ORIGINAL ARTICLE

Salmonella bloodstream infection in Ghanaian children

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Objective: To examine the frequency of community-acquired salmonella bloodstream infection in Ghanaian children and the occurrence of antibiotic resistance in salmonellae.

Methods: The study comprised 472 patients with a blood culture obtained within 48 h of admission to the pediatric department of Korle Bu Teaching Hospital in Accra, Ghana, over a 3-month period. All *Salmonella* isolates from blood cultures were speciated and antibiotic susceptibility tests were performed. Clinical data of children with salmonella bloodstream infection were compared to those of controls. Two control groups were identified: all children enrolled in the study without salmonella bloodstream infection (group 1), and those with bloodstream infection due to other organisms (group 2).

Results: A pathogen was isolated from 111 children (23.5%), and salmonellae were among the most common isolates (n=24; 21.6%). Among *Salmonella* strains, *S. enteritidis* (n=14; 59%) predominated over *S. typhi* (n=6; 25%). Resistance to several antibiotics was only found in *S. enteritidis* isolates (n=8; 57%). Children with salmonella bloodstream infection presented more often than controls with severe anemia, jaundice, abdominal pain and distension as well as hepatomegaly and splenomegaly. They were also hospitalized for a significantly longer period, but the case-fatality rate was similar.

Conclusions: Salmonella bloodstream infection, especially due to non-typhoidal strains, is a potential health problem for Ghanaian children and may be complicated by resistance to the commonly available antibiotics.

Key words: Non-typhoidal salmonella bloodstream infection, multiple antibiotic resistance, risk factors, clinical features

Salmonella bloodstream infections represent a major health problem worldwide but particularly in developing countries [1,2]. Typhoid fever is very common in South and East Asia [3], and West and Central Africa. In Africa there is also a high frequency of non-typhoidal salmonella bloodstream infections [4,5]. The emergence of multi-drug-resistant non-typhoidal salmonellae in several West and Central African countries such as Rwanda, Liberia and Senegal has been reported with increasing frequency over the last decade [6–8]. It is not known whether resistant strains have already spread to the West African country of Ghana. We report the results of a prospective study performed at the Korle Bu Teaching Hospital in Accra to evaluate the importance of drug-resistant salmonella infection in Ghanaian children.

PATIENTS AND METHODS

Background

Situated in the national capital of Accra, Korle Bu Teaching Hospital is the largest hospital in Ghana, with approximately 1550 beds. Patients mostly come from the densely populated Greater Accra Region and belong to the urban population, but some are also referred from other hospitals all over the country. Between 100 and 200 children up to the age of 12 years are seen daily at the department of paediatrics, which provides about 175 beds for inpatients. The study was performed during the dry season, with temperatures approximating 28°C.

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Study design

All patients between the ages of 1 week and 12 years, who presented at the department of paediatrics from 7 December 1993 to 7 March 1994 with a blood culture taken within 48 h of admission, were eligible for the study. The indications for obtaining a blood culture were those of the usual practice at the department, including a rectal temperature >38°C, severe malnutrition in acutely ill children (weight for age < 5th percentile), sickle cell disease or congenital heart disease even in the absence of fever. Information was recorded relating to the patients' name, date of admission, age, sex, weight for age (according to the National Centre for Health Statistics (NCHS) growth charts [9]), feeding practice, geographic origin, number of children in the family and professions of the carers. The presenting complaints of the patients were noted, as well as the findings of the physical examination on admission. All children enrolled in the study were followed up until they were discharged or died. The length of stay in the hospital, the duration of fever and the treatment modalities were recorded. The clinical data were evaluated by comparing patients with salmonella bloodstream infection due to both non-typhoidal salmonellae and *S. typhi* (cases) to all other children without salmonella infection (control group 1) and to all children with bloodstream infection due to any other pathogen (control group 2). Children comprising control group 2 are therefore a subgroup of children constituting control group 1.

Laboratory studies

Blood was examined for hemoglobin, sickle cell disease and malaria parasites for most of the patients. A sample of about 2 mL of blood for culture was inoculated into a bottle containing 10 mL of thioglycolate broth and incubated at 35–37°C. Subcultures and Gram-staining were performed routinely on days 1 and 7 and if bottles showed turbidity. Salmonellae were identified using standard criteria and were further specified with antisera manufactured by Behring (Marburg, Germany) according to the Kauffmann–White scheme [10]. Antibiotic susceptibility was tested on Mueller–Hinton agar by the disk diffusion method [11].

Statistics

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) 6.0 for Windows. Risk factors and clinical features were studied by univariate analysis. For categorical variables, the chi-squared test was employed, and the Mann–Whitney U test was used for continuous variables. $p<0.05$ was considered significant, and $p<0.01$ was taken as highly significant.

Table 1 Bacterial species isolated from blood cultures

Species	Number of isolates	Percentage
Gram-negative isolates		
Salmonella spp.	24	21.6
Enterobacter spp.	26	23.4
Acinetobacter spp.	12	10.8
Klebsiella spp.	11	9.9
Citrobacter spp.	4	3.6
Pseudomonas spp.	2	1.8
Proteus spp.	1	0.9
Haemophilus influenzae	1	0.9
Escherichia coli	1	0.9
Gram-positive isolates		
Staphylococcus aureus	23	20.7
Enterococcus faecalis	3	2.7
Streptococcus pneumoniae	3	2.7
Total	111	100

RESULTS

Four hundred and seventy-two children between the ages of 1 week and 12 years were included in the study. *Staphylococcus epidermidis* and *Bacillus* spp. were recovered from 70 and nine blood cultures respectively, and both were considered to be contaminants. A significant pathogen was isolated from 111 blood cultures (23.5%). Salmonellae were among the most common pathogens (n=24; 21.6%), second only to *Enterobacter* spp. (n=26; 23.4%) (Table 1). The majority of *Salmonella* isolates were identified as *S. enteritidis* (n=14; 59%), followed by *S. typhi* (n=6; 25%), whereas other serotypes occurred only occasionally (one isolate each of *S. oakland*, *S. paratyphi* A, *S. typhimurium* and *S. wien*).

Among *S. enteritidis* isolates, eight (57%) had identical resistance patterns. They exhibited resistance to ampicillin, mezlocillin, trimethoprim–sulfamethoxazole, and tetracycline. *Salmonella* spp. other than *S. enteritidis* were all susceptible to ampicillin, trimethoprim-sulfamethoxazole, tetracycline, mezlocillin, chloramphenicol, augmentin, aztreonam, amikacin, gentamicin, cefazolin, cefuroxime, cefotaxime and ofloxacin. No resistance to chloramphenicol was recorded in any of the *Salmonella* strains, and none of the *S. typhi* isolates was resistant to any of the antibiotics tested.

The mean age of patients with salmonella bloodstream infection (all species, including *S. typhi*) was significantly higher than that of the two control groups (5 years versus 3.2 years in control group 1 and 3.3 years in control group 2). Few cases of non-typhoid salmonella bloodstream infection occurred in children younger than 1 year, and all children with typhoid fever were older than 3 years. There were more male (54%)

Table 2 Clinical data at presentation and outcome in children with salmonella bloodstream infection (cases) and in controls

	No. of cases	Control Group 1		Control Group 2	
		No.	*p*-values	No.	*p*-values
Total	24 (100%)	448 (100%)		87 (100%)	
Mean age (years)	5	3.2	< 0.01	3.3	< 0.01
Female sex	9 (37.5%)	207 (46%)	NS	40 (46%)	NS
Sickle cell disease	6 (25%)	58 (13%)	NS	8 (9%)	NS
Fever (> 38.5°C)	16 (67%)	212 (47%)	NS	41 (47%)	NS
Severe anemia (hemoglobin ≤5 g%)	8 (33%)	76 (17%)	< 0.05	16 (18%)	NS
Jaundice	9 (38%)	66 (15%)	< 0.01	15 (17%)	< 0.05
Abdominal pain	11 (46%)	72 (16%)	< 0.001	17 (20%)	< 0.01
Abdominal distension	6 (25%)	37 (8%)	< 0.01	6 (7%)	< 0.01
Hepatomegaly ≥5 cm	10 (42%)	46 (10%)	< 0.001	11 (13%)	< 0.001
Splenomegaly	12 (50%)	92 (21%)	< 0.001	22 (25%)	< 0.01
Length of hospitalization (days)	11.2	8.4	< 0.01	10.2	< 0.01
Pyrexia > 3 days	12 (50%)	107 (24%)	< 0.001	26 (30%)	< 0.05
Death	3 (12.5%)	57 (13%)	NS	14 (16%)	NS

NS=not significant.

than female children enrolled, but no difference in the frequency of salmonella bloodstream infection was observed. Only a small proportion of children were well nourished, and the weight for age was above the 50th percentile in no more than 40 patients (8.5%). An influence of low weight for age on the occurrence of salmonella bloodstream infection could not be observed (data not shown).

Fever (>38°C) was one of the major criteria for inclusion in this study. However, comparing patients with high-grade fever (>38.5°C) to those with low grade fever (≤38.5°C) at the time of admission, we observed that children with salmonella bloodstream infection were more likely to present with high-grade fever, even though the correlation was not significant (Table 2). The blood film of 83 patients in this study (18%) revealed malaria parasites.

Severe anemia (Hb ≤5 g%), jaundice, abdominal pain, abdominal distension, hepatomegaly (≥5 cm below the costal margin) and splenomegaly were significantly more common in patients with salmonella bloodstream infection than in controls (Table 2). Most of these physical signs were also associated with sickle cell disease (data not shown). However, there was no difference in the frequency of salmonella bloodstream infection between those with and those without sickle cell disease, and the correlation between the physical signs mentioned and salmonella bloodstream infection remained significant even after excluding all 64 patients (14%) with sickle cell disease.

Two hundred and fifty children in this study (53%) were treated with chloramphenicol. Most of them received this drug as empirical treatment for suspected bloodstream infection. Ninety-nine children (21%) were treated for at least 7 days. Chloramphenicol was also given to most of the patients with salmonella bloodstream infection (79%).

Patients with salmonella bloodstream infection were hospitalized for a significantly longer period than the controls, and extended pyrexia (>3 days) was more often recorded. The mean length of their hospital stay was 11.2 days compared to 8.4 in control group 1 and 10.2 in control group 2. Nevertheless, the case-fatality rate did not differ between cases and controls. The crude mortality of patients with salmonella bloodstream infection was 12.5%, and it was 13% and 16% in the respective control groups (Table 2). Several children died during the first few days or even the first few hours after admission, due to the advanced state of their diseases and the critical condition in which they arrived at the hospital.

DISCUSSION

Salmonella bloodstream infection was a common cause of illness among the children in this study. It has previously been observed that salmonella infection in Ghana occurs more frequently during the rainy season than during the dry season [12,13]. But even though this study was performed during the dry season, salmonellae were still among the most common pathogens, accounting for 24% of blood culture isolates. These figures are comparable to other reports on salmonella bloodstream infection. In a study conducted in South Africa, *Salmonella* spp. were isolated from 22% of 315 children with bloodstream infection, and only

Streptococcus pneumoniae was more frequent (24%) [14]. In Nigeria, salmonella bloodstream infection was diagnosed in 24% of 146 bacteremic patients [15]. In a study including 900 febrile children in Rwanda, the blood cultures of 112 patients grew a pathogen (12.4%), and *Salmonella* spp. accounted for 74% of these isolates [4].

Six *Salmonella* strains (25%) in this study were *S. typhi*, but the majority were non-typhoidal *Salmonella* spp., with *S. enteritidis* being the most common serotype (59%). The predominance of non-typhoidal salmonellae among blood culture isolates was also reported from other African countries such as Kenya [5], South Africa [14] and Zaire [16], with frequencies ranging from 43% to 88%. In contrast, the majority of isolates in Rwanda were *S. typhi*, and only 43% were non-typhoidal salmonellae [4].

In this study, *S. typhi* isolates were susceptible to all drugs tested. Antibiotic resistance was only found in *S. enteritidis*. Most of these isolates were resistant to ampicillin, mezlocillin, tetracycline and trimethoprim–sulfamethoxazole, but all remained susceptible to chloramphenicol. These strains were, by definition, not multi-drug resistant, since multi-drug resistance in salmonellae is defined as resistance to chloramphenicol, ampicillin and trimethoprim–sulfamethoxazole [17]. Antibiotic resistance, especially in non-typhoidal salmonellae, is of increasing importance worldwide [18] and has been reported from other West and Central African countries such as Kenya [5], Rwanda [7] and Liberia [8]. Antibiotic resistance to chloramphenicol was not found during the study period but has been observed during an earlier survey in Accra (M. J. Newman, personal communication). As it is the only commonly available drug to treat drug-resistant salmonella bloodstream infection, the probable spread of resistance to chloramphenicol will become a matter of great concern. More than half of the children in this study (53%) were given chloramphenicol as empirical treatment.

Early diagnosis and appropriate treatment of salmonella bloodstream infection is essential to improve the outcome of patients and limit the spread of drug-resistant strains. Therefore, risk factors and common clinical features of salmonella bloodstream infection were investigated and compared to controls. It has frequently been claimed that infants and children in the first year of life are especially at risk for salmonella bloodstream infection [19,20]. Others could not confirm this finding [21]. The results of this study did not support the view that infants are at increased risk. The mean age of children with salmonella bloodstream infection was 5 years, versus 3.2 and 3.3 years in the respective control groups. Previous years' data at Korle Bu Teaching Hospital showed that non-typhoidal salmonella infection was most common in children between the ages of 1 and 3 years, whereas the frequency of typhoid fever rose continuously with age. Children with salmonella bloodstream infection were hospitalized for a significantly longer period than controls. Despite adequate treatment, fever persisted, often for more than 3 days. Three children died of salmonella bloodstream infection, accounting for a case-fatality rate of 12.5%. Comparable mortality rates of 12–20% have been reported from other African countries [4,5,14,16]. The fact that mortality in children with salmonella bloodstream infection was not increased compared to controls may be influenced by the occurrence of benign bacteremia during diarrheal illness.

Clinical findings associated with salmonella bloodstream infection were severe anemia, jaundice, abdominal pain, abdominal distension, hepatomegaly and splenomegaly. However, from this series no clinical signs were assumed to be pathognomonic. Even cardinal signs of typhoid fever such as fever, splenomegaly, relative bradycardia and rose spots are not reliable in an area where malaria is endemic and the dark skin of patients may make rose spots difficult to detect [18,22]. Apart from abdominal distension, all these signs are also commonly found in patients with sickle cell disease. Children with sickle cell disease are generally predisposed to salmonella infection [23,24] and to develop complications such as septic arthritis and osteomyelitis [25]. However, the association with salmonellosis was still significant after excluding the sickle cell patients. Due to its frequency and protean clinical presentation, salmonellosis should be considered as a differential diagnosis in cases of severe febrile illness in children in endemic areas.

In conclusion, salmonella bloodstream infection, especially due to non-typhoidal species, may have a significant impact on children's health in Ghana. All *Salmonella* isolates in the present study were susceptible to chloramphenicol, the most frequently employed antibiotic for salmonella bloodstream infection. However, substantial effort will be necessary to limit the occurrence of multi-drug resistant non-typhoidal salmonellae that have already emerged in other West and Central African countries [5–7] and may become a therapeutic challenge in the near future also in Ghana. This is especially important in a country where people cannot generally afford to be treated with the newer, more expensive, drugs such as third-generation cephalosporins or quinolones [17]. Since our survey was limited in time and confined to the Greater Accra Region, no firm conclusions may be drawn regarding the situation in the whole of the country. In addition,

since no epidemiologic strain typing was performed, one cannot exclude the possibility that resistant *S. enteritidis* isolates belonged to one strain. Further studies of salmonellosis involving healthcare centers in various areas of the country are therefore necessary to more completely understand the full extent of this potentially serious health problem in Ghana.

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