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Typhoid Fever Complicated by Intestinal Perforation: A Persisting Fatal Disease Requiring Surgical Management

Thomas Butler, Joseph Knight, Samir K. Nath, Peter Speelman, Swapan K. Roy, and M. A. K. Azad

From the International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh; and the Department of Medicine, Case Western Reserve University, Cleveland, Ohio

In Bangladesh, clinical records of 323 patients with typhoid fever were reviewed to study the incidence, fatality, and optimal therapy of the complication of intestinal perforation. Fifteen patients (4.6%) developed intestinal perforation. Case-fatality rates were six of nine patients treated medically and one of four patients treated surgically for whom the postoperative courses were known. A literature review of 57,864 cases of typhoid fever in developing countries in the antibiotic era revealed that perforation developed in 2.5% of patients, a percentage that was similar to the incidence of 2.8% reported in the preantibiotic era. The median of case-fatality rates in these reports was 43% and the proportion of all reported typhoid deaths attributable to perforation was 25%. The case-fatality rates for patients with perforation were 70% for 410 patients managed medically and 26% for 1,835 patients managed surgically. Although some reports were biased toward placing patients at lower risk into surgical treatment, the large number of patients treated successfully by surgery suggests real improvement in surgical techniques in countries with endemic typhoid fever. These results indicate that intestinal perforation persists as a major cause of death in cases of typhoid fever in developing countries in the antibiotic era and that surgical treatment with use of antibiotic therapy is optimal for this complication.

Typhoid fever has been almost eliminated from developed countries but remains a common disease in developing countries. Just as typhoid fever was a lethal disease in the preantibiotic era with an estimated case-fatality rate of 11% that was calculated by Osler in the United States [1], typhoid fever in developing countries in the antibiotic era is associated with a persistent risk of fatality at a similar magnitude despite the widespread use of antibiotics in most developing countries [2]. One of the reasons for the high case-fatality rate of typhoid fever in both the preantibiotic era and the antibiotic era is the development of serious complications, which include intestinal hemorrhage, intestinal perforation, myocarditis, and pneumonia. Intestinal perforation occurred in ~3% of all cases of typhoid fever in the United States during the preantibiotic era [3] and was the most feared complication, which carried a fatality risk of nearly 100%.

The chances of survival in patients with intestinal perforation seemed to improve in the antibiotic era, leading Woodward and Smadel [4] and Huckstep [5] in the 1950s and 1960s to advocate medical therapy without surgery for this condition. In 1964, Woodward and Smadel [4] advised:

> Exploratory laparotomy with suture of the intestinal lesion can now be avoided in most instances with reliance placed upon (*1*) control of infection with antibiotics, (*2*) well-established supportive measures such as fluid replacement to combat shock, and (*3*) the institution of gastric suction to decompress the distended bowel. . . . Should it become obvious to the clinician and surgeon in attendance that the infectious process is failing to localize as evidenced by the findings on examination, persistence of shock, continued leukocytosis, and other signs, it may be surmised that the ulcer is not healing and that surgical intervention is indicated.

At the International Centre for Diarrhoeal Disease Research (ICDDR), B Hospital in Dhaka, Bangladesh, where no surgical facilities are present, patients with typhoid fever complicated by intesti-

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Please address requests for reprints to Dr. Thomas Butler, International Centre for Diarrhoeal Disease Research, G. P. O. Box 128, Dhaka-2, Bangladesh.

nal perforation have usually been treated with antibiotics and no surgery. The recent occurrence of several fatalities with this treatment prompted us to review our own cases and to make a reassessment of optimal therapy from reports in the literature.

Materials and Methods

The Hospital of the ICDDR,B provides care to patients with diarrhea from Dhaka and surrounding areas. Blood samples for culture are obtained from patients who are admitted and have fever. The medical records of 323 patients with blood cultures positive for *Salmonella typhi* during the period 1975–1983 were reviewed. The diagnosis of perforation was sought from evidence on roentgenogram, surgical and postmortem observations, and clinical impressions of physicians. The age, sex, and outcome of treatment for each patient with typhoid fever were recorded.

For the literature review, papers were selected that based the diagnosis of typhoid fever on culture or serologic results. Papers that were listed in *Index Medicus* and *MEDLINE* were obtained. The impressions of perforations were based on surgical or roentgenographic evidence. Included in the analysis of incidence and fatality were papers describing ≥50 cases of typhoid fever. For the outcome of management, papers were selected that included ≥5 cases with information on therapy and survival.

Results

Clinical and epidemiologic features of typhoid fever with perforation. Out of 323 patients with fever, diarrhea, and blood cultures positive for *S. typhi*, 15 cases (4.6%) were identified as complicated by intestinal perforation. The diagnosis of perforation was made in nine patients by demonstrating pneumoperitoneum by roentgenogram; in the remaining six patients, one had a perforation demonstrated during surgery and the others showed clinical signs of abdominal distention, absent bowel sounds, or loss of liver dullness.

The 15 cases with intestinal perforation consisted of 12 males and three females. The mean age was 25.7 years. By recorded histories, these patients had a mean duration of fever of 15.0 days before admission to the hospital and had the onset of diarrhea a mean of 6.9 days before admission. Signs of perforation were present at the time of admission in only two patients. In the remaining patients, the perforations were detected in the hospital after two to 15 days of treatment. The mean time after hospitalization within which perforation occurred was 5.5 days. When this period is added to the mean duration of preadmission illness of 15.0 days, the mean of 20.5 days was the average duration of illness before perforation.

Table 1. Contrasting features of patients with typhoid fever as shown by positive blood culture with intestinal perforation and without perforation.

Feature	Intestinal perforation	No perforation
No. of patients	15	308
Mean age (years)	25.7*	12.4
Sex distribution (M:F)	12:3 = 4.0	197:111 = 1.8
Mean duration (days) of fever before admission	15.0	10.3
Mean duration (days) of diarrhea before admission	6.9	7.3
Case-fatality rate†	7/15 (47)‡	11/308 (3.6)

* Mean age of patients with perforation is greater than that for patients without perforation (Student's t test, $P < .005$).

† Case-fatality rate is expressed as the number of patients who died/the total number of patients with typhoid fever (%).

‡ Case-fatality rate is higher for perforated cases than nonperforated cases (χ^2-test, $P < .005$).

Contrasting features of patients with typhoid fever with and without perforation. The 15 patients with typhoid fever and perforation were compared with 308 patients with typhoid fever and both diarrhea and blood cultures positive for *S. typhi* who were hospitalized during the same period and did not show signs of perforation. As shown in table 1, the mean age of the patients with perforation, 25.7 years, was significantly greater than the mean age of the patients without perforations, which was 12.4 years ($P < .005$, Student's t test). Other differences included a greater male preponderance and a longer duration of preadmission fever in the patients with perforations. The case-fatality rate among those patients with perforations was 47%, compared with 3.6% among those patients without perforations ($P < .005$, χ^2 test). These data on fatalities in cases of typhoid fever show that seven out of a total of 18 deaths among these patients with typhoid fever occurred in patients with perforation, a rate indicating a strong influence of perforation on mortality in this group of patients.

Treatment and Outcome

During the period of this chart review, the physicians of the ICDDR,B Hospital did not follow a uniform treatment regimen for typhoid fever complicated by intestinal perforation but used their individual judgment. Patients who required surgical treatment were transferred to other hospitals in Dhaka because the Hospital of the ICDDR,B has no surgical facilities. Of the 15 patients with perforations, six were referred for surgery and, in these, the case-fatality rate among those for whom follow-up information was available was one of four or 25%. Nine patients were treated medically, and six of them died, a fatality rate of 67%. The actual case-fatality rates may have been higher because information on the postoperative courses of two patients was not available and two of the medically treated patients discharged themselves before they were fully recovered.

Illustrative Case Reports

Of the four cases that are summarized, the first two are examples of failure of medical therapy with postmortem findings. The next two cases show successful results of surgery.

Case no. 1. A 15-year-old girl was admitted with a history of fever for 30 days. The fever had been high with intermittent patterns that included evening rises and shaking chills. Ten days before admission, diarrhea occurred that resulted in the passage of yellow, watery stools about six times a day. On the day of admission, she noted swelling of her abdomen.

She was prostrate, stuporous, and confused. Her temperature was 36.0 C, pulse rate 100 beats/min, respirations 32/min, and blood pressure 90/60 mm Hg. The skin of her face, trunk, and extremities showed an ecchymotic rash. The abdomen was moderately distended, tender, and rigid. Bowel sounds were decreased.

The hematocrit was 37%, white blood cell (WBC) count 5,950/mm^3 with differential count showing 37% polymorphonuclear leukocytes, 50% band forms, and 13% lymphocytes. The platelet count was 40,000/mm^3. The concentrations of serum electrolytes were sodium, 115 meq/liter; potassium, 4.8 meq/liter; chloride, 85 meq/liter; and CO_2 content, 18 mmol/liter. The blood culture was positive for *S. typhi*, and the *Salmonella* O agglutinin titer was 1:320. The abdominal roentgenogram showed free air under the diaphragm.

She was treated with nasogastric tube suction and iv normal saline. Chloramphenicol (60 mg/kg of body weight) was administered iv in four divided doses each day and gentamicin (5 mg/kg) was given iv in three divided doses each day. She remained febrile, on the third hospital day developed shock, and died.

The postmortem examination revealed that the peritoneal cavity contained approximately three liters of purulent fluid, which was tinged with blood. The pelvic cavity contained about one liter of grossly bloody fluid. The peritoneum was inflamed and the omentum was adhering to the spleen. The spleen was enlarged to 185 g, and its surface showed a linear rupture that was 3 cm long and extended 2 cm deep into the substance of the spleen. The edges of the rupture line were gray, and the omentum was adherent along the edges of the rupture. The distal ileum contained many gray oval ulcers that were deep and confluent. About 70 cm proximal to the ileocecal valve there was an ileal perforation. In the cecum and ascending colon, there were ~20 round ulcers up to 1 cm in diameter that were shallow with gray bases. The liver was enlarged to 1,348 g, and its surface was mottled with brown and yellow patches. Twenty adult *Ascaris* worms were present in the small intestine.

Microscopically, the ileal ulcers consisted of deep areas of necrosis up to the serosal surface. The necrotic areas contained vascular thrombi and mononuclear cell infiltration. The colonic ulcers consisted of necrosis of the lamina propria with polymorphonuclear leukocytes at the base of the ulcers. The spleen showed areas of necrosis and vascular thrombi in the white pulp. The liver contained typhoid granulomas and showed severe macrovesicular fatty change.

Case no. 2. A 17-year-old male farmer's helper developed fever and chills 12 days before admission. The fever was continuous and accompanied by anorexia and cough. Ten days before admission, diarrhea developed and was characterized by mucoid soft stools five times a day, changing later to yellow, liquid stools.

He appeared thin and prostrate but was mentally oriented. His temperature was 38.3 C, pulse rate 100 beats/min, respirations 26/min, and blood pressure 100/60 mm Hg. The lungs contained scattered rhonchi and rales without signs of consolidation. The abdomen was slightly tender and firm with guarding. The liver was palpable 1 cm below the right costal margin, and bowel sounds were present.

The hematocrit was 43% and the WBC count

12,200/mm³ with a differential count showing 59% polymorphonuclear leukocytes, 12% bands, 28% lymphocytes, and 1% eosinophils. The platelet count was 145,000/mm³. The serum electrolyte concentrations were sodium, 123 meq/liter; potassium, 3.6 meq/liter; chloride, 94 meq/liter; and CO_2 content, 22 mmol/liter. The blood culture was positive for *S. typhi*. The serum *Salmonella* O agglutinin titer was 1:1,280. A chest roentgenogram showed clear lung fields, and an abdominal roentgenogram showed gaseous distention with air-fluid levels in loops of the small bowel.

Treatment was started with 60 mg of chloramphenicol/kg per day. On the second hospital day, intestinal perforation was suspected and confirmed by the roentgenographic evidence of free air under the diaphragm. Suction by nasogastric tube was started, and treatment with 5 mg of gentamicin/kg per day was instituted. The condition of the patient failed to improve and he died five days later.

The postmortem examination revealed an inflamed peritoneal surface with purulent liquid and fecal material in the peritoneal cavity. In the distal 100 cm of the ileum there were ~20 oval ulcers that were shallow and up to 3 cm in diameter. The ulcers became confluent in the final 10 cm of the ileum. About 60 cm from the ileocecal junction, there was a perforation measuring 1.5 cm in diameter on the antimesenteric surface of the ileum. In the proximal colonic mucosa, there were ~10 oval ulcers up to 1 cm in diameter. Mesenteric lymph nodes were enlarged up to 1.5 cm. The liver was enlarged to 1,440 g, and the spleen was enlarged to 112 g with a soft consistency. The lungs showed consolidation in the right upper lobe and abscesses up to 2 cm in diameter in all lobes.

Microscopically, the ileal ulcers consisted of necrosis up to the muscularis layer with mononuclear cell inflammation and vascular thrombosis. The colonic ulcers were superficial, showing necrosis of the epithelial cells with edema and mononuclear inflammatory cells in the submuscoa. The spleen showed congestion and necrosis in the red pulp. The lungs showed extensive areas of necrotizing pneumonia. The adrenal glands had areas of hemorrhage and necrosis. Postmortem cultures of the intestinal contents and mesenteric lymph node were positive for *S. typhi*.

Case no. 3. A 15-year-old boy was admitted with the complaints of fever and diarrhea. Ten days before admission, the patient noted fever, which was accompanied by chills, prostration, and anorexia. These symptoms persisted, and three days before admission, he developed watery diarrhea, which occurred 15–20 times a day. The patient appeared lethargic but was mentally oriented. His pulse rate was 104 beats/min, temperature was 40 C, respiration 32/min, and blood pressure 110/70 mm Hg. Three rose spots were present over the upper chest. The abdomen was distended slightly, and there was tenderness around the umbilicus. The liver was palpable 2.5 cm below the right costal margin and was tender. The spleen was palpable 6 cm below the left costal margin and was tender.

The WBC count was 3,500/mm³, with a differential of 40% polymorphonuclear leukocytes, 19% band forms, 38% lymphocytes, and 3% monocytes. The platelet count was 50,000/mm³. The hematocrit was 34%. The typhoid "O" agglutinin titer was 1:160.

Treatment with 60 mg of chloramphenicol/kg per day divided in six hourly doses per os was started. Cultures of blood and stool specimens obtained on admission yielded *S. typhi* that was sensitive to chloramphenicol. The patient improved with the treatment. He became afebrile after 3.5 days of chloramphenicol treatment and gained weight; the rose spots faded away, and the sizes of the liver and spleen were reduced. Abdominal distention and tenderness disappeared on the second hospital day.

The patient had been afebrile for 24 hr when on the fifth hospital day his temperature rose to 39.4 C. He complained of severe abdominal pain, there was marked tenderness and rigidity over the abdomen, bowel sounds were absent, and there was rebound tenderness. A roentgenogram of the abdomen showed free gas under the right hemidiaphragm. The patient was transferred to a surgical unit where surgery was performed ~12 hr after the perforation had been detected. About 150 ml of straw-colored, nonhemorrhagic exudate was found in the peritoneal cavity. The entire ileum was hyperemic. There were two perforation sites, round in shape (diameter, ~0.2 cm), on the antimesenteric surface of the terminal ileum. They were sutured with chromic catgut without omentum. He received 500 ml of blood during the operation and 500 ml of blood postoperatively. He was discharged seven days after the operation without complication other than weight loss of 4 kg.

One month after the surgery, the patient regained his original weight and returned to his work. Two months after the surgery, he was fully recovered.

Case no. 4. A 35-year-old male shopkeeper presented with complaints of fever and diarrhea. Ten

Table 2. Frequency of perforation in cases of typhoid fever in developing countries from the antibiotic era (after 1950).

Country	Year [reference]	No. of cases with perforation/total no. of cases of typhoid fever (%)	Case-fatality rate (%) of all typhoid cases	Case-fatality rate (%) of cases of perforation
Bangladesh	Present study	15/323 (4.6)	5.6	54
Brazil	1961 [36]	7/60 (12)	6.7	43
Chile	1959 [37]	2/95 (2.1)	2.1	50
	1967 [40]	11/3,036 (0.4)	0.8	45
	1979 [24]	14/185 (7.6)	12	36
	1981 [38]	3/311 (1.0)	0.6	33
	1981 [39]	3/782 (0.4)	0.1	0
Egypt	1950 [41]	7/200 (3.5)	6.5	29
Ethiopia	1981 [42]	3/50 (6.0)	12	100
Ghana	1969 [10]	141/789 (18)	NA	30
	1976 [20]	309/1,542 (21)	NA	24
India	1963 [43]	4/111 (3.6)	7.2	75
	1965 [44]	3/334 (1.0)	5.7	67
	1968 [45]	3/98 (3.1)	13	67
	1970 [26]	60/3,800 (1.6)	4.5	72
	1972 [46]	2/54 (3.7)	1.9	NA
	1975 [25]	15/899 (1.7)	NA	NA
	1977 [14]	30/270 (11)	NA	60
	1977 [47]	4/500 (0.8)	NA	NA
	1977 [48]	0/78 (0)	1.3	. . .
	1982 [6]	344/38,932 (0.9)	NA	72
Indonesia	1978 [49]	75/540 (14)	NA	NA
	1982 [50]	2/158 (1.6)	NA	100
Iran	1961 [51]	8/530 (1.5)	3.6	25
Israel	1954 [52]	3/244 (1.2)	3.3	67
Kenya	1960 [5]	20/240 (8.3)	5.4	20
Lebanon	1978 [53]	1/104 (1.0)	1.0	0
Malaysia	1952 [54]	3/58 (5.1)	1.7	33
Nigeria	1966 [55]	26/214 (12)	24	54
	1966 [11]	12/262 (4.6)	NA	42
	1971 [56]	10/150 (6.7)	10	30
	1972 [18]	91/630 (14)	NA	41
	1972 [16]	76/224 (34)	NA	43
	1975 [21]	0/57 (0)	18	. . .
	1981 [57]	5/64 (7.8)	22	NA
	1981 [28]	46/117 (39)	41	41
Rhodesia	1971 [30]	13/243 (5.3)	7.0	23
South Africa	1954 [58]	2/110 (1.8)	5.5	50
	1969 [29]	12/316 (3.8)	7.3	67
	1975 [9]	38/754 (5.0)	11	32
Zambia	1978 [59]	25/400 (6.3)	9.8	56

NOTE. Studies were chosen that reported at least 50 patients with confirmed typhoid fever who were examined for perforation. When available, the case-fatality rates for all cases of typhoid fever and cases of perforation are recorded. NA = not available. The total number of cases of typhoid fever is 57,864; the total number of cases of perforation is 1,448 or 2.5% of the total number of cases of typhoid; the median case-fatality rate for all studies is 6.1%; and the median case-fatality rates for all cases of perforation is 43%.

days earlier he noted the onset of fever that was accompanied by chills and anorexia. Three days before admission he started to have watery mucoid stools five to six times per day. The patient appeared toxic but was mentally oriented. The pulse rate was 100 beats/min, and respirations 30/min. The temperature was 39.4 C. The abdomen was soft and slightly tender on deep palpation around the umbilicus. The liver and spleen were not palpable, and bowel sounds were present. The WBC count was

7,600/mm³ with a differential showing 66% polymorphonuclear leukocytes, 26% band forms, and 8% lymphocytes. The platelet count was 300,000/mm³. The hematocrit was 40%. The typhoid "O" agglutinin titer was 1:40. A blood culture yielded *S. typhi* sensitive to chloramphenicol. Stool culture and urine culture were negative. On the day of admission, 60 mg of chloramphenicol/kg of body weight per day divided in six hourly equal doses was started by the iv route.

On the second hospital day, he developed severe abdominal pain. The abdomen was very tender and rigid with rebound tenderness. Bowel sounds were absent. A roentgenogram of the abdomen showed free gas under the right hemidiaphragm. The patient was immediately sent to a surgical unit where he was operated on.

About 300 ml of straw-colored, nonhemorrhagic fluid was found in the peritoneal cavity. The entire ileum was hyperemic. There were two round perforation sites, which were located ~10 cm proximal to the cecum, with diameters of 0.2 cm and 0.4 cm. The perforation sites were sutured.

On the eighth day after surgery, he was discharged in good health. One month after surgery, he had gained 3 kg in body weight and was working again.

Incidence and Fatality of Intestinal Perforation in Developing Countries

In published reports of cases of typhoid fever in developing countries after 1950, the rate of perforation was recorded in 41 reports (table 2). Combining these reports with our results, there were 1,448 cases of perforation out of 57,864 cases of typhoid, giving an overall incidence of 2.5%. In individual reports the rates varied from 0% to 39%. The largest number of cases, reported by Chouhan et al. [6], was 344 perforations out of 38,932 cases of typhoid, giving a perforation rate of 0.9%. If these cases were not included, then the overall rate of perforation would increase to 5.8%. Geographic differences are suggested by low rates of perforation in Chile and India and high rates in Nigeria.

The reported case-fatality rates for all cases of typhoid fever in developing countries varied from 0.1% to 41% with a median rate of 6.1% (table 2). Among cases of typhoid fever complicated by intestinal perforation, the median of the case-fatality rates was 43%.

To assess the effects of antibiotic availability in developing countries on the incidence and fatality of intestinal perforation, we compiled reports of typhoid fever before 1950 (table 3). The overall incidence of perforation in 15,980 cases was 2.8%. The similarity of this rate to the rate of 2.5% in developing countries after 1950 (table 2) suggests that treatment with antibiotics in developing countries had no effect on the incidence of intestinal perforation in cases of tyhpoid fever. In the reports from the preantibiotic era, the medians of the case-fatality rates were 11% for all typhoid cases and 66% for perforated cases (table 3). These rates are considerably higher than the respective median rates of 6.1% and 43% for developing countries after 1950 and thus suggest that antibiotics in developing countries have had some favorable effect on mortality of all cases of typhoid fever and of typhoid fever with perforation.

In developed countries, on the other hand, the clinical experience with typhoid fever after 1950 has been different. Most of the reported 1,234 cases shown in table 4 developed during well-defined outbreaks or occurred in returned travelers. There were no cases

Table 3. Summary of data from reports of typhoid fever in the preantibiotic era (before 1950).

Country	Year [reference]	No. of typhoid cases	No. of cases of perforation (%)	Case-fatality rate (%) of all typhoid cases	Case-fatality rate (%) of cases of perforation
Great Britain	1917 [60]	1,118	9 (0.8)	7.5	100
India	1946 [61]	1,077	11 (1.0)	7.8	55
Mexico	1948 [62]	457	29 (6.3)	NA	66
Philippines	1929 [63]	3,255	38 (1.2)	19	97
United States	1935 [1]	9,713	351 (3.6)	11	NA
United States	1946 [3]	360	9 (2.5)	13	56

NOTE. The total number of cases of typhoid fever is 15,980; the total number of cases of perforation is 447 or 2.8% of the total number of cases of typhoid; the median case-fatality rate for all studies is 11%; and the median case-fatality rate for cases of perforation is 66%.

Table 4. Summary of data from reports of typhoid fever in developed countries in the antibiotic era (after 1950).

Country	Year [reference]	No. of typhoid cases	No. of cases of perforation	Case-fatality rate (%) of all cases of typhoid
Scotland	1965 [64]	507	0	0.6
Sweden	1982 [65]	61	0	0
Switzerland	1965 [66]	437	0	0.7
Switzerland	1981 [67]	124	0	0
United States	1975 [68]	105	0	0

NOTE. The total number of cases of typhoid fever is 1,234, and the median case-fatality rate for cases of perforation is 0.5%.

of perforation in these reports, and the case-fatality rates also approached 0%. The low incidence of perforation in developed countries could suggest that early antibiotic treatment did prevent perforation.

Underestimation of True Incidence of Intestinal Perforation

The diagnostic techniques that can establish the presence of intestinal perforation are visual inspection of the intestine during surgery or postmortem examination and the demonstration of pneumoperitoneum by roentgenogram. The roentgenographic evidence for perforation is the most widely used technique, but it has proved to be insensitive. In studies that documented perforation at surgery, prior abdominal roentgenograms showed pneumoperitoneum in only 10 of 20 cases reported by Li [7], and in only 10 of 165 cases reported by Badejo and Arigbabu [8]. In 11 different reports [7–17] 622 patients with proven perforation had roentgenograms taken, and only 286 (46%) of these roentgenograms showed free peritoneal air. These findings indicated that about half of the cases of intestinal perforations will be detected when roentgenograms are taken. Even fewer will be diagnosed because roentgenograms are seldom taken in cases of typhoid fever with abdominal distention and abdominal tenderness and since these signs are considered typical of cases of typhoid fever without perforation by most physicians.

Results and Management

In 39 published reports from developing countries after 1950 that described treatment and outcome in at least five cases of typhoid fever complicated by intestinal perforation (table 5), a total of 2,245 patients were included. Medical treatment without surgery was provided for 410 patients, of which 285 (70%) died. The range of case-fatality rates was 17%–100%, indicating that there was a variety of selection criteria and risk factors present in these groups of patients. There were 1,835 surgically treated patients of which 483 (26%) died. The range of surgical case-fatality rates was 0%–100% in these reports, indicating also a great variety of selection criteria, risk factors, and surgical techniques. In 20 of the surgical reports, no medically treated patients were included for comparison; in 11 reports, both surgical and medical results were given for comparison, but in none of these was any attempt made to select patients equally or randomly in order to allow one to compare objectively two methods of treatment.

In 13 of the surgical reports, the kinds of operations performed were described (table 6). The most commonly performed operation was simple closure of the perforation, followed in decreasing frequency by ileostomy and/or ileocolostomy. The case-fatality rates for each operation ranged from 14% to 28%. The small number of cases treated with wedge resection with closure and the similarity of the case-fatality rates associated with the other types of surgery do not permit conclusions about which operation is preferable.

Other Epidemiologic and Clinical Features of Intestinal Perforation

The ages and sex distribution of patients with typhoid fever complicated by intestinal perforation were given in 23 reports from developing countries in the antibiotic era (table 7). In only three reports, including the present series of cases in Bangladesh, were the age and sex distributions of the patients with nonperforated typhoid also given. The median of the mean ages for the series of patients without perfo-

Table 5. Case-fatality rates of cases of typhoid with perforation in the antibiotic era (after 1950).

Country	Year [reference]	No. of deaths/total no. of patients (%) for indicated type of patient management: Medical (without surgery)	Surgical
Bangladesh	Present study	6/9 (67)	1/4 (25)
Chile	1967 [40]	. . .	4/10 (40)
Egypt	1950 [41]	2/4 (50)	0/3 (0)
Ghana	1969 [10]	. . .	36/121 (30)
	1976 [20]	. . .	68/283 (24)
Guatemala	1981 [15]	. . .	18/59 (31)
Hong Kong	1963 [7]	. . .	2/20 (10)
India	1967 [22]	. . .	14/29 (48)
	1967 [72]	. . .	9/40 (23)
	1970 [26]	39/50 (78)	4/10 (40)
	1975 [25]	3/5 (60)	2/7 (29)
	1975 [13]	. . .	2/9 (22)
	1975 [69]	. . .	3/15 (20)
	1977 [14]	10/22 (45)	8/8 (100)
	1978 [70]	1/6 (17)	5/25 (20)
	1981 [71]	. . .	25/85 (29)
	1982 [6]	165/206 (80)	81/138 (59)
Iran	1961 [51]	. . .	2/8 (25)
Kenya	1960 [5]	4/20 (20)	. . .
Korea	1970 [12]	. . .	28/213 (13)
	1975 [73]	. . .	16/161 (9.9)
Malaysia	1964 [4]	1/6 (17)	. . .
Mexico	1983 [34]	. . .	0/8 (0)
Nigeria	1964 [27]	7/7 (100)	15/31 (48)
	1966 [55]	9/12 (75)	5/13 (38)
	1966 [11]	1/1 (100)	4/11 (36)
	1972 [16]	15/18 (83)	18/58 (31)
	1972 [18]	8/12 (67)	27/63 (43)
	1980 [8]	. . .	10/165 (6.1)
	1981 [28]	. . .	19/39 (49)
	1982 [19]	. . .	8/32 (25)
Pakistan	1982 [74]	. . .	4/22 (18)
Rhodesia	1971 [30]	0/5 (0)	3/6 (50)
Senegal	1979 [75]	. . .	7/26 (27)
South Africa	1969 [29]	5/8 (63)	3/4 (75)
	1975 [9]	5/14 (36)	7/24 (29)
Thailand	1975 [17]	. . .	11/50 (22)
USSR	1982 [76]	. . .	6/17 (35)
Zambia	1978 [59]	4/5 (80)	8/18 (44)
Total		285/410 (70)	483/1,835 (26)

NOTE. Studies were chosen that reported at least five cases of typhoid fever complicated by intestinal perforation after 1950 and in which the kind of patient management and outcome were described.

ration was 12.4 years, compared to 22 years for those with perforation. This age difference suggests that young children with typhoid fever are less susceptible to intestinal perforation than are older children and adults. Alternatively, the diagnosis of perforation is harder to make in young children, and in many countries these children are less likely to undergo surgical procedures. On the other hand, some of the studies that included young children suggested that older children were more susceptible to typhoid perforation. Mulligan [18] found perforation to be rare in children younger than five years. In these reports, the youngest children with perforations were 18 months [19] and two years [15, 20], whereas infants have been frequently reported to have typhoid fever without perforation [21]. The sex distribution of patients with intestinal perforation in developing countries showed a male-to-female ratio of 2.9. This male preponderance was greater than that of 1.4 for patients with typhoid including those without perforation.

The clinical histories of patients with perforation indicated that perforation occurred most frequently after the second week of illness (table 8). Earlier occurrences of perforation, however, have also been recorded, with totals of 94 cases in the first week and 122 cases in the second week of illness. The perforations have been located in the terminal ileum and were most frequently single perforations. At least two perforations were found in smaller proportions of the cases (table 8).

Prognostic Factors in Typhoid Perforation

In patients undergoing surgery for perforation, the best results were obtained when operations were promptly performed within 24 hr after the onset of signs and symptoms of perforation [10, 20, 22–25]. When surgery was delayed 24–48 hr after the time of perforation, case-fatality rates increased to >50% in some reports [22, 26], and even higher fatality rates occurred when surgery was performed >72 hr after perforation occurred [6, 10, 20, 22, 23]. Another prognostic factor is the time of perforation in relation to the onset of typhoid fever. In the reports of Singh and Singh [25] and Eggleston et al. [23] lower case-fatality rates were obtained with surgery in patients in whom perforation occurred during the first week of illness. Perforations occurring after the third week were associated with higher case-fatality rates [25, 27]. Other bad prognostic factors that have been

Table 6. Types of surgery performed in cases of typhoid fever complicated by perforation in developing countries in the antibiotic era (after 1950) and associated case-fatality rates (%).

Country	Year [reference]	No. of deaths/no. of patients who received indicated surgery (%)			
		Simple closure	Ileal resection	Ileostomy and/or ileocolostomy	Wedge resection with closure
Ghana	1969 [10]	36/121 (30)	. . .	. . .	. . .
Guatemala	1981 [15]	. . .	. . .	18/59 (31)	. . .
Hong Kong	1963 [7]	2/20 (10)	. . .	. . .	. . .
	1967 [22]	14/29 (48)	. . .	. . .	. . .
	1967 [72]	9/40 (23)	. . .	. . .	. . .
	1975 [69]	. . .	. . .	3/15 (20)	. . .
India	1979 [70]	1/7 (14)	1/11 (9)	1/2 (50)	. . .
	1981 [71]	13/43 (30)	2/3 (67)	9/29 (31)	. . .
Korea	1975 [73]	11/103 (11)	3/43 (7)	1/10 (10)	. . .
Nigeria	1964 [27]	10/23 (44)	5/7 (71)	. . .	. . .
	1972 [16]	9/40 (23)	2/4 (50)	1/2 (50)	2/9 (22)
Thailand	1975 [17]	4/11 (36)	3/20 (15)	2/7 (29)	1/12 (8)
Zambia	1978 [59]	7/16 (44)	. . .	. . .	. . .
Total		116/453 (26)	16/88 (18)	35/124 (28)	3/21 (14)

NOTE. Studies were chosen that reported at least 10 cases of typhoid fever complicated by intestinal perforation after 1950 in which results of surgery were described.

reported include renal failure [10], intestinal hemorrhage [9, 25], anemia [9], and lack of experience of the operating surgeons with this disease [9].

Influence of Perforation on Overall Mortality in Typhoid Fever

In 21 reports from developing countries after 1950, the numbers of deaths due to typhoid fever and numbers of patients with perforations were recorded. The percentage of deaths due to intestinal perforation ranged from 0% to 40% (table 9). The overall proportion of the deaths due to perforation was 25%. However, this percentage is certainly less than the true number because postmortem examinations were carried out consistently in only three of these studies of mortality [28–30].

Discussion

The 15 patients with intestinal perforation in Bangladesh were detected among a group of 323 patients with fever and blood cultures positive for *S. typhi*. This incidence of perforation in cases of typhoid fever of 4.6% is probably an underestimation of the actual incidence because roentgenograms were not regularly taken in patients with abdominal symptoms and because pneumoperitoneum can be insensitive as a test for perforation. These 15 patients with typhoid fever complicated by intestinal perforation were characterized by a mean age of 25.7 years, which was more than twice that of 12.4 years in the cases of typhoid fever without perforation, a male-to-female ratio of 4.0, and a high case-fatality rate of 7/15 or 47%. The case-fatality rate was lower in those patients treated surgically (25%) than in those receiving medical treatment alone (67%). These findings in our patients, when compared with large experiences with typhoid fever complicated by intestinal perforation, appear to be typical of recent experiences in other developing countries during the antibiotic era.

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 a condition of hyperplasia this lymphoid tissue bridges the distance from the luminal epithelium to the serosa. During the course of typhoid fever, *S. typhi* is in the mononuclear phagocytes of Peyer's patches, and in cases with intestinal perforation, this tissue and surrounding tissues show hemorrhagic necrosis and vascular thrombosis. This complication occurs most often in the third week of typhoid fever, suggesting that it is a late event that requires time for bacteria to invade the tissue and, perhaps, for the immune response to contribute to the pathogenesis of the lesions. The most serious consequence of intestinal perforation is the leakage of intestinal contents with

Table 7. Ages and sex distribution of patients with typhoid with or without intestinal perforation in developing countries in the antibiotic era (after 1950).

Country	Year [reference]	Mean age (years)/sex distribution (M:F) for patients with typhoid fever	
		With perforation	Without perforation*
Bangladesh	Present study	25.7/12:3	12.4/197:111
Chile	1967 [40]	NA/9:2	NA/2,004:1,467†
Ghana	1969 [10]	18/91:30	NA/NA
Guatemala	1981 [15]	7/35:24	NA/NA
Hong Kong	1963 [7]	25/16:4	NA/NA
India	1967 [22]	~30/27:2	NA/NA
	1967 [72]	NA/36:4	NA/NA
	1970 [26]	NA/46:14	NA/NA
	1975 [25]	20/11:4	NA/NA
	1975 [69]	14/13:2	NA/NA
	1977 [14]	22/27:3	NA/NA
	1981 [71]	24/62:23	NA/NA
Indonesia	1978 [49]	26/142:42	NA/NA
Iran	1961 [51]	20/8:0	NA/NA
Korea	1975 [73]	30/113:48	NA/NA
Mexico	1983 [34]	NA/3:5	NA/10:9
Nigeria	1964 [27]	26/27:11	NA/NA
	1971 [56]	5.3/NA	4.2/81:69
	1972 [16]	22/59:17	NA/NA
	1972 [18]	20/61:22	NA/NA
	1980 [8]	27/108:57	24/28:17
	1982 [21]	21/23:5	NA/NA
Senegal	1979 [75]	16/22:4	NA/NA

NOTE. For all those patients with typhoid fever complicated by intestinal perforation the median age is 22 years and the sex ratio is 951 males to 326 females (2.9). For all patients without perforation the median age is 12.4 years and the sex ratio is 2,320 males to 1,673 females (1.4). NA = not available.

* Or total number of patients with typhoid fever reported.

† Includes cases of paratyphoid A and B, which were 12.6% of all cases.

bacteria other than *S. typhi* into the peritoneum, giving rise to generalized peritonitis and often fatal septicemia. Perforations occur most commonly on the antimesenteric surface of the ileum and, thus, may remain open without any covering of the mesentery for prolonged periods.

The epidemiologic features of our patients in Bangladesh and of other experiences in developing countries could have a bearing on the pathogenesis of intestinal perforation in typhoid fever. When patients with typhoid fever with perforation were compared with patients without perforation, the group of patients with perforations showed greater male preponderance and older mean ages. These differences could have resulted from reporting biases, such as selective underreporting of female cases due to referral patterns and underdiagnosis of perforation in young children due to less specific symptomatology. On the other hand, the consistency of these trends from different kinds of hospitals in several countries suggests that the sex and age differentials are real. The greater male preponderance and older ages among patients with perforations are consistent with a requirement for multiple exposures to *S. typhi* to produce perforation. If males are exposed slightly more frequently to *S. typhi*, giving a male-to-female ratio of 1.4 during the first exposure to result in typhoid fever without perforation, then two additional infections per person at the same sex ratio of exposure resulting in perforation would give the greater male-to-female ratio of 2.9 ($\sim 1.4^3$) that prevails for this disease (table 7). The older mean age of patients with perforations is also consistent with multiple exposures, which require time. Young children with typhoid fever would be expected more frequently to be suffering from their first exposure. Also consistent with this viewpoint is the virtual elimination of perforation from typhoid fever in developed countries (table 4), where the rare occurrence of this disease, as in returned travelers, makes multiple exposures to the infection almost impossible.

An alternative explanation to multiple exposures for the age and sex distribution of patients with perforation is that there is a genetic predisopostion to this complication. If there are genes that govern the immune response to antigens of *S. typhi*, certain individuals with typhoid fever might develop an exaggerated hyperplasia in Peyer's patches that could result in perforation. If these genes occurred preferentially in males, the male preponderance could be explained. In mouse typhoid, there are inbred genetic strains that are either more susceptible or resistant to lethal *S. typhimurium* infection than are outbred mice [31], and one of the genes controlling susceptibility to infection is X-linked [32]. Multiple exposures, however, still might be necessary to trigger the enhanced immune responses and to explain the more advanced ages of the patients with perforation. A case report in favor of a genetic predisposition for typhoid perforation was made by Vyas et al. [33], who noted typhoid fever with perforation in two identical twin brothers aged 21 years in India. In Mexico, Vogel et al. [34] reported perforations also in two sisters with typhoid fever.

The optimal treatment of typhoid fever compli-

Table 8. Time of perforation in relation to onset of disease and the number of perforations in the intestine from five reports of typhoid perforations from developing countries in the antibiotic era (after 1950).

Country	Year [reference]	No. of cases with perforations occurring during indicated interval			No. of cases with indicated no. of perforations in intestine		
		1 Week	2 Weeks	After 2 weeks	1	2	>2
Guatemala	1981 [15]	8	32	19	46	6	6
India	1967 [22]	9	13	4	27	1	1
	1979 [23]	15	25	38	67	6	1
Korea	1975 [73]	6	34	121	111	30	20
Nigeria	1972 [16]	56	18	8	36	11	6
Total		94	122	190	287	54	34

cated by perforation has been controversial. In the preantibiotic era, Osler [1, 35] advised early surgery and suggested that about one-third of patients who received surgery would survive compared with universal fatality for those who did not receive surgical treatment. In the antibiotic era, however, both Woodward and Smadel [4] and Huckstep [5] emphasized the great risk that surgery imposed and suggested that most patients could be managed by antibiotic treatment without surgery. Huckstep [5] advised that surgery be limited to those cases in which surgery could be carried out promptly within 6 hr of the perforation and in cases in which intestinal obstruction or abscess formation necessitated surgery. Actual experiences in developing countries that are reviewed in this paper, however, indicate that medical therapy carried a high case-fatality rate and that surgical intervention has produced more encouraging results. The cumulative case-fatality rates were 70% for 410 patients undergoing medical treatment and 26% for 1,835 patients who received surgical treatment (table 5). Although many of the reports had a bias toward placing patients who were poor surgical risks into medical therapy, the overall result indicates that the surgical approach to treating patients is preferred.

Table 9. Percentage of typhoid deaths attributed to intestinal perforation in developing countries in the antibiotic era (after 1950).

Country	Year [reference]	No. of deaths due to perforations/total no. of deaths due to typhoid fever (%)
Bangladesh	Present study	7/18 (39)
Chile	1967 [40]	5/24 (21)
	1979 [24]	5/22 (23)
Egypt	1981 [38]	2/13 (15)
Ethiopia	1981 [42]	3/6 (50)
India	1963 [43]	3/8 (38)
	1965 [44]	2/19 (11)
	1968 [45]	2/13 (15)
	1970 [26]	43/170 (25)
Indonesia	1982 [50]	2/3 (67)
Iran	1961 [51]	2/19 (11)
Kenya	1960 [5]	4/13 (31)
Nigeria	1966 [55]	14/52 (27)
	1971 [56]	3/15 (20)
	1975 [21]	0/10 (0)
	1981 [28]	19/48 (40)
Rhodesia	1971 [30]	3/17 (18)
South Africa	1954 [58]	1/6 (17)
	1969 [29]	8/23 (35)
	1975 [9]	12/84 (14)
Zambia	1978 [59]	14/39 (36)
Total		154/622 (25)

The more favorable prognosis of patients receiving surgery may also reflect an improvement in surgical facilities and skills of surgeons available now in countries with endemic typhoid fever. The prognosis was adversely affected by delaying surgery for 24 hr after the perforation, but it would seem advisable to attempt operations on all patients after preparation with fluid therapy, therapy with broad-spectrum antibiotics, and blood transfusion, as required. The choice of operation should depend on the number of perforations and condition of the ileum.

The most frequently performed operation was simple closure of the perforations; patients with extensive necrosis or multiple perforations may require ileostomy or ileocolostomy, but ileal resection should probably be avoided. Medical therapy without surgery should not be deliberately chosen for patients with proven perforation because of the poor results documented in many studies (table 5). The earlier recommendations of medical therapy without sur-

gery in most instances [4, 5] do not conform to our understanding of the pathogenesis of this disease in which fecal spillage onto the peritoneal surface causes peritonitis and, often, fatal sepsis.

Another therapeutic implication of the reported experiences with intestinal perforations is that about half the cases of perforation can be missed if pneumoperitoneum is used as the diagnostic criterion. Large numbers of patients have been proved to have perforation at surgery after a roentgenogram showed only dilated loops of bowel or peritoneal fluid without free peritoneal air [8]. Early perforations that are small, or even microscopic, could leak bacteria without air onto the peritoneum to start peritonitis. This implies that early laparotomy should be considered for certain patients with typhoid fever who have signs of peritonitis, sepsis, or ileus, although they do not have pneumoperitoneum. This advice of surgery in cases without pneumoperitoneum was made by Li in 1963 [7].

Further studies of causes of death in patients with typhoid fever are needed to determine whether this surgical approach is correct. Postmortem examinations will be required in fatal cases of typhoid to establish the true incidence of perforation. For now, intestinal perforation, which was the established diagnosis in 25% of fatal cases of typhoid fever in developing countries, must be considered a major cause of death – if not the most frequent cause of death – in patients with typhoid fever in endemic areas of the world.

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