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Changing characteristics of typhoid fever in Taiwan

Chan-Ping Su[1], Yee-Chun Chen[2], Shan-Chwen Chang[2]

[1]Department of Emergency Medicine and [2]Section of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, Taipei; Taiwan, ROC

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Typhoid fever, a systemic disease caused by *Salmonella typhi*, is classically characterized by fever and abdominal symptoms. Although now considered uncommon, it seems to have re-emerged in Taiwan in recent years. We conducted a retrospective study of the clinical characteristics and microbiologic findings in 24 confirmed cases of typhoid fever treated over a 7-year period at a medical center in northern Taiwan. There were 11 males and 13 females, including 15 adults (over 18 years in age) and 9 children. Their mean age was 24.7 years (range, 9 months to 58 years). Twelve patients had recently returned from abroad, mostly from Southeast Asia. The most common complaints were fever (24/24), diarrhea (18/24), abdominal pain (10/24), and cough (10/24). The average duration of fever before diagnosis was 14.1 days, with a maximum of 30 days. Relative bradycardia was noted in 6 patients. Leukopenia was noted in 2 patients. *S. typhi* was isolated from blood culture in 20 cases, from stool culture in 3 cases, and from bone marrow culture in 1 case. Widal test was only positive initially in 7/18 cases. Fever of unknown origin was the most common initial diagnosis. Typhoid or enteric fever was impressed initially in only 2 cases. Almost all isolates of *S. typhi* were susceptible to antibiotics currently used for typhoid fever, with only 1 isolate resistant to chloramphenicol. All patients survived after antibiotic treatment. Only 1 patient developed recurrence after a 10-day course of ceftriaxone. In conclusion, the diagnosis of typhoid fever is often challenging due to non-specific symptoms and lack of an immediate confirmatory test. It is important to include this disease in the differential diagnosis of febrile patients with abdominal symptoms.

Key words: Differential diagnosis, fever of unknown origin, *Salmonella typhi*, typhoid fever

Typhoid fever, a systemic disease caused by *Salmonella typhi*, is an acute illness characterized by fever and gastrointestinal symptoms. It has become an uncommon disease in Taiwan during recent years, and younger physicians may have never encountered a patient with typhoid fever, or be unfamiliar with the features of this disease.

Patients with typhoid fever usually present with a history of prolonged fever, headache, and abdominal discomfort. There are no distinctive clinical features, and definite diagnosis requires isolation of *S. typhi* from blood, bone marrow, stool, or urine cultures. Fever is the most common finding and is seen in 75 to 100% of cases [1].

The classic findings of relative bradycardia and rose spots were noted in less than half of patients [2]. Laboratory findings such as leukopenia, thrombocytopenia, proteinuria, and elevated transaminases are also non-specific and uncommon. Diminished awareness of the clinical features among physicians and lack of specific clinical characteristics may delay the diagnosis and treatment of this disease. In addition, greater participation in travel to developing areas may result in increased incidence. Familiarity with the clinical features of this disease and a high index of suspicion are required for an early diagnosis and provision of appropriate management.

This study analyzed the clinical characteristics and microbiologic findings in cases of typhoid fever treated at a medical center during a 7-year period.

Materials and Methods

There were a total of 24 cases of culture-confirmed typhoid fever at National Taiwan University Hospital, a 2000-bed medical center in northern Taiwan, during the period from January 1993 to December 1999. All of the cases included in this study had fever or other symptoms or signs compatible with systemic infectious disease and at least 1 positive culture of *S. typhi* from their specimens (20 from blood, 3 from stool, and 1

Corresponding author: Dr. Shan-Chwen Chang, Section of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan 100, ROC.
E-mail: sc4030@ha.mc.ntu.edu.tw

from bone marrow). The medical records were reviewed and data were collected, including age, gender, underlying medical conditions, travel history in the recent 1 month, type and duration of symptoms, and findings of physical examination. The highest temperature recorded during hospitalization and associated heart rates were noted. Relative bradycardia was defined as a pulse rate of less than 100 beats/min associated with the highest body temperature [3]. Data from the first laboratory tests including the white blood cell (WBC) count, serum transaminases, and any other abnormal test results were recorded.

The results of confirmatory blood, bone marrow, stool cultures, and Widal test were also reviewed. A positive Widal test was defined as a titer of *S. typhi* O antigen ≥1:320 or a titer of *S. typhi* H antigen ≥1:640 or 4-fold change of follow-up titer [4]. Admission and discharge diagnosis, treatment, outcome, and complications were also recorded. *S. typhi* was identified by conventional methods [5]. Antimicrobial susceptibility was tested by the disk-diffusion method and interpreted according the criteria of National Committee for Clinical Laboratory Standards [6].

Results

Patient characteristics

Among the 24 patients with culture-confirmed typhoid fever, 11 were males and 13 were females (Table 1). Fifteen patients were adults (≥18 years old) and 9 were children. The mean age was 24.7 years (range, 9 months to 58 years). Most cases occurred in autumn (11 cases), followed by summer (6 cases), winter (4 cases), and spring (3 cases). Twelve patients had a recent travel history, including 4 males and 8 females. The areas recently traveled to included Southeast Asia (9 cases), Northeast Asia (1 case), North America (1 case), and Europe (1 case). The average age of the returned travelers was 27.7 years (range, 2 to 42 years), and that of the non-travelers 21.7 years (range, 9 months to 58 years). The 9-month-old patient had biliary atresia and no recent travel history. Only 1 patient had received gastrectomy and this patient had just returned from Japan. Other associated underlying conditions included bronchial asthma (1 case), IgA nephropathy (1 case), and hepatitis C carrier (1 case). None of the patients had ever received glucocorticosteroid or any immunosuppressive therapy.

Table 1. Patient characteristics

Case no.	Age (years)	Gender	Time of visit	Recent travel	Culture site	Underlying disease	Initial impression
1	21	M	May 1992	No	Blood	No	URI
2	42	F	Sep 1992	USA	Blood	No	Pelvic abscess
3	13	F	Sep 1992	No	Blood	No	UTI
4	33	M	Jun 1993	No	Blood	No	Cholangitis
5	36	F	Jul 1993	France	Blood	No	Enteric fever
6	30	F	Nov 1993	No	Stool	No	Sepsis
7	6	M	Mar 1994	Myanmar	Blood	No	FUO
8	21	F	Jul 1994	No	Blood	No	Infectious diarrhea
9	30	M	Mar 1995	Japan	Blood	Gastrectomy	FUO
10	9	F	May 1995	No	Blood	No	AGE
11	48	F	Aug 1995	Indonesia	Blood	No	FUO
12	9	F	Jan 1996	Thailand	Stool	No	FUO
13	14	M	Dec 1996	No	Blood	Asthma	Rickettsial disease
14	16	M	Apr 1997	Philippines	Blood	No	Sepsis
15	2	F	Sep 1997	Myanmar	Blood	No	AGE
16	9 months	M	Sep 1997	No	Blood	Biliary atresia	Pneumonia
17	26	F	Sep 1997	No	Stool	No	Endocarditis
18	14	M	Sep 1997	No	Marrow	PSVT	Encephalitis
19	58	M	Oct 1997	No	Blood	HCV	FUO
20	21	M	May 1998	No	Blood	No	Hepatitis
21	25	F	Aug 1998	Southeast Asia	Blood	No	URI
22	36	F	Jan 1999	Southeast Asia	Blood	IgA nephropathy	FUO
23	41	F	Jul 1999	Indonesia	Blood	No	FUO
24	41	M	Aug 1999	Indonesia	Blood	No	Typhoid fever

Abbreviations: PSVT = paroxysmal supraventricular tachyarrhythmia; HCV = hepatitis C virus; URI = upper respiratory tract infection; UTI = urinary tract infection; FUO = fever of unknown origin; AGE = acute gastroenteritis; IgA = immunoglobulin A

Table 2. Symptoms and physical findings in 24 patients with typhoid fever

Symptom/sign	Adults n = 15 (%)	Children n = 9 (%)	Total n = 24 (%)
Fever	15 (100)	9	24 (100)
Diarrhea	10 (66.7)	8	18 (75)
Abdominal pain	8 (53.3)	3	11 (45.8)
Abdominal tenderness	8 (53.3)	3	11 (45.8)
Cough	7 (46.7)	3	10 (41.7)
Sore throat	4 (26.7)	2	7 (29.2)
Relative bradycardia	5 (33.3)	1	6 (25)
Headache	3 (20)	0	3 (12.5)
Rose spots	1 (6.7)	2	3 (12.5)
Splenomegaly	2 (13.3)	0	2 (8.3)
Hepatomegaly	1 (6.7)	1	2 (8.3)
Nausea/vomiting	1 (6.7)	0	1 (4.2)
Constipation	0 (0)	1	1 (4.2)
Coryza	1 (6.7)	0	1 (4.2)
Mental change	0 (0)	1	1 (4.2)

Clinical features

The most common symptoms were fever (24/24, 100%), diarrhea (18/24, 75%), abdominal pain (10/24, 41.7%), and cough (10/24, 41.7%) [Table 2]. However, many cases presented with upper airway symptoms, such as cough (10 cases), sore throat (7 cases), and even coryza (1 case). Headache was noted in only 3 adult patients (12.5%), nausea/vomiting in 1 adult case, and constipation in 1 pediatric case. The most common physical findings were fever (24/24, 100%), abdominal tenderness (10/24, 41.7%), relative bradycardia (6/24, 25%), and rose spots (3/24, 12.5%) [Table 2]. Relative bradycardia was noted in only 1 pediatric patient. Hepatomegaly and splenomegaly were noted in 2 cases each. One patient with biliary atresia presented with hepatomegaly, and 1 patient who presented with splenomegaly was a hepatitis C carrier.

Laboratory and microbiologic features

Initial WBC count was normal in 18 patients, and elevated (>10 K/mm^3) in 4; leukopenia (<4 K/mm^3) was noted in 2 patients. Elevated transaminases (>40 U/L) was noted in only 2 cases. Blood culture was the most common confirmatory test (20/24). Of the 18 patients presenting with diarrhea, only 3 had positive stool cultures. Positive bone marrow culture with hemophagocytosis was noted in 1 patient. Almost all of the isolates were susceptible to current antibiotics used for typhoid fever, including ampicillin, chloramphenicol, cotrimoxazole, third-generation cephalosporins, and fluoroquinolones, except for 1 strain which was resistant to chloramphenicol. The only resistant strain was isolated from a male traveler who had returned from Japan. This patient had received subtotal gastrectomy for perforated peptic duodenal ulcer 17 years previously, and had not received any antibiotic treatment before the onset of symptoms. Initial Widal test was positive in 6 of 17 patients (35.3%). Follow-up Widal tests showed 4-fold change (either increase or decrease) in 6 of 8 patients (75%). The average duration from symptom onset to diagnosis was 14.8 days (range, 5 to 30 days) for the 6 patients with positive initial Widal test, and 15.5 days (range, 7 to 26 days) for the 11 patients with negative initial Widal test. There was no significant difference in febrile duration between these 2 groups of patients (p=0.87).

Clinical course, treatment, and outcome

Typhoid fever or enteric fever was the initial diagnosis in only 2 cases (Table 1). The most common initial diagnosis (7 cases) was fever of unknown origin. Acute gastroenteritis or infectious diarrhea was suspected in 3 patients. Upper or lower airway infection was diagnosed in 3 patients. Other initial diagnoses included: sepsis (2 cases), rickettsial disease (1 case), cholangitis (1 case), hepatitis (1 case), acute pyelonephritis (1 case), pelvic abscess (1 case), endocarditis (1 case), and encephalitis (1 case). The average duration from disease onset to diagnosis of typhoid fever was 14.5 days (range, 5 to 30 days). Only 4 cases were diagnosed within 7 days. The diagnosis was obtained more than 2 weeks after symptom onset in 10 cases, and the maximal duration was as long as 30 days (Fig. 1). Five patients were lost to follow-up, and the other 19 patients were admitted and treated. Among the 19 admitted patients, only 3 received a single antibiotic. Eight patients received more than 2 kinds of antibiotics, mainly due to the uncertainty of the diagnosis. Five patients were treated with third-generation cephalosporins, including cefotaxime, ceftriaxone, and ceftizoxime, 2 patients were treated with ampicillin/amoxicillin, and 2 patients with ciprofloxacin. The other 9 patients received more than 1 of the 5 classes of antibiotics currently used in the treatment of typhoid fever (Table 3). The duration of antibiotic therapy was quite variable, ranging from 3 to 21 days. The average duration of the febrile period from disease onset was 16.4 days (range, 3 to 34 days). The average duration from starting treatment to defervescence was 3.86 days, ranging from 1 to 7 days. No deaths occurred among the admitted patients. Recurrence, defined as reappearance of the symptoms in association with a positive culture

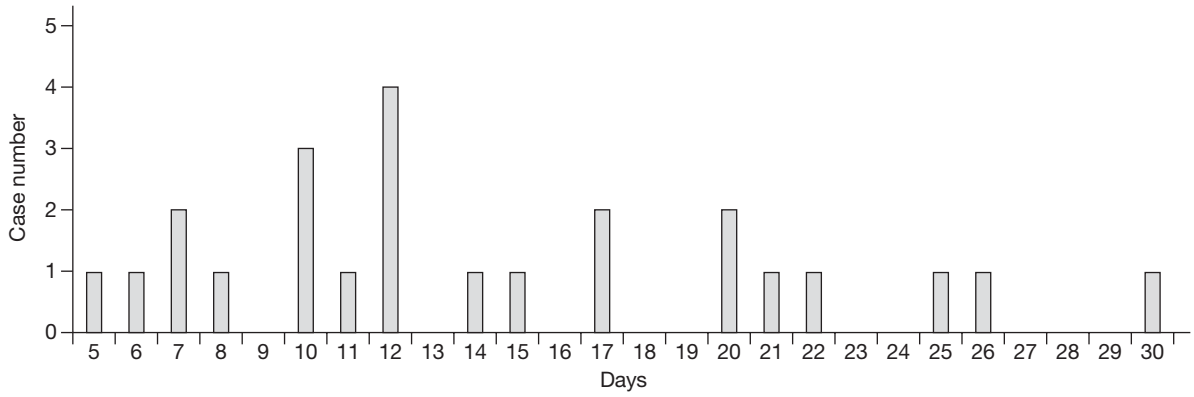

Fig. 1. Period from symptom onset to diagnosis in 24 patients with typhoid fever.

Table 3. Antimicrobial therapy in the 19 patients with typhoid fever admitted to the hospital

Antibiotic regimen	No. of cases n = 19 (%)
3-Ceph	5 (26.3)
Amp	2 (10.5)
Cip	2 (10.5)
3-Ceph + Amp	1 (5.3)
Amp + 3-Ceph	4 (21.1)
Cip + Amp	1 (5.3)
3-Ceph + Cip	3 (15.8)
Cot + 3-Ceph	1 (5.3)

Abbreviations: 3-Ceph = third-generation cephalosporin; Amp = ampicillin/amoxicillin; Cip = ciprofloxacin; Cot = cotrimoxazole; + indicates a change was made from the former to the latter antimicrobial agent

after a course of antibiotic treatment, was observed only in 1 female patient, 36 days after a 10-day-course of ceftriaxone therapy. One pediatric case developed the complications of encephalitis and infection-associated hemophagocytotic syndrome. One adult patient developed the complication of gallbladder empyema and was treated surgically. Stool cultures were collected in 16 of 19 admitted patients from 2 to 18 weeks (mean, 37.5 days) after admission and none was positive.

Discussion

Typhoid fever, a systemic infectious disease caused by *S. typhi*, is an acute illness characterized by protean and non-specific symptoms, including prolonged fever, abdominal pain, diarrhea, headache, sore throat, cough, constipation, and a rose-colored rash [7]. The incubation period ranges from 5 to 21 days [4]. *S. typhi* colonizes and infects only human beings; infection usually follows ingestion of food or water contaminated with the feces of those with active disease, or those who are asymptomatic carriers. The disease remains a serious public health problem throughout the world. There are several types of typhoid fever disease patterns: epidemic, endemic, or sporadic. The clinical features, incidence of complications, and mortality associated with typhoid fever vary considerably depending on the type of pattern [2,7,8-14]. In Taiwan, typhoid fever occurs mainly as a sporadic disease in patients of any age and gender, and at any time of the year. The prevalence rate of typhoid fever in Taiwan has markedly decreased, from nearly 200 documented cases annually in the 1950s to several tens of cases annually in the 1990s [8,15-17]. Half of our patients had a recent travel history, mostly to Southeast Asia; a lower percentage than in studies from the United States (72%) [18]. Imported cases have become the major patient source of typhoid fever in Taiwan. There were more cases in summer and autumn in this series, similar to other studies conducted in Taiwan [8,15].

The most common clinical manifestations seen in this series were prolonged fever with diarrhea (75%), followed by abdominal pain (41.7%), and cough (41. 7%). Headache was reported by only 12% of our patients, compared to about 47% in other series [8,15]. Fever without any other associated gastrointestinal symptoms was present in 25% of patients, which is higher than that of Chiu et al's study (15%) [8]. Fever with upper airway symptoms was present in 41.7% of the patients, which is higher than in previous studies (23 to 33%) [13,15]. The most common physical sign was abdominal tenderness (41.7%). Unlike the results as high as 31 to 61% in other series [8,12,15], hepatosplenomegaly was uncommon in this study (8.3%). The more specific physical sign of rose spots was noted in only one-eighth of our patients, while this sign occurred in 15 to 29% of patients in previous series

from Taiwan [8,15]. Relative bradycardia was noted in 25% of our patients; however, it has been regarded as an unreliable feature of enteric fever [19]. Comparison of our data with other studies [8,15-17] suggests that atypical cases may be increasing in Taiwan.

The mean duration of fever from onset to diagnosis was as long as 14.5 days in this series, which was similar to data from other series in Taiwan and Japan [12,15]. Most patients had normal leukocyte count (75%), and leukopenia was found in only 8.3% of patients. Leukopenia was quite non-specific for typhoid fever in this series. Elevated serum transaminases were noted in only 8.3% of patients. The initial Widal test was positive in only 35.3% of our patients, although the proportion of positive results might have increased to about 75% if paired sera titers were compared. However, treatment decisions must be made before the second test. No significant difference in duration from symptom onset to diagnosis was observed between the 2 groups of patients with positive or negative initial Widal test. In untreated patients with typhoid fever, antibody titers are often not detected until the second week of illness and are usually elevated by the third week. In some cases, no titer elevation is ever documented. Early treatment often attenuated the immunologic response to the infection. Thus, a low or negative titer does not exclude the diagnosis of typhoid fever [20]. In addition, because the test has serious cross-reactivity with many other infectious agents, it may produce false-positive results. Thus, Reynolds et al noted that the Widal test is unreliable in clinical practice [21].

The most common admitting diagnosis was fever of unknown origin. Typhoid fever or enteric fever was impressed at admission in only 2 patients, including the wife of a man who had returned from travel to Indonesia. Compared to other studies reported from Taiwan, our patients seemed to have more atypical presentations [8, 15]. A relatively low incidence of the classical symptoms in this study is consistent with other reports [22,23]. Because of delayed visits to the hospital by the patients, lack of physician familiarity with this disease, and the increase in patients with atypical symptoms, the diagnosis of typhoid fever has become a challenge for physicians [7].

Detection of *S. typhi* is most frequent in blood culture (83.3%), followed by stool culture (12.5%). The low *S. typhi* detection rate in urine in this study was consistent with other data [22]. The average duration (14.5, 15, and 10 days for blood, stool, and bone marrow, respectively) from onset to diagnosis was not well correlated with the positive culture sites (p=0.91). Although bone marrow aspiration was performed in only 1 patient in this series, it had the greatest sensitivity in a previous study [7]. In patients with prolonged fever who have received antibiotic therapy, bone marrow culture should be considered as an effective diagnostic method [24]. Almost all of the strains isolated in this series were susceptible to all antimicrobial agents, except for 1 strain which was resistant to chloramphenicol. These results are similar to those of other reports from Taiwan. [8,15]

Until the 1980s, chloramphenicol had been the drug of choice for typhoid fever. However, after the documentation of chloramphenicol-resistant strains in 1974 [25], the increasing rate of relapse with chloramphenicol therapy necessitated the use of ampicillin or cotrimoxazole. However, the use of ampicillin and cotrimoxazole has been increasingly compromised due to multidrug resistance [18,23,26], and these agents are now replaced mostly by fluoroquinolones and sometimes by third-generation cephalosporins [27]. Most of our patients were treated with third-generation cephalosporins (10 cases) or fluoroquinolones (5 cases); 4 patients were treated successfully with ampicillin. No mortality occurred in our patients. Although fluoroquinolone-resistant *S. typhi* is reported to be increasing in United Kingdom [28], such resistance has not been reported in our country. However, the efficacies of therapeutic regimens for typhoid fever need constant monitoring, because of the growing number of travelers from Taiwan to various areas of the world.

Despite a 10-day course ceftriaxone therapy, 1 woman developed recurrence 36 days later. She and her husband developed typhoid fever after returning from Indonesia. Her husband developed symptoms after her first discharge from the hospital. Her symptoms then recurred and *S. typhi* was isolated from blood culture again. Because of the time sequence, cross-transmission between these 2 patients was suspected and recurrence due to treatment failure was considered less likely. Typhoid fever in 1 adult patient was complicated by gallbladder empyema requiring surgical intervention. One pediatric patient developed the complications of encephalitis and infection-associated hemophagocytotic syndrome. There have been several previous reports of typhoid fever associated hemophagocytotic syndrome [29-31]. Furthermore, hemophagocytosis may be an important mechanism in producing neutropenia and thrombocytopenia in typhoid fever [32].

Fever of unknown origin was the most common initial diagnosis, and typhoid fever was impressed initially only in 2 patients in this study. Delayed

diagnosis may occur due to the delay visiting the hospital by the patient and failure to recognize symptoms by the physician. Lack of familiarity with the increasing atypical presentations of typhoid fever made it difficult to diagnose this disease in many cases in this series. As cultures are time-consuming and the use of Widal test should not be encouraged, the diagnosis of typhoid fever continues to be a great challenge. In order to make a correct and fast diagnosis, physicians need to maintain awareness and suspicion of this disease, and to perform appropriate cultures of bacteria.

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