ORIGINAL ARTICLE 10.1111/j.1469-0691.2005.01200.x

Non-Typhi *Salmonella* gastroenteritis in children presenting to the emergency department: characteristics of patients with associated bacteraemia

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ABSTRACT

The records of children with *Salmonella* gastroenteritis only (n = 97), and those with associated bacteraemia (n = 64), seen in one medical centre during a 12-year period, were analysed retrospectively. Mean patient age was 2.24 ± 2.8 years (range, 0.05–16 years), and 49% were male. Children with bacteraemia presented after a longer duration of symptoms (7.0 ± 6.9 vs. 3.9 ± 4.6 days, p 0.0002), and had higher erythrocyte sedimentation rates (45 ± 22 vs. 33 ± 22 mm/h, $p < 0.02$) and lactate dehydrogenase values (924 ± 113 vs. 685 ± 165 IU/L, p 0.001). There was a trend in bacteraemic children towards immunosuppression (6.3% vs. 1.0%, p 0.08) and a lower number of siblings (2.9 ± 1.9 vs. 3.8 ± 2.7, p 0.063). Non-bacteraemic children had a more severe clinical appearance, and a higher percentage had a moderate to bad general appearance (51.5 vs. 29.7%, $p < 0.01$), with dehydration (37.1 vs. 18.8%, p 0.02) and vomiting (58.8 vs. 39.0%, p 0.02). Laboratory dehydration indicators were also markedly worse in non-bacteraemic children, with urine specific gravity of 1020 ± 9.4 vs. 1013 ± 9.0 (p 0.0002), base excess of −4.2 ± 3.0 vs. −2.5 ± 3.4 mEq/L (p 0.01), and blood urea nitrogen of 10.1 ± 7.0 vs. 7.4 ± 4.5 mg% (p 0.002). Thus, the clinical presentation of bacteraemic children was more gradual, and associated gastroenteritis and dehydration was less pronounced. These findings may contribute in part to the inadvertent discharge of bacteraemic children from the emergency department.

Keywords Bacteraemia, children, diagnosis, gastroenteritis, *Salmonella*

Original Submission: 19 September 2004; **Revised Submission:** 15 February 2005; **Accepted:** 23 March 2005

Clin Microbiol Infect 2005; 11: 651–655

INTRODUCTION

Childhood infection with non-Typhi *Salmonella* (NTS) commonly causes acute gastroenteritis, which is generally self-limited, but can result occasionally in bacteraemia. The reported incidence of bacteraemia among children with gastroenteritis caused by NTS varies between 3.3% and 41% [1–7]. It is agreed generally that children aged >2 months with NTS gastroenteritis should not be treated with antimicrobial agents, because therapy is ineffective, may prolong the carrier state and could induce drug resistance [8]. There is no simple clinical sign or laboratory test for the reliable detection of bacteraemic patients.

Previous studies have identified certain high-risk groups that are more susceptible to extra-intestinal disease (e.g., young infants and immunocompromised patients). However, previous studies of paediatric populations have either not compared bacteraemic with non-bacteraemic patients, or have performed blood culture only in a subgroup of patients assumed to be non-bacteraemic [6,9–12]. A case-control study that compared bacteraemic and non-bacteraemic children did so only in patients with NTS infection [2]. Therefore, the aim of the present study was to define the clinical characteristics of children presenting to the emergency department with NTS

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bacteraemia, and to compare them with those of children with non-bacteraemic NTS gastroenteritis.

MATERIALS AND METHODS

Patients

The records of the microbiology laboratory at Shaare Zedek Medical Center, a 550-bed community hospital in Jerusalem, Israel, were reviewed from 1990 to 2001. During this period, the policy in the emergency department was to obtain one blood culture set from each febrile child with diarrhoea. Seventy-five children (aged ≤16 years) with a positive blood culture for NTS were identified. Of these, 11 children whose medical records were not available were excluded from analysis. Children with acute *Salmonella* gastroenteritis, but with negative blood cultures, were the reference population. The medical records of the patients were reviewed with respect to demographics, clinical presentation, laboratory results, bacteriology and outcome. The patients were considered to appear ill if they were described by emergency department staff as irritable, lethargic or toxic, and considered to appear well if they were described as active, alert, playful, etc.

Bacteriology

Blood cultures were performed using the BACTEC 9240 (Becton Dickenson, Sparks, MD, USA). Blood isolates of *Salmonella* were identified with common biochemical tests [13]. Serogrouping was performed by agglutination testing. Serovars were determined in the Central Laboratories, National *Salmonella* Center (Ministry of Health, Jerusalem, Israel). Susceptibilities were tested using the Kirby–Bauer disk-diffusion technique.

Statistical analysis

Data were stored and analysed using EPIINFO v. 6.04 (CDC, Atlanta, GA, USA). Physical findings between bacteraemic and non-bacteraemic patients were compared by chi-square analysis, with $p < 0.05$ considered to be significant. Continuous variables were compared with the *t*-test. Logistic regression analysis was performed using SPSS v. 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Sixty-four patients (31 males, 48.4%) were included in the NTS bacteraemia group, and 97 patients (51 males, 52.6%) were included in the NTS gastroenteritis group. The mean age of patients in the two groups was similar (Table 1). Of the 64 bacteraemic patients, 37 (58%) were aged ≤12 months (one patient aged <3 months), compared to 30% of the non-bacteraemic patients (five patients aged <3 months). Table 1 compares the clinical characteristics and outcome of the patients in both groups, while Table 2 compares the laboratory characteristics of the two groups. Six of the patients included in the study, four in the bacteraemic group and two in the non-bacteraemic group, were immunocompromised. These included one patient with juvenile rheumatoid arthritis, one with systemic lupus erythematosus, one with acute lymphocytic leukaemia, one infected with human immunodeficiency virus and suffering from severe malnutrition, and two with congenital nephrotic syndrome.

Three patients in the bacteraemic group suffered complications. A patient with systemic lupus erythematosus who developed abdominal

Table 1. Clinical characteristics and outcome of children presenting to the emergency department with *Salmonella* gastroenteritis with and without associated bacteraemia

	***Salmonella* gastroenteritis (*n* = 161)**		
Characteristic	**Bacteraemic (*n* = 64)**	**Non-bacteraemic (*n* = 97)**	**p value**
Age (years) at presentation (mean ± SD)	1.92 ± 2.9	2.44 ± 2.6	NS
Immunocompromised, *n* (%)	4 (6.2)	2 (2)	NS
Days until diagnosis (mean ± SD)	7.0 ± 6.9	3.9 ± 4.6	0.0002
Ill appearance, *n* (%)	19 (29.6)	50 (51.5)	0.007
Dehydration, *n* (%)	12 (18.7)	36 (37.1)	0.02
Highest temperature (°C, mean ± SD)	39.5 ± 0.86	39.2 ± 0.91	0.029
Diarrhoea, *n* (%)	54 (84)	89 (91.7)	NS
Vomiting, *n* (%)	25 (39)	57 (58.7)	0.02
Empirical antibiotic treatment, *n* (%)	49 (77)	70 (72)	NS

NS, not significant.

Table 2. Laboratory data of children presenting to the emergency department with *Salmonella* gastroenteritis with and without associated bacteraemia

	***Salmonella* gastroenteritis (*n* = 161)**		
Characteristic	**Bacteraemic (*n* = 64) Mean ± SD**	**Non-bacteraemic (*n* = 97) Mean ± SD**	**p value**
WBC	14.4 ± 6.9	13.2 ± 6.1	NS
ESR	44.7 ± 22.4	33.5 ± 22.0	0.016
Urine specific gravity	1013 ± 9.0	1020 ± 9.0	0.0002
BUN	7.4 ± 4.5	10.1 ± 7.0	0.002
Creatinine	0.4 ± 0.13	0.42 ± 0.14	NS
pH	7.36 ± 0.04	7.35 ± 0.05	NS
HCO_3	20.8 ± 3.5	19.5 ± 3.4	0.04
Base excess	− 2.5 ± 3.4	− 4.2 ± 3.0	0.01
LDH	924 ± 113	685 ± 165	0.001
NTS serogroup *n* (%)			
Group B	15 (23)	28 (29)	NS
Group C	32 (50)	44 (45)	NS
Group D	17 (27)	25 (26)	NS

NS, not significant; WBC, white blood cell count (1000/mL); ESR, erythrocyte sedimentation rate (mm/h); BUN, blood urea nitrogen (mg/dL); HCO_3, serum bicarbonate; LDH, lactate dehydrogenase (IU/L).

tenderness, with evidence of pancolitis on CT scan, was treated conservatively and recovered uneventfully. One patient who underwent tetralogy of Fallot repair became septic and was diagnosed with acute endocarditis. One patient with polycystic disease of the liver developed an NTS liver abscess. No mortality occurred in the study population.

Non-bacteraemic patients were more likely to be dehydrated (p 0.02) and to appear ill upon physical examination (p 0.007). Although patients with NTS bacteraemia tended to have a higher fever, most appeared well, and the duration of the illness before diagnosis was significantly longer compared to non-bacteraemic patients (p 0.0002). Moreover, 31 (48%) of the patients with bacteraemia were discharged after their initial visit to the emergency department, compared to 29 (30%) non-bacteraemic patients (p 0.02). Most bacteraemic patients were discharged with a diagnosis of a virus infection, and were recalled and admitted only when the blood culture was positive for a Gram-negative bacillus. There were no infectious complications among the patients with bacteraemia, including those who were initially discharged from the emergency department.

The clinical differences between the two groups were supported by the laboratory findings; non-bacteraemic patients had higher blood urea nitrogen levels (p 0.002) and urine specific gravity (p 0.0002), and lower bicarbonate values (p 0.04). The latter two differences were also significant in multivariate analysis. Bacteraemic patients had a higher erythrocyte sedimentation rate (ESR) (p 0.016), but the white blood cell count was similar in both groups. No differences in levels of transaminases were observed, but lactate dehydrogenase was elevated significantly in patients with bacteraemia (p 0.001). *Salmonella* group C was the most common group, accounting for *c.* 50% of isolates.

DISCUSSION

The data from the present study suggest that although younger children with NTS gastroenteritis are more likely to be bacteraemic, the course of their disease is usually benign, and complications in previously healthy children are rare. This concurs with studies published previously, which have shown that although bacteraemia can be persistent, it does not usually evolve to meningitis or metastatic foci of infection [3,14].

Sirinavin *et al.* [6,10,11] studied Thai children with extra-intestinal salmonellosis, and suggested that infants aged < 6 months, and those who are immunocompromised, have a higher probability of extra-intestinal infection, and show a higher case fatality rate. These studies included children with bacteraemia and a large subgroup of patients with localised infection, such as NTS meningitis, arthritis and osteomyelitis. Data analysis did not differentiate between the latter groups.

It has also been shown that NTS bacteraemia in children is different in several respects from that in adults. Adult patients are more likely to have predisposing conditions, a higher rate of immunosuppression and incidence of primary bacteraemia, extra-intestinal organ involvement, and show a relatively high mortality rate [15,16]. End-organ complications of *Salmonella* bacteraemia in the elderly in the Shaare-Zedek Medical Center have been described previously [17,18]. In the present study period, none of the bacteraemic children developed meningitis, and there was no mortality associated with bacteraemia. The two children who did develop focal infection had a predisposing condition.

The incidence of NTS bacteraemia in Israel, in both children and adults, increased significantly during the period 1987–1996. In a study from southern Israel, this increase correlated with an increased frequency of *Salmonella* Virchow and *Salmonella* Enteritidis infections [19]. Most of the bacteraemic children in the present study had *Salmonella* C infection, with *Salmonella* Virchow accounting for only a minority of infections.

According to these data, although there is no single test that could differentiate reliably between children with NTS gastroenteritis alone and those with associated bacteraemia, the clinical picture in these two groups is often different. Bacteraemic patients tended to have more prolonged and higher fever, but most appeared well on presentation. Although most children presented with diarrhoea, they were usually not dehydrated, and almost half were discharged from the emergency department. In contrast, half of the non-bacteraemic children appeared ill, and were more likely to be dehydrated, with corresponding laboratory findings of concentrated urine and lower bicarbonate levels. In contrast, Meadow *et al.* [2] reviewed the

clinical course of children with NTS bacteraemia, compared to that of children with gastroenteritis alone, and did not demonstrate any difference in clinical characteristics or outcome between these two groups. Although the ESR was significantly higher in bacteraemic children, there was an overlap in ESR values from children with gastroenteritis alone. The combination of fever and gastroenteritis with an elevated ESR (> 40 mm/h), and possibly an elevated level of lactate dehydrogenase, could raise a suspicion of associated bacteraemia.

The present data show that bacteraemic children had a mean duration of fever of 1 week before presentation at the emergency department, compared to 4 days in children with gastroenteritis alone. Similarly, a previous study [20] also suggested that children with NTS bacteraemia differed from those with gastroenteritis alone by having a fever duration of >5 days. Because of the prolonged fever, bacteraemic children may present to the emergency department later in the course of their illness, despite improved acute clinical signs. Hence, the clinical signs and laboratory indicators for dehydration may be less pronounced than for those children with gastroenteritis alone, who present earlier during the acute disease.

Empirical antibiotic therapy of gastroenteritis in children has not been shown to decrease the risk of persistent bacteraemia [12,21], and, in view of the low risk of complications and the favourable outcome, is not justified. Instead, children suspected of having NTS gastroenteritis should be evaluated carefully for signs of toxicity or dehydration and, if they appear well and hydrated, may be managed safely as outpatients until blood culture results are obtained. Epstein *et al.* [22] showed that *Salmonella* was second only to *Streptococcus pneumoniae* as a cause of occult bacteraemia in children discharged from the emergency department, accounting for seven (25%) of 28 such cases. None of these discharged children suffered complications. This was also true for children aged <1 year. As the present study included only six patients aged <3 months, it is not possible to draw general conclusions regarding the proper management of this age group. In contrast, Galofre *et al.* [23] studied 172 adult patients with *Salmonella* bacteraemia, and reported that 12% died and 16% developed septic metastases, which was especially the case for immunocompromised patients.

The present study had several limitations, associated primarily with its retrospective nature. First, although many variables were highly significant in the bivariate analysis, most (except for urine specific gravity and serum bicarbonate level) were not significant in multivariate analysis, mainly because some of the data were not available for many of the patients studied. Nevertheless, these highly significant differences in the bivariate analysis were considered to be clinically relevant. Second, as this study focused on children presenting to the emergency department from whom at least one blood culture was obtained, it is likely that both patient groups were more severely ill than patients with NTS gastroenteritis cared for in the community. Hence, both the severity of the clinical and laboratory characteristics of the patients in the two groups and the percentage of patients with associated bacteraemia may be overestimated. Yet, in an emergency department, this is the group of patients who would be suspected to have an associated bacteraemia and who should therefore be evaluated.

In summary, the present study demonstrated that children with NTS gastroenteritis and associated bacteraemia tended to have a more prolonged and indolent course of disease, compared with children with NTS gastroenteritis without bacteraemia. This finding, which is somewhat contrary to what might be expected, may be important for clinicians who care for young children with febrile gastroenteritis.

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