MULTIDRUG-RESISTANT TYPHOID FEVER IN SINGAPORE

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ABSTRACT

A study was conducted to determine the clinical and epidemiological characteristics of multidrug-resistant (MDR) typhoid fever in Singapore. Twenty-one of 121 patients with typhoid fever had MDR typhoid fever after recent travel to the Indian subcontinent. Fifty patients with drug susceptible typhoid fever were also analysed for comparison. Nineteen of the MDR S. typhi isolates had resistance to ampicillin, chloramphenicol and trimethoprim – sulphamethoxazole (TMP-SMX) while the remainder had resistance to ampicillin and TMP-SMX. The predominant presenting symptoms were fever and diarrhoea. Eleven patients with MDR typhoid fever were treated with oral ciprofloxacin and nine with intravenous ceftriaxone. The patients with MDR typhoid fever had a longer duration of fever defervescence (8 ±5 days) compared to those with drug-susceptible typhoid fever (5.7 ±4.16 days) ($p < 0.01$). Eighteen patients were cured and one patient defaulted treatment. Two patients relapsed within two months of treatment. The study showed that 17.4% of patients with typhoid fever had imported MDR S. typhi after recent travel to the Indian subcontinent where MDR typhoid fever is prevalent.

Keywords: *multi-drug resistant typhoid, travel*

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INTRODUCTION

Most recent cases of typhoid fever in developed countries are related to international travel or contacts[1]. Typhoid fever, however, remains prevalent in developing countries[2].

The emergence of drug resistance in typhoid fever has been of major concern in recent years. Since 1989, multidrug-resistant *Salmonella typhi* have been reported in India[3-5], Pakistan[6], and China[7]. These strains are resistant to chloramphenicol, ampicillin and trimethoprim-sulphamethoxazole (TMP-SMZ).

In Singapore, there are 110 to 190 cases of typhoid fever annually. More than half of typhoid fever cases reported during the period 1982-1991 were imported from the Indian subcontinent and Southeast Asia[8]. Until recently, multidrug-resistant (MDR) *Salmonella typhi* was uncommon in Singapore.

The objective of our study was to determine the clinical and epidemiological characteristics of MDR typhoid fever in Singapore.

MATERIALS AND METHODS

Communicable Disease Centre (CDC) is a 130-bed tertiary referral centre. For this study, we retrospectively analysed the medical records of all culture-proven multidrug-resistant typhoid fever admitted to the CDC between 1 November 1990 and 30 June 1992. The patients were located from a database kept by the outpatient clinic and a computerised medical records system. Fifty patients, with culture-proven drug-susceptible typhoid fever, were randomly selected for analysis.

The medical records were analysed for mode of presentation, travel history, clinical features, treatment and outcome. Time to fever defervescence was defined as the interval from initiation of appropriate antibiotic therapy until the documentation of normal body temperature for more than 24 hours. The outcomes were divided into cure and relapse. An infection was considered cured if clinical signs and symptoms resolved, blood cultures became negative and the patient remained well during follow-up. A patient was considered to have relapsed if, after an appropriate clinical and bacteriologic response (the latter being a negative blood culture), fever or other clinical signs of infection recurred in association with a blood culture positive for the same organism within two months of completion of treatment.

The patients were generally followed up for 3 months post-treatment in order to detect faecal carrier state. All strains of *Salmonella typhi* isolated from patients in CDC were routinely phage typed.

Significance testing between groups was done where applicable with Fisher's exact test.

RESULTS

A total of 121 patients with culture-proven typhoid fever were admitted to CDC during the 20-month study period. Twenty-one patients (17.4%) had MDR typhoid fever. Fifty patients with drug-susceptible typhoid fever were also analysed.

The two groups were comparable with respect to age and sex (Table I). All the patients with MDR typhoid fever were of Indian ethnic origin.

Table I – Population characteristics

Characteristic	MDR typhoid fever (n = 21)	Drug-susceptible typhoid fever (n = 50)
Age in years: mean ± SD	27 ± 13	27 ± 10
Sex : M:F	12:9	32:18
Race: Chinese	–	18 (36%)
Indian	21 (100%)	14 (28%)
Malay	–	13 (26%)
Others	–	5 (10%)

The mode of presentation was analysed in the 21 patients with MDR typhoid fever. The mean duration of fever at

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presentation was 11.0 ± 5.7 days. Two patients had underlying medical conditions, one had discoid lupus erythematosus and another had epilepsy. A history of contact was sought in all cases and was found in only 4. Three patients were part of a family consisting of parents and a child who had recently travelled to India. Four patients had received antibiotics in the 4 weeks prior to presentation (19%). None of the patients had received prior typhoid vaccination.

Travel to the Indian subcontinent (India and Bangladesh) accounted for all of the cases of MDR typhoid fever and 33.3% of drug-susceptible typhoid fever (Table II). Sixteen percent (8 of 50) of the drug-susceptible typhoid fever were domestically acquired.

Table II – Major sources of travel-associated typhoid fever

Country	No. of patients (%)	
	MDR typhoid fever (n = 21)	Drug-susceptible typhoid fever (n = 50)
Bangladesh	1 (4.8%)	–
India	20* (95.2%)	14 (28%)
Indonesia	–	20 (40%)
Malaysia	–	4 (8%)
Philippines	–	2 (4%)
Thailand	–	2 (4%)

*This number included:
i) 3 tourists from India visiting Singapore
ii) 2 foreign workers from India
iii) 15 local residents who visited India

Table III shows the clinical features of the patients with MDR typhoid fever at presentation. The predominant symptoms were fever (100%) and diarrhoea (71%). Hepatomegaly was detected in 10 (48%) and splenomegaly in 7 patients (33%). At presentation, only one patient was leucopenic and 3 were thrombocytopenic.

Table III – Clinical and laboratory findings at presentation in patients with MDR typhoid fever

Feature		No. of patients (%)
I Clinical		
Symptoms:	Fever	21 (100)
	Diarrhoea	15 (71)
	Chills	14 (67)
	Vomiting	9 (43)
	Abdominal pain	7 (33)
	Headache	6 (29)
	Cough	3 (14)
	Constipation	1 (4.8)
Signs:	Hepatomegaly	10 (48)
	Splenomegaly	7 (33)
	Rose spots	3 (14)
	Jaundice	2 (9.5)
II Laboratory		
Leucopenia (<4000 WBC/mm³)		1 (4.8)
Thrombocytopenia (<100,000 platelets/mm³)		3 (14)
Alanine aminotransferase level (>50 IU/ml)		9 (43)

In all cases, blood and stool cultures were obtained at admission. The organism was isolated from the blood of 20 patients (95%) with MDR typhoid fever and 50 patients (100%) of the drug-susceptible group (Table IV). A single Widal's agglutination test was performed in 16 patients with MDR typhoid fever and 38 patients with drug-susceptible typhoid fever. The test was positive (O antigen titre more than 1:160) in 6 instances in MDR typhoid group and 20 instances in drug-susceptible group. Vi-phage typing was also performed on 17 MDR *Salmonella typhi* strains isolated (Table V). Thirteen of the strains belonged to Vi-phage type E_1. An unusual Vi-phage type E_3 was detected in one isolate.

Table IV – Laboratory methods of diagnosis in patients with the MDR typhoid and drug-susceptible typhoid fever

Method of diagnosis	No. of isolates	
	MDR (n = 21)	Drug-susceptible (n = 50)
Blood culture	20	50
Stool culture	3	3
Serological (Widal test)		
O antigen titre > 1:160	6/16 (37.5%)	20/38 (52.6%)
H antigen titre > 1:320	13/16 (81.3%)	26/38 (68.4%)

Table V – Vi phage types of MDR *Salmonella typhi* isolated

Phage types	No. of patients
E_1	13
E_3	1
UVS 1	2
UVS 4	1
Total	17

Nineteen of the 21 MDR *S. typhi* isolates were resistant to ampicillin, TMP-SMX and chloramphenicol and the remainder 2 isolates were resistant to both ampicillin and TMP-SMX.

Table VI compares patients infected by MDR strains with drug-susceptible strains in terms of treatment and outcome. Of the patients with MDR typhoid fever, 11 received oral ciprofloxacin and 10 received iv ceftriaxone. Twenty patients were cured (95%). One patient had absconded on the third day of ciprofloxacin therapy and was, therefore, lost to follow-up.

Table VI – Differences in treatment and outcome of typhoid fever caused by MDR and drug-susceptible strains of *Salmonella typhi*

	MDR	Drug-susceptible	P value
Follow up reported	20 patients	49 patients	
Antibiotic therapy:			
IV ampicillin	–	5	
Oral chloramphenicol	–	6	
Oral ciprofloxacin	11	15	
Oral pefloxacin	–	1	
IV ceftriaxone	10	23	
Mean duration (days) of antibiotic therapy	10	8.7	
Number of days to fever defervescence : Mean ± SD	8 ± 5	5.7 ± 4.16	>0.01
Cure	18	46	NS
Relapse	2	3	
Complications: Gastro-intestinal bleeding	1	1	

NS: Not significant

The mean duration of antibiotic treatment was 10 days and the mean time to fever defervescence was 8 ± 5 days. Two relapses occurred, one treated with ciprofloxacin and the other with ceftriaxone, 4 and 8 weeks respectively after completion of treatment. Repeat blood cultures yielded *S. typhi* with similar sensitivity patterns and Vi-phage type as in the primary illness.

Of the 50 patients with drug-susceptible typhoid fever, 39 were given second-line drugs from the time that typhoid was first suspected clinically. The agents used were ampicillin (5 patients), chloramphenicol (6 patients), ciprofloxacin (15 patients), pefloxacin (one patient) and ceftriaxone (10 patients). One patient was discharged against medical advice on day 7 of ceftriaxone therapy and was lost to follow-up. The mean time to fever defervescence was 5.7 ± 4.16 days. Three patients relapsed 5 to 7 weeks after completion of treatment. Repeat blood cultures yielded sensitive *S. typhi* strains.

Only 2 patients developed complications in the form of gastrointestinal bleeding (one from each group).

DISCUSSION

Until recently, multidrug-resistant *Salmonella typhi* was uncommon in Singapore. In our study, 21 of 121 (17.4%) patients with typhoid fever had MDR *Salmonella typhi* isolated. It is particularly relevant that all patients from whom such strains were isolated had a history of recent travel to the Indian subcontinent.

Numerous factors are responsible for the emergence of MDR *Salmonella* strains, namely administration of antibiotic therapy to farm animals and antibiotic treatment of animals and humans with *Salmonella* gastroenteritis[9]. In our study, only 4 patients had received antibiotics before presentation. Bhutta et al, on the other hand, found that the majority of their patients had received at least one antibiotic before presentation[6].

The predominant presenting symptoms in our patients were fever (100%) and diarrhoea (71%). The frequency of occurrence of diarrhoea is higher than the 37% – 57% reported from Aberdeen[10] and Florida[11]. Bhutta et al (1991) reported a fairly high incidence of diarrhoea among children (less than 2 years of age) with MDR typhoid[6].

The fairly high incidences of hepatomegaly and splenomegaly with elevation of alanine aminotransferase levels in liver function among our MDR typhoid cases probably reflect greater persistence and proliferation of salmonella in the reticuloendothelial system.

Haemotologic investigations were not helpful in suggesting a diagnosis of typhoid fever. Results of the Widal's test appear to be of limited value in the diagnosis of typhoid fever. The 0 agglutination titre of 1:160 was chosen as a cut-off limit between typhoid and non-typhoid patients[12]. Pang et al (1983) had also reported on the limitations of Widal's test in the rapid diagnosis of typhoid[13]. Of the 17 strains of *S. typhi* examined, 13 belonged to the Vi-phage type E_1. This result concurs with the common phage type found in India[14].

Traditional treatment of typhoid fever is with primary antibiotics such as chloramphenicol, ampicillin and trimethoprim-sulphamethoxazole. Resistance to all three antibiotics have been reported from the Indian sub-continent. Third generation cephalosporins and quinolones have emerged as effective agents in the treatment of multidrug-resistant typhoid fever [15,16]. In our study, the patients with MDR typhoid fever received either oral ciprofloxacin or IV ceftriaxone with a 95% cure rate.

The advantages of the quinolones are that they can be administered orally, penetrate into macrophages (the site of salmonella replication) and have a low risk of plasmid-mediated resistance. Additional advantages are the low relapse rate and low carriage rate following clinical cure of typhoid fever.

The patients with MDR typhoid fever had a longer duration of fever defervescence (8 ± 5 days) compared to those with drug-susceptible typhoid fever (5.7 ± 4.16 days) ($p < 0.01$). The persistence of fever in most patients may be maintained by the release of pyrogenic cytokines from macrophages and necrotic tissue[17].

In conclusion, MDR typhoid fever in Singapore is largely imported, occurring in patients who had recently travelled to the Indian subcontinent. In comparison with drug-susceptible typhoid fever, it appears to be a more severe illness with a longer duration of fever. Our limited experience indicates that ciprofloxacin and ceftriaxone seem to be effective agents in the treatment of MDR typhoid fever.

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