BLOOD CULTURE CONFIRMED TYPHOID FEVER IN A PROVINCIAL HOSPITAL IN THE PHILIPPINES

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Abstract. Epidemiological features of blood culture confirmed typhoid fever and antibiotic sensitivity of isolated Salmonella typhi strains were investigated in Bohol Province in Central Philippines from where no earlier information of these was avialable. Typhoid fever is endemic elsewhere in the Philippines (eg Metropolitan Manila and surroundings) where also multidrug resistant S. typhi strains have been detected. A laboratory for surveillance of invasive bacterial infections was established in a tertiary care government hospital, in Bohol, Central Philippines, in 1994. Patients with suspected typhoid fever or other serious infection were managed and blood cultures from them were taken according to clinicians' judgment. Blood cultures were processed and the isolated bacteria identified using generally accepted mothods. S. typhi and other Salmonella isolates were identified using commercial antisera. Patient data were collected from hospital records. Of a total of 4,699 blood cultures done during a period of 3 3/4 years, 1,530 (32%) were requested for suspected typhoid fever. S. typhi was the most common pathogen isolated from 422 patients (8.9%), followed by S. paratyphi A from 55 patients (1%). Most patients were young adults (43%) and school age children (28%). Male:female ratio was 1.5:1. Among the 422 patients, there were 9 (2%) deaths due to typhoid fever, all with complications. All S. typhi isolates were sensitive to chloramphenicol, cotrimoxazole, and ampicillin. Our observation on blood culture confirmed typhoid fever demonstrates its importance as a major infectious disease in Bohol and gives a sound basis for treatment of typhoid patients and for further clinical and epidemiologic studies of typhoid fever and for following antibiotic sensitivity S. typhi in Bohol and elsewhere in the Philippines.

INTRODUCTION

Typhoid fever is a major health problem in developing countries where safe water supplies and adequate sewage disposal are often lacking (Hornick, 1985). Epidemiologic data on typhoid fever in endemic countries is lacking or incomplete. Case identification may be based on clinical, bacteriological or serologic diagnosis; or typhoid fever may be clumped with other diseases or conditions such as fever of unknown origin (Hornick, 1985). A definite diagnosis can only be obtained by isolating the

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causative agent, *Salmonella typhi*, from the blood, stool, urine, or bone marrow culture. In studies of the efficacy of vaccines against typhoid fever, blood culture positive typhoid fever has usually been the endpoint (Bodhidatta *et al*, 1987; Simajuntak *et al*, 1991). Appearance of resistant *S. typhi* strains in many countries (Rowe *et al*, 1997) has made the isolation and sensitivity testing of the organism important in the management of patients.

Typhoid fever is endemic in the Philippines, and strains resistant to one or more antibiotics have been isolated in Metropolitan Manila (Saniel, 1993), and Rizal, Laguna, Cavite and Bulacan Provinces which are surrounding Metropolitan Manila (Saniel, 1995). Data on the epidemiology and risk factors of typhoid fever in Metropolitan Manila is available (Saniel,

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1993), but not from other urban or rural parts of the country.

In this paper, we report some clinical and epidemiological observations on patients from whom *S. typhi* was isolated by blood cultures at Governor Celestino Gallares Memorial Hospital (Gallares Hospital), which is a government tertiary care hospital in Bohol Province, Central Philippines, 1994-1997 after the bacteriological laboratory had been updated.

MATERIALS AND METHODS

Bohol, an island in the Visayan region, is the tenth largest province in the Philippines. It has a population of about one million, 85% living in rural areas. The Gallares Hospital in the provincial capital, Tagbilaran City, is the only tertiary care hospital in Bohol and has a total bed capacity of 200 with departments of internal medicine (65 beds), surgery (55 beds), obstetrics and gynecology (40 beds) and pediatrics (40 beds). The Gallares Hospital serves as the secondary care hospital for Tagbilaran and surrounding municipalities, with the majority of patients being walk-in patients.

A bacteriological research laboratory (ARIVAC laboratory) was established at the Gallares Hospital in early 1994 as part of an ARI vaccine project (Herva *et al*, 1999). The laboratory offered its service of blood cultures for all patients of the hospital, and this study was based on blood cultures yielding *S. typhi* between April 1, 1994 and December 31, 1997. Results of a separate study on invasive bacterial infections in children has been reported elsewhere (Lupisan *et al*, 2000).

Patients were admitted, diagnosed and treated according to the routing practices of the hospital. Blood cultures were requested by clinicians according to their judgment. Only one blood culture was taken from each patient, and because the blood culture bottles were principally for pediatric use, only 1-2 ml of blood was taken and added into the 20-ml brain-heart infusion broth bottle. The bottle was incubated for a total of seven days and subcultured on sheep blood agar, chocolate agar and MacConkey agar plates after overnight, 3 days and 5-7 days of incubation. Salmonellae were presumptively identified by biochemical tests and confirmed by serology using O group antisera (BBL Becton Dickinson, USA) in the ARIVAC laboratory. The identifications were later confirmed at the Research Institute for Tropical Medicine, Metro Manila, using O:9 and H:d (*S. typhi*) and O:2 and H:a (*S. paratyphi* A) typing sera (Denka Sieken, Japan). Antibiotic sensitivity testing was performed using diffusion method and following the National Committee for Clinical Standard (NCCLS) recommendations. Clinical data of the patients were collected from hospital records.

RESULTS

Salmonella typhi was isolated from 422 (9%) and *S. paratyphi* A from 55 (1%) of the 4,699 patients with blood cultures taken at Gallares Hospital between April 1, 1994 and December 31, 1997. Of other major pathogens, *Escherichia coli* was isolated from 36 (0.8%), *Streptococcus pneumoniae* from 37 (0.8%), *Klebsiella pneumoniae* from 33 (0.7%), *Staphylococcus aureus* from 23 (0.5%), *Streptococcus pyogenes* from eight, *Haemophilus influenzae* from three and *Neisseria meningitidis* from one of the patients.

Patients with *S. typhi* were seen throughout the year, the number varying from one to 22 (mean 9.3) patients per month. The largest numbers of monthly isolations were in the latter half of the year, the rainy months of July to December (Fig 1). Most *S. paratyphi* A infections occurred in two periods, from September 1996 to March 1997 (N=33) and in October and November 1997 (N=12).

The number of *S. typhi* in blood cultures increased in the course of the study period. However, the proportion of blood cultures yielding *S. typhi* did not increase being 14.8%, 10.4%, 7.3% and 8.2% in the years 1994, 1995, 1996 and 1997, respectively, reflecting the increasing number of blood cultures from 413 during the 9 months in 1994 to 1,857 in 1997. Thus, there probably was no true in-



Fig 1–Monthly numbers of 422 patients with blood culture confirmed typhoid fever in the Gallares Hospital, Bohol, Central Philippines, in 1994-1997.

Age (years)



Fig 2–Age and sex distribution of 422 patients with blood culture confirmed typhoid fever in the Gallares Hospital, Central Phillippines, in 1994-1997.

crease in typhoid fever during the study period. Almost half (44%) of the blood culture confirmed typhoid fever patients came from Tagbilaran City and the four surrounding towns (combined population about 150,000), all within 15 km distance from Gallares Hospital. In 1997, a total of 153 patients with typhoid fever were confirmed by blood culture, 67 of them from that population of 150,000, giving 45 per 100,000 per year as the incidence of confirmed typhoid fever in this population.

Most patients with blood culture confirmed typhoid fever were young adults (15-29 yrs) and school age children (5-14 yrs) (Fig 2).

Table 1								
Signs	and	symp	otoms	in	422	patien	ts	with
bloo	d cu	lture	confi	rme	ed ty	phoid	fev	ver.

Signs and symptoms	No. of patients (%)				
Fever	420 (99.5)				
Chills	153 (36)				
Headache	162 (38)				
Diarrhea	104 (25)				
Constipation	7 (2)				
Anorexia	108 (26)				
Malaise	100 (24)				
Cough	99 (23)				
Vomiting	88 (21)				
Abdominal pain	79 (19)				
Hepatomegaly	24 (6)				
Gastrointestinal bleeding	g 11 (3)				
Changes in sensorium	22 (5)				
Rashes	4 (1)				
Seizures	2 (0.5)				

Only 29 (7%) of the patients were under five years old, whereas 24% of all blood cultures were taken from this age group. Only three (0.5%) patients were infants less than one year of age. Two hundred and fifty-five (60%) were males and 167 (40%) females.

Clinical suspicion of typhiod fever was the most common (1,530, 32%) reason for requesting blood culture among the total of 4,699 patients with blood culture taken. On the other hand, in 338 (80%) of the 422 blood culture confirmed typhoid fever, the clinical diagnosis on request of blood culture was typhoid fever. Other initial diagnoses for the confirmed typhoid fever cases were pneumonia, sepsis, systemic viral infection, urinary tract infection, dengue hemorrhagic fever, acute gastroenteritis, and meningitis. Isolations of S. typhi were done mostly in the first (183, 43%) and the second (103, 24%) weeks of fever. On admission, almost all patients had fever. Other frequent manifestations of the illness were diarrhea, cough and malaise (Table 1).

All *S. typhi* isolates were sensitive to chloramphenicol, cotrimoxazole and ampicillin, the first-line drugs for typhoid fever, and to ceftriaxone, ciprofloxacin and ofloxacin. Of

the 422 patients, 71 (17%) had a history of pre-admission antibiotic intake, mostly chloramphemicol (23; 5%) or amoxycillin/ampicillin (22; 5%). In the hospital, the patients were treated with chloramphenicol (288; 68%) or amoxycillin/ampicillin (33; 8%); sometimes with other antibiotics such as ceftriaxone or the quinolones.

Three hundred and forty-five patients (81%) recovered without complications, whereas 77 (18%) had complications such as ileitis in 21 (5%), psychosis in 16 (4%) and gastrointestinal bleeding in 11 (2.6%) with only one case of confirmed intestinal perforation. There were nine (2.1%) deaths, two of them in the age group 5-14 years, four in the group 15-29 years, and one in each older age group. All patients with fatal outcome had complications.

DISCUSSION

Our results show that typhoid fever is endemic in Bohol as it is known to be endemic in Metropolitan Manila and surrounding urban or semiurban municipalities (Saniel, 1993; 1995). Typhoid fever was the most common clinical diagnosis for blood culture requests, and S. typhi was by far the most common pathogen isolated from blood cultures in our newly established bacteriological laboratory at the tertiary hospital of Bohol Province. Also in Indonesia, S. typhi has been found to be the most common finding in blood cultures from febrile patients (Sudarmono and Radji, 1991). Typhoid fever is endemic with high incidence fugures in Indonesia (Simanjuntak et al, 1991), Malaysia (Chee et al, 1991) and widely in Southern Asia (Hornick, 1985). These observations point out the importance of typhoid fever among infectious diseases requiring hospital treatment in Southeast Asian countries.

In our study, *S. typhi* grew in blood cultures from 20% of the 1,530 patients with clinical diagnosis of typhoid fever. In other studies with varying clinical definitions, *S. typhi* has been isolated from up to 80% of clinically suspected typhoid patients (Gilman *et al*, 1975), less often (40-60%) (Gilman *et al*, 1975; Hoffman *et al*, 1984; Farooqui *et al*, 1991), if a proportion of the patients had received antibiotic treatment before blood culture. The amount of blood collected for culture has a significant effect on the detection of bacteremia (Isaacman, 1996). We collected only 1-2 ml per patient instead of the recommeded 5-10 ml (Tsang and Chau, 1991). Also by increasing the number of blood cultures from one to three the isolation rate in clinically typical typhoid can be increased from 60-70% to 85-90% (Sudarmono and Radji, 1991).

In our study, most blood culture isolations of S. typhi were from school age children (5-14 years) (28%) and young adults (15-29 years) (42%). Typhoid fever is mainly a disease of school-age children and young adults also in Malaysia (Chee et al, 1991), Indonesia (Simanjuntak et al, 1991) and other endemic areas where the disease burden is intermediate and the infection usually acquired outside home (Mahle and Levine, 1993). In our study only 6% were from 1-4 years old and 0.5% from under one year old children in contrast to Bangladesh, in which one third (32%) of hospitalized blood culture confirmed typhoid patients were children less than 6 years of age (Butler et al, 1991). Also in Indonesia typhoid frequently occurred in the age group 3-6 years (Simanjuntak et al, 1991).

In our study, the low percentage (7%) of S. typhi blood isolations from children under 5 years old is not due to small number of blood cultures since 24% of all blood cultures were from this age group. In a prospective two-year study on all children less than 5 years old admitted to the same hospital because of suspected serious infections (clinically severe or very severe pneumonia, suspected meningitis, or suspected sepsis) there were only two isolations of S. typhi among 956 patients (Lupisan et al, 2000). Thus, S. typhi infection in infants and young children, presenting atypically as pneumonia (Butler et al, 1991; Tupasi et al, 1990; O'Dempsey et al, 1994) or as mild "viral syndrome" (Mahle and Levine, 1993), was uncommon in Bohol.

The incidence (45 per 100,000 per year in 1997) of blood culture confirmed typhoid fever in Bohol is a minimum because we do not know what proportion of typhoid patients in Tagbilaran and its immediate surroundings sought care at the Gallares Hospital. Closely similar incidences of blood culture confirmed typhoid fever have been reported among Egyptian (age 6 to 7 years; 49 per 100,000 per year) (Wahdan et al, 1982) and Chilean school children (age 6-19 years, in whom also bone marrow and duodenal fluid were cultured; 103 per 100,000 per year) (Levine et al, 1987). Much higher incidence figures of blood culture confirmed typhoid fever have been observed in South African (850/100,000/year: age 5-16 years) (Klugman et al, 1987) and Indonesian children (1,307, 1,352, 1,150 and 987/100,000/ year in age groups 3-6, 7-9, 10-14 and 15-19 years, respectively) (Simanjuntak et al, 1991). Even higher incidence (2,730/100,000/year) in less than 5 years old children was observed in a recent prospective study in New Delhi, India (Sinha et al, 1999).

Regarding the appearance and spread of *S. typhi* strains resistant to first-line antimicrobials (Rowe *et al*, 1997) and recently also to ciprofloxacin (Threlfall *et al*, 1999; Threlfall, 1999; Chitnis *et al*, 1999), it was an unexpected finding that all isolated *S. typhi* strains were sensitive to the first-line and second-line antimicrobials tested. Thus, the resistant *S. typhi* strains found in Metropolitan Manila and the surroundings (Saniel, 1993; 1994) have not yet invaded the Philippines as a whole. Treatment of patients with chlorampenicol (68%) or amoxycillin (8%) was adequate.

In conclusion, *S. typhi* infection is endemic even outside major urban centers in the Philippines. However, the susceptibility of the isolates is excellent despite common previous use of antibiotics and enables treatment with first-line antibiotics.

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