65.1	114	53.0		
Female	123	22	34.9	101	47.0	0.090	
Age	232	50		182			
<1 year	42	8	16.0	34	18.7	0.663	
1–5 years	77	24	48.0	53	29.1	0.012	
6–15 years	59	10	20.0	49	26.9	0.319	
16–25 years	11	0	0	11	6.0	0.075	
26–45 years	14	4	8.0	10	5.5	0.510	
>45 years	29	4	8.0	25	13.7	0.277	
Signs and symptoms	266	61		205			
Self-reported fever	120	34	55.7	86	42.0	0.057	0.468
Anaemia	55	15	24.6	40	19.5	0.390	0.139
Convulsions	43	15	24.6	28	13.7	0.042	0.482
Dyspnoea	17	2	3.3	15	7.3	0.375	0.892
Abdominal pain	10	4	6.6	6	2.9	0.244	0.396
Vomiting	8	3	5.0	5	2.4	0.389	0.129
Axillary temperature	190	47		143			
≥38°C	160	37	78.7	123	86.0	0.234	0.388
≥39°C	121	29	61.7	92	64.3	0.745	0.311
≥40°C	56	16	34.0	40	28.0	0.428	0.076
≥41°C	7	3	6.4	4	2.8	0.367	0.201
Microscopy for malaria	74	16		58			
Positive	24	9	56.3	15	25.9	0.022	

[a]Data were obtained between June 2012 and September 2014.
[b]Missing data are due to incomplete patient records.
[c]Based on partial correlation test.

patients (thiamphenicol, n = 2; cotrimoxazole, n = 1; imipenem, n = 1; metronidazole, n = 1).

In this study, analysis of a single blood culture obtained from acutely ill patients in central Côte d'Ivoire revealed a high prevalence (22.5%) of bacterial BSI. Sixty-five percent of bacteraemia cases were detected in male patients, which is in line with recent research shedding new light on gender differences in the susceptibility towards bacterial infections [14,15]. *Enterobacteriaceae* accounted for over 90% of all significant bacteraemia episodes. Such a strong predominance of Gram-negative pathogens has also been reported from other African settings, including Burkina Faso [16] and the Democratic Republic of the Congo [17].

In our patient sample, *K. pneumoniae* was the most commonly isolated pathogen, which may be explained by distinct geographical idiosyncrasy. Indeed, although *K. pneumoniae* is an important agent of nosocomial infections worldwide, recent studies have highlighted its potential to cause community-onset infections across Africa and Asia [18]. Invasive infections due to typhoidal and particularly non-typhoidal *S. enterica* strains are endemic to sub-Saharan Africa [19,20] and constitute the second most common pathogen in the present study. Hence, our findings underscore previous calls for in-depth investigations to elucidate the epidemiology of *S. enterica* in Africa [21], with a particular focus on multidrug-resistant strains, potential human-to-human transmission and complex interactions with highly co-endemic infections such as HIV and schistosomiasis [22].

In the current setting, children were disproportionately affected by BSI. Interestingly, no infections with *Streptococcus pneumoniae* and only a few *S. aureus* cases were detected. In contrast, a recent meta-analysis revealed that *S. pneumoniae* is the most common cause of bacteraemia in African children [8], but this observation does not apply to all African settings [17].

Our study has several limitations. First, the examination of only a single blood culture per patient as performed here is relatively insensitive, particularly for the detection of *S. pneumoniae* [23] and invasive salmonellosis [24]. Second, the use of a more sophisticated blood culture detection system (e.g. automated blood culture incubation and growth detection) may have further increased the sensitivity of the microbiological analysis. Third, it was not systematically assessed whether the patients had received any anti-infective treatment before they sought care at the hospital. In many regions of sub-Saharan Africa, antibiotics are readily sold as over-the-counter drugs and without a medical prescription [25,26]. Hence, it is likely that many patients in our study had been self-treated before admission. Many Gram-positive (e.g. *S. aureus* and *S. pneumoniae*) and some Gram-negative pathogens (e.g. *Haemophilus influenzae*), which commonly cause community-acquired infections, are sensitive to many empirically used antibiotics (e.g. penicillin derivatives such as

amoxicillin/clavulanic acid), while Gram-negative *Enterobacteriaceae* are more frequently resistant. Hence, such pre-treatment may have caused a selection bias in our study sample that may partially explain the low number of the aforementioned pathogens.

Fourth, this retrospective observational study had incomplete patient chart data, and information on clinical and epidemiological parameters was thus not fully available to investigate the association between clinical features and bacteraemia. Additionally, the high rates of malaria co-infections in bacteraemic individuals precluded any distinct attribution of clinical signs and symptoms to bacterial BSI. Fifth, the number of obtained blood cultures during the study period was low. Blood culture diagnostics were re-introduced in the study hospital after a decade of absent laboratory services, and not all attending physicians may thus have been aware of this diagnostic tool. Moreover, costs for laboratory tests in Côte d'Ivoire have to be incurred by the patients themselves or their families, which could have prevented a wider use of blood culture sampling in febrile but less severely ill patients, thereby leading to selection bias.

Our study is further limited by the unavailability of serotyping methods to differentiate non-typhoidal *S. enterica* from typhoidal serovars (*Salmonella* Typhi and *Salmonella* Paratyphi) and by the lack of antimicrobial susceptibility testing for the detected pathogens. However, these limitations reflect the reality of many hospital settings in sub-Saharan Africa, where the lack of laboratory infrastructure and accurate diagnostic testing constitutes a significant, yet insufficiently addressed barrier to improved patient management [27]. Indeed, allocation of funds towards an improved availability of reliable data on antimicrobial resistance patterns in resource-constrained tropical countries would be highly cost-effective and could significantly affect the mortality and morbidity rates due to bacterial BSI [28]. The paramount importance of microbiologic diagnostics is further underscored by our observation that clinical parameters alone (e.g. fever) were not sufficiently sensitive to predict BSI, thereby confirming previous findings from paediatric studies in Guinea-Bissau [29] and Kenya [30].

In conclusion, we provide the first report on the aetiology of BSI in central Côte d'Ivoire after a decade-long disruption of diagnostic laboratory activities due to political unrest and armed conflict. We identified a high prevalence of BSI that was almost exclusively attributable to *Enterobacteriaceae. K. pneumoniae* and *S. enterica* accounted for >50% of all detected pathogens. Further research on these bacteria is warranted to elucidate their epidemiology, virulence characteristics, resistance patterns and clinical presentation in Côte d'Ivoire and elsewhere in sub-Saharan Africa.

Conflict of interest

None declared.

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