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Typhoid Intestinal Perforations: Twenty-six Year Experience

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Abstract
Background Typhoid fever (TF) is a severe febrile illness caused by *Salmonella typhi*. One of the most lethal complications of TF is ileal perforation (TIP). Although the mortality of associated with TIP has decreased slightly over the past decade, it is still high.
Methods and Results The records of the 82 surgically treated patients with TIP were evaluated retrospectively. There were 64 men with the mean age of 36.3 years (range: 7–68 years). In surgical treatment, debridement with primary closure was performed in 32 patients (39.0%), and wedge resection with primary closure was performed in 9 (11. 0%), resection with primary anastomosis in 9 (11.0%), and resection with ileostomy in 32 (39.0%). The most common postoperative complication was wound infection, which occurred in 24 patients (29.3%). The overall morbidity was highest in the ileostomy group. The overall mortality was 11.0% (9 patients). Age, gender, number, and localization of the perforations ($p > 0.05$) were not found to affect mortality, but prolonged preoperative period ($p < 0.001$), extended peritoneal contamination ($p < 0.01$), and ileostomy procedure ($p < 0.001$) were found to influence the increase in mortality.
Conclusions Early and appropriate surgical intervention with effective preoperative and postoperative care may improve survival in TIP.

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Typhoid fever (TF) is a severe febrile illness caused primarily by the gram-negative bacillus *Salmonella enteritidis* serovar Typhi [1]. In developing countries, typhoid fever still remains a major health problem because of poor sanitary conditions [2]. According to the best global estimates, there are at least 16 million new cases of typhoid fever around the world [3], and approximately 10,000 patients are hospitalized annually for this infection in Turkey [1]. The most lethal complications of TF are intestinal bleeding and ileal perforations, both arising from necrosis of Peyer's patches in the terminal ileum [1, 4]. The mortality associated with typhoid ileal perforations (TIP) ranges between 5% and 80% in various series [4, 5]. Though surgery is accepted as the definitive treatment of TIP, there is no general agreement regarding the choice of procedure [4–6]. Many factors, such as presentation time, adequacy of preoperative resuscitation, number of perforations and extent of fecal peritonitis, operation time, and technique, have been investigated for their possible effect on prognosis [3–5], but the effect of the location of ileal perforations is not clear. For the present study we reviewed our patients with TIP to determine the factors that affect mortality and morbidity.

Patients and methods

The clinical records of 82 patients who underwent surgery because of TIP in the Department of General Surgery, School of Medicine, Ataturk University, in an about 26-year period between June 1978 and December 2004, were reviewed retrospectively with respect to age, gender, symptom duration, perforation number, perforation location,

extent of peritoneal contamination, performed surgical procedures, morbidity, and mortality.

The diagnosis of TF was established on the basis of history, clinical examination, isolation of *Salmonella typhi*, and a positive Widal test. It was also confirmed intraoperatively by the typical findings of antimesenteric perforations of the ileum, and postoperatively by the pathologic examination that showed histological evidence of typhoid inflammation in the tissue obtained from the edges of perforations.

The diagnosis of patients with TIP was investigated by the presence of rebound tenderness and abdominal rigidity during physical examination, air fluid levels and gas under the diaphragm in plain abdominal radiography, free abdominal fluid and hepatosplenomegaly in abdominal ultrasonography and computed tomography, and typical features of enteric perforation containing free abdominal fluid in paracentesis. Patients with temperature ≥38°C or ≤36°C, heart rate ≥90 beats/min, respiratory rate ≥20 breaths/min, white blood cell count ≥12,000/μl or ≤4,000/μl were treated even though they were in sepsis.

All patients were resuscitated with intravenous fluids, received placement of a nasogastric tube to decompress the stomach, and had a urethral catheter to monitor urine output. Intravenous antibiotics, generally comprising chloramphenicol or ciproflocsasin were administered preoperatively and dueing the first 7 postoperative days.

Abdominal exploration was performed through a right paramedian or midline incision. The amount of pus/fecal matter drained from the peritoneal cavity reflected the extent of contamination [3]. Peritoneal contamination was accepted as severe when the drainage amount was more than 1,000 ml, whereas the contamination was accepted as moderate when the amount was between 500 and 1,000 ml, and mild when the amount was less than 500 ml. The peritoneal cavity was irrigated with normal saline. No intraperitoneal antibiotic was used. In general, debridement and two-layered primary closure or wedge resection with primary closure was the first choice of surgical treatment. Resection with primary anastomosis was performed in the patients with multiple perforations, but it was avoided if severe abdominal contamination, or ischemic, inflamed, or edematous intestine was present. Resection with or without ileostomy was used in patients with severe peritonitis, edematous or ischemic bowel, or associated problems (severe pulmonary or cardiac disease, sepsis or shock, hypoproteinemia). After the surgical procedures, the drains were inserted to right paracolic area and pelvic cavity. The incision was cleaned with povidone iodine and the abdominal layers were closed continuously by polidioxanone, while the skin was closed separately by silk. Tension sutures were not used in any patient.

The chi-square test was used for statistical analyses. A value of $p < 0.05$ was accepted as significant.

Results

Patients were between 7 and 68 years of age (mean: 36.3 years). There were 64 male patients and 18 females (3.6 : 1). Patients with TIP were generally presented to the hospital during the second (55 patients, 67.1%) and third week of their illness.

Some findings of the study and the correlations between them were given in Table 1. Ten patients (12.2%) had associated diseases (chronic obstructive pulmonary disease in 6 patients, hypertension in 4 patients, cardiac or coronary disease in 3 patients, renal insufficiency in 1 patient). The mean interval between presentation and surgery was 37.6 h (range: 660 h), and 27 patients (32.9%) suffered from shock or sepsis. Operative findings included severe peritoneal contamination in 34 patients (41.5%), moderate in 29 (35.4%), and mild in 19 (23.2%). There was a single perforation in 67 patients (81.7%), and 15 others had multiple perforations (18.3%). The perforations were located between 0 and 60 cm from the ileocecal valve in 70 patients (85.4%) and more than 60 cm from the valve in 12 others (14.6%).

Surgical procedures included debridement with primary closure in 32 patients (39.0%), wedge resection with primary closure in 9 patients (11. 0%), resection with primary anastomosis in 9 patients (11.0%), and ileostomy in 32 patients (39.0%; terminal ileostomy with resection in 28 patients; exteriorization in 4).

In mild cases, histopathological studies showed nonspecific changes consisting of edema, congestion, and focal inflammation. More severe cases showed crypt abscesses with prominent neutrophilic infiltrates in degenerating crypts. There were also extensive areas of mucosal necrosis and hemorrhage with punched–out mucosal ulcerations or erosions with elevated borders, crypt abscesses in the nonulcerated areas, and extensive mucosal and submucosal necrosis with hemorrhage.

The most common postoperative complications were superficial incision site infections in 24 patients (29.3%) and deep incision site infections in 21 patients (25.6%) incision dehiscence in 15 and intra-abdominal abscess in 6. Five (33.3%) of the patients with incision dehiscence had hypoproteinemia. Postoperative leakage was seen in 7 patients (8.5%). Leakage was from the primary closure in 3. The other 4 were in the ileostomy group, and these patients underwent reoperation. The overall morbidity rate was highest in ileostomy group. The mean hospitalization time was 11.7 days (range: 5–25 days).

Table 1 The findings of the patients with TIP and the correlations between the findings

Criterion	PC	WRA	RA	RI	Total	Mortality
Preoperative interval						
0–6 h	6	–	4	–	10	0 (0.0 %)
7–12 h	5	–	2	–	7	0 (0.0 %)
13–24 h	12	3	1	1	17	0 (0.0 %)
25–48 h	4	2	1	9	16	2 (12.5 %)
49–72 h	4	3	1	10	18	2 (11.1 %)
73-h	1	1	–	12	14	5 (35.7 %)
Severity of contamination						
Mild	10	3	6	–	19	1 (5.3 %)
Moderate	16	4	3	6	29	2 (6.9 %)
Severe	6	2	–	26	34	8 (23.5 %)
Number of perforations						
Single	32	9	1	25	67	8 (11.9 %)
Multiple	–	–	8	7	15	3 (20.0 %)
Surgical site infection						
Superficial	11	2	2	9	24	1 (4.2 %)
Deep	3	1	2	15	21	1 (4.8 %)
Total	14 (43.8 %)	3 (33.3 %)	4 (44.4 %)	24 (75.0 %)	45 (54.9 %)	9 (20.0 %)
Mortality	2 (6.3 %)	0 (0.0 %)	0 (0.0 %)	7 (21.9 %)	9 (11.0 %)	9 (11.0 %)

PC primary closure; *WRA* wedge resection and anastomosis; *RA* resection and anastomosis; *RI* resection and ileostomy

Overall, mortality was 11.0% (9 patients). Three (33.3%) of the dead patients were over 50 years of age, 6 patients (66.7%) were male, 7 patients (77.8%) had surgery 48 h or later after the onset of the symptoms, 7 patients (77.8%) had shock or sepsis, 3 patients (33.3%) had associated disease, 8 patients (88.9%) had severe peritoneal contamination, 3 patients (33.3%) had multiple bowel perforations, 3 patients (33.3%) had perforations located over 60 cm from the ileocecal valve, and 7 patients (77.8%) had ileostomy. The cause of death was shock and sepsis in 6 patients (66.7%), intestinal leakage and peritonitis in 2 patients (22.2%), and pulmonary insufficiency in 1 patient (11.1%). Although the mortality rate was higher in patients older than 50 years of age, there was not a significant statistical correlation (χ^2: 2.32; $p > 0.05$). Similarly, no correlation was found between gender and mortality rate (χ^2: 0.77; $p > 0.05$), but mortality was higher among female patients than males (16.7% and 9.4%, respectively). The prolonged interval between the onset of the symptoms and surgery was found to be an important causative factor in increased mortality rate (for a delay longer than 48 h, χ^2: 32.23; $p < 0.001$). In addition, there was a significant correlation between the extent of peritoneal contamination and mortality rate (χ^2: 9.37; $p < 0.01$); 8 of 34 patients in the severe contamination group (23.5%) were lost. Six of 67 patients in the single perforation group (9.0%) died, and 3 of 15 patients in the multiple perforation group (20.0%) died. A correlation between the number of perforations and mortality rate was not found to be significant (χ^2: 1.53; $p > 0.05$).

Although the mortality rate was higher in the group with perforations located more than 60 cm from the ileocecal valve (3 of 12 patients, 25.0%; versus 6 of 70 patients with perforations closer to the ileocecal valve, 8.6%), no significant correlation was seen (χ^2: 2.83; $p > 0.05$). Eight patients in the ileostomy group died, and there was a very significant correlation between ileostomy procedure and mortality rate (χ^2: 22.28; $p < 0.001$).

Some characteristics of the 70 patients with TIP who were treated between 1978 and 1990 and the 12 new cases treated between 1991 and 2004, are given in Table 2. Resection with primary anastomosis was the preferred operation in the cases treated during the last 14 years of the study, and none of those patients died.

Discussion

One of the most lethal complications of TF is ileal perforation arising from necrosis of the Peyer's patches in terminal ileum [1]. The incidence of TIP has been reported to be between 0.8% and 18% [7]. Although the mortality of TIP has decreased slightly over the past decade, it still ranges between 9% and 50% with surgical treatment and over 40% with conservative treatment in various series [5, 8]. Turkey, especially East Anatolia is an endemic region for TF, and the causative organism, *Salmonella typhi*, is very sensitive to the antimicrobial agents commonly used in this region. Therefore the early use of effective antibiotics in patients with TF has probably led to the decrease the TIP

Table 2 The findings of the previously reported cases and the new added patients with TIP, and their comparison

Criterion	1978–1990	1991–2004	Total
Number	70	12	82
Age (mean year)	33.7	51.4	36.3
Gender (male/female)	56/14 (4/1)	8/4 (2/1)	64/18 (3.6/1)
Preoperative interval (mean hour)	38.1	34.7	37.6
Severe peritoneal contamination	31 (44.3 %)	3 (25.0 %)	34 (41.5 %)
Multiple perforations	11 (15.7 %)	4 (33.3 %)	15 (18.3 %)
Operative procedure			
Primary closure	29 (41.4 %)	3 (25.0 %)	32 (39.0 %)
Wedge resection and anastomosis	7 (10.0 %)	2 (16.7 %)	9 (11.0 %)
Resection and anastomosis	3 (4.3 %)	6 (50.0 %)	9 (11.0 %)
Ileostomy	31 (44.3 %)	1 (8.3 %)	32 (39.0 %)
Surgical site infection	38 (54.3 %)	7 (58.3 %)	45 (54.9 %)
Mortality	9 (12.9 %)	0 (0.0 %)	9 (11.0 %)

incidence in recent years [1]. While Oren and Atamanalp [9] have reported 70 cases of TIP in the 12-year period between 1978 and 1990, in our department, the number of new cases is only 12 in the 14 years between 1991 and 2004.

Typhoid ileal perforation commonly affects young adults in the second and third decades of the life [5, 6], as found in the present series. It is also more common in males [1,10–12]; a possible explanation could be that males spend more time than females in outdoor activities, and males more often eat outdoors [12]. While Rahman et al. [2] have found that the mortality associated with TIP was increasing in children younger than 5 years of age, no correlation was found between age and mortality rate in the reports of Adesunkanmi and Ajao [5] and Meier and Tarpley [12], or in our study. On the other hand, TIP usually occurs in the second or third week of the fever, as was true in the present study [1, 10], and this is related to mechanism of perforation in Peyer's patches of terminal ileum [1].

Although nonoperative management was at one time considered the best treatment for patients with TIP, surgical treatment is now universally accepted as the standard of treatment [5, 7, 9, 10, 12]. One of the many factors that affect the success of the treatment may be the interval between the onset of the illness or the patient presentation and surgery. Rahman et al. [2], Saxe and Cropsey [4], Adesunkanmi and Ajao [5], Onen et al. [7], Abantanga and Wiafe-Addai [8], and Akgun et al. [13] have found that early surgical intervention can reduce morbidity and mortality in TIP. SimilarIy, in the present study, the prolonged delay between presentation and operation was found to be a causative factor in increased mortality rate. In our opinion, it plays a big role in the development of peritonitis, sepsis, or shock. Likewise, Rahman et al. [2], Saxe and Cropsey [4], Shukla et al. [6], and Meier and Tarpley [12] have shown that the prognosis of these patients is related mainly to overwhelming sepsis and shock. Further, operative abdominal findings may be effective in establishing the prognosis of TIP. Saxe and Cropsey [4], Adesunkanmi and Ajao [5], Shukla et al. [6], Onen et al. [7], and Meier et al. [14] have reported that severe peritoneal contamination is associated with poor prognosis, with a mortality rate ranging between 28% and 80%. In our study, we found a mortality rate as high as 23.5% in the group of patients with severe peritoneal contamination, and this result supports the findings mentioned above.

In TIP, the number and location of the perforations may be two other factors influencing prognosis. Beniwal et al. [10] have found that the number of perforations affects the mortality. Similarly, Adesunkanmi and Ajao [5] report a high incidence of residual abscess in patients with single perforation (mortality rate: 16.7%), noting that the incidence of fecal fistula is higher in patients with multiple perforations (mortality rate: 100%). In contrast, Rahman et al. [2] reported that the number of perforations does not significantly affect the outcome and mortality. The results of the present study are similar to those of Rahman et al.; no statistically significant correlation was found between the number of perforations and mortality rate. It has been showed that TIP classically occurs on the antimesenteric border of the ileum, generally at distance 0–80 cm from the ileocecal junction [4, 6, 8, 15, 16]. We could not find any published date about the relation between the location of the perforations and mortality. In the present study, the mortality rate was found to be higher in the group with perforations located more than 60 cm from the ileocecal valve, but no significant correlation was seen. In our opinion, the distance of the perforations from the ileocecal junction may not affect the prognosis directly, but it may influence the choice of operative technique.

Although early surgical intervention with active preoperative resuscitation and postoperative care is accepted as the standard of treatment in TIP, there is no general agreement

regarding the choice of operative procedure. Such choice is best determined by the laparotomy findings and the general condition of the patient. The main options include simple closure with or without a serosal or omental patch, wedge resection with primary anastomosis, resection with primary ileoileal or ileotransverse anastomosis, resection with ileostomy, and ileal exclusion or tube ileostomy through perforations, with extensive washing out and debridment of the abscess peels, all with or without drainage [2–10,16–18].

The different operative techniques have been discussed in different reports. Rahman et al. [2] have reported that the kind of surgical procedure does not appear to reduce the mortality associated with TIP. However, Beniwal et al. [10] have recommended primary repair as the first choice. Similarly, Shukla et al. [6] use the single-layer closure technique and have noted a reduction in the mortality rate from 35% to 10.8%. Adesunkanmi and Ajao [5] have shown the two-layer closure technique with or without an omental patch to be the most successful approach, whereas Ameh [16] has reported that resection with primary anastomosis is the preferred technique, Meier and Tarpley [12] and Eustach and Kreis [18] report that the best policy is routine debridement and closure for single perforation, cautioning that resection must be reserved for multiple perforations and a severely diseased short segment of bowel. Similarly, Saxe and Cropsey [4] recommend primary closure for single perforation, and resection with primary anastomosis for multiple perforations. In contrast, Meier and Tarpley [12] have advised ileostomy in cases with multiple perforations and severe abdominal contamination. From their experience, an ileostomy minimizes the need for reoperation for fecal fistula and also shortens the paralytic ileus. Similarly, Adesunkanmi and Ajao [5] report that a significant reduction in the morality rate can be obtained by using tube ileostomy in such conditions, and Onen et al. [7] advise that ileostomy appears to be an effective procedure in patients with delayed presentation and severe abdominal contamination. However, as noted by Beniwal et al. [10], ileostomy is more expensive, as all the patients not only have to undergo reoperation for closure of the ileostomy but also require specialized care prior to closure. Therefore, it should be considered as a secondary procedure in patients who have developed fecal fistula. In our opinion, in spite of the high morbidity rate associated with stoma, ileostomy may be a life-saving procedure in patients with severe abdominal contamination or with ischemic, inflamed, or edematous intestine. The high mortality and morbidity rates found in the ileostomy group in the present study may be associated with the poor general condition of patients treated with this technique.

Laparoscopy also has a big role in the treatment of TIP [19, 20]. Ramanchandran et al. [19] report successful treatment of 6 patients by the laparoscopic primary closure technique. Similarly, Sinha et al. [20] treated 25 patients with TIP laparoscopically, with an 8% port-site infection rate and no mortality.

The mortality rate of TIP ranges from 5%–80% in various series [2–10, 16–18], and operative treatment has clearly afforded a survival advantage in patients with TIP [4]. In our previous series, reported by Oren and Atamanalp [9], the mortality rate was 12.9%; in the latter 14 years of the present study, this rate was 0% in the 12 patients treated, and overall mortality was 11.0% in the present series. This success probably depends on effective preoperative support and postoperative care, safe anesthesia, broad-spectrum antibiotics, and early and suitable surgical intervention.

The most frequent postoperative complication of TIP is wound infection, and the most severe is fecal fistula. Others report wound dehiscence, intestinal obstruction, intraabdominal abscess, empyema, bleeding diathesis, and psychosis as significant complications [8–10, 12]. Fecal fistula is a catastrophic complication. It significantly increases the risk of death, and at the least, it requires reoperation [12]. In the present study, the most common postoperative complication was wound infection, with the highest incidence in the ileostomy group.

When we compared the previously reported data [9] with the new cases added between 1991 and 2004, we determined that resection with primary anastomosis has become the preferred operation. No mortality was seen in the last group of patients included in our study. Use of effective antibiotics, better preoperative and postoperative care, and operative techniques have probably afforded this survival advantage.

In conclusion, TIP still has a grave prognosis with high rates of associated mortality and morbidity. Active preoperative resuscitation, early and appropriate surgical intervention, and excellent postoperative care may improve the survival. Prolonged presentation time and severe peritoneal contamination may increase the mortality rate. In surgical treatment, primary closure is the most frequently recommended procedure. Resection may be reserved for patients with multiple perforations or a severely diseased short bowel segment, but it should be avoided in the presence of severe abdominal contamination or an ischemic, inflamed, or edematous intestine is present. Although ileostomy is associated with high mortality and morbidity, it may be life-saving in patients with severe abdominal contamination or an ischemic, inflamed, or edematous intestine.

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