Antibiotic resistance pattern of pediatric Typhoid fever patients at Harapan Kita Children and Maternity Hospital Jakarta, 1996 P-6

Sri Kusumo Amdani

Abstrak

Sejak 1 Januari sampai 31 Desember 1996, telah dirawat 552 pasien anak di RS Harapan Kita dengan diagnosis klinik demam tifoid. Dari jumlah tersebut, hanya 133 (24,1%) yang dipastikan secara bakteriologis, yaitu 114 S. typhi, *18* S. paratyphi A *dan 1* S. paratyphi B. *Rendahnya hasil kultur positif mungkin disebabkan oleh pemberian terapi antibiotika sebelum pasien dirawat. Hasil uji sensitivitas dari* S. typhi *menunjukkan: 97,4% sensitif terhadap kloramfenikol dan kotrimoksasol, 96,5% terhadap amoksisilin, 99,1% terhadap sefotaksim dan seftriakson, 96,9% terhadap sefmetasol. 100% terhadap siprofloksasin.* S. paratyphi A *100% sensitif terhadap kloramfenikol, kotrimoksasol, amoksisilin, sefotaksim, seftriakson, sefmetasol dan siprofloksasin. Kami mempelajari 118 orang pasien dengan kultur positif. Pasien tersebut berumur antara 6 bulan dan 16 tahun: 28% kurang dari 5 tahun, 42,4% berumur antara 5-9 tahun dan 45,8% adalah perempuan. Lama demam rata-rata sebelum dirawat adalah 6,9 hari (2-30 hari), dan demam turun setelah 5,7 hari perawatan (2-12 hari). Kloramfenikol diberikan pada 84% pasien, setengah dari jumlah tersebut diberikan dalam kombinasi dengan amoksisilin atau kotrimoksasol. Semua pasien sembuh dan hanya 2,5 % pasien yang mengalami komplikasi berat. Dari data yang diperoleh, diambil kesimpulan:* S. typhi *dan* S. paratyphi A *di Jakarta masih sensitif terhadap obat-obat standar yang digunakan untuk pasien anak dengan demam tifoid. Lebih dari seperempat pasien berumur kurang dari 5 tahun, dan manifestasi klinik penderita pada penelitian ini ringan.*

Abstract

From 1 January to 31 December 1996, 552 pediatric patients were hospitalized at our hospital with typhoid fever diagnosed clinically. From those, only 133 (24.1%) were confirmed bacteriologically, 114 with S. typhi, *18 with* S. paratyphi A *and one with* S. paratyphi B. *This low positive culture might be caused by antibiotic therapy given before admission. Results of sensitivity test of* S. typhi *showed that 97.4 % were sensitive to chloramphenicol and co-trimoxazole. 96.5 % to amoxicillin. 99.1 % to cefotaxime and ceftriaxone, 96.9 % to cefmetazole, 100% to ciprofloxacine. For* S. paratyphi A *the sensitivity test results were as follow: 100% to chloramphenicol, co-trimoxazole, amoxicillin cefotaxime, ceftriaxone, cefmetazole and ciprofloxacine. We reviewed 118 patients with positive culture. The patients age ranged from 6 months to 16 years, 28% were less than 5 years, 42.4% were between 5-9 years, and 45.8 % were females.The mean duration of fever before admission was 6.9 days (2-30 days), and fever disappeared after 5.7 days of treatment (2-12 days). Chloramphenicol were given in 84% of patients, half of those were in combination with amoxycillin or co-trimoxazole. All patients survived and only 2.5% of patients had severe complications in this series. From these data we concluded that* S. typhi *and* S. paratyphi A *in Jakarta still had high sensitivity to common drugs used for pediatric typhoid fever. More than onefourth of the patients were less than 5 years old, and the clinical manifestations of patients in this series were mild.*

INTRODUCTION

Unless other wise stated, the term typhoid fever used in this paper refers either to typhoid and paratyphoid fever. Typhoid fever is endemic in Indonesia with an incidence rate of 350-810 cases reported per 100,000 population or about 600,000 to 1.5 million patients per year. Mortality was estimated at 50,000 deaths per year[1]. In the Department of Pediatric Dr. Cipto Mangunkusumo Hospital Jakarta, the case fatality rate reported was 3 to 7.3%[2]. Clinical picture of the disease may vary widely, from mild to severe forms. The clasical clinical picture was seen in approximately 88% of cases and the highest attack rate was in children and adolescents between the ages of 5 to 15 years[3]. Social factor, eating attitude, environmental hygiene and physical status probably affect the incidence of typhoid fever. The diagnosis of typhoid fever in children largerly depends on the clinical manifestations. Blood culture and serological test are frequently not helpful in the diagnosis. Another factor is the irrational use of antibiotics by physicians causes difficulties in microbiological and serological diagnosis of typhoid fever[4].

The drug of choice for typhoid fever in many studies and also in our hospital is still chloramphenicol with ampicillin and co-trimoxazole as the first alternative drugs[5-6]. The aim of this present study is to know the resistance pattern of *S.typhi* and *S.paratyphi* to various antibiotics and the other alternative antibiotics for the resistant strains.

Harapan Kita Children's and Maternity Hospital, Jakarta

METHODS

A retrospective study was carried out on all typhoid fever patients admitted to Harapan Kita Children's and Maternity Hospital during the period of 1 January to 31 December 1996 with bacteriological confirmation. We recorded all of the positive blood culture results with *S.typhi* and *S.paratyphi* in that period, and then collected the medical records of the concordant patients. The adult patients (more than 18 years old) and patients whose medical records were not found were excluded from this study. Results of sensitivity test for *Salmonella* on several antibiotics were recorded from all positive culture results. We also recorded the patient history of illness and clinical monitoring during hospitalization until the patient was discharged or died. Blood culture for *Salmonella* was carried out by using bile media and the determination of bacterilogical sensitivity was carried out by using criteria established by The National Committee for Clinical Laboratory Standards (NCCLS) in the USA[4].

A patient was considered cured if fever and other clinical manifestations disappeared, the general conditions was going better, and there was no complications[4]. Anemia was defined as hemoglobin concentration of less than 11 g/dl for children 6 months 6 years, or less than 12 g/dl for children more than 6 years old[7]. Leukopenia was defined if the leucocyte count was <5000/µl, while lymphocytosis referred to lymphocyte count of more than 33% of total WBC, and thrombocytopenia was defined as the platelet count of less than 150,000/µl[8].

RESULTS

From 1 January to 31 December 1996, 552 pediatrics patients were hospitalized at Harapan Kita Children's and Maternity Hospital with typhoid fever diagnosed clinically and 3 of them died (CFR 0.5%). Among those, only 133 (24.1%) were confirmed bacteriologicaly, 114 with *S.typhi,* 18 with *S.paratyphi* A and one with *S.paratyphi* B. From those 133 bacteriological confirmed patient, we could found only 118 medical records. Further description and analysis of clinical features were limited to 118 patients with medical record, while antibiotic sensitivity test were recorded from 133 patients with positive culture.

Table 1 shows that there were 64 (54.2%) male and 54 (45.8%) female children. The age ranged from 6 months to 16 years, 28% were less than 5 years, 42.4% were between 59 years, and the rest were more than 10 years. The history of illness, clinical and laboratory features of those patients are shown in Table 2. Table 3 shows complication and other diseases of typhoid fever patients, while the treatment results are depicted in Table 4.

Table 1. Age and sex distribution of typhoid fever patients

Age Group (yr)	Number of cases		Total
	Male (%)	Female (%)	(%)
0 - 4	19 (16.1)	14 (11.9)	33 (28)
5 - 9	29 (24.6)	21 (17.8)	50 (42.4)
> 10	16 (13.6)	19 (16.1)	35 (29.7)
Total	64 (54.2)	54 (45.8)	118 (100)

Tabel 2. Clinical and laboratory features of children with typhoid fever

Clinical manifestation	
* Fever before admission (day), mean ± SD	6.9 ± 4.3
* Temperature (°C), mean ± SD	39.2 ± 0.6
* Diarrhea	43.5 %
* Constipation	52.5 %
* Nausea / vomit	69.5 %
* Abdominal pain	85.6 %
* Coated tongue	60.2 %
* Abdominal distension	40.7 %
* Hepatomegaly	27.1 %
* Splenomegaly	0 %
Laboratory features	
* Anemia – < 6 years	39.4 %
– > 6 years	36.5 %
* Leukopenia	21.1 %
* Lymphocytosis	47 %
* Thrombocytopenia	21.2 %

Tabel 3. Complications of pediatric typhoid fever patients

* Bronchopneumoniae	12 (10.2%)
* Encephalopaty	2 (1.7%)
* Peritonitis	1 (0.8%)
* Cholecystitis	1 (0.8%)

Tabel 4. Results of treatment of pediatric typhoid fever patients

Antibotic	N (%)	Defervescence of temperature (day), mean + SD
All patients*	97 (100%)	5.7 + 2.3
Chloramphenicol	34 (35%)	5.1 + 2.1
Chloramphenicol + Ampicillin / Amoxycillin	32 (33%)	5.9 + 2.3
Chloramphenicol + Co-trimoxazole	16 (16.5%)	6.1 + 2.4
Others	15 (15.5%)	6.5 + 2.4

** 21 patients still have fever when discharged*

The sensitivity pattern of *S.typhi* on various antibiotics were obtained from 114 isolates, 97.4% were

sensitive to chloramphenicol and co-trimoxazole, 96.5% to amoxicillin, 99.1% to cefotaxime and ceftriaxone, 96.9% to cefmetazole and 100% to ciprofloxacine. The pattern of sensitivity on antibiotics of *S.paratyphi* were obtained from 19 isolates and the sensitivity test were 100% toward all antibiotics mentioned above (Table 5).

Tabel 5. Sensitivity pattern of *Salmonella* from 133 pediatric typhoid fever patients for several antibiotics

Antibiotic	*S.typhi* (%) n = 114	S.paratyphi (%) n = 19
Chloramphenicol	97.4	100
Ampicillin / amoxycillin	96.5	100
Co-trimoxazole	97.4	100
Cefotaxime	99.1	100
Ceftriaxone	99.1	100
Cefoperazone	96.9	100
Cefmetazole	97.7	100
Ciprofloxacin	100	100

DISCUSSION

The diagnosis of typhoid fever is proven by culture of the offending pathogen. In this present study, we only found 24.1% positive culture, similar to Nathin's series (20.3%)[4]. Hendarwanto reported that positive bone marrow cultures were more frequently obtained than positive blood cultures in adult patients (70-78 % vs 40-50 %), but bone marrow punction procedure maybe to invasive for children[9].

The case fatality rate of all pediatric typhoid fever patients in this series is 0.5%, whereas the overall mortality in Dr. Cipto Mangunkusumo Hospital Jakarta is 3-7.3%[4] and in Dr. Sutomo General Hospital Surabaya is 0-0.95%[4,10].

In this series, 50 (42.4%) patients were between 5-9 years, and 33 (28%) patients were less than 5 years of age. Compared to Nathin's series which only has 13.6%, our series has higher incidence of patients less than 5 years, but lower incidence of cases more than 10 years (29.7% vs 37.5%)[4]. Reports from many hospital in Indonesia indicated that the peak age incidence was in adolescents and young adults, while Jusuf et al reported that the highest attact rate was in children and adolescents between the ages of 5-15 years[3,9]. According to Hendarwanto, there was no significant difference in sex distribution of typhoid fever patients in Indonesia, which was also in this present study, with 54.2% male and 45.8% female[9].

The clinical manifestation of typhoid fever in children are generally milder than in those of adults. In our series, the mean duration of fever before admission was 6.9 ± 4.3 days, lower than Nathin's study (9.1 ± 5.4 days) and Rivai's series in pediatric patients (9.2 days)[4,9]. The mean of temperature on admission in present study was 39.2 ± 0.6°C, similar to report by Pape et al that all their patients had temperature of more than 39°C in the beginning of hospitalization, but higher than Nathin's series (38.6 ± 0.6°C)[4].

Gastrointestinal disorders are common in patients with typhoid fever. Our series shows that diarrhea was less frequent than constipation (43.5% vs 52.5%). This finding is different with report by Nathin et al which showed that diarrhea was more frequent than constipation (42.0% vs 34.4%), but similar to the finding of other investigators in Jakarta and Surabaya in adult patients[4,9]. Coated tongue was found in 60.2% of patients, very similar to Nathin's study (61.1%). Report of Hendarwanto showed that coated tongue in adult patients occured in 72-100% of patients[4,9].

Hepatomegaly and splenomegaly were subsequently found in 27.1% and 0% of patients in our series. This finding is lower than Nathin's study which found hepatomegaly in 40.5% and splenomegaly in 1.5% of their patients[4]. As reported by Hendarwanto, in adult patients hepatomegaly was found in 35-82% and splenomegaly in 23-36% of the patients[9].

Peripheral blood finding in typhoid fever patients are characterized by leucopenia with relative lymphocytosis. In this series, leucopenia was found only in 21.2% of patients, while Nathin's series found in 36.6% of patients and Rivai's series in children found in 54% of their patients[4,10]. In children below 6 years of age, anemia was found in 39.4% of patients, while in children over 6 years of age anemia was found in 36.5% of patients. These findings are very low compare to Nathin's study which found that anemia in children below and over 6 years of age were 54.8% and 70.8% of patients subsequently[4]. Anemia typhoid fever in general is of the normocytic-normochromic type, especially if intestinal blood loss occurs. Anemia is often found in severe acute infections which is characterized by inflammation and can be measured by BSR[4].

Typhoid fever is a systemic infectious disease, which can cause various complications in almost all organ systems of the host. In our series bronchopneumoniae was the most frequent complication occured in patients (10.2%), while encephalopathy, peritonitis and cholecystitis were the other complications which oc-

cured only in a few patients (3.3%). In Hendarwanto's report of adult patients, bronchopneumoniae only happened in 2.2 % - 7.1% of patients[9]. Complications of pediatric typhoid patients at Dr. Sutomo Hospital Surabaya were intestinal hemorrhage, hepatitis, febrile convulsion and septic shock[10].

Drug of choice for typhoid fever at the moment is still chloramphenicol, with the alternative drugs are ampicillin/amoxycillin, thiamphenicol and co-trimoxazole. The resistance of *S.typhi* to chloramphenicol, ampicillin, amoxycillin, co-trimoxazole and multidrugs resistant *S.typhi* (MDRST) is a problem now[4]. The sensitivity pattern of *S.typhi* to some antibiotics is shown in Table 5. Small percentage of *S.typhi* was resistant to the following antibiotics: chloramphenicol (2.6%), ampicillin/amoxycillin (3.5%) and co-trimoxazole (2.6%). There were three isolates of *S.typhi* resistant toward two or more drugs commonly used in the treatment of pediatric typhoid fever (chloramphenicol, ampicillin/amoxycillin, co-trimoxazole), but the patients were succesfuly treated with combination of chloramphenicol and co-trimoxazole (two patients) and amoxycillin and co-trimoxazole (one patient). These data indicate that there is resistance of *S.typhi* to commonly used antibiotics, but the percentage is small. This finding were very similar to a study from Dr. Cipto Mangunkusumo Hospital 1991-1994[4].

Other antibiotics clinically effective in the treatment of pediatric typhoid fever are cefotaxime, ceftriaxone, cefoperazone, cefmetazole and ciprofloxacin. The resistance rate of *S.typhi* to these antibiotics was remarkably low, i.e. cefotaxime 0.9%, ceftriaxone 0.9%, cefoperazone (3.1%), cefmetazole (2.3%) and ciprofloxacin (0%).

Since the prevalence of resistance of *S.typhi* to chloramphenicol is negligible, chloramphenicol is still considered as a drug of choice for the treatment of pediatric typhoid fever, followed by ampicillin/amoxycillin and co-trimoxazole.

In this study, 21 patients still had fever when they were discharged in the 2nd - 11th days after hospitalization as requested by their parents. All 97 patients left were succesfully cured, 34 (35%) with chloramphenicol, 32 (33%) with combination of chloramphenicol and ampicillin/amoxycillin, 16 (16.5%) with combination of chloramphenicol and co-trimoxazole and the rest with other antibiotics combination. In patients treated with chloramphenicol fever disappeared after 5.1 ± 2.1 days of treatment, not different with previous studies in defervescence of temperature point of view[4].

CONCLUSIONS

From 552 patients clinically suspected typhoid fever, 133 (24.1%) were confirmed bacteriologically. More than one fourth of the patients were less than 5 years old, and the clinical manifestations of patients in this series were mild.

Resistance of *S.typhi* to commonly used antibiotics did occur in small percentage. There were three isolates of *S.typhi* resistant toward two or more drugs commonly used in the treatment of pediatric typhoid fever, but the patients were succesfuly treated with combination of that drugs. Chloramphenicol is still considered as a drug of choice for the treatment of typoid fever in children.

REFERENCES

1. Soemarmo SP. Opening remarks In: Nelwan RHH ed. Typhoid fever: profle diagnosis and treatment in the1990's. Papers presented at the first ISAC International Symposium; Bali (Balai Penerbit FKUI Jakarta, 1992) p. xvii-xviii.
2. Nathin MA, Hadinegoro SR. Ceftriaxone in the treatment of typhoid fever in children. In: Nelwan RHH ed. Typhoid fever: profle diagnosis and treatment in the 1990's. Papers presented at the first ISAC International Symposium; Bali (Balai Penerbit FKUI Jakarta, 1992) p. 133-9.
3. Jusuf H, Sudjana P. Cerebral complication of typhoid fever, Acta Med Indones 1996; XXVIII:179-83.
4. Nathin MA, Ringoringo HP, Tambunan T, Hadinegoro SR, Abdoerrachman HM, Tumbelaka AR, et al. Antibiotic resistance pattern of pediatric typhoid fever patients at the Department of child health, Cipto Mangunkusumo Hospital, Jakarta in 1990-1994, Paediatr Indones 1996; 36: 193-207.
5. Nicholson JF, Pesce MA. References ranges for laboratory tests. In: Behrman RE, Kliegman RM, Nelson WE, Vaughan lil VC eds. Nelson's textbook of pediatrics 14th ed. (WB Saunders Company Philadelphia, 1994): 1799-827.
6. Utji R. Antimicrobial therapy of typhoid fever and susceptibility of *Salmonella typhi* to antimicrobials Acta Med Indones 1996; XXVIII: 185-8.
7. Markum AH, Abdulsalam M, Moeslichan Mz. Dampak anemia gizi den pencegahannya pada anak balita Presented at: Temu Karya Anemia Gizi, Semarang 1986.
8. Feigin RD. Typhoid fever. In: Behrman RE, Kliegman RM, Nelson WE, Vaughan lil VC, eds. Nelson's textbook of pediatrics 14th ed. (WB Saunders Company Philadelphia, 1994): 731-4.
9. Soewandojo E. Typhoid fever: Management of complications and short overview of cases in Dr. Sutomo General Hospital Surabaya Indonesia, Acta Med Indones 1996; XXVIII: 159-66.
10. Hendarwanto. Clinical picture of typhoid fever. Acta Med Indones 1996; XXVIII: 151-7.