Surgical Complications of Typhoid Fever: Enteric Perforation

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Typhoid fever remains a prevalent disease in developing nations as the result of adverse socioeconomic factors. The most frequent complication, and principal cause of mortality, is perforation of the terminal ileum. This report presents our experience with 96 patients surgically treated at Cayetano Heredia University Hospital in Lima, Peru from 1972 to 1986. The clinical characteristics and the diverse surgical procedures utilized in the management of these patients are reviewed.

Typhoid fever, a severe febrile infectious disease caused primarily by the gram-negative bacillus *Salmonella typhi* and occasionally by other types of salmonallae, occurs with high endemic prevalence in many areas where depressed socioeconomic levels and unsanitary environmental conditions prevail. The disease is acquired through the ingestion of contaminated water and food. The intraluminal intestinal infection is followed by multiplication of the microorganisms in the reticuloendothelial system (RES) during an incubation period of 1–14 days; clinical manifestations start with bacteremia, high fever, and signs of systemic sepsis with characteristic normal or low white blood cell counts and anemia. From the RES infection, the organism reemerges in the form of episodes of bacteremia and reaches the gut to become localized in Peyer's patches, which become severely inflamed, producing mesenteric adenitis and ulceration of the mucosa. Ulceration and hemorrhage occur, principally in the terminal ileum and, less frequently, in the cecum.

Perforation is heralded by exacerbation of abdominal pain associated with tenderness, rigidity, and guarding, most pronounced over the right iliac fossa; however, for many patients in a severe toxic state, these signs may be obscured, with resultant delays in diagnosis and adequate surgical intervention.

Surgical intervention in this most devastating complication of typhoid fever continues to be associated with high morbidity and mortality rates, and the choice of the specific operative procedure is still a matter of debate. In 1978, our group reviewed the results of treatment in a series of 20 cases of typhoid perforation managed since January 1, 1972. In the present article, we review our experience extending to December 31, 1986.

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Material and Methods

A retrospective analysis of 96 patients operated on for typhoid perforation of the bowel at the Cayetano Heredia University Hospital between January 1, 1972 and December 31, 1986 was carried out. The study included analysis of the characteristics of our patient population, seasonal incidence, interval of illness before perforation, interval between perforation and surgical intervention, presenting clinical features, antecedent management, findings at operation, type of operation performed, and complication and mortality rates.

Results

The incidence of typhoid bowel perforation in the overall series was 7.8%. The highest incidence occurred in the second and third decades of life, with age limits between 4 and 56 years. There was a clear male predominance in a proportion of 6:1 (Table 1).

Although a study carried out in 1977 had shown that the incidence of bowel perforation was highest during the Summer season (corresponding to the first 3 months of the year in the southern hemisphere), the review up to December of 1986 showed a higher incidence for the Fall and Winter months.

The great majority of our patients developed the perforation within the first 2 weeks of illness, with 1 patient doing so after only 24 hours of symptomatic illness. Most patients were operated on within the first 24 hours following perforation, with a complication rate of 66.6%. Two patients came to operation after 5 days of illness.

Seventy (72.9%) patients were operated on within the first 48 hours after presentation: 17 (17.7%) between 48 and 120 hours, and 2 (2.1%) after the fifth day. There was a correlation between the interval from presentation to operation and the mortality rate (although the 2 patients that were operated on 5 or more days after presentation constitute too small a number to derive an entirely valid conclusion): <48 hr: 70 patients, 1 death (1.4%); 48–120 hr: 17 patients, 4 deaths (23.5%); >120 hr: 2 patients, no deaths (Table 2).

The diagnosis of perforation was established fundamentally by the clinical features indicative of an abdominal catastrophe, even when the patient had had signs, in some cases, for as long as 2 or 3 weeks. Fever and abdominal pain were the 2 most

Table 1. Age-related incidence of typhoid fever.

Age (yr)	No. of patients (%)
<10	14 (14.6)
11–20	23 (24.0)
21–30	27 (28.1)
31–40	19 (19.8)
>41	13 (13.5)
Total	96 (100)

Table 2. Interval between perforation and operation.

Hours	No. of patients	
	Total	Died
<48	70	1
48–120	21	4
>120	2	0
No data	3	0
Total	96	5

Table 3. Surgical procedures in patients with typhoid enteric perforations.

Procedure	No. of patients	Mortality	Cause of death
Wedge resection and closure	43	1[a]	Sepsis
Intestinal resection	26	2	Sepsis consequent to anastomotic failure
Intestinal resection, closure of distal stump, and ileotransverse colostomy	15	0	
Intestinal resection and right colectomy	3	0	
Ileostomy	4	1 + 1[a]	Sepsis
Drainage	2	0	
Serous patch	3	0	

[a] Dehiscence of appendiceal stump.

frequently observed symptoms: 94.32% and 83.78%, respectively. Headache, severe malaise, anorexia, nausea, vomiting, and diarrhea were also frequent. Transient melena occurred in 6 patients. Signs of acute abdominal catastrophe were present in all cases, with absent hepatic dullness on percussion in 8 cases.

Leukocytosis with left-sided shift was recorded in 59.5% of the patients, and leukopenia with left-sided shift in 36.4.%. Serum agglutinins appeared positive in only 38% of our cases. Surprisingly, blood cultures and bone marrow cultures were negative in 54% and 52%, respectively; however, these cultures were not obtained in all patients. All patients exhibited moderate anemia.

Eight patients in this series received treatment with chloramphenicol before coming to our hospital—none for longer than 4 days. One patient received amoxicillin for 4 days. In all cases, an aggressive regimen intended to correct hemodynamic, metabolic, and fluid and electrolyte alterations was undertaken upon admission, with efforts oriented toward the control of sepsis.

Findings at Laparotomy

Generalized peritonitis with large quantities of pus varying from 500 ml to 4,000 ml was found at operation in the majority of our cases. A sealed perforation with localized peritonitis was encountered in 5 patients. Edema and inflammatory signs over the mesentery were common, particularly along the terminal ileum, together with a variable number of enlarged mesenteric nodes close to the ileum and to the ascending colon.

A single perforation was found in 78% of the patients; 2 perforations were found in 16%, and multiple perforations in 6%. The antimesenteric border of the bowel was the site of perforation in all cases in this series. Reperforation occurred in 1 patient, 1.04% of the entire series. Most perforations (63%) were located within 30 cm of the ileocecal valve, with the closest one at 2 cm, 4 beyond 40 cm, and 1 at 120 cm.

A diversity of surgical procedures was utilized: (a) wedge

resection of the perforation and its indurated margin with transverse 2-plane closure in 43 patients; (b) resection of the affected segment of ileum with end-to-end anastomosis in 26 patients; (c) resection of the affected segment of the terminal ileum with closure of the distal stump and end-to-side ileotransverse colostomy in 15 patients; (d) resection of the terminal ileum with right colectomy and end-to-side ileotransverse colostomy in 3 patients; (e) ileostomy in 4 patients; (f) drainage of the peritoneal cavity alone in 2 patients; (g) serous patch in 3 patients (Table 3).

Profuse intraoperative peritoneal lavage was done in all cases. Vertical and transverse incisions were utilized, and the laparotomy wound was left open according to the operating surgeon's individual judgment.

Clinical Course

The postoperative course was favorable and free of complications in 34 (35.4) patients. Mortality rates for the different procedures are summarized in Table 3. Overall, complications occurred in 69 patients (71.9%), the majority (40.6%) being wound infections. There were also 3 enterocutaneous fistulas that closed spontaneously under parenteral nutritional support; 10 patients developed respiratory tract complications, 8 with atelectasis and 2 with pneumonitis; 1 patient suffered pulmonary embolism; 2 had residual abscesses; 2 developed renal insufficiency, 1 recovered and 1 died with progressive sepsis. Two patients exhibited transient melena. Two others developed icterus due to granulomatous hepatitis, and 2 more developed partial intestinal obstruction that subsided under nonoperative management. Three patients presented with a severe systemic septic syndrome, and 3 others had frank septic shock (Table 4).

Chloramphenicol was utilized perioperatively as the drug of choice in doses of 50–100 mg/kg per day, combined with gentamicin in doses of 5 mg/kg per day. The combination with amikacin and amoxicillin was utilized in some cases. Ampicillin was an alternate drug in a few cases at the beginning of the study period.

Discussion and Comment

An epidemiologic study carried out by Gottuzo [1] in Peru in 1980 reported an incidence of 209 cases of typhoid fever per

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Table 4. Postoperative complications.

Complication	No. of patients (%)
Wound infection	39 (40.6)
Respiratory complication	10 (10.4)
Enterocutaneous fistula	3 (3.1)
Residual abscess	2 (2.1)
Renal failure	2 (2.1)
Melena (transient)	2 (2.1)
Icterus	2 (2.1)
Partial intestinal obstruction (transient)	2 (2.1)
Pulmonary embolism	1 (1.0)
Severe sepsis	3 (3.1)
Septic shock	3 (3.1)

Table 5. Perforation and mortality rates in typhoid fever.[a]

Country	Year	Perforated/total No. of cases (%)	Fatality (%) of all cases	Fatality (%) of perforation
Bangladesh	1985	15/323 (4.6)	5.6	54
Brazil	1961	7/60 (11.7)	6.7	43
Chile	1959	2/95 (2.1)	2.1	50
Chile	1967	11/3,036 (0.4)	0.8	45
Chile	1979	14/185 (7.6)	12.0	36
Chile	1981	3/311 (1.0)	0.6	33
Chile	1981	3/782 (0.4)	0.1	0
Ghana	1976	309/1,542 (20)	NA	24
India	1963	4/111 (3.6)	7.2	75
India	1982	344/38,932 (0.9)	NA	72
Israel	1954	3/224 (1.3)	3.3	67
Nigeria	1981	46/117 (39.3)	41	41
Zambia	1978	25/400 (6.3)	9.8	56

NA: not available.
[a]According to Butler and associates [5].

100,000 inhabitants, a prevalence 4 times larger than the figures reported for the Mexican epidemic of 1972. According to the same Peruvian author, the incidence increased up to the year 1984, when it began to decline to a stable rate of 105 cases/100,000, with a hospital admission rate of 200 cases per annum, 20% of them occurring in children.

The rate of bowel perforation in our environment is 6–10%. The 96 cases that constitute the present series represent a perforation rate of 7.8%. Badejo and Arigbabu [2] of Nigeria reported the highest rate of bowel perforation found in the literature: 78.6%; at the Baptist Medical Center of Ogbomoso, Nigeria [3], approximately 75% of all hospital admissions for typhoid fever required surgical intervention for bowel perforation. Chouhan and Pande [4] reported the largest series of perforations—344 among 38,962 cases of typhoid fever—which was a perforation rate of only 0.9%. Butler and associates [5], in a review of 57,864 collected cases from developing countries reported after 1950, encountered 1,448 perforations, which was a rate of 2.5%. If we exclude the Chouhan report, the rate for the collective series would be 5.8%. There are no clear explanations for the variable perforation rates according to geographic regions, as is seen in Table 5 (data taken from Butler and colleagues [5]).

Bowel perforation tends to occur during the second week of illness. This was observed in our series. In our series, the

highest prevalence of bowel perforation was in the younger age groups in the second and third decades of life. Huaraz Loyola [6] reports that in 78.8% of the patients seen at Hospital Guillermo Almenara of Lima, Peru, bowel perforation occurred in the third and fourth decades of life, which is a finding that is similar to those of Kim and coworkers [7] and of Eggleston and Santoshi [8]. Our difference in comparison to Huara Loyola is explained on the basis of the different population groups that are admitted at the 2 Lima hospitals: no children are admitted at the Almenara hospital.

Our finding of male preponderance of typhoid perforation agrees with the different reports from the world literature. In the years 1984–1989, we admitted 378 women and 446 men with typhoid fever; although at a lower level, the high male:female ratio was maintained.

There is no clear explanation for the sex and age distribution. Immune mechanisms and genetic predisposition factors have been proposed; individuals with genetic governance of the immune response to the Salmonella typhi antigen could undergo an exaggerated hyperplastic response of Peyer's patches, with an increased risk of necrosis and perforation. The male preponderance would be explained by the fact that men would possess more of this genetic pattern. In fact, one of the genes that controls susceptibility to infection is linked to the X chromosome [5].

It appears that repeated exposures are necessary for the activation and stimulation of the immune response; this would explain the increasing incidence of the complication parallel with advancing age, to attain the highest prevalence in the second to fourth decades of life. The interesting report by Vyas and associates [9] on the occurrence of typhoid perforation in identical twins 21 years of age gives additional support to the genetic predisposition in the pathogenesis of the disease.

Until 1978, we recorded a higher incidence of typhoid perforation in the southern hemisphere during the Summer months (December 21–March 21). The Gottuzo [1] epidemiologic study indicated a higher prevalence during the second quarter of the year, corresponding to the Fall, coincident with the start of school classes, a time of being out-of-home and a time of high risk of infection. Analysis of the overall series in the present study shows the largest number of cases occurring during the Fall and Winter. The majority of our patients were operated on during the initial 48 hours of presentation, with 2 patients being operated on after the fifth day, indicative of the difficulty in establishing the diagnosis of perforation.

The diagnosis in our group of patients was established primarily on the basis of the clinical picture, with all of our patients exhibiting an "acute abdomen." In the report by Meier and colleagues [3] on 108 patients managed at the Baptist Medical Center of Ogbomoso, Nigeria, an institution with apparently similar facilities as our own, 27% of the patients presented with a nondistended abdomen despite the severe peritoneal pathology encountered at operation. These authors also reported active intestinal bowel sounds in the presence of severe peritonitis, and of negative laparotomies in patients with silent abdomens. In our series, 8 patients presented with absence of hepatic dullness and radiologic demonstration of pneumoperitoneum was present in only 1 case. Li [10] has reported that in 20 cases of perforation, only 10 had roentgenographic demonstration of pneumoperitoneum, which also oc-

curred in 10 of the 165 patients reported by Bedejo and Rigbabu [2]. These reports would indicate that on the basis of radiologic findings alone, only about one half of the cases of perforation would be accurately diagnosed. Not many radiographs are usually obtained in our city because many practicing physicians do not order radiographs in the presence of a febrile patient with abdominal distension because they consider this a "normal finding" in a person with a presumptive diagnosis of uncomplicated typhoid fever.

The usual complaint upon presentation is a change in the type of abdominal pain: the vague, transient, generalized abdominal pain becomes acute and intense, coincident with deterioration in the general condition. In a few cases, the abdominal pain, which generally occurs over the right lower quadrant, starts over the epigastrium, and radiates to the genitalia; 1 patient suffered severe pain over the penis. It is common to observe nausea and vomiting of increasing severity, but we have not seen the high incidence of diarrhea reported by Butler and coworkers et al [5] in Bangladesh. Two of our patients presented to the emergency room free of symptoms; this has also been reported by Pons [11]. The severe septic condition that was present in 30% of our patients is a common finding in the literature since typhoid fever is more of a systemic septic entity than an intestinal disease.

Leukocytosis and left-sided shift is observed more frequently than the well known leukopenia [4]; leukopenia may even be found in the presence of acute perforation. Anemia is also a frequent finding, due to underlying malnutrition or to actual blood loss; melena was recorded in 6 patients in the preoperative evaluation, and occurred postoperatively in 2 other patients. The low percentage of positive serum agglutinin titers is a well recognized fact, so that this test has been abandoned at many institutions; however, noteworthy is the low percentage of positive blood and bone marrow cultures in our series. Until, 1980 the bone marrow culture was positive in about 90% of our cases; the reason for the recent lower positivity rate of this most specific test [12] remains unexplained. Olobuyide and associates [13] of Nigeria reported, in a study of 28 patients, on the predictive value of the C-reactive protein level. This finding deserves further investigation.

The vast majority of our patients, coming from economically deprived sectors of our population, did not receive treatment prior to presentation; it is frequent to see many stoic patients, accustomed to social hardship, seeking care late in the course of their illness. Overall mortality rates for untreated typhoid fever are around 15%; mortality declines to about 1% when proper treatment is undertaken.

Generalized peritonitis with abundant peritoneal fluid is the usual finding in typhoid perforation. The majority of patients exhibit a single perforation, but multiple perforations are far from infrequent, making it obligatory to execute a meticulous bowel inspection at the time of laparotomy. Reperforation is also not infrequent, although in some cases the "recurrent" peritonitis is truly persistent peritonitis due to missed perforations.

Weller Van Hook [14] was the first to propose, in 1891, that laparotomy should be carried out in patients with typhoid perforation. Although typhoid perforation was probably recognized before 1829, it was not until that year that it was clearly

described by Louis, as cited by Bitar and Tarpley in their historical review [15]. The first operation for typhoid perforation was probably performed in 1885; the patient did not survive. The first successful operation motivated the report by van Hook. Operative mortality rates progressively declined from 1885 to 1948, when reported figures indicated a prevailing mortality rate of about 29%. Surgery then became established as a valid treatment modality for this entity.

With the advent of chloramphenicol in 1948, Woodward and colleagues [16] reported on the recovery of a patient treated nonoperatively with this agent, plus streptomycin and penicillin. Bitar and Tarpley [15] collected 16 patients treated conservatively with antibiotics between 1948 and 1950, with a mortality rate of 31.2%. During the same period, a report of 6 patients treated with operation and antibiotics revealed a mortality rate of 16.7%. Unfortunately, many reports on the mortality of medical treatment were compared with figures of surgical mortality in the preantibiotic era, causing considerable confusion [17].

By 1965, the preferred treatment of typhoid perforation had become surgical intervention. Although mortality figures ranged from 10 to 25%, there were no comparable studies to define the superiority of one method over the other. Li [10], Archampong [18], Olurin and coworkers [19], Mulligan [20], and Eggleston and Santoshi [8] were among those who defended the surgical approach, on grounds reviewed by Bitar and Tarpley [15]. It is obvious that, currently, it would be ethically difficult to propose a randomized trial to compare medical and surgical treatment.

Olurin [19] points out that surgeons face 3 main problems when treating a patient with typhoid perforation: (1) septicemia, (2) generalized peritonitis, and (3) dehydration and electrolyte imbalance. Because these patients are critically ill, they are best managed in an intensive care setting, with full hemodynamic monitoring including pulmonary artery catheterization.

Antimicrobial therapy must be directed against 3 main groups of organisms: (1) gram-negative bacilli, (2) anaerobes, and (3) typhoid bacillus. Chloramphenicol remains the standard therapy; its low cost and proven efficacy, combined with the scarcity of resistant strains in our environment, makes this antibiotic the largely preferred agent. An aminoglycoside, likely gentamicin, is added to cover the enteric aerobic gram-negative organisms, and metronidazole or clindamycin to cover against the anaerobes. The following outline, after Bitar and Tarpley [15], constitutes a simple and practical therapeutic guide.

Salmonella typhi	*Chloramphenicol:* 12.5 mg/kg q 6 hr (usually 1 g q 6 hr, but up to 2 g q 4 hr in the very ill) or
	Ampicillin: 25 mg/kg q 6 hr (usually 2 g q 6 hr) or
	Amoxicillin: 12.5–25 mg/kg q 6 hr (maximum 2 g q 6 hr) or
	Trimethoprim-sulfamethoxazole: 2–4 tabs 2 × day (80 mg–400 mg) or 160 mg–800 mg to 320–1,600 mg IV 2 × day (doses must be adjusted in renal insufficiency)

Enteric aerobic gram-negative bacilli	*Gentamicin*: 2 mg/kg loading dose; 1.3–1.7 mg/kg q 8 hr (doses must be adjusted in renal insufficiency)
Anaerobes	*Metronidazole*: 2 g/kg loading dose; 7.5 mg/kg q 6 hr (up to 4 g/day) or 500 mg q 6 hr or *Clindamycin*: 600 mg q 6 hr

We agree with Hoffman and colleagues [21] in the use of dexamethasone in patients in a severe septic state or in septic shock. We have utilized an adult schedule of 3 mg/kg as a starting dose, followed by 1 mg/kg every 6 hours for 48 hours.

A variety of surgical procedures have been utilized in the treatment of typhoid perforation [22]: simple closure, resection of the perforation and closure, wedge resection and closure, resection of the affected terminal ileum and end-to-end anastomosis, resection with ileotransverse colostomy, and resection with right colectomy. Simple closure was performed in 92% of Meier's 108 patients, with 8 patients developing anastomotic leaks and 6 deaths; wedge resection is our preferred method for single perforations less than 0.5 cm in diameter, with transverse closure in 2 layers. The same procedure is favored for multiple perforations more than 30 cm apart. Large perforations (more than 0.5 cm in diameter) or multiple perforations are best treated by resection of the affected bowel segment and primary anastomosis. Some authors [5] argue against ileal resection. Resection with ileotransverse colostomy is not an ideal procedure because it leaves a blind loop of large bowel, with its corresponding problems. Right colectomy has to be undertaken when there is perforation of the cecum. Exteriorization of the affected ileum or ileostomy is performed in patients in an extremely critical condition; intestinal continuity is reestablished no less than 6 weeks later. Serous patching using adjacent bowel loops, a procedure performed initially in our series, has been abandoned and we do not think that it has any indication.

Reperforation is reported in about 12% of cases in some series [23]. For this reason, some authors favor intestinal resection of the severely inflamed bowel and for patients with multiple perforations [10], a technique that we have also preferred.

Occasionally, one encounters an intraabdominal abscess and no evidence of bowel perforation. In such a situation, we favor simple drainage of the abscess cavity and continued antibiotic coverage. We have utilized profuse lavage following repair or resection, but have no experience with postoperative continuous peritoneal lavage. Our trend is toward leaving the wound open for delayed primary closure, considering the high incidence of postoperative wound infection. Incidental appendectomy was performed in 2 patients early in the study period with disastrous results. This procedure is strongly condemned.

Enterocutaneous fistulas have responded well to total parenteral nutrition. Unfortunately, this important therapeutic modality is not widely available in many public hospitals because of its considerable expense. Enteral nutrition utilizing autochthonous material, such as soybean "milk," molasses, and other inexpensive nutrients, has been successfully utilized for the nutritional support of patients with other types of distal enteric fistulas, but not for any of the patients in the present series [24].

Our global mortality rate (5.2%) and the mortality rates for the different surgical procedures (Table 3) are considered acceptable for our patient population, with a background of malnutrition and economic deprivation. It would have been lower without the 2 patients who had the totally ill-advised incidental appendectomy.

Résumé

La fièvre typhoïde reste une maladie fréquente dans les pays en voie de développement en raison des facteurs économiques et sociaux. La principale complication et cause de mortalité est la perforation de l'iléon terminal. Ce travail rapporte notre expérience chez 96 patients traités chirurgicalement à l'hôpital Universitaire Cayétano Hérédia à Lima, Pérou, pour la période de 1972 à 1986. Les caractéristiques cliniques et les différents procédés chirurgicaux employés pour le traitement de ces patients sont passés en revue.

Resumen

La fiebre tifoidea sigue siendo una entidad clínica prevalente en las naciones en desarrollo, como expresión de factores socio-económicos adversos. La complicación más frecuente, que también representa la mayor causa de mortalidad, es la perforación del ileon terminal. Se presenta nuestra experiencia con 96 pacientes intervenidos quirúrgicamente en el Hospital de la Universidad Cayetano Heredia de Lima, Peru, en el período 1972–1986. Se hace una revisión de las características clínicas y de los diversos procedimientos operatorios utilizados en el manejo de estos pacientes.

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