Risk Factors for Enteric Perforation in Patients with Typhoid Fever

Salih Hosoglu¹, Mustafa Aldemir², Serife Akalin¹, Mehmet Faruk Geyik¹, Ibrahim H. Tacyildiz², and Mark Loeb³

¹ Department of Clinical Microbiology and Infectious Diseases, Dicle University Hospital, Diyarbakir, Turkey.  
² Department of Emergency Medicine, Dicle University Hospital, Diyarbakir, Turkey.  
³ Departments of Pathology and Molecular Medicine and Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada.

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A case-control study was performed using the records of patients hospitalized for typhoid fever at Dicle University Hospital, Diyarbakir, Turkey, between 1994 and 1998. Case patients with enteric perforation were compared with control patients with typhoid fever but no enteric perforation. Risk factors for perforation were determined using logistic regression modeling. Forty case patients who had surgery because of typhoid enteric perforation were compared with 80 control patients. In univariate analyses, male sex (p = 0.01), age (p = 0.01), leukopenia (p = 0.01), inadequate antimicrobial therapy prior to admission (p = 0.01), and short duration of symptoms (p = 0.01) were significantly associated with perforation. In multivariate analysis, male sex (odds ratio (OR) = 4.39, 95% confidence interval (CI): 1.37, 14.09; p = 0.01), leukopenia (OR = 3.88, 95% CI: 1.46, 10.33; p = 0.04), inadequate treatment prior to admission (OR = 4.58, 95% CI: 1.14, 18.35; p = 0.03), and short duration of symptoms (OR = 1.22, 95% CI: 1.10, 1.35; p = 0.001) were significant predictors of perforation. A short duration of symptoms, inadequate antimicrobial therapy, male sex, and leukopenia are independent risk factors for enteric perforation in patients with typhoid fever.

intestinal perforation; multivariate analysis; risk factors; typhoid fever

Abbreviations: CI, confidence interval; OR, odds ratio.

Typhoid fever is a severe febrile illness caused primarily by the gram-negative bacillus Salmonella enteritidis serovar Typhi. It is a global health problem that can have a devastating impact on resource-poor countries. Regions with contaminated water supplies and inadequate waste disposal have a high incidence of typhoid fever (1–4). Approximately 10,000 patients are hospitalized annually for this infection in Turkey, and more than 60 percent of these cases are reported from the southeast region (5–7). The incidence of typhoid fever in southeastern Turkey ranges from 210 to 320 cases per 100,000 population (5). The most lethal complications of typhoid fever are intestinal bleeding and ileal perforations, both arising from necrosis of Peyer’s patches in the terminal ileum (8–10).

Despite this high morbidity, relatively little is known about risk factors for enteric perforation in patients with typhoid fever. Previous studies have suggested that male sex and leukocytosis predispose patients to enteric perforation (11–13). However, these studies were limited in that they did not adjust for confounding variables. To determine risk factors for enteric perforation among patients admitted to the hospital with typhoid fever in southeastern Turkey, we conducted a case-control study.

MATERIALS AND METHODS

Selection of case and control patients

Our study was conducted at Dicle University Hospital, a 1,050-bed tertiary referral center that provides care for the vast majority of patients with typhoid fever in southeastern Turkey. Using a standardized data collection form, we abstracted data from the medical records of all inpatients with typhoid fever hospitalized over a 5-year period (January
1994–December 1998). During this time period, all typhoid fever patients with acute abdomen seen in the emergency department had their cases investigated by abdominal ultrasonography, plain abdominal radiography, and paracentesis for typical features of enteric perforation: free abdominal fluid, hepatosplenomegaly, air-fluid levels, and gas under the diaphragm. The diagnosis of typhoid fever was based on the isolation of S. Typhi using standard methods from blood, urine, bone marrow, or stool, in conjunction with a compatible clinical presentation—that is, persistent fever and at least two of the following: constipation or diarrhea, anorexia, abdominal pain, abdominal rigidity, relative bradycardia, and changes in consciousness. Case patients were those with typhoid fever who had evidence of enteric perforation based on compatible clinical presenting and imaging with a positive S. Typhi culture from blood, urine, bone marrow, or stool. The diagnosis in culture-negative cases was based on a standardized clinical definition (i.e., persistent fever and at least two of the following: constipation or diarrhea, anorexia, abdominal pain, abdominal rigidity, relative bradycardia, and changes in consciousness) and intraoperative findings (anterior mesenteric perforation of the distal ileum with histologic evidence of typhoid inflammation in the tissue obtained from the edge of the perforation). Standard criteria (rebound tenderness, abdominal rigidity, the presence of free intraabdominal gas upon radiography, fecaloid or purulent fluid upon paracentesis) were used in the decision to perform a laparatomy in patients with suspected enteric perforation. If an inpatient with typhoid fever developed an acute abdomen during the hospitalization period, ultrasonography, radiography, and paracentesis were performed to determine whether the ileum had been perforated. Patients with generalized peritonitis due to other causes (intestinal tuberculosis, traumatic perforation, perforated appendicitis, duodenal ulcer perforation) were excluded from this study. For each case patient, the next two patients admitted to the hospital with typhoid fever who did not have clinical or radiologic evidence of enteric perforation were selected as controls.

**Measurements**

Information on demographic factors and clinical presentation was abstracted from all patients. Data on time of onset of symptoms, prehospital therapy, and hospital clinical and laboratory findings were abstracted. Duration of illness prior to admission was defined in days from the onset of symptoms to hospital admission. Inadequate therapy was defined as not being given a minimum of 3 days of effective antimicrobial treatment for S. Typhi at the correct dose prior to admission.

On the basis of clinical relevance and a review of the literature, the following potential risk factors were evaluated: age (>40 years), gender, inadequate treatment, duration of symptoms, high fever (>38.5°C), elevated transaminase levels (>1.5 times normal values), hepatosplenomegaly, leukopenia (<3,000 white blood cells/µl), anemia (hemoglobin level <8 g/dl), and elevated erythrocyte sedimentation rate.

**Statistical analysis**

For univariate analyses, a chi-squared test was used for categorical variables and a Student’s t test for continuous variables. For assessment of predictors of perforation, multivariate analysis using logistic regression was performed. Candidate variables with a p value less than 0.1 were entered using a backwards, stepwise approach. Variables were kept in the final model if the p value was less than 0.05.

**RESULTS**

Forty-eight patients met our case definition for typhoid fever with enteric perforation (mean age = 28.2 years; range, 16–74 years; 80 percent males). Eight typhoid fever patients with enteric perforation were excluded from the study because of data insufficiency. During this 5-year period, 459 typhoid fever patients were hospitalized. The rate of perforation was 10.5 percent among all inpatients. Twenty-six case patients (65 percent) had S. Typhi detected from blood; one (2.5 percent) had it detected from bone marrow, six (15 percent) from stool, and two (5 percent) from urine. All case patients had rebound tenderness and abdominal rigidity (table 1). The mean duration of symptoms for case patients was 13.9 days (standard deviation, 5.3; range, 1–30 days). The mean interval between presentation at the emergency department and surgery was 1.5 hours (standard deviation, 0.7; range, 1–6 hours). Perforation occurred during the course of hospitalization in 10 case patients (25 percent). Twenty-six (87 percent) of 30 patients with perforation prior to hospital admission had thrombocytopenia as compared with three patients (10 percent) with perforation after hospitalization (p = 0.002). Hepatosplenomegaly was more common among patients with perforation prior to hospitalization than among those who developed perforation as inpatients (43 percent vs. 10 percent; p = 0.056). In plain abdominal radiographs, all case patients had air-fluid levels, and 28 (70 percent) had air under the diaphragm. The most frequent laboratory findings were elevated transaminase levels (22 patients; 55 percent) and leukopenia (21 patients; 53 percent) (table 1). Management of case patients included aggressive fluid-electrolyte and acid-base balancing, preoperative administration of antimicrobial agents (chloramphenicol or ciprofloxacin), nasogastric tube decompression, and administration of total parenteral or enteral nutrition postoperatively.

Eighty patients (66.7 percent) were selected as control patients. All of the control patients had S. Typhi detected from blood; one (1.3 percent) had it detected from bone marrow and five (6.3 percent) from stool. The mean duration of symptoms for control patients was 18.8 days (standard deviation, 6.0; range, 8–32 days). Management of control patients included hospitalization and antimicrobial therapy with chloramphenicol, ciprofloxacin, or ceftriaxone for either 7 or 10 days. Three case patients (8 percent) died in the hospital; all control patients survived.

Risk factors were determined by comparing case patients with control patients. In univariate analyses, male sex (odds ratio (OR) = 1.39, 95 percent confidence interval (CI): 1.09, 1.78; p = 0.01), age (>40 years) (OR = 4.67, 95 percent CI: 287, 1324; p = 0.0002), high fever (>38.5°C) (OR = 2.74, 95 percent CI: 1.18, 6.33; p = 0.02), and inadequate therapy (OR = 4.44, 95 percent CI: 1.09, 17.73; p = 0.04) were significant (table 2). In the multivariate analysis, high fever (OR = 2.86, 95 percent CI: 1.13, 7.27; p = 0.025) and inadequate therapy (OR = 5.43, 95 percent CI: 1.31, 21.8; p = 0.025) were retained in the final model.
1.27, 17.10; \( p = 0.01 \)), leukopenia (<3,000 white blood cells/µl) (OR = 2.00, 95 percent CI: 1.25, 3.20; \( p = 0.01 \)), inadequate antimicrobial therapy prior to admission (OR = 4.24, 95 percent CI: 1.29, 13.95; \( p = 0.01 \)), and short duration of symptoms (\( \leq 15 \) days) (OR = 1.84 (95 percent CI: 1.21, 2.80; \( p = 0.01 \)) were significantly associated with perforation (table 2).

The following variables, on the basis of an a priori decision, were entered into the logistic regression model: male sex, age, leukopenia, inadequate treatment, duration of symptoms, and hepatosplenomegaly. In multivariate analysis, male sex (OR = 4.39, 95 percent CI: 1.37, 14.09; \( p = 0.01 \)), leukopenia (OR = 3.88, 95 percent CI: 1.46, 10.33; \( p = 0.04 \)), inadequate treatment prior to admission (OR = 4.58, 95 percent CI: 1.14, 18.35; \( p = 0.03 \)), and short duration of symptoms (OR = 1.22, 95 percent CI: 1.10, 1.35; \( p = 0.001 \)) were kept in the model as significant predictors of perforation. A Pearson’s correlation coefficient test was used to assess the correlation between inadequate treatment prior to admission and short duration of symptoms. The correlation was not significant at the 0.05 level (\( r = -0.197 \)).

DISCUSSION

Risk factors for perforation among patients with typhoid fever have been previously assessed (1, 3, 14–16). However, to our knowledge, this was the first study to determine independent risk factors for perforation using multivariate analysis. An important finding was the significant association between short duration of symptoms and perforation. This is consistent with the clinical evidence in published case series (1, 2, 14–16). For example, Khan et al. (15) reported that among patients with typhoid fever confirmed by blood culture, the mean duration of symptoms was lower in patients with enteric perforation than in those without it. In contrast to these findings, other investigators have reported an association between longer duration of symptoms and perforation (2, 17, 18). For example, in a case series from Bangladesh, Butler et al. (2) reported a longer mean duration of symptoms prior to admission among patients with enteric perforation. It is notable that in their report, only two of the 15 patients who eventually developed perforation did so prior to admission, whereas in our study the majority of perforations occurred prior to hospital admission. In resource-poor countries, difficulties in diagnosis, patient transfer, and subtherapeutic antibiotic treatment often result in delayed presentation to a hospital (2, 16). This may explain the delays in the report by Butler et al. (2). The patients in our study appear to have had a more fulminant course, with early perforation, and because of the severity of their illness they may have been more likely to receive hospital care earlier than typhoid fever patients who did not present with signs of perforation.

### TABLE 1. Symptoms, clinical signs, and laboratory findings in hospitalized patients with typhoid fever, Diyarbakir, Turkey, 1994–1998

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case patients (enteric perforation)</th>
<th>Control patients (no enteric perforation)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(( n = 40 ))</td>
<td>(( n = 80 ))</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>40</td>
<td>100</td>
<td>32</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29</td>
<td>72.5</td>
<td>33</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>30.0</td>
<td>26</td>
</tr>
<tr>
<td>Constipation</td>
<td>27</td>
<td>67.5</td>
<td>12</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High fever (&gt;38.3°C)</td>
<td>37</td>
<td>92.5</td>
<td>76</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>14</td>
<td>35.0</td>
<td>41</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>35</td>
<td>87.5</td>
<td>35</td>
</tr>
<tr>
<td>Rebound tenderness</td>
<td>40</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal rigidity</td>
<td>40</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Confusion</td>
<td>20</td>
<td>50.0</td>
<td>7</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air-fluid levels</td>
<td>40</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>Gas under diaphragm</td>
<td>28</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>21</td>
<td>52.5</td>
<td>21</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>29</td>
<td>72.5</td>
<td>17</td>
</tr>
<tr>
<td>Anemia</td>
<td>7</td>
<td>17.5</td>
<td>12</td>
</tr>
<tr>
<td>Elevated transaminase levels</td>
<td>22</td>
<td>55.0</td>
<td>38</td>
</tr>
</tbody>
</table>
The majority of typhoid fever patients who develop perforation do so within the first 2 weeks of the illness (3, 16). It is possible, as our results suggest, that patients with perforation have a disease pathogenesis that is more fulminant. The mechanism of intestinal perforation in typhoid fever is hyperplasia and necrosis of Peyer’s patches of the terminal ileum. The lymphoid aggregates of Peyer’s patches extend from the lamina propria to the submucosa, so that in the presence of hyperplasia the distance from the luminal epithelium to the serosa is bridged by lymphoid tissue. During the course of typhoid fever, S. Typhi is found within mononuclear phagocytes of Peyer’s patches, and in cases with intestinal perforation, both this tissue and surrounding tissues show hemorrhagic areas, most often during the third week of the illness (2). Tissue damage in Peyer’s patches occurs, resulting in ulceration, bleeding, necrosis, and, in extreme cases, full-thickness perforation. The process leading to tissue damage is probably multifactorial, involving both bacterial factors and host inflammatory response (2, 18, 19).

The fact that inadequate treatment was independently associated with enteric perforation is important, since this is a potentially modifiable factor. In patients with typhoid fever, antimicrobial treatment needs to be started early and to be used for a sufficient amount of time. The causative organism, S. Typhi, is very sensitive to antimicrobial agents commonly used in Turkey (20, 21). The timing of antimicrobial therapy could be critical in preventing serious complications such as perforation. Enteric perforation among patients with typhoid fever has been extremely rare in developed countries during the era of antibiotic use (2). This observation supports the early use of effective antibiotics in patients with typhoid fever.

Leukopenia was also found to be an independent risk factor for enteric perforation in our study. This is in contrast to other reports, in which leukocytosis has predominated in patients with enteric perforation. Among patients with typhoid fever who do not have enteric perforation, leukopenia is known to be a very common laboratory finding. For example, a white blood cell count of less than 4.5 × 10^9/liter was found in 18 percent of all children in one study (20). In another case series of patients with typhoid fever, white blood cell counts were normal in 12 patients and elevated in two, and leukopenia (4,000 white blood cells/µl) was noted in seven patients (14). In yet another study (15), wherein five of 21 patients had intestinal perforation, the rate of leukopenia was higher among patients with no complications. Given the fact that none of the case patients in our study died, perhaps leukocytosis is associated with an increased severity of enteric perforation and leukopenia in milder forms of the illness.

This study showed that being male is an independent risk factor for intestinal perforation. Our findings are consistent with previous reports in which a high male:female ratio among patients with typhoid enteric perforation was documented (9, 16–20). Khan et al. (11) reported that intestinal perforation occurred significantly more frequently in males than in females. The male:female ratio was found to be 2.5 in one study (22) and 4 in another (23). The exact reason for a higher rate of enteric perforation in males is unclear.

Hepatosplenomegaly is common among patients with typhoid fever. In a study by Chiu et al. (24), hepatosplenomegaly was the most common finding upon physical examination. However, we did not find hepatosplenomegaly to be a significant predictor of typhoid perforation.

The effect of older age on typhoid enteric perforation is unclear. In the study by Butler et al. (2), the mean age of patients with perforation was 25.7 years as opposed to 12.4 years among those with no perforation (p < 0.005). Although Khan et al. (11) reported a mean age difference between patients with and without complications (mean ages were 5 years among those with no perforation (p < 0.005).
30.2 years (standard deviation, 8.4) vs. 28.9 years (standard deviation, 12.0), respectively), this difference was not statistically significant \( (p = 0.08) \). Although we found a significant difference between the two groups in univariate analyses, age did not remain in our final multivariate model.

In conclusion, a short duration of symptoms prior to admission, leukopenia, inadequate treatment, and male gender are independent risk factors for perforation among hospitalized patients with typhoid fever. Typhoid fever and its complications remain an important cause of morbidity in resource-poor countries.

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REFERENCES