ORIGINAL ARTICLE

Typhoid Fever in Malaysian Children

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Summary

A prospective study of 102 children with bacteriologically confirmed typhoid fever, admitted to Hospital Universiti Sains Malaysia over 5 years was conducted. The average age at presentation was 91.3 (range 6 - 159) months. Fever (90%), abdominal pain (56%) and diarrhoea (44%) were common symptoms. Findings included: hepatomegaly (85.3%), splenomegaly (27.5%), anaemia (31%), leukopenia (15%), thrombocytopenia (26%), positive Widal (62.5%) and Typhidot test (96%). Patients were treated with ampicillin (n=54) or chloramphenicol (n=49) and 1/3 developed complications like hepatitis (n=19), bone marrow suppression (n=8) and paralytic ileus (n=7). A patient with splenomegaly, thrombocytopenia or leukopenia was at higher risk of developing complications.

Key Words: Typhoid fever, Malaysian children, Clinical features, Typhidot, Predictors of complications

Introduction

Typhoid fever is still an important health problem in developing countries with an estimated incidence of 540-cases/100,000 population[1]. In more affluent regions of the world, proper sanitation has successfully diminished infection with *Salmonella typhi (S. typhi).* Nevertheless both sporadic cases and outbreaks of typhoid fever have been encountered in the developed countries over the years[2].

Although the number of reported cases has dropped over the years, typhoid is still a common febrile illness in Malaysia[3,4] (Fig I). In year 1998 and 1999 the highest number of cases were reported from Kelantan followed by Sabah, Terengganu, Selangor and Sarawak and majority of the patients was children[4].

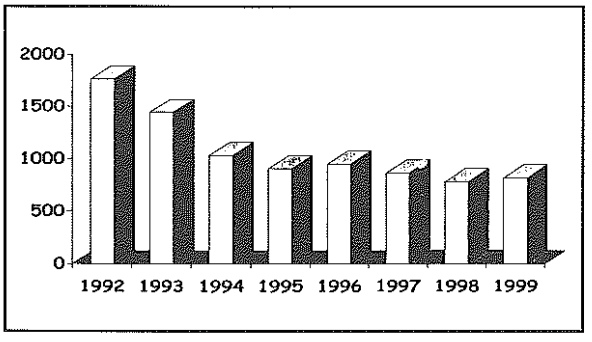

Fig. 1: No. of typhoid cases reported in Malaysian from 1992 - 99[4].

In Kelantan epidemics of typhoid are common[5]. The annual incidence rates of typhoid in Kelantan show a baseline endemicity of 20 to 30 cases per 100,000 population[6].

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The emergence and spread of *S. typhi* resistant to multiple antibiotics is now a subject of international concern. Not only has it become endemic in many developing countries, causing enormous morbidity and exorbitant costs of treatment, resistant Salmonella is also being increasingly reported from the developed world[7,8].

This paper presents the results of a prospective study, which was conducted over a period of nearly five years in Hospital Universiti Sains Malaysia (HUSM), which is one of the two referral centres for the state of Kelantan. The aim of this investigation was to study the incidence and nature of complications of typhoid fever in children and also to identify the risk predictors / markers of these complications. We also reviewed the published data about typhoid fever in Malaysian and other children.

Materials and Methods

A prospective study of children with bacteriologically confirmed typhoid fever caused by *S. typhi* or *Salmonella paratyphi (S. paratyphi)*, admitted to HUSM between 1st October 1993 and 31st August 1998 was conducted. Children with immune deficiency, malignancy, major congenital abnormalities or syndromes, chronic illnesses like tuberculosis or chronic renal failure or receiving steroids were excluded from the study. Statistical analysis was performed using Chi- squares test and statistical significance was defined as $P<0.05$. Fishers exact test was used where indicated. It was computed using programme "STATCALC calculator" in software package Epi-info 6.04b.

A diagnosis of hepatitis was made when the transaminase levels were raised to at least twice the normal value for that age group. Patients with pancytopenia were diagnosed to have bone marrow suppression and a diagnosis of paralytic ileus was based on clinical and radiological features such as abdominal distension, absent bowel sounds, dilated bowel loops etc.

Results

There were a total of 9292 admissions to paediatric medical wards during the study period (this does not include admissions to special care nursery or neonatal intensive care); 159 of them were treated for typhoid fever including 102 with cultures positive for *S. typhi*. Blood culture was positive in 77, stool culture in 14 and both blood and stool cultures in 11 children (Table I). All the isolates of *S. typhi* were sensitive to common antibiotics like ampicillin, chloramphenicol and

Table I
Epidemiological Data of 102 children, with Bacteriologically Confirmed Typhoid Fever, Admitted to HUSM (1.10.93 - 31.8.98)

Aver age	91.3 (6 - 159 months)
Male : female	1.2 : 1
Duration of illness before admission	11.5 (1 - 35 days)
Positive history of contact	47%
Contact with siblings	40%
Contact with parents	7%
Contact with cousins	38%
Contact with others	15%
Piped water supply	50%
Well water supply	50%
Usage of boiled water for drinking	98%
Positive blood culture	77
Positive stool culture	14
Both blood and stool culture positive	11
Duration of hospitalisation	16.6 (3 - 32days)
Follow-up	50%
Rate of complications	33%
Nutritional status	
>50th percentile	41%
10th - 50th percentile	29%
3rd - 10th percentile	10%
<3rd percentile	20%

co-trimoxazole. These patients were seen throughout the year including 3 small outbreaks: July 1997, October 1997 and March 1998.

A positive history of contact was obtained in 47 (47%) cases and 20 (20%) children had their weight less than 3rd percentile for age. The median age of these 102 children was 90.5 months (range 6 - 159 months). The male to female ratio was 1.2:1 and average duration of illness before admission was 11.5 days (range 1 - 35 days) (Table I).

Apart from fever (n=90) other common symptoms were abdominal pain or discomfort (n=56), diarrhoea (n=44) and cough (n=41). On physical examination 85.3% were found to have hepatomegaly, 27.5% splenomegaly and 6 patients had jaundice (Table II).

Anaemia (haemoglobin <10 g/L) was present in 31%, leukopenia (total white count <5x10^9/L) in 15%, leukocytosis (total white count >12x10^9/L) in 18% and thrombocytopenia (platelet count <150x10^9/L) in 26% of patients. Widal test was positive [T(O)>1/80] in 62.5% and IgM using dot enzyme assay[9] was detected in 80% children (Table II).

Half of the patients had received antibiotics before admission. After admission 54% were treated with ampicillin and defervescence was achieved after an average period of 6.2 days (maximum up to 21 days) of treatment. They were hospitalised for an average of 16.6 days (range 3 - 32 days) and half of them came for at least one follow-up visit. One patient was treated surgically for bowel perforation and peritonitis and there was no mortality (Table I).

One third of patients developed complications (Table III). Anicteric hepatitis was the most common complication followed by bone

Table II
Clinical and Laboratory Findings* in 102 Children, with Bacteriologically Confirmed Typhoid Fever, Admitted to HUSM (1.10.93 - 31.8.98)

Fever	90
Abdominal pain or discomfort	56
Diarrhoea	44
Cough	41
Headache	37
Constipation	24
Hepatomegaly	85.3
Splenomegaly	27.5
Jaundice	6
Anaemia (Hb <10g/L)	31
Leukopenia (total white count <5x10^9/L)	15
Leukocytosis (total white count >12x10^9/L)	18
Thrombocytopenia (platelet count <150x10^9/L)	26
Pancytopenia	8
TO >1/80 (Widal test)	62.5
TH >1/80 (Widal test)	66.6
IgG (typhidot test)	92.5
IgM (typhidot test)	80.0
IgM (typhidot - M test)	96.2

** percentage*

Table III
Complications* of Bacteriologically Confirmed Typhoid Fever in 102 Children Admitted to HUSM (1.10.93 - 31.8.98)**

Hepatitis	19
Bone marrow suppression	8
Paralytic Ileus	7
Myocarditis	4
Psychosis	4
Cholecystitis	3
Osteomyelitis	2
Peritonitis	1
Other complications	4

** percentage*
*** 12 patients developed multiple complications*

marrow suppression, paralytic ileus, myocarditis, psychosis and osteomyelitis. Twelve patients developed multiple complications. These complications were not related to age of patient, duration of illness before admission, nutritional status of patient, level of "O" or "H" titre, positivity for IgG or IgM or treatment with ampicillin or chloramphenicol. However patients with splenomegaly, thrombocytopenia or leukopenia were at higher risk of developing these complications. Nearly 54% of children with splenomegaly, 60% with thrombocytopenia, 70.6% with leukopenia, 77.8% with both splenomegaly and leukopenia and 78.6% with splenomegaly and thrombocytopenia developed complications (Table IV).

Discussion

It has been estimated that 12 - 33 million cases of typhoid fever occur annually throughout the developing world. It causes more than half a million deaths every year, mainly in school going children, and unless sanitary and nutritional conditions improve, it is impossible to eradicate this disease[1,10]. In patients whose cause of fever could be established/diagnosed, typhoid was reported to be the second most common cause of fever in Malaysia[11]. There was a range of 1715 to 2962 reported cases from 1978 to 1990 with an annual incidence of 10.2 to 17.9 per 100,000 population[12] but the number of reported cases has gradually dropped to 818 in 1999[4] (Fig. I). In our study 1.7% of children admitted to paediatric medical wards of HUSM were treated for typhoid fever.

Table IV
Features Related to Rate of Complications* in 102 Children with Bacteriologically Confirmed Typhoid Fever Admitted to HUSM (1.10.93 - 31.8.98)

Clinical and Laboratory Features	Developed Complications	No Complications	P value
Splenomegaly			
Yes	15	13	0.012
No	17	52	
Trombocytopenia			
Yes	18	12	0.000
No	15	53	
Leukopenia			
Yes	12	5	0.002
No (normal WBC)	17	45	
Splenomegaly and thrombocytopenia			
Yes	11	3	0.041
No	11	43	
Splenomegaly and leukopenia			
Yes	7	2	0.002
No	9	36	

53.6% of children with splenomegaly developed complications.
60% of children with thrombocytopenia developed complications.
70.6% of children with leukopenia developed complications.
78.6% of children with splenomegaly and thrombocytopenia developed complication.
77.8% of children with splenomegaly and thrombocytopenia developed complications.

Typhoid is mainly a disease of children. The reported age incidence shows considerable variation but most reports indicate a peak in the first two decades of life with emphasis on the 5 - 15 year age range. In our study the average age was 7.5 years (Table I). *Choo et al* in their retrospective study of paediatric patients from the same centre reported a mean age of 7.3 years[3]. Many reports stress the occurrence of typhoid fever in the under 5-year olds with up to 50% of cases occurring in the first 2 years of life[13]. Only 3 of our patients were less than 2 years old. In a study from India the incidence rate of typhoid fever per 1000 person-years was 27.3 at age under 5 years, 11.7 at 5 - 19 years, and 1.1 between 19 and 40 years[14]. In a report form United States, 35% of patients suffering from typhoid were less than 5-years old[15]. Many investigators have reported typhoid in neonates[16,17]. The youngest patient reported by *Choo et al* in their study from Kelantan was 48 days old[3]. In another retrospective study of Malaysian children, youngest patient reported was 2-month-old[18]. As we did not include neonates in our study, our youngest patient was 6-month old.

Humans are the only natural reservoirs of *S. typhi*. To get typhoid fever implicates a direct or indirect contact with a patient or carrier of *S. typhi*. Nearly half of our patients had positive history of contact (Table I). Majority of the contacts was with siblings and cousins, not only showing higher incidence of disease in children but also relatively poor hygienic habits in this age group. *Choo et al* reported a positive history of contact in 22.6% of their patients, a quarter of them had their first-degree relatives suffering from typhoid fever[3]. Male to female ratio in our patients was 1.2:1, which was similar to previous reports from Malaysia[3,18].

All our patients were Malays (representative of Kelantan population) and half of them used well water at home. However 98% of them, when at home, used boiled water for drinking. Eating out is quite common in Kelantan and there is no strict control over "sporadic" food stalls. *S. typhi* not only spreads through water but also can be transmitted through raw or half cooked food[19]. During our study period there were three small outbreaks and all of them were related to "Kenduri" - the feast following marriage ceremony.

Of the 102 children, 41% had a body weight more than 50th percentile for age and 20% had less than 3rd percentile. Similar findings were reported earlier from our centre[3]. It seems that poor nutritional status does not particularly predispose children to this infection.

Nearly half of our patients came from families of low socio-economic status (monthly income <RM500/month) and 1/3rd from families with high income (monthly income >RM1000/month). We also analysed data based on income per person per month for these families (total income of the family - house rent / no. of family members dependent on total income) and found similar results. Nearly 18% of patients came from families with income >RM200/person/month, showing that in Malaysia typhoid fever affects all classes of society and apart from poor socio-economic status, also relates to life style and eating habits of the family.

Average duration of illness before admission to hospital was 11.5 days; some patients reported after up to 35 days of illness. Similar findings are reported in previous investigations related to Malaysian patients[18]. Majority of population in Kelantan lives in rural areas and prefers to receive treatment from "Bomoh", the traditional healer, before seeking help from general practitioners or hospitals[20]. The average duration of hospitalisation was 16.6 days. It was the hospital policy to complete the antibiotic treatment (usually for two weeks) and get "stool clearance" (three stool specimens to be collected for Salmonella culture, first specimen 24 hours after completion of antibiotic treatment) before patient is discharged from the hospital. For the same reason *Choo et al* [3] reported the mean duration of hospitalisation of 17.2 days.

Seasonal Variations

It is believed that typhoid fever shows a seasonal pattern usually with greater prevalence in the rainy season[21,22]. In contrast *Choo et al* in an earlier study from Kelantan reported a high incidence during the hot dry season[3]. *Yap et al* did not find any seasonal variation but about half of their cases were admitted during dry months of May, June and July[18]. In our study patients were seen throughout the year and there was no significant seasonal variations.

Symptoms and Signs

The concept of a 'typical' clinical picture in childhood typhoid is inappropriate and misleading. The severity and duration of illness varies greatly from child-to-child. As typhoid is both a septicaemia and toxaemia, any tissue or organ system can be involved in a variety of ways. At presentation, patient may be a sick looking child with 'toxic' appearance or a comfortable healthy looking child who does not have any symptom except fever.

Fever is the most constant presenting symptom; 90% of our patients presented with this complaint. *Choo et al* [3] reported fever in 100% and *Yap et al* 18 in 98% of their patients. Fever is usually high (39 - 40°C) and may be intermittent or remittent. Rigors or chills may occur with high fever and it is safe to use acetaminophen or ibuprofen to control fever[23], however generally it does not respond to acetaminophen or there is only a partial response. As noted in previous reports[3,13] we also did not find any evidence of relative bradycardia and none of our patients was found to have rose spots.

Apart from fever the other common symptoms in our patients were abdominal pain or discomfort followed by diarrhoea, cough, vomiting, headache and constipation (Table II). In an earlier report from our centre[3] the five most common symptoms (apart from fever) included; diarrhoea, vomiting, cough abdominal pain and headache. *Yap et al* also reported similar frequency of these clinical features[18]. Contrary to common belief, diarrhoea is a relatively common presentation than constipation; 44% of our patients had diarrhoea and only 24% presented with constipation. Other authors[3,15,18] have reported similar findings. However *Sinha et al* in their prospective study in Delhi, did not report diarrhoea in their 5-year-old and above patients and only in 14% of their younger patients[14]. Reported frequency of diarrhoea in typhoid fever reveals geographic variations of between 30% and 50%[21,22,24]. Cough has been reported as a common symptom of typhoid fever in children[3,18] and our investigation provided similar results (Table II).

Hepatomegaly (85.3% of patients) followed by splenomegaly (27.5%) was the most common clinical findings in our investigation. All the patients who had splenomegaly also had hepatomegaly. Two other investigations of Malaysian children reported similar findings[3,18]. *Sinha et al* [14] reported splenomegaly in 26% of their 5-years-old and above patients and in 14% of their younger patients.

Diagnosis

To make a diagnosis of typhoid fever, blood and stool specimens of all 159 children, suspected to have this illness, were cultured and only 102 (64%) had positive results. Blood culture was positive in 77, stool culture in 14 and both blood and stool cultures were positive in 11 children (Table I). Since blood and stool cultures were positive in the 1st, 2nd and 3rd week of illness, as also shown previously[3,14], it is important to culture blood and stool regardless of the stage of illness. All urine cultures were negative for *S. typhi* and similar results have been reported previously as well[18]. *S. paratyphi A* was isolated form one patient.

As 54% of 159 children had received antibiotics before admission, our culture positivity rate was low (64%). However it is interesting to note that 50% of the children who were treated with

antibiotics before admission had positive blood or stool culture. Many reasons including sub-optimum doses taken by these patients can explain this inconsistency. This finding underscores the importance of cultures of *S. typhi* even in patients who had received antibiotics before admission.

Widal agglutination test was done in 96, typhidot in 80 and typhidot-M[9] in 26 of these 102 culture positive patients. In Widal test "O" or "H" titre of ≥=1/80 was interpreted as positive (Table II). As controversy surrounds the "significant levels" of "O" or "H" titre[3,25] it is not possible to compare the results of different investigations. *Choo et al* [25] found that an "O" and /or "H" titre of ≥1/40 carries a sensitivity and specificity of 89%. *Yap et al* chose higher titres of "O", yet 99% of their patients had positive Widal test[18].

The rise in "H" titres often higher than that of "O" titres, as seen in our children (Table II), was also reported previously[3]. Contrary to common belief that raised "O" titres are of higher diagnostic value than "H" titre[26], *Choo et al* [27] found that a raised "H" titre is more sensitive than a raised "O" titre yet with a similar high specificity. Rise in both "O" and "H" titre was found to be of equal significance by other investigators[28].

Typically Widal titres are believed to rise to diagnostic values in the second week of illness. Our investigations showed that significant number of patients achieved that titre within first week of illness. Other investigators have reported similar findings[3,25,26].

From the above discussion it is reasonable to conclude that: (1) Widal agglutination test is a useful diagnostic tool, (2) the length of history of fever does not affect the initial Widal titre in culture positive cases and (3) rise in both "O" and "H" should be given equal significance.

Typhidot and Typhidot-M tests detect antibodies to a 50-kD outer membrane protein of *S. typhi* [29,30]. These IgM and IgG antibodies persist in circulation for 2.6 and 5.4 months respectively[31]. These tests were developed in School of Medical Sciences of Universiti Sains Malaysia[32] and have been evaluated by many investigators[9,33]. Results of these tests in our patients are summarised in Table II. Our findings of usefulness of these tests and their superiority to Widal test both in early and later part of illness confirm the results of earlier reports.

Haematological Abnormalities

Haematological derangements are common in typhoid fever. Significant changes include anaemia, leukopenia, eosinophilia, thrombocytopenia and sub-clinical disseminated intravascular coagulation[34]. Anaemia and thrombocytopenia were the most common abnormalities in our patients (Table II). Majority had normal leukocyte count. Yap et al reported similar results in their paediatric patients[18]. Slightly higher figures were reported from our centre previously[3]. None of our patients developed clinical manifestations of disseminated intravascular coagulation.

Children with typhoid, initially not anaemic, may rapidly develop severe anaemia because of combination of haemolysis, toxic marrow depression and occult blood loss[13]. Anaemia in our patients may not be entirely due to typhoid fever, as we did not investigate these patients for other causes but none of them had frank rectal bleeding or had occult blood positive in their stools. *Khosla et al* [34] reported similar results in their adult patients except leukopenia, which was more common in their series.

Treatment and Outcome

Although resistance to common antibiotics has been reported[35,36], it is not a major problem in Malaysia like other countries[14,15,37,38]. All the isolates in our investigation were sensitive to commonly used antibiotics (ampicillin, chloramphenicol, co-trimoxazole). During our study period it was the hospital policy not to use

the cephalosporin group of antibiotics for treatment of typhoid fever. Chloramphenicol and ampicillin were used without any specific criteria for their selection. Fifty four percent of our patients were treated with ampicillin and rest with chloramphenicol. Both these antibiotics were tolerated well by children without any significant side effects. In only one patient, who developed pancytopenia after hospitalisation, treatment was changed from chloramphenicol to ampicillin. There was no mortality or permanent disability. Clinical and bacteriological relapse occurred in 4 (4%) patients. All of them were initially treated with ampicillin and were successfully retreated with the same antibiotic. Other investigators[18] have reported similar incidence of relapse. Two patients became carriers and were being followed up closely. Due to intermittent excretion of *S. typhi* in stool of carriers and with poor follow-up rate (50% in this study), the carrier rate in our study is likely to be an underestimate.

Complications

Reports based on retrospective data have shown that complications of typhoid fever are common both in children[3] and adults[39]. However some complications are more common in children than in adults[13].

The incidence of complications of typhoid fever (both in adults & children) is reported from 13% to 38%[39]. In our investigation, 1/3 of culture positive children developed complications (Table III). Anicteric hepatitis was the most common complication followed by bone marrow suppression, paralytic ileus, myocarditis, psychosis and cholecystitis. *Choo et al*[3] in their retrospective data from the same area in 1988 reported gastritis, bronchitis, ileus, psychosis, encephalopathy, gastrointestinal bleeding and myocarditis as complications of typhoid fever in children.

Hepatitis

The documented incidence of hepatitis in typhoid fever (both in adults and children) varies widely from less than 1% to 26% of patients[39]. In our investigation 19% of children developed this complication. Six of these patients were investigated for other viral causes of hepatitis (hepatitis A, B, C & E virus) and were found to be negative. The liver function tests were repeated in 3 of these children before being released from hospital and were documented to be normal. Of these 19 children, 11 were males, blood culture was positive in 17 and 12 of them were treated with ampicillin. Only 4 patients developed clinical jaundice. The level of serum bilirubin was low or normal in majority of patients, which may explain the failure to identify this complication in a retrospective study conducted earlier in the same centre[3]. Seven of these patients developed multiple complications.

In contrast to the previous view[40], in our study, development of this complication was not related to delay in treatment, nutritional status or sex of patients and clinical jaundice was not a common feature however hepatomegaly was detected in all of these patients.

Bone Marrow Suppression

Eight of our patients who presented with pancytopenia were diagnosed to have bone marrow suppression. The blood culture was positive in 7 and stool culture in 2 of these patients; 5 of them were males. These children were not investigated for other causes of pancytopenia but all of them had normal blood counts at the end of treatment for typhoid fever. As samples for blood investigations were collected before treatment with antibiotics was started, pancytopenia was therefore unlikely due to chloramphenicol therapy. Two patients with pancytopenia, who were treated with chloramphenicol under close monitoring,

responded well to the treatment. One patient who developed pancytopenia after receiving chloramphenicol is not included in this group.

Gastrointestinal Complications

Salmonella infection in the gut involves local inflammation, lymphatic absorption of toxins and direct portal spread of infection so that there is intestinal infection of variable extent. Intestinal perforation and paralytic ileus are commonly reported complications. Intestinal perforation can occur at almost any time and may be the precipitative cause for admission[41]. In our series peritonitis was diagnosed in only one patient who was directly admitted to paediatric surgical ward and needed laparotomy. Seven other patients developed paralytic ileus (Table III) and were treated conservatively with fluids, electrolytes and antibiotics. All our patients recovered completely.

Myocarditis

Electrocardiographic changes suggestive of myocarditis are rather common in typhoid fever but the incidence of true myocarditis is low both in adult patients[42] and children. *Yap et al* in their retrospective study of 54 Malaysian children did not report any case of myocarditis[18]. We made the diagnosis of myocarditis based on clinical features, ECG changes and echocardiography findings and only 4 children fulfilled the criteria. A previous study from the same institution reported only one of 137 children developing this complication[3]. On the other hand in another series from Kelantan, *Kean et al* reported ECG abnormalities in half and myocarditis in 1/3 of their 60 patients[43]. This discrepancy could be due to difference in definition of myocarditis as well as in methodology of studies.

Psychosis

Four children who presented with emotional upset and derangement of personality and loss of contact with reality and with delusions, hallucinations or illusions were diagnosed to have psychosis. These symptoms were not related to drug ingestion and settled within few days after treatment for typhoid was started. No antipsychotic drugs were used for treatment in these children.

Neuropsychiatric complications have been reported in from as low as 2.3% to as high as 84% of typhoid patients, with acute psychosis in 0.6% of these patients[44]. In an earlier retrospective study from our centre, psychosis was reported in 2.2% of paediatric patients[3]. None of our patients developed other reported neuropsychiatric complications such as cerebellitis, meningo-encephalitis, aphasia or deafness[44]. Neuropsychiatric complications have been reported more common in patients with multidrug-resistant *S. typhi* infection[44]; none of our patients had infection with resistant *S. typhi*.

Cholecystitis

Enteric fever associated with cholecystitis has a reported incidence of 2.8% to 12.5%; 60% of these patients have acalculus disease[45]. It is usually due to toxic dilatation of gallbladder. In our series ultrasonography was performed on patients with one or more of the following features: right hypochondrial or diffuse abdominal pain; abdominal distension, tender hepatomegaly; positive Murphy's sign or a palpable gallbladder. Based on the presence of increased gallbladder size, gallbladder thickness and other findings[46] a diagnosis of acalculus cholecystitis was made in 2 patients. Both of these children were also icteric and had elevated serum alkaline phosphatase levels and were managed conservatively. One of these patients had elevated transaminase levels bringing in the possibility of hepatitis as well. Another patient who presented with ileal perforation and peritonitis was, on laparotomy, found to have gangrenous necrosis of gallbladder. *S. typhi* was cultured from the gallbladder fluid in this child. A similar case of a Malaysian patient was reported earlier[18]. In another earlier retrospective study of 137 typhoid patients from

our centre cholecystitis was not reported as a complication[3]. With the widespread use of abdominal ultrasonography, acute acalculus cholecystitis in typhoid fever is becoming increasingly easy to recognise.

Osteomyelitis

Salmonella usually causes osteomyelitis in patients with sickle cell disease[47], haematological malignancy or with pre-existing bone pathology; sites usually affected are femur or tibia. Two of our patients developed this complication affecting their tibiae. One patient had congenital aniridia and optic atrophy of the right eye. There was no evidence of Wilm's tumor or any other malignancy in this patient. The other patient had evidence of haemolytic jaundice (jaundice with haemoglobinuria and increased reticulocyte count). His G6PD level was normal and there was no evidence of thalassaemia, spherocytosis or sickle cell disease and actual cause of haemolysis could not be established. His transaminase levels were raised but screening for hepatitis viruses was negative. In the course of treatment this patient developed pancytopenia and the treatment was changed from chloramphenicol to ampicillin. Choo et al in their retrospective study from our centre did not report any case with this complication[3].

Other Complications

Other complications in our patients included: pneumonia, haemolytic anaemia, and syndrome of inappropriate release of antidiuretic hormone (SIADH). Many pulmonary complications of typhoid fever such as bronchitis, pneumonia, lung abscess, empyema and adult respiratory distress syndrome (ARDS) have been reported[48]. Pneumonia may occur very early in the disease and may indeed be the presenting feature or may arise later. Radiological evidence of pneumonia occurs in up to 1/3 of cases and may be evident in 50% or more of autopsies on fatal cases[8]. Surprisingly very few pulmonary complications have been reported in Malaysian patients. Choo et al reported bronchitis in 3.7% of their paediatric patients[3]. *Yap et al* did not report any pulmonary complication in their series[18]. In many patients who have other complications of typhoid fever pneumonia may be an indirect complication or "complication of a complication". Only one patient in our series developed pneumonia but this patient also had paralytic ileus and might have developed pneumonia due to aspiration.

Haemolysis is a rare reported complication of typhoid fever4[9]. Probably if all cases of anaemia due to typhoid fever are investigated, more patients may be identified to have haemolysis as it contributes to development of anaemia in typhoid fever[13]. One of our patients developed this complication. This patient had other complications as well but there was no obvious predisposing factor for haemolysis in this patient.

Two of our patients developed SIADH and both of them had other complications as well. Both these patients developed severe hyponatraemia (<120mmol/L) and were found to have low plasma osmolality. *Choo et al* in their retrospective study reported hyponatraemia (<130mmol/L) in 16.1% of their patients[3]. It was not possible to establish whether SIADH was a direct or indirect complication in our patients.

Predictors of Complications

Following factors did not influence the rate of complications in our patients: age at admission, duration of illness before admission, use of antibiotics before admission, nutritional status of patient at the time of admission, level of "O" or "H" titre, presence or absence of IgM or IgG and treatment with chloramphenicol or ampicillin after admission.

However it was found that a child with splenomegaly, leukopenia or thrombocytopenia had higher risk of developing a complication. A

child with both splenomegaly and thrombocytopenia or leukopenia had nearly 2.5 times higher risk of developing a complication (Table IV).

From above discussion it is concluded that (1) complications of childhood typhoid fever are common, (2) anicteric hepatitis, bone marrow suppression and paralytic ileus are three most common complications and (3) a child with splenomegaly, leukopenia or thrombocytopenia is more likely to develop complications.

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