Invasive non-typhoidal salmonellosis in immunocompetent infants and children

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Bacteremia; Childhood; Immunocompetent hosts; Infancy; Invasive salmonellosis; Non-typhoidal Salmonellae

Summary
Objective: To investigate the extraintestinal manifestations of non-typhoidal Salmonellae (NTS) infection in immunocompetent infants and children.
Method: The study took place at the University General Hospital at Heraklion, Crete. Over a 10-year period from 1993—2002 we studied 1087 patients, of whom 443 were children less than 14 years old, with a culture-proven diagnosis of NTS infection. Stool and blood cultures were routinely obtained in patients presenting with fever and diarrhea. The cases of invasive infection in otherwise well children, including bacteremia and/or extraintestinal focal infections were further analyzed.
Results: Invasive cases were less common in children than adults (4.06% vs. 8.7%; relative risk 0.467; 95% confidence intervals (CI) 0.279—0.784; p = 0.0033). Furthermore, invasive cases were much less common in the otherwise well than in immunocompromised children (3.5% vs. 21.4%; relative risk 0.163; 95% CI 0.053—0.500; p = 0.0008). The 15 otherwise well children with invasive NTS infection were aged from 3 weeks to 7.5 years, and nine were aged less than 12 months. Among them, 11 presented with bacteremia, and four with focal extraintestinal infections (rectal abscess, deep neck abscess, urinary tract infection, elbow arthritis). Salmonella enterica subsp. enterica serovars Enteritidis and Virchow were the most common invasive serotypes. All invasive strains were susceptible to beta-lactams including ampicillin, and to cotrimoxazole. All patients made a complete recovery with intravenous antibiotics and did not present with relapses or major infections during long-term follow-up.
Conclusion: Invasive non-typhoidal salmonellosis in immunocompetent children is less frequent than in both immunocompromised children and in adulthood. However, invasive cases may well
Introduction

The usual clinical presentation of non-typhoidal Salmonellae (NTS) infection is self-limited gastroenteritis, however bacteremia and focal extraintestinal infections may occur. Incidence rates of invasive salmonellosis vary widely and are higher in individuals at the extremes of age, the immunocompromised, and patients with hemoglobinopathies and hemolytic anemias.\(^1^\)–\(^5^\) In contrast to NTS gastroenteritis, invasive disease has a guarded outcome and prompt antibiotic treatment is essential.\(^6^\)–\(^10^\) In this study we investigated the frequency, presentation and outcome of invasive NTS infections in otherwise well children being treated at a referral general hospital, in a well-defined geographical area, and over a long period.

Population and methods

Study setting and design

The University General Hospital at Heraklion, Crete is the main tertiary care setting in the island covering a population of 611,000, of whom 132,000 are children aged 0–14 years (2001 census data). The mean annual admission rate during the study period was 45,104 patients, of whom 4,574 were children less than 14 years old. The study included all patients hospitalized from January 1993 to December 2002 with a culture positive for NTS. Stool and blood cultures were routinely obtained in patients presenting with fever and diarrhea. The cases of invasive infection in otherwise well children, including bacteremia and/or extraintestinal focal infections were further analyzed.

Bacteriology

Blood cultures were performed using the BacT/Alert System (Organon Teknika Corporation, North Carolina, USA). Stool specimens were cultured on routine bacteriologic media employed for enteric pathogens according to usual protocols (all media products of BioMérieux, Marcy l’Etoile, France). The isolated organisms were identified biochemically according to standard methods, the API system (BioMérieux), and commercial antisera (Bio-Rad, Marnes-la-Coquette, France). Susceptibility to antimicrobial agents was determined by the disk diffusion method recommended by the Clinical and Laboratory Standards Institute.\(^12^\)

Statistics

Relative risks with 95% confidence intervals (CI) were calculated to compare incidence differences between groups. The Chi-square test was used to estimate the statistical significance of differences, and values of \(p < 0.05\) were considered to be significant.

Results

NTS infection

A culture-proven NTS infection was documented in 1,087 patients, 443 (41%) of whom were children under 14 years of age, and 644 (59%) adolescents and adults. Eighteen children (4.1%) and 56 adolescents and adults (8.7%) presented with bacteremia and/or focal infection. The relative risk for invasive disease among children was 0.467 as compared to the adult patients (95% CI 0.279–0.784; \(p = 0.0033\)). Among the 443 children, 14 (3.2%) were immunocompromised and 429 (96.8%) were otherwise well. Three children from the first group and 15 from the second presented with invasive NTS infection (21.4% and 3.5%, respectively). Otherwise well children had a significantly lower risk for invasive NTS infection than their immunocompromised peers (relative risk 0.163, 95% CI 0.053–0.500; \(p = 0.0008\)).

Of the 429 children with a culture positive for NTS, four (0.9%) were aged less than 4 weeks, presenting with gastroenteritis (3) and urinary tract infection (1). NTS were the most common bacterial isolates in childhood gastroenteritis in the area of the study, accounting for 36.5% of all stool bacterial isolates during the study period.

Invasive NTS infection

Among the 15 children with invasive NTS infection seven (47%) were girls and eight (53%) were boys. The median age was 0.9 years (range 24 days–7.5 years) and nine (60%) were infants aged less than 1 year. Medical history did not reveal underlying predisposing conditions in any of the children. A history of prematurity was recalled in a single child. Thirteen children (87%) presented with fever \(>39\) °C, 11 (73%) with gastrointestinal symptoms, two (13%) with a maculopapular rash, and one (7%) with febrile seizures. Bacteremia occurred in 11 (73%) and focal infections were documented in four (27%) patients. A 5-month-old boy presented with vomiting, bloody diarrhea, and a rectal abscess without fever; a 4-year-old girl presented with fever, left-side torticollis, and a deep neck abscess; a 24-day-old infant presented with fever and failure to thrive and grew Salmonella spp in urine; a 5-year-old boy presented with left elbow swelling, a history of gastroenteritis a month ago, and grew Salmonella enterica subsp. enterica ser. Virchow in synovial fluid.

Serotypes and susceptibility

The frequency of serotypes in stool and blood/focal cultures is shown in Table 1. All cases were community-acquired. S. enterica subsp. enterica serovars Typhi and Paratyphi were not isolated from infants or children. By contrast, S. enterica subsp. enterica ser. Typhi was isolated...
from three adults and \textit{S. enterica} subsp. \textit{enterica} ser. \textit{Paratyphi B} from four adults. The overall resistance rates of NTS strains were 26.3% to ampicillin, 29.9% to tetracycline, 6.8% to chloramphenicol, and 3.6% to cotrimoxazole. All isolates were susceptible to quinolones and third generation cephalosporins. All invasive strains were sensitive to beta-lactams including ampicillin, and to cotrimoxazole.

**Laboratory findings**

The mean white blood cell count in the 15 infants and children with invasive NTS infection was 10.4 \(\times\) 10\(^9\)/L (range 7.8—15.7), the mean neutrophil count 4.9 \(\times\) 10\(^9\)/L (range 2.2—9.1), and the mean erythrocyte sedimentation rate was 59.4 (range 30—92) mm/h. Only four (27%) children had leukocytosis (white cell count >12.0 \(\times\) 10\(^9\)/L) and none had leukopenia. All bacteremic patients had a sterile repeat blood culture. Serum immunoglobulin determination and had leukopenia. All bacteremic patients had a sterile repeat

<table>
<thead>
<tr>
<th>Serovar</th>
<th>Stool</th>
<th>Blood</th>
<th>Focal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteritidis</td>
<td>335</td>
<td>6</td>
<td>0</td>
<td>335 (6)</td>
</tr>
<tr>
<td>Typhimurium</td>
<td>61</td>
<td>1</td>
<td>0</td>
<td>61 (1)</td>
</tr>
<tr>
<td>Virchow</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Newport</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Glostrup</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Heidelberg</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Infantis</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Kottbus</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Agona</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Blockley</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Braenderup</td>
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<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bredeney</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Hador</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ramsey</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>\textit{Salmonella spp}</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total (patients)</td>
<td>424</td>
<td>13</td>
<td>2</td>
<td>429 (10)</td>
</tr>
</tbody>
</table>

**Management and outcome**

All children received intravenous antibiotics, mostly a third generation cephalosporin, for 7—30 days. All had an excellent outcome and did not present with relapses or any other infections during the follow-up period.

**Discussion**

In recent studies NTS were found to be the most common bacterial enteropathogens in children in Greece \cite{13,14,15} and this was confirmed by our findings. In a recent study conducted by our team, it was found that \textit{S. enterica} subsp. \textit{enterica} were the most commonly isolated bacterial enteropathogens accounting for up to 6% of the total diarrheal patients in Crete, and being more frequently detected in patients over 15 years of age. \cite{14} Among children, salmonellosis was diagnosed more frequently in those aged between 5 and 9 years. \cite{14} In the present study, invasive disease occurred in 3.5% and 21.4% of immunocompetent and immunocompromised children with NTS infection, respectively. Incidence values varying from 2% to 47% have been reported. \cite{16,17,18} Neonates and infants less than 3 months of age with NTS gastroenteritis are widely considered to be more prone to bacteremia and focal infection. Our findings suggest that this susceptibility extends throughout infancy, as most of our patients with invasive infection were infants less than 1 year old, although there was only one infant of less than 3 months. First line laboratory investigation in children with invasive NTS infection was commonly non-specific. The findings in children with NTS bacteremia are not extremely helpful as they are generally similar to those in uncomplicated gastroenteritis. \cite{10,19,20}

Salmonellae are particularly capable of causing focal suppuration of infections of almost any organ. \cite{21,22,23,24,25} The urinary tract infection in our patient was considered to be hematojenous as the neonate had no diarrhea or NTS isolation from stool. The infant with bacteremia and rectal abscess was afebrile. We are not aware of any detailed description of a rectal abscess due to NTS infection. Deep neck abscesses are extremely rare, although the skeletal system is a common site of focal infection, mainly in individuals with pre-existing skeletal abnormalities, immune disorders, or sickle cell disease.

Several studies have suggested particular virulence and invasiveness of certain NTS serovars including \textit{S. enterica} subsp. \textit{enterica} serovars Enteritidis and Typhimurium. \cite{1,5,10,16,26,28} The invasiveness of \textit{S. enterica} subsp. \textit{enterica} ser. Virchow has increased especially among children, although the strain has not been shown to harbor a virulence plasmid. \cite{5,23,27} Interestingly, \textit{S. enterica} subsp. \textit{enterica} ser. Choleraesuis, a well-recognized invasive serovar, was not isolated from any adult or child, including the immunocompromised patients, and no \textit{S. enterica} subsp. \textit{enterica} serovars Typhi or Paratyphi were isolated from children.

Antimicrobial resistance of NTS has been increasing through the 1990s and is a major problem in several countries. \cite{28} NTS isolates from stools demonstrated broad antibiotic resistance in this study, similar to that previously reported, \cite{14} however all invasive isolates were sensitive to cotrimoxazole and all beta-lactams. All our patients had a favorable outcome, however persistent bacteremia or relapse despite adequate antibiotic administration has been reported. \cite{15}

In conclusion, NTS invasive infection is much less common in otherwise well children as compared both to their immunocompromised peers and to adults. However, invasive infection may well occur among otherwise well infants and children with gastroenteritis, requiring hospitalization. Infants aged less than 12 months are more susceptible than older children to invasive infection. In our setting, \textit{S. enterica} subsp. \textit{enterica} serovars Enteritidis and Virchow but not Typhimurium strains were associated with high invasiveness. An immunological work-up does not seem necessary for otherwise healthy children with NTS invasive infection and the outcome is favorable with appropriate antibiotic treatment.

**Conflict of interest:** No conflict of interest to declare.
References