Risk factors for mortality caused by nontyphoidal Salmonella sp. in children

Maria Teresa Rosanova,(1) Hugo Paganini,(1) Rosa Bologna,(1) Horacio Lopardo,(2) and Gabriela Ensinck(1)

Objective: To identify the risk factors for mortality in extraintestinal nontyphoidal Salmonella (NTS) infections in infants and children.

Methods: We performed a retrospective analysis of 107 patients with at least one nonfecal culture for NTS seen from January 1988 to December 1995.

Results: The median age was 12 (range 1–216) months. Malnutrition was found in 55 patients (51%), and 22 (20%) displayed severe features (weight loss >40%). Seventy-two patients (67%) had previously been hospitalized, and 59 (55%) had received antibiotics during the month before admission. Fever (85%) and diarrhea (56%) were the most frequent clinical manifestations. Nineteen children (18%) had leukopenia. Forty-nine patients (46%) had only bacteremia, 33 (31%) bacteremia with focal infections, and 25 (23%) focal infections with negative blood cultures. Forty-seven strains (44%) were multiresistant, and 40 of them were nosocomially acquired. Eight patients (7%) had received inappropriate antibiotic treatment, and two of them died. Thirteen (12%) children died. Age, underlying disease, previous admission, previous antibiotic therapy, type of infection, susceptibility of the strains and inappropriate antibiotic treatment were not statistically significant risk factors for mortality. A logistic regression analysis selected the following variables as independently influencing outcome: malnutrition (P<0.01), leukopenia (P<0.002) and presence of diarrhea (P<0.02).

Conclusions: Children with extraintestinal infections by NTS with leukopenia, malnutrition and presence of diarrhea have a higher risk of death.


INTRODUCTION

Nontyphoidal Salmonella (NTS) infections are usually limited to simple gastroenteritis, but a higher risk of bacteremia and other extraintestinal infections can occur and result in serious sequelae and death. The potential predisposing factors for extraintestinal infections include extremes of age and immunocompromising conditions. Since the 1960s, Salmonella species resistant to antibiotics have been reported with increasing frequency all over the world, and are of great concern. During the study period, we had in our hospital an increasing number of extraintestinal infections by NTS and resistance to antibiotics, like other pediatric centers in Argentina.

Episodes of Salmonella sp. bacteremia are associated with a relatively high crude mortality rate; however, very few studies have focused on the analysis of prognostic factors in extraintestinal salmonellosis. In some reports, mortality has been related to extreme age, absence of fever, presence of shock or coma, underlying diseases, and inappropriate antimicrobial treatment. In the present study, we analyzed the epidemiologic, bacteriologic and clinical features and outcome of 107 extraintestinal infections by NTS.

METHODS

Setting

The Hospital de Pediatría Profesor Dr. Juan P. Garrahan is a 560-bed tertiary-care pediatric general hospital in Argentina.

Study design

A retrospective analysis of clinical and bacteriologic data for all patients with NTS extraintestinal infections between January 1988 and December 1995 was carried out. Patients were included in the study if they had had at least one nonfecal culture positive for NTS. The medical records of patients were reviewed regarding epidemiologic, clinical, bacteriologic and outcome features.
Definitions

Extraintestinal localization

NTS was isolated from at least one nonfecal culture.

Degree of malnutrition

This was defined according to the Gomez et al classification as: first degree, 10–24% deficit weight/age (w/a); second degree, 25–39% deficit w/a; and third degree, ≥40% w/a.

Nosocomial acquisition

This was considered to have occurred when the cultures were positive after 72 h from admission with prior negative cultures, or when patients had been hospitalized within 30 days before the onset of infection.

Prior use of antibiotics

This was considered to have occurred when the patient had received any kind of antibiotic 30 days before NTS infection. The appropriateness of antimicrobial therapy was determined for the first 3 days of extraintestinal infection due to NTS. Appropriate antimicrobial therapy included administration of trimethoprim-sulfamethoxazole, ampicillin or amoxicillin, chloramphenicol, ciprofloxacin, imipenem or third-generation cephalosporins, if organisms were susceptible to the drug in vitro. Inappropriate antimicrobial therapy included use of a regimen without any appropriate drug, a drug to which the causative organism was resistant, or no antimicrobial therapy.

Bacteriology

Conventional methods were used for the isolation and identification of *Salmonella* strains. Test of susceptibility were done using diffusion and dilution techniques as defined by the National Committee for Clinical Laboratory Standards (NCCLS) guidelines. A multiresistant *Salmonella* sp was defined when resistance to two or more groups of antibiotics was found. Two patterns of multiresistance were detected: multiresistant 1 (MR1), with resistance to trimethoprim-sulfamethoxazole; and multiresistant 2 (MR2), with susceptibility to this drug (Table 3). Final serovar identification was performed at the Instituto de Microbiologia Carlos Malbrán in 37 strains.

A patient’s death was attributed to extraintestinal infection by *Salmonella* sp if cultures were positive at the time of death or if death occurred within the first 2 weeks of documented infection without any other explanation.

Statistical analysis

Fisher’s exact test was considered for comparison of proportions when at least one expected value was <5; otherwise, the uncorrected chi square was used and P-values ≤0.05 were considered significant. The ORs and their 95% CI were calculated by logistic regression. Stata statistical software was used for all calculations.

**RESULTS**

During the study period, 107 patients with extra-intestinal infections by NTS were recorded. The median age was 12 (range 1–216) months. Sixty-seven (63%) were male. Seventy-two (67%) had underlying diseases, mainly hematologic and oncologic disorders. Eleven (10%) were HIV infected. According to nutritional status classified by weight for age on admission, 55 (51%) were malnourished, and 22 of these (20%) had third-degree malnutrition. Seventy-two (67%) had previously been hospitalized, and 59 (55%) had received antibiotics during the month before admission (Table 1). Fever (85%) and diarrhea (56%) were the most frequent clinical features. Nineteen children (18%) had leukopenia, and 15 of these had immunocompromising conditions. Blood cultures were positive in 82 patients (77%), and fecal cultures in 42 (40%). Forty-nine children (46%) had only bacteremia, 33 (31%) had bacteremia with focal infection, and 25 (23%) had focal infection with negative blood cultures. The most frequent clinical foci were the central nervous system and genitourinary tract (Table 2). Forty-seven strains (44%) were multiresistant; 40 of these were nosocomially acquired (Table 3). Eight patients (7%) had received inappropriate antimicrobial treatment, and two of these...

### Table 1. Clinical characteristics of 107 children with extraintestinal NTS infections

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Male/Female</td>
<td>67/40</td>
<td>67/40</td>
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<tr>
<td>Median age in months (range)</td>
<td>12 (1–216)</td>
<td>12 (1–216)</td>
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<tr>
<td>Normal weight for age</td>
<td>52</td>
<td>49</td>
</tr>
<tr>
<td>Degree of malnutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Second</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Third</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Prior hospitalization</td>
<td></td>
<td></td>
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<tr>
<td>Underlying diseases</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>91</td>
<td>85</td>
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<tr>
<td>Diarrhea</td>
<td>60</td>
<td>56</td>
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### Table 2. Clinical localizations in 107 children with extraintestinal NTS infections

<table>
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<tr>
<th>Localization</th>
<th>n</th>
<th>Percentage</th>
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<tr>
<td>Bacteremia without localization</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>Clinical focus</td>
<td>98</td>
<td>54</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>13</td>
<td>22</td>
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<tr>
<td>Urinary tract</td>
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<td>22</td>
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<tr>
<td>Osteoarticular</td>
<td>9</td>
<td>10</td>
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<tr>
<td>Skin</td>
<td>8</td>
<td>14</td>
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<tr>
<td>Lower respiratory tract</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Others</td>
<td>8</td>
<td>14</td>
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died. Thirteen children (12%) died. Univariate analysis of factors associated with death demonstrated that there were statistically significant differences in certain factors associated with death: malnutrition, presence of diarrhea, and leukopenia (P<0.05). Age <12 months, underlying disease, previous hospital admission, previous antibiotic therapy, localization of infection, susceptibility of the strains and inappropriate antimicrobial therapy were not significant. Malnutrition, leukopenia and presence of diarrhea were statistically associated with mortality according to the logistic regression model (P<0.05) (Tables 4 and 5).

**DISCUSSION**

Although NTS infections are usually limited to simple gastroenteritis, a higher risk of bacteremia and other extraintestinal infections can occur and result in serious sequelae and death.1,2

*Salmonella* infections are common in Argentina. However, little information is available from descriptive studies, and there are few comparative studies concerning the clinical course and prognosis of extraintestinal infections by NTS.9-15 The potential predisposing factors for extraintestinal infections include extremes of age and immunocompromising factors.1,2,5 The incidence of NTS infections is greater in the first year of life than at any other time.3,4

**Table 3. Patterns of resistance in 107 strains of NTS**

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<thead>
<tr>
<th></th>
<th>AMP</th>
<th>CTX</th>
<th>AKN</th>
<th>TMS</th>
<th>CMP</th>
<th>IMP</th>
<th>NOR</th>
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<tbody>
<tr>
<td>MR1</td>
<td>R</td>
<td>R</td>
<td>R</td>
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<td>MR2</td>
<td>R</td>
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MR1, Multiresistant (TMS resistant); MR2, Multiresistant (TMS susceptible); S, susceptible; R, resistant; AMP, ampicillin; CTX, cefotaxime; AKN, amikacin; TMS, trimethoprim-sulfamethoxazol; CMP, chloramphenicol; IMP, imipenem; NOR, norfloxacin.

In the general population, suppurative complications have been recognized in 7–10% of all cases of salmonellosis.1 NTS may involve any organ system. Meningitis due to NTS has been most commonly found in infants and the elderly, and is associated with complications and a higher risk of mortality.1-5

Case-fatality rates for extraintestinal infection due to NTS in previous reports vary from 0% to 66%, and are associated with many factors.9-15 Our study showed that malnutrition, leukopenia and diarrhea were predictors of death.

Sirinavin et al21 reported that severe malnutrition was a predictor for extraintestinal infection in children with *Salmonella* enteritis but not for mortality; however, Riley et al9 showed that malnutrition was a risk factor for mortality, as we did.

Leukopenia was a predictor of infectious relapse in adult patients with NTS bacteremia,12 and for more severe clinical presentations in children.14 Ramos et al12 noted in a comparative study of patients with bacteremia due to NTS that there were more deaths in the group without preceding diarrhea. Leukopenia and diarrhea were risk factors for death in our series.

Previous studies have suggested that age less than 1 year,14 localization of infection (pneumonia and meningitis)12,13 and immunocompromised status4 were variables associated with risk of death in children with NTS infections, but in our series there were no significant differences for these conditions.

Different *Salmonella* serovars were reported as being associated with invasiveness and high death rates,15 but serovar identification is not possible in all cases, so we cannot draw definitive conclusions concerning this point. During the past two decades, several species of *Salmonella* have shown an alarming ability to acquire high resistance levels to antibiotics.7,8 In Argentina, multiresistant NTS were detected at the beginning 1989 in pediatric hospitals.8 Several authors suggested that multiresistant NTS infections were not more severe when compared with antibiotic-susceptible strains,22 but other authors have reported outbreaks of multiresistant NTS with high morbidity and mortality rates.23 Our data did not show differences between resistant and antibiotic-susceptible strains. Sirinavin et al14 showed that inappropriate antibiotic therapy was a risk factor for mortality, but this variable did not achieve statistical significance in our study.

In summary, our results suggest that pediatric patients with extraintestinal infections by NTS associ-
ated with malnutrition, leukopenia and or the presence of diarrhea have more risk of mortality.

ACKNOWLEDGEMENTS

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REFERENCES