Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage:www.elsevier.com/locate/apjtm

Document heading

Relapse typhoid fever in North-eastern state in Malaysia

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ARTICLE INFO

Article history:
Received 9 July 2009
Received in revised form 7 August 2009
Accepted 10 October 2009
Available online 20 January 2010

Keywords:
Recurrence
Typhoid fever
Salmonella Typhi
Malaysia

ABSTRACT

Objective: To discuss the prevalence, clinical and laboratory presentations of relapse typhoid fever. **Methods**: All relapse cases were reviewed to identify the clinical and laboratory presentation of the relapse typhoid fever. **Results**: Two hundred and forty six patients were admitted to a teaching tertiary hospital in North-eastern state of Malaysia and fourteen (5.69%) relapse cases were identified. The duration of relapse after the patient was discharged was (25.0±9.9) d. The patients presented with fever, diarrhoea, headache, abdominal pain and constipation. The duration of fever before admission in the initial episode [(8.6±4.2) d] was significantly longer than the relapse episode [(5.0±2.5) d] (P=0.019). Four patients have hepatomegaly in initial episode and ten in relapse episode (P=0.852). The defervescence days of initial episodes was (3.2±2.2) d, comparing to relapse episode [(2.0±1.8) d] which was statistically not significant (P=0.124). **Conclusion**: Assumption of the relapse typhoid fever is milder comparing to original episodes based on observation and is not supported by statistical analysis.

1. Introduction

Typhoid fever is a systemic disease caused by *Salmonella enterica* serotype *Typhi* (*Salmonella typhi*). This fever is an important public health problem in many underdeveloped and developing countries. It is endemic in Malaysia, and periodically gives rise to outbreaks. The annual incidence in Malaysia is 10.2 to 17.9 per 100 000 population [1].

The most common clinical manifestations seen in typhoid patients are prolonged fevers and headaches, followed by abdominal pain and diarrhea. Other associated symptoms less commonly reported are a non-productive cough, constipation, meningismus, deafness, confusion, and weight loss. Death from typhoid fever has been independently associated with seizures, intestinal perforation, pneumonia, delirium, and coma [2].

With early and appropriate antibiotic therapy, the case-fatality-rate for typhoid is less than 1%. Relapse of typhoid fever might occur in 5-10% of cases. Most of the relapse cases occurred after 2-3 weeks of resolution of initial fever and more often following antibiotic treatment. The clinical severity of relapse episode is much lower [3, 4]. Unfortunately, the relapse cases were not regularly studied and reported. The incidence is unknown at most of the endemic area and data on relapse typhoid fever are limited especially in term of clinical presentation and laboratory findings.

2. Materials and methods

Two hundred and forty six patients were admitted to Hospital Universiti Sains Malaysia that located at North-eastern part of Malaysia in an outbreak in 2005 and fourteen (5.69%) relapse cases were identified. A review of all relapse cases was done to identify the clinical and laboratory presentation. Relapse typhoid fever was defined as the reccurrence of typhoid fever after clinical resolution or culture-negative of the initial episode of typhoid fever. The sensitivity pattern of initial episodes and relapse episodes should exclude reinfection. No molecular typing was done in this study.

All blood samples were inoculated into Bactec® blood culture system (Becton Dickinson, UK). If the inoculation showed any growth by automated detection system, Gram stain, primary sensitivity test and subculture onto blood agar, chocolate blood agar and McConkey agar were done. Stool cultures were inoculated onto MacConkey agar and deoxycholate agar. *Salmonella enterica* serotype *Typhi* (*Salmonella typhi*) was identified by biochemical reaction, API 20 E system (bioMerieux, US) and serotyping

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(Remel Europe Ltd., England). The sensitivity test was done according to the Clinical and Laboratory Standards Institutes (CLSI) protocol using Kirby-Bauer disc diffusion method.

IgM rapid test was done using TYPHIrapid™ (MBDr, Malaysia) and TYPHIdot™ (MBDr, Malaysia). TYPHIrapid™ is an extension of TYPHIdot™ which already well evaluated[5, 6]. These methods were based on the recombinant protein produced from the gene sequence of the 50 kD OMP.

3. Results

Twelve cases of relapse were diagnosed by a positive blood culture for *Salmonella* typhi. Two cases were diagnosed clinically and supported by serological marker (Table 1). *Salmonella* typhi isolated from blood culture, both initial and relapse, were sensitive to all tested antibiotics including ceftriaxone and ciproflaxacin.

The youngest patient was four year-old and the eldest was sixty year-old. The duration of relapse after the patient was discharged was (25.0±9.9) d. All patients presented with fever in first episode and relapse episode. Other clinical presentations were diarrhea (64.3% in initial episode and 50.0% in relapse episode), headache (28.6% and 14.3%), abdominal pain (28.6% and 7.1%), and constipation (7.1% and 21.4%). In initial episode, seven patients presented with more than two complaints where as only three patients presented with more than two complaints in relapse episode (P=0.115).

In initial episode, the patients have shorter hospitalization [(7.29±1.98) d] compared to relapse episode [(8.29±1.90) d] but without statistically significant difference (P=0.152). The total white count (TWC) was almost similar between the initial episode and the relapse episode, which was (6.15 ±2.36)×10^3/μL and (6.28±1.85)×10^3/μL, respectively (P=0.867). The haemoglobin (Hb) of initial episode was (12.22±1.45) g/dL and of relapse episode was (11.73±1.63) g/dL (P=0.413). The platelet count is (179±120)×10^3/μL for initial episode and (236±89)×10^3/μL for relapse episode (P=0.164). Four patients have hepatomegaly in initial episode and ten in relapse episode but the difference was not statistically significant (P=0.852).

The defervescence days of initial episodes was (3.2± 2.2) d compared to relapse episode [(2.0±1.8) d] without statistically significant difference(P=0.124). The duration of fever before admission in the initial episode was (8.6±4.2) d and relapse episode was (5.0±2.5) d (P=0.019).

In initial episodes, thirteen cases were treated with ceftriaxone and one case was treated with ciprofloxacin. As in usual practice, the short duration of therapy for typhoid fever was used. The duration for ceftriaxone therapy was continued until five days fever subside whereas for ciprofloxacin the total seven days therapy [7, 8].

The antibody test (IgM to 50 kDa protein) was negative in five patients in both initial and relapse episodes (Patient 6, 7, 9, 11 and 14). Another three patients have positive in initial episodes but later negative in relapse episodes.

No patient in either initial or relapse episode need intensive care management during the admission or any time during the illness. No complication documented during the initial or relapse episode. All patients were screened for *Salmonella typhi* in stool specimen before discharge and found negative.

4. Discussion

The occurrence of relapse typhoid fever in this study is similar with previous report that relapse typhoid fever occurs in 5-10% of cases. The relapse episode is milder and less severe than original attack[3, 4]. Only one case of leukopenia (TWC<3×10^9/mm^3) was identified. All cases in this report failed to demonstrate an elevated WBC during their illness. This is consistent with previous report that reported in 95% of cases the TWC was in normal range or leukopenia[2]. The risk factor of relapse was not evaluated in this series.

The patients had longer period of fever in initial episode comparing to relapse episode. It is probably due to the thorough investigation and more careful management the relapse episode comparing to initial episode. The patients were also admitted to hospital longer in relapse episode comparing to initial episode. This was due to longer duration of antibiotics used in treatment of relapse attack comparing to original attack and more careful management as discharging.

The choice and duration of antibiotics therapy remain controversial. A report in 1992 had shown that 7-day ciproflaxacin is a good drug to treat typhoid fever with a mean of 3-21 days defervescence time with no relapse[8]. But later study have shown that it is associated with high treatment failure rate (17.4% microbiological failure rate) and longer defervescence time (12.4 days mean)[9].

An earlier study in Egypt showed that five-day course of ceftriaxone is associated with lower relapse rate (95% cure rate) and earlier defervescence time (3.9 days mean) [10]. There was a report of one patient failed to respond to ceftrioxone in the neighbour country, Singapore[11]. The newer study suggested that 14-day cefriaxone therapy can reduce the relapse rate of multidrug resistant typhoid[12]. Flexible duration of ceftriaxone is said to be comparable with traditional chloramphenicol therapy[7]. The controversial antibiotic regime showed the need of local clinical trial and treatment protocol.

The phenomenon of relapse could result from recrudescence of bacteria that lie quiescent within host tissues, reinfection with the same strain, or infection with a different strain. Although simple methods, such as comparison of antibiotic sensitivity patterns, may give some clues to the identities of the organisms, the organisms are not always susceptible to antibiotics [13].

In this study, five patients (35.7%) had not developed antibody (IgM) at any time during the course of infection. Previous studies had shown that the sensitivity of the test was 90.3-93.1%[5, 6]. The low sensitivity in this study probably due to no significant IgM response was stimulated by the infection at any time. Prompt reinfection with *Salmonella typhi* and other immunomodulating factors such as the presence of concomitant illness and nutritional status may alter the magnitude and timing of the IgM response [6]. This finding also suggested that some portions of the population are at risk of relapse because they are unable to develop the specific antibody and deserves further study to confirm.

The limitations of this review include the retrospective study design and a small case review. Thus, the study was subject to recording bias and selection bias. Molecular genotyping such as Pulse Field Gel Electrophoresis is also recommended in this kind of review to ascertain that all of the patients are actually having relapse typhoid fever in

Table 1

Case summaries of relapse typhoid fever in Hospital Universiti Sains Malaysia.

Case No.	Age Years	Relapse days after discharge	Admission day*	Clinical Presentation*		Days of fever*	Defervesence days*	Hb* (g/dL)	TWC* ($\times 10^3$/L)	Blood culture*	IgM rapid test*	Treatment for initial episode
				Relapse episode	Initial episode							
1	24	27	9(7)	Fever	Fever diarrhea	2(7)	0(1)	12.7 (12.2)	5.7 (5.2)	+ (+)	+ (−)	Ceftriaxone
2	5	9(7)	9(7)	Fever constipation	Fever diarrhea	3(12)	5(3)	8.2 (9.7)	5.3 (4.5)	+ (+)	+ (+)	Ceftriaxone
3	16	11(10)	11(10)	Fever	Fever	3(4)	1(4)	13.4 (12.2)	4.1 (3.6)	+ (+)	NA (+)	Ciproflaxacin
4	10	7(7)	7(7)	Fever constipation	Fever	7(9)	1(3)	11.6 (13.7)	6.0 (6.8)	+ (+)	+ (+)	Ceftriaxone
5	31	10(7)	10(7)	Fever headache diarrhea	Fever headache diarrhea	3(7)	0(4)	12.5 (13.6)	10.6 (6.5)	+ (+)	− (NA)	Ceftriaxone
6	16	6(6)	6(6)	Fever diarrhea	Fever	7(4)	5(3)	11.7 (13.7)	4.7 (6.9)	+ (+)	− (−)	Ceftriaxone
7	10	8(8)	8(8)	Fever diarrhea	Fever diarrhea abdominal pain	3(10)	5(3)	9.5 (11.0)	6.4 (10.9)	+ (+)	− (−)	Ceftriaxone
8	10	6(8)	6(8)	Fever	Fever diarrhea abdominal pain	NA(21)	1(6)	9.7 (10.0)	7.9 (4.5)	− (+)	+ (+)	Ceftriaxone
9	32	8(9)	8(9)	Fever diarrhea	Fever diarrhea abdominal pain	7 (14)	2(2)	13.3 (12.8)	7.3 (8.9)	+ (−)	− (−)	Ceftriaxone
10	15	7(7)	7(7)	Fever diarrhea abdominal pain	Fever diarrhea abdominal pain	7(14)	2(5)	12.9 (10.4)	6.0 (3.9)	− (+)	(−)	Ceftriaxone
11	60	11(10)	11(10)	Fever headache diarrhea constipation	Fever headache	NA(9)	5 (8)	10.6 (12.2)	2.9 (2.9)	+ (+)	− (−)	Ceftriaxone
12	33	6(4)	6(4)	Fever	Fever diarrhea	3(3)	2(0)	12.9 (13.3)	7.4 (7.3)	+ (+)	+ (−)	Ceftriaxone
13	31	7(7)	7(7)	Fever	Fever headache diarrhea	5(5)	1(5)	13.2 (14.1)	6.8 (4.9)	+ (+)	+ (+)	Ceftriaxone

*: The result/duration in the initial episode, NA: not available.

contrast to re-infection.

Acknowledgement

We thank Ms Fadzilah Ahmad and Ms Rosliza Abdul Rahman for technical support during the outbreak.

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Executive Editor: Beijia Tan