

Enteric Fever in a Tertiary Paediatric Hospital: A Retrospective Six-Year Review

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Abstract

Introduction: Enteric fever is a multisystemic infection which largely affects children. This study aimed to analyse the epidemiology, clinical presentation, treatment and outcome of paediatric enteric fever in Singapore. **Materials and Methods:** A retrospective review of children diagnosed with enteric fever in a tertiary paediatric hospital in Singapore was conducted from January 2006 to January 2012. Patients with positive blood cultures for *Salmonella typhi* or *paratyphi* were identified from the microbiology laboratory information system. Data was extracted from their case records. **Results:** Of 50 enteric fever cases, 86% were due to *Salmonella typhi*, with 16.3% being multidrug resistant (MDR) strains. Sixty-two percent of *S. typhi* isolates were of decreased ciprofloxacin susceptibility (DCS). Five cases were both MDR and DCS. The remaining 14% were *Salmonella paratyphi* A. There were only 3 indigenous cases. Ninety-four percent had travelled to typhoid-endemic countries, 70.2% to the Indian subcontinent and the rest to Indonesia and Malaysia. All patients infected with MDR strains had travelled to the Indian subcontinent. Anaemia was a significant finding in children with typhoid, as compared to paratyphoid fever ($P = 0.04$). Although all children were previously well, 14% suffered severe complications including shock, pericardial effusion and enterocolitis. None had typhoid vaccination prior to their travel to developing countries. **Conclusion:** Enteric fever is largely an imported disease in Singapore and has contributed to significant morbidity in children. The use of typhoid vaccine, as well as education on food and water hygiene to children travelling to developing countries, needs to be emphasised.

Ann Acad Med Singapore 2016;45:297-302

Key words: Children, Fever, Paratyphoid, Typhoid

Introduction

Enteric fever refers collectively to typhoid and paratyphoid fever. It is a potentially fatal multisystemic infection caused by bloodstream invasion with the bacteria *Salmonella enterica* serotype *typhi* (*S. typhi*) or *Salmonella enterica* serotype *paratyphi* (*S. paratyphi*).^{1,2}

Transmission occurs via the faecal-oral route through contact with food handled by infected individuals or from ingestion of sewage-contaminated water or shellfish.³ As such, enteric fever is endemic in areas with low socioeconomic indices where sanitary conditions are suboptimal.⁴ Globally, the estimated total number of

enteric fever episodes in 2010 was 13.5 million, with a large majority concentrated in Asia, Africa, Latin America and the Caribbean. The median enteric fever incidence rate per 100,000 was <0.1 in Europe and 0.3 in North America, compared to 394.2 and 724.6 in South Asia and Sub-Saharan Africa, respectively.⁵

Enteric fever is largely a disease affecting the young.^{6,7} The incidence peaks in school-age children aged 5 to 19 years.⁸ The incubation period is typically 8 to 14 days and the illness begins with fever associated with constitutional and abdominal symptoms.⁹ Approximately 20% of patients develop a rash known as "rose spots" due to bacterial emboli

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in the dermis.^{10,11} If left untreated, the disease progresses to involve multiple systems and may even lead to death.^{12,13} Both typhoid and paratyphoid fever share similar clinical features, although paratyphoid fever usually follows a more benign course. Crump et al estimated that without effective treatment, enteric fever had a case fatality rate of 10% to 30%.⁴ This number was reduced to 1% to 4% in those receiving appropriate therapy.

This is a retrospective review of children diagnosed with enteric fever in a tertiary paediatric hospital in Singapore, over a 6-year period from January 2006 to January 2012. The aim of this study was to describe the epidemiology, clinical presentation, treatment and outcome of paediatric enteric fever in Singapore, and thus, review the current standard of care.

Materials and Methods

We conducted a search of our microbiology laboratory information system for positive blood cultures for *S. typhi* or *S. paratyphi* among children less than 17 years of age admitted to our hospital for treatment between 1 January 2006 and 31 January 2012. Data was then extracted from their case records.

Imported cases were defined as those with a travel history to a typhoid-endemic country within the preceding 3 months before the onset of illness. We reported the nationality of the study cases, as a significant proportion of them were found to be foreigners or tourists. Fever was defined as an axillary or tympanic temperature more than or equal to 38°C. The finding of Faget's sign described sphygmothermic dissociation, or fever associated with relative bradycardia.¹⁴

We analysed blood culture, stool culture, and Widal and Weil-Felix serology results in our patients, in addition to relevant haematological and biochemical laboratory parameters. Blood results analysed were those taken on admission to the hospital. In our institution, antibiotic susceptibility testing to ampicillin, sulfamethoxazole/trimethoprim and ceftriaxone was routinely performed for all cases of blood culture-positive enteric fever. Our laboratory has ceased antibiotic susceptibility testing to chloramphenicol. Multidrug resistant (MDR) typhoid fever was defined as infection with a strain of *S. typhi* resistant to both traditional first-line antibiotics of ampicillin and sulfamethoxazole/trimethoprim.^{15,16} Additionally, isolates were screened for decreased ciprofloxacin susceptibility (minimum inhibitory concentration [MIC] ≥ 0.125 mg/L) based on resistance to nalidixic acid.¹⁷

Widal and Weil-Felix serology was interpreted as significant if O and H antigen titres were more than 1/320.^{18,19} Anaemia was defined as a haemoglobin value more than 2 standard deviations (SD) below the mean for the reference

population.²⁰ Normal values for platelets, leucocytes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and liver transaminases were defined based on the standard reference ranges employed by our laboratory.²¹

Outcome was assessed in terms of time to fever defervescence, disease complications, need for intensive care, length of hospital stay and mortality. Time to fever defervescence was defined as the number of days for fever to lyse completely for at least 24 hours, after starting therapeutic doses of culture-sensitive intravenous antibiotics.²²

Statistical analysis was performed using the SPSS statistical software programme, version 20 (IBM Corporation, Armonk, NY, USA). Chi-square and Fisher's exact tests were used for categorical data, while Mann-Whitney U and SPSS independent samples median tests were used for continuous data. *P* values <0.05 were considered statistically significant. This study was approved by the SingHealth Institutional Review Board and approval was obtained for waiver of consent.

Results

A total of 43 cases of typhoid and 7 cases of paratyphoid fever were identified over this 6-year period. All paratyphoid cases involved *S. paratyphi* A. The median age of patients was 7.8 years. Males accounted for 60% of cases. Ninety-four percent of cases were imported. Three cases were indigenous, with all 3 being citizens or permanent residents without any contact history with a known infected person, nor any returning traveller from a typhoid-endemic country (Table 1).

All 50 cases presented with fever, with a median duration of 9.0 days (interquartile range [IQR]: 6.0 to 11.3 days). Table 1 lists the significant clinical findings. There were no cases of typhoid encephalopathy and none had the characteristic rose spots described in classic typhoid fever. Forty-eight percent were tachycardic on arrival to the children's emergency department. Of these, 87.5% had tachycardia in proportion to the degree of fever.²³ Three had tachycardia in association with hypotension, all of whom were infected with *S. typhi*. None of the affected children demonstrated relative bradycardia (Faget's sign).

Of the 43 typhoid fever cases, 14% were infected with MDR strains. Sixty-two percent of isolates tested were found to have decreased ciprofloxacin susceptibility (DCS). Five cases were both MDR and DCS, and these patients were found to have had recent travel to India or Pakistan. While there were no MDR *S. paratyphi* A strains, 60% of isolates tested were DCS. All strains were sensitive to ceftriaxone (Table 2).

Anaemia was present in the majority (74%) of children, with a median lowest haemoglobin level of 11.1 g/dL.

Table 1. Population Characteristics and Clinical Signs at Presentation

	Enteric Fever (n = 50)
Age in years	
Median	7.8
Interquartile range	(5.1 – 11.5)
Males, n (%)	30 (60.0)
Nationality, n (%)	
Singaporean	29 (58.0)
Indian	10 (20.0)
Indonesian	7 (14.0)
Bangladeshi	2 (4.0)
Nepalese	1 (2.0)
Pakistani	1 (2.0)
Positive travel history, n (%)	47 (94.0)
Country of travel	
India	29 (61.6)
Indonesia	13 (27.7)
Bangladesh	2 (4.1)
Nepal	1 (2.2)
Pakistan	1 (2.2)
Malaysia	1 (2.2)
Symptoms	
Headache	10 (20.0)
Lethargy	8 (16.0)
Anorexia/weight loss	18 (36.0)
Myalgia	4 (8.0)
Abdominal pain or discomfort	27 (54.0)
Vomiting	29 (58.0)
Diarrhoea	32 (64.0)
Constipation	2 (4.0)
Signs	
Tachycardia	24 (48.0)
Hypotension	3 (6.0)
Abdominal distension	6 (12.0)
Abdominal tenderness	20 (40.0)
Hepatomegaly	16 (32.0)
Splenomegaly	2 (4.0)

Patients with typhoid fever had lower haemoglobin levels than those with paratyphoid fever ($P = 0.04$). However, thrombocytopenia and leucopenia occurred in only 10% and 14% of patients, respectively, of which all were typhoid fever (Table 3). Although full blood count readings were done on all 50 patients, not all had inflammatory markers or liver function tests. Among the patients who did have values for ESR and CRP, all were raised, with median highest readings of 45 mm/hr (IQR: 21.5 to 70 mm/hr) and

Table 2. Antibiotic Resistance and Other Investigations for Enteric Fever

	<i>S. typhi</i> (n = 43)	<i>S. paratyphi A</i> (n = 7)
Antibiotic resistance, n (%)		
Ampicillin	6 (14.0)	0
Sulfamethoxazole/trimethoprim	7 (16.3)	0
Ceftriaxone	0	0
MDR*	6 (14.0)	0
DCS†	18/29 (62.1)	3/5 (60.0)
MDR and DCS	5/29 (17.2)	0
Stool culture‡, n	43	7
Positive, n (%)	18 (41.9)	0
Serological (Widal and Weil-Felix test), n	37	6
Significant titres, n (%)		
O antigen titre >1/320	21 (48.8)	2 (28.6)
H antigen titre >1/320	31 (72.1)	5 (71.4)

DCS: Decreased ciprofloxacin susceptibility; MDR: Multi-drug resistant

*Ampicillin and sulfamethoxazole/trimethoprim resistance.

†Minimum inhibitory concentration (MIC) ≥ 0.125 mg/L.

‡Results for stool cultures taken before initiation of antibiotic treatment.

94.8 mg/L (IQR: 53.4 to 173.8 mg/L) respectively. Raised liver transaminases were a feature in the majority (69.7%) of patients, with median highest alanine transaminase levels at 71.5 U/L (IQR: 40.3 to 100.8 U/L) and median highest aspartate transaminase levels at 85.5 U/L (IQR: 54.6 to 127.3 U/L).

All study cases received intravenous (IV) ceftriaxone once culture results were confirmed, at a median duration of 7 days (IQR: 5 to 10 days). The dosages of IV ceftriaxone ranged from 50 to 100 mg/kg/day. This was followed by a course of oral antibiotics, of which 82.5% were prescribed sulfamethoxazole/trimethoprim at dosages of between 8 to 12 mg/kg/day (trimethoprim) in 2 divided doses. The rest received azithromycin at 10 mg/kg/day (10%), cefibuten at 10 mg/kg/day (7.5%), amoxicillin at 50 mg/kg/day (2.5%) or cefuroxime at 30 mg/kg/day (2.5%). The median duration of total antibiotics received (IV and oral) was 14 days (IQR: 14 to 16 days).

The median value for time to fever defervescence from initiation of appropriate antibiotic treatment was 5 days (IQR: 3 to 7 days). We observed that the time to fever defervescence did not differ significantly among children with typhoid or paratyphoid fever.

Depending on the clinical presentation and progress, some patients underwent imaging studies during their hospital stay. About half (48%) had ultrasound scans of the abdomen performed, while 8 (16%) underwent computed tomography (CT) scans of the abdomen. Indications for performing

Table 3. Haematological Parameters and Outcomes of Enteric Fever

	<i>S. typhi</i> (n = 43)	<i>S. paratyphi A</i> (n = 7)	P Value
Haematological indices			
Anaemia: n, %	34 (79.1)	3 (42.9)	0.04
Lowest Hb (g/dL): median (IQR)	10.7 (10.0 – 12.0)	12.7 (12.0 – 13.7)	0.004
Thrombocytopenia: n, %	5 (11.6)	-	-
Leucopaenia: n, %	7 (16.3)	-	-
Leucocytosis: n, %	2 (4.7)	-	-
Duration of treatment (days)	14	17	0.796
Median, IQR	(14 – 15)	(10 – 20)	
Time to fever defervescence (days)	5	5	0.642
Median, IQR	(3 – 7)	(3 – 5)	
Length of hospital stay (days)	8	10	0.516
Median, IQR	(7 – 9)	(6 – 11)	
Complicated cases (n)	6	1	0.895
Complications			
Ascites	3	1	
Enterocolitis	2	1	
Haemodynamic shock*	2	-	
Pleural/pericardial effusion	2	-	
Ileus	1	-	
Pyelonephritis	1	-	
Relapse (n)	1	0	0.655

IQR: Interquartile range; *S.*: *Salmonella enterica*

*Acute circulatory failure with hypotension.

the above studies included significant abdominal pain or distension, persistent fever, and uncertainty regarding the initial clinical diagnosis. Of the 7 patients with complications, only 1 was infected with paratyphoid fever. Table 3 lists the significant complications noted. The finding of pleural effusion was detected on abdominal ultrasound, while the pericardial effusion was seen on a 2-dimensional (2D) echocardiogram. Both did not require drainage. Urine culture performed for the child with pyelonephritis did not yield significant growth.

Repeat blood cultures to document clearance of infection were not routinely done. Criteria for discharge were mainly resolution of fever and stable clinical status. The median duration of hospital stay was 8 days (IQR: 7 to 10 days). In our study, there was no significant difference between the duration of hospital stay for typhoid versus paratyphoid fever.

Discharged patients were planned for follow-up in the outpatient clinic for a period of between 3 to 6 months. However, only 14% returned for follow-up. One child infected with a drug-susceptible strain of *S. typhi* was re-admitted for a relapse despite being discharged on resolution of initial fever. He had completed 5 days of IV ceftriaxone at a dose of 100 mg/kg/day followed by 7

days of oral sulfamethoxazole/trimethoprim at a dose of 8 mg/kg/day (trimethoprim). He presented to the children's emergency department a month later in view of recurrent fever. A repeat blood culture yielded *S. typhi* with the same sensitivity as previously documented. Abdominal ultrasound showed mild hepatosplenomegaly; no further work-up was done as he was otherwise well. He received an additional 7 days of IV ceftriaxone at 100 mg/kg/day followed by 7 days of oral sulfamethoxazole/trimethoprim at 8 mg/kg/day (trimethoprim). In this case, there was documented clearance on repeat blood and stool cultures after the relapse.

None of the children required intensive care and there were no cases of mortality from enteric fever in our study. On examination of their immunisation records, none were vaccinated against typhoid fever.

Discussion

Although enteric fever is more common in children, few studies focusing on the paediatric population have been done in Singapore. Singapore is a developed city-state where enteric fever is non-endemic. It is however, located in Southeast Asia, where enteric fever rates are among

the highest in the world.²⁴ A previous epidemiological study of enteric fever in Singapore by Ty et al (1990 to 2009) reported the incidence of indigenous enteric fever in Singapore as 0.26 per 100,000 in 2009.^{25,26} This was comparable to that of Europe and North America. However, the disease burden was still significant as more than 90% of cases were imported.

In our study, we found that 94% of paediatric enteric fever cases were imported, mainly from India and Indonesia. Only 3 cases did not have any significant travel or contact history. These results are comparable to the findings by Ty et al, whereby the majority of cases were imported from India and Indonesia. A separate study of 121 patients in Singapore infected with *S. typhi* demonstrated that 17.4% were MDR strains.²⁷ The study reported that all patients from whom these strains were isolated had a history of recent travel to the Indian subcontinent. In our study, MDR *S. typhi* was detected in 14% of paediatric patients. Interestingly, all these patients had also recently travelled to India, Bangladesh or Pakistan. This echoes the conclusion that MDR typhoid fever in Singapore is mainly imported from countries in the Indian subcontinent.

Until the mid-1980s, ampicillin, chloramphenicol or sulfamethoxazole/trimethoprim was the standard treatment for enteric fever.²⁸ Due to the emergence of MDR strains, ciprofloxacin was recommended as an alternative antibiotic in 1990.^{29,30} However, nalidixic acid-resistant strains with DCS started to emerge in the literature in 1992, and these were found to be associated with treatment failure.^{31,32} In our study, DCS was observed in a majority of *S. typhi* isolates tested; however, all strains were sensitive to ceftriaxone.

In our institution, the recommended first-line empirical antibiotic for suspected enteric fever is IV ceftriaxone at a dose of 80 to 100 mg/kg/day. A similar regimen of initial IV ceftriaxone therapy followed by oral therapy once there is adequate clinical response is also recommended by the Department of Health and Human Services of Victoria, Australia.³³ Although this is a recommendation for the adult population, we have adapted it for use in our institution. To date, this has been our practice for years and our study has demonstrated only 1 case of relapse (2%) in this 6-year period.

In terms of clinical presentation, persistent fever was a feature in all our paediatric cases despite some patients having been pretreated with oral antibiotics from primary care physicians. Abdominal symptoms and signs were also seen in 92% of patients. Thus, enteric fever should be considered as a differential diagnosis in children with unexplained or prolonged fever, in association with any abdominal complaints, especially in the presence of positive travel history.

Typical haematological and biochemical manifestations reported in enteric fever include pancytopenia, raised acute inflammatory markers^{34,35} and raised liver transaminases.³⁶ Our study has demonstrated that anaemia is a significant feature of paediatric enteric fever, particularly in cases of *S. typhi* infection. In addition, raised inflammatory markers were seen in all patients who had these tests done. The majority had isolated raised liver transaminases as well. Although non-specific, when analysed as a whole together with the relevant clinical presentation, these findings may aid in a decision to treat empirically for enteric fever while awaiting confirmatory cultures.

Despite inpatient treatment with appropriate antibiotics at recommended doses, our study has shown that morbidity is substantial as significant complications arose among the affected paediatric population. Thus, it is important that primary disease prevention in the form of immunisation is emphasised. In our analysis, none of the 47 affected patients who travelled to typhoid-endemic countries received immunisation against typhoid fever.³⁷ This occurred despite the World Health Organisation (WHO) specifically recommending typhoid fever vaccination for those travelling to destinations where the risk of typhoid fever is high.³⁸ Of the 2 typhoid vaccines with demonstrated safety and efficacy available on the market, the injectable vaccine is licensed for individuals aged above 2 years, with a protective efficacy 1.5 years after vaccination of about 72%.

A review of 580 cases of vaccine-preventable diseases among returned international travellers by the GeoSentinel Surveillance Network (1997 to 2007) reported that confirmed or probable enteric fever was the most common disease acquired.³⁹ Yet immunisation against typhoid disease was not routinely practised for individuals who travelled to typhoid-endemic countries. These findings are likely contributed by the fact that a significant number of travellers may have been visiting friends and/or relatives in these countries which they consider to be their home, and would not have visited travel clinics. Therefore, while primary prevention in the form of typhoid vaccination for travellers to typhoid-endemic countries needs to be strongly emphasised,⁴⁰ education on food and water hygiene should not be neglected.

To date, this is the first study on paediatric enteric fever in Singapore. Our study was purely observational in nature, and one limitation was that we only included patients with blood culture positivity in our analysis, potentially missing culture negative cases treated for possible enteric fever.

Conclusion

Although Singapore has low rates of indigenous enteric fever, additional imported cases contributed to an average of

10 cases of paediatric enteric fever per year in our hospital. Through advocating for routine vaccination of children above 2 years prior to travel to typhoid-endemic areas as well as emphasising on the education of food and water hygiene, we hope to reduce the prevalence of imported enteric fever in Singapore.

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