Typhoid fever and typhoid hepatitis in Taiwan

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SUMMARY

The annual incidence of typhoid fever in Taiwan was 2·1–3·6 cases per 1 000 000 population
from 1995 to 2002. More than 80 % of 45 patients with typhoid fever treated at National Taiwan
University Hospital from 1996 to 2002 had elevated serum aminotransferase levels at
presentation. Ten of these patients were treated during an outbreak in Taipei County in 2002,
and seven of them who did not have pre-existing liver disease developed hepatitis, which was
unrelated to other aetiologies. All *Salmonella typhi* isolates were susceptible to extended-spectrum
cephalosporins and fluoroquinolones. Multidrug resistance (intermediate resistance to ampicillin,
trimethoprim–sulphamethoxazole, and chloramphenicol) was found in one (2·5 %) of the 40
isolates studied. Pulsed-field gel electrophoresis analysis demonstrated a high genetic diversity
among *S. typhi* isolates and identified a novel clone associated with the 2002 outbreak.
Physicians should be alert to the possibility of typhoid fever when patients, without other
gastrointestinal symptoms, present with sustained fever and hepatitis.

INTRODUCTION

Typhoid fever affects 17 million people worldwide
every year, with an annual mortality rate of approximately
600 000 [1]. This disease can be transmitted by
contaminated drinking water and food and is associated
with inadequate hygiene and sanitary conditions
[2, 3]. The clinical manifestations of typhoid
fever are protean and most are non-specific, such as
sustained fever with fatigue, headache, or anorexia
[1, 4]. As a result, the disease is easily overlooked
initially and this delayed diagnosis presents a threat to
the public health.

Although typhoid fever is prevalent in developing
countries in South America and Asian countries such
as Indonesia and Vietnam [1, 5, 6], it rarely occurs in
industrialized regions [7, 8]. Travel makes the transmission
of typhoid fever more unpredictable and is
the major cause of acquiring typhoid fever in developed
countries [7, 8]. Furthermore, since 1990, there
have been increasing reports of *Salmonella typhi* isolates
being resistant to most previously useful antibiotics
[9–11].

In Taiwan, typhoid fever has been listed as one of
the 38 notifiable communicable diseases in the
National Surveillance and Report System of the
Centre for Disease Control (CDC) of the Department
of Health since the 1950s. From 1995 to 2002, 40–80
cases of typhoid fever were reported annually to the
CDC in Taiwan. This study analysed the clinical

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manifestations and laboratory findings of 45 patients with typhoid fever who were treated at the National Taiwan University Hospital (NTUH) from 1996 to 2002, including 10 patients involved in an outbreak of typhoid fever in Taipei County in 2002. The high prevalence of hepatitis in patients with typhoid fever was emphasized and microbiological characteristics (including antimicrobial susceptibilities and genotyping) of the isolates from these patients were also examined.

MATERIAL AND METHODS

Patients and bacterial isolates

Yearly trends of confirmed cases of typhoid fever from 1995 to 2002 in Taiwan were evaluated. These data are available on the Taiwan CDC website (http://www.cdc.gov.tw). To understand the clinical features and laboratory characteristics of Taiwanese patients with typhoid fever, 45 patients with typhoid fever who were treated from January 1996 to December 2002 at NTUH, a tertiary-care referral centre with 2000 beds in northern Taiwan, were analysed. In June 2002, an outbreak of typhoid fever occurred involving 12 patients in Taipei County. Ten of these 12 patients were admitted to NTUH. Household members of these patients were asked if they had experienced any symptoms of typhoid fever and their faecal samples and blood specimens were collected for bacterial culture. Data on demographic characteristics, travel history, clinical manifestations, duration of fever before admission, laboratory data and outcome of these patients were recorded. Diarrhoea was defined as watery or loose stool of more than three times per day. Infections were considered indigenous if patients had no history of residence or travel to another country during the 1 month preceding the onset of illness.

A total of 40 isolates *S. typhi* from various clinical specimens (stool and blood) from 40 of the 45 patients treated at NTUH from 1996 to 2002 were preserved for use in this study. These isolates were identified as *S. typhi* by standard biochemical methods and the Phoenix System (Becton Dickinson, Cockeysville, MD, USA).

Aetiology of hepatitis

Sera (paired serum samples collected at an intervals ranging from 2 to 4 weeks) of 10 patients with typhoid fever involved in the outbreak were also studied for the presence of HBsAg, IgM anti-HBc, IgM anti-HAV, hepatitis C virus (HCV) antibody (Abbott Diagnostics Division, Dartford, UK), and RNA of HEV and HCV by reverse transcriptase–PCR (RT–PCR) [12]. Testing for the presence of indirect haemagglutination antibody (IHA) (Cellognost Amoebiasis, Dade Behring, Marburg, Germany) for amoebiasis was also performed.

Antimicrobial susceptibility testing

Minimum inhibitory concentrations (MICs) of 40 isolates to 12 antimicrobial agents were determined by the standard agar dilution method according to the guidelines provided by the National Committee for Clinical Laboratory Standards (NCCLS) [13]. These agents included ampicillin, ceftriaxone, cefotaxime, cefepime, cefpirome, azetreonam, imipenam, ciprofloxacin, levofloxacin, moxifloxacin, trimethoprim–sulphamethoxazole (TMP–SMX), and chloramphenicol. *Salmonella typhimrium* American Type Culture Collection (ATCC 14028) and *Escherichia coli* ATCC 25922 were used as control strains.
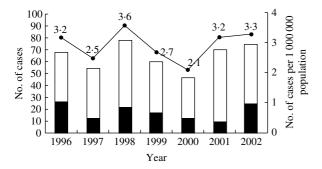
Genotyping

Genotyping of the 40 isolates was performed using pulsotypes generated by pulsed-field gel electrophoresis (PFGE) [14, 15]. The DNA was digested by three restriction enzymes (*Xba*I, *Spe*I and *Bln*I) and the restriction fragments were separated in a CHEF-DRIII unit (Bio-Rad, Hercules, CA, USA) [15].

RESULTS

Disease incidence

The annual case numbers of typhoid fever in Taiwan and the proportion related to foreign travel are shown in Figure 1 [16]. The annual incidence was 2·1–3·6 cases per 1 000 000 population from 1995 to 2002 [16]. The mean number of cases with typhoid fever from 1995 to 2002 was 64 per year and 27% (121/450) were imported. Indonesia, China, and Burma were the leading countries from which typhoid fever cases were imported [16].

Among the 45 patients treated at NTUH, 25 (55·6%) were male. The mean age of the 45 patients was 29·0 years (range 1–77 years). Eighteen (40%)

Fig. 1. Incidence [cases per 1 000 000 population (–●–)] and annual number of imported and indigenous cases (□) of typhoid fever from 1995 to 2000 in Taiwan.

patients acquired *S. typhi* infection imported from Southeast Asian countries (Indonesia 9, China 3, Burma 2, Philippines 1), Africa (Swaziland 1, Senegal 1), and Okinawa (1 patient) and 27 infections were indigenous. Among the 27 patients with domestic typhoid fever, 10 patients were related to an outbreak in Taipei County in 2002 and 17 patients acquired *S. typhi* infections in different parts of Taiwan which were not linked to any known outbreaks.

The mean days of fever before presentation was 10·5 (ranging from 1 to 30 days). Twenty-two (48·9%) patients had diarrhoea before admission. Laboratory data were available for 42 patients. Leukopenia (white blood cell count <4000/mm³) was found in seven patients (16·7%). Initial serum aspartate amino-transferase (AST) was elevated in 36 patients (85·7%) with a mean level of 145·2 U/l (range 25–826 U/l) (reference values <40 U/l). Twenty (47·6%) of these patients had AST levels within one- to threefold of the upper normal limit (40–120 U/l) and 16 (38·0%) had elevated AST values of more than threefold of the upper normal limits. The mean serum alanine aminotransferase (ALT) was 109·9 U/l (reference range 21–425 U/l). The mean ALP was 345·9 U/l (reference range 69–1587 U/l). Abnormal bilirubin (total bilirubin >1·0 mg/ml) was found in three patients (7·1%). Abdominal sonography was per-formed in 22 patients and 13 had abnormal findings. These findings included splenomegaly in five patients, hepatomegaly in three patients, and gall bladder abnormality in five patients including one patient with gallbladder empyema who underwent surgery.

All of these patients received either a β-lactam antibiotic or a fluoroquinolone (ciprofloxacin) and responded well. Abnormal aminotransferase levels returned to the normal range 2–3 weeks after antimicrobial treatment in all patients except for one

with underlying liver disease (biliary atresia). Only two (4·5%) patients had relapse during follow-up.

Antimicrobial susceptibilities

Susceptibilities of 40 *S. typhi* isolates recovered from patients treated from 1996 to 2002 are shown in Table 1. All isolates were susceptible to cephalo-sporins, imipenem, aztreonam and fluoroquinolones. Two isolates (≤5%) were intermediate to ampicillin (MICs, 8 μg/ml) and one of them was also inter-mediate to TMP–SMX (MIC, 4/76 μg/ml) and chloramphenicol (MIC, 16 μg/ml).

Genotypes

Among the 40 isolates of *S. typhi*, a total of 31 PFGE profiles were identified. Ten isolates, which exhibited an identical profile were associated with an outbreak of typhoid fever in 10 patients in Taipei County in 2002.

Investigation of the outbreak in Taipei County

Investigation of the outbreak of typhoid fever started in early June 2002 in Taipei County when a shortage of water supply occurred (Fig. 2). Epidemiological and microbiological investigations conducted by Taiwan CDC were started immediately at the begin-ning of the outbreak. At least 24 (58·5%) of 41 members in seven families (families A–G), all of whom resided in the urban area of the county, were reported to have diarrhoea and/or fever, with date of onset from 5 June to 28 July (Table 2). Patient no. 2 had travelled to Indonesia in January 2002 while the other patients had not travelled abroad during the 1-year period prior to the onset of illness. They shared neither common recreational or social activities nor visited the same grocery stores or restaurants; how-ever, all of these persons used drinking water from the same water supply system.

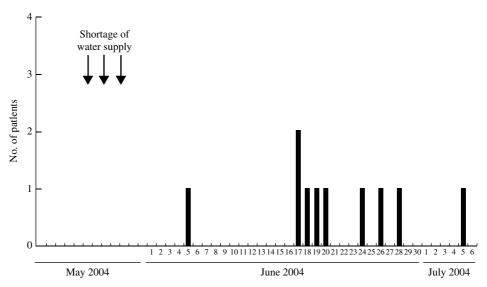Among these 24 patients, 12 had positive cultures for *S. typhi*: 11 from blood and one from a faecal sample. Ten of the 12 patients with laboratory-confirmed typhoid fever were treated at NTUH (Table 2). Two household members each of families B, D and E respectively, had positive cultures of *S. typhi*.

Among the 10 patients hospitalized at NTUH, all had fever (>38 °C), three had headache, and two had

Table 1. *Susceptibility of 40 blood isolates of* S. typhi *recovered from 40 out of 45 patients treated at National Taiwan University Hospital from 1996 to 2002*

Antimicrobial agent	MIC (µg/ml) Range	50%	90%	% of isolates Susceptible	Resistant
Ampicillin	2–16	2	8	95	0
Cefotaxime	≤0·03–0·25	0·06	0·25	100	0
Ceftriaxone	≤0·03–0·12	≤0·03	0·12	100	0
Cefepime	≤0·03–0·12	≤0·03	0·12	100	0
Cefpirome	≤0·03–0·25	≤0·03	0·12	100	0
Aztreonam	0·06–1	0·12	1	100	0
Imipenem	0·06–0·12	0·06	0·12	100	0
Ciprofloxacin	≤0·03	≤0·03	≤0·03	100	0
Levofloxacin	≤0·03	≤0·03	≤0·03	100	0
Moxifloxacin	≤0·03–0·06	≤0·03	≤0·03	100	0
TMP–SMX*	0·5–4	2	2	97	0
Chloramphenicol	4–16	4	8	97	0

* TMP–SMX, trimethoprim–sulphamethoxazole.

Fig. 2. Epidemic curve of an outbreak of typhoid fever involving 10 patients who were treated at National Taiwan University Hospital. Arrows indicate the date (16, 21 and 26 May 2004) of shortage of drinking water supply in the area where the patients resided.

non-productive cough. Five patients had constitutional symptoms such as fatigue and general weakness. Patient no. 5 had transient altered mental status but cerebrospinal fluid study revealed negative findings.

All patients except one (patient no. 2) had no known liver disease prior to admission. Patient no. 2 had pre-existing liver disease (hepatitis B virus-associated liver cirrhosis) with elevated levels of serum AST (range 49–422 U/l). Seven (77·8%) of the nine patients without pre-existing liver disease had elevated levels of serum AST (ranging from 50–422 U/l)

and ALT (ranging from 55–425 U/l) at presentation. Serum studies of the 10 patients for HAV IgM antibody, HBsAg, IgM anti-HBc, Anti-HBs, RNA of HCV and HEV, and IHA for amoebiasis were all negative except for patient no. 1, who had positive HbsAg. Abdominal sonography was performed in six adult patients and revealed thickening of the wall of the ileum with enlarged mesenteric lymph node in three patients and splenomegaly in three patients.

All isolates had an identical antibiotype and were susceptible to ampicillin (MICs, 2 µg/ml), chloro-amphinical (MICs, 4 µg/ml), ceftriaxone (MICs,

Table 2. *Characteristics of 10 patients with typhoid fever involving in an outbreak of typhoid fever in Taipei County, Taiwan, 2002 (presented in chronological order)*

Patient no.	Age (yr)/ sex	Family (no. of members/ no. of members with fever/ no.of members with diarrhoea)	Date of onset of fever	Date of positive culture (blood/ stool)	Duration (days) of diarrhoea (presence of stool occult blood)	WBC (/mm³)	Total bilirubin (mg/dl)	AST/ALT (U/l)	ALP (U/l)	CRP (mg/dl)	Antibiotic treatment (days)
1	38/F	A (5/0/0)	5 June	26 June (−/+)	14 (+)	4580	0·7	198/265	427	1·2	Ceftriaxone (14)
2	53/M	B (8/4/1)	17 June	24 June (+/−)	30 (−)*	3850	0·8	32/34	219	7·0	Ceftriaxone (14)
3	9/M	C (?/?/?)	18 June	25 June (+/−)	7 (+)	7500	n.a.	49/55	n.a.	0·8	Cettriaxone (14)
4	25/F	D (3/2/0)	19 June	1 July (+/−)	14 (−)*	5290	1·1	127/90	284	1·7	Ceftriaxone, Ciprofloxacin (14)
5	77/F	E (5/2/4)	20 June	2 July (+/−)	1 (−)	6680	0·5	50/28	145	8·0	Ciprofloxacin (10)
6	28/M	F (7/1/2)	24 June	7 July (+/−)	5 (+)	5640	0·7	62/81	485	8·7	Ciprofloxacin (10)
7	1/M	E (5/2/4)	26 June	5 July (+/−)	0 (+)	9920	n.a.	116/87	n.a.	5·7	Ceftriaxone (14)
8	38/M	G (8/1/3)	28 June	1 July (+/−)	2 (+)	11010	0·4	422/425	419	8·4	Ceftriaxone (5)
9	1/M	B	5 July	7 July (+/−)	14 (+)*	9880	n.a.	82/59	n.a.	n.a.	Ceftriaxone (5)
10	48/F	D	17 June (28 July)†	29 July (+/−)	0 (+)	3270	0·4	63/53	162	4·4	Ciprofloxacin (10)

WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; CRP, C-reactive protein; n.a., not available.

* Patient nos. 2, 4, and 9 had loose stool for 30, 14, and 14 days respectively.

† Patient no. 10 had fever from June 17 to June 27 and remained afebrile until July 28 when fever occurred again and was admitted.

$\leqslant 0.03\ \mu g/ml$), TMP–SMX (MICs, $0.05–2\ \mu g/ml$), and ciprofloxacin (MICs, $\leqslant 0.03\ \mu g/ml$). The PFGE profiles of the 10 isolates from the 10 patients were identical and belonged to a unique clone.

More than 4500 persons in the county were investigated by Taiwan CDC. Stool samples from symptomatic persons (diarrhoea, fever) and all household contacts of infected persons, and tap water from the homes of the symptomatic persons were studied for enteric pathogens. All faecal and water samples were negative for *S. typhi* or other pathogens (such as *Shigella* spp. or amoeba). The Health Department of Taipei County made public announcements about the need to improve personal hygiene and increased chlorine concentration in the water supply system. During 2 months follow-up, no additional cases were found in Taipei County.

DISCUSSION

In Taiwan, the annual incidence of typhoid fever was more than 10 cases per 1 000 000 population in 1940s [16]. Similar to other countries in the Western Pacific Region (Japan, Hong Kong and Korea), continuous improvement in sanitary conditions in Taiwan have significantly decreased the incidence of this disease [17]. Improvements of sanitation of water supply and sewage disposal systems in Taiwan have lead to a relatively stable incidence of typhoid fever in recent years (2–3 per 1 000 000 population). However, due to frequent international travel of Taiwanese to neighbouring Southeast Asian countries, importation of typhoid fever from these countries is still a crucial problem in Taiwan.

A study of laboratory-based surveillance of typhoid fever in the United States found that 81% of typhoid fever was associated with travel and 19% was domestically acquired [7]. In Taiwan, about 25% of cases of typhoid fever were imported from Southeast Asian countries. India, which is reported to have multidrug-resistant *S. typhi* strains and to be the leading country responsible for the importation of typhoid fever to the United States and the United Kingdom, was rarely the country responsible for typhoid fever importation to Taiwan [7, 8]. India is not a popular holiday destination for Taiwanese.

A high incidence of hepatitis associated with paratyphoid fever has been reported in Taiwan [12]. Hepatic manifestations in patients with typhoid fever were mild and with good prognosis [18], but some patients had sufficient hepatic involvement to mimic a

clinical picture of viral hepatitis, amoebic liver disease, leptospirosis, or rickettsial infection. More than 80% of our patients had abnormal liver function, which was the most common significant laboratory abnormality. Incidence of abnormal liver function in patients with typhoid fever ranged from 25 to 94% of cases [18–22]. Jaundice was reported in 0·5–7·6% of cases [18, 20, 21]. In our series, 38% of patients had AST elevation of more than threefold of the upper normal limit, which mimicked hepatitis while jaundice was rarely found in our patients. In the reported 2002 outbreak in Taipei County, the elevated liver function test was the most common feature occurring in conjunction with sustained fever. Our observations from the outbreak indicate that the combination of fever with hepatitis accelerated the differential diagnosis of typhoid fever before culture results became available and could be important in providing effective and early identification of a possible outbreak for public health officials in non-endemic or low-endemic areas.

The factors predisposing to varying degrees of hepatic injury in typhoid fever were unknown [20–23]. Mixed infection with hepatitis A or hepatitis E, both of which are enterically transmitted diseases, has been reported [24, 25]. Differences in the timing of specimen collection for obtaining biochemistry data may contribute to these variations. Morgenstern et al. [23] found that liver involvement in typhoid fever is constant, occurring during the second and third week of symptoms, and is characterized by a moderate to marked increase in serum alkaline phosphatase and aminotransferases. When patients from an endemic or outbreak area presented acute febrile hepatitis with or without diarrhoea, typhoid fever should be a consideration.

Since 1989, 11 countries have reported epidemics of typhoid fever due to multidrug-resistant S. typhi (resistant to ampicillin, TMP–SMX, and chloramphenicol). [8–11, 26]. Since 1993, strains of S. typhi with decreased susceptibility to ciprofloxacin have been isolated with increasing frequency in Vietnam and other countries [10, 26]. Taiwan has an established high prevalence of antimicrobial drug resistance in organisms such as non-typhoid Salmonella and pneumococcus [15, 27, 28], however, multiple resistance in S. typhi (imported or domestic isolates) is rare [29, 30]. Although one (2·5%) of our isolates was not susceptible to ampicillin, TMP–SMX, and chloramphenicol, all isolates were susceptible to fluoroquinolones and extended-spectrum cephalosporins.

Several molecular typing methods have been applied to S. typhi to evaluate the strain relatedness for epidemiological analysis [14, 31–34]. Previous PFGE-based studies of S. typhi from Southeast Asian countries (including Taiwan) demonstrated that multiple genetic variants of S. typhi isolates associated with sporadic cases and occasional outbreaks are simultaneously present in that area [14, 34]. The high genetic heterogeneity among S. typhi isolates from several Asian countries was also demonstrated by Liu et al. [33] using a multiplex PCR assay on variable-number tandem repeats. Interestingly, few isolates obtained from Malaysia, Indonesia, and Thailand shared the same PFGE profiles indicating that diffusion of these strains within these regions of Southeast Asia did occur [14]. In this study, the PFGE profiles of the isolates from the 2002 outbreak were identical and unique compared to those generated for other isolates from imported or indigenous cases collected from 1996 to 2002. These results imply that this outbreak was caused by a strain of S. typhi, different from those circulating in Taiwan prior to the 2002 outbreak, although the source of this strain was unclear.

In conclusion, Taiwan remains a low-prevalence area for typhoid fever with little evidence for multiple-drug resistance or decreased susceptibility to ciprofloxacin among S. typhi, even though it is a neighbour to highly endemic countries in Southeast Asia and imported cases represent 25% of all reported cases of typhoid fever. Physicians should be alert to the possibility of typhoid fever when patients present with sustained fever and hepatitis even in the absence of other gastrointestinal symptoms, and notify governmental surveillance systems of the need to act to prevent the spread of typhoid fever.

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