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Original Article

Impact of an antimicrobial resistance control program: pre- and post-training antibiotic use in children with typhoid fever

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Abstract

Background Antibiotics are the main treatment for typhoid fever. Inappropriate use of antibiotics may lead to antimicrobial resistance. In 2012, Dr. Soetomo Hospital conducted training for pediatric residents on the proper use of antibiotics to limit antimicrobial resistance.

Objective To evaluate the impact of a rational, antibiotic-use training program for pediatric residents on their antibiotic prescriptions for patients with typhoid fever.

Methods A cross-sectional, analytic study was conducted. We collected data from children with typhoid fever who were hospitalized in Dr. Soetomo Hospital, pre- and post-training on antibiotic prescriptions. Children with other known bacterial infections or who were discharged on request were excluded. Antibiotic prescriptions were evaluated using Gyssens algorithm based on the local protocol. Chi-square test was used to compare the quality of antibiotic prescriptions, before (year 2012) and after (year 2013) the training.

Results Forty-nine patients with 67 prescriptions in 2012 and 34 patients with 48 prescriptions in 2013 fulfilled the inclusion criteria. Patients' ages ranged from 1-18 years. Diagnoses of uncomplicated and complicated typhoid were found in 74% and 26% of subjects, respectively. First line (chloramphenicol, thiamphenicol, ampicillin, trimetroprim and sulfametoxazol) and second line (ceftriaxone and cefixime) use were 72% and 28%, respectively. All patients were discharged in good condition. Appropriate use of antibiotics was noted in 61% of subjects in 2012 and in 81% of subjects in 2013 (P=0.036). The most common type of error in 2012 and 2013 was dosage imprecision (25% and 17%, respectively).

Conclusion Training on appropriate use of antibiotics significantly improved the quality of antibiotics prescribed in children with typhoid fever in Dr. Soetomo Hospital. **[Paediatr Indones. 2016;56:205-10. doi: 10.14238/pi56.4.2016.205-10]**.

Keywords: *antimicrobial use; Gyssens algorithm; resistance; S. typhi; typhoid fever*

Typhoid fever is a systemic infection caused by *Salmonella enterica* serotype *typhi* (*S. typhi*). This disease is endemic to Indonesia, with an incidence of 350-810 cases/100,000 residents.[1] It mostly affects children aged 3 to 19 years.[2] Antibiotic treatment is the major therapy for typhoid fever. Development of *S. typhi* strains that are multidrug resistant (MDR) to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP-SMX) has been reported in India and some other Asian Country.[2] However, a study in the Pediatrics Department of Hasan Sadikin Hospital, Indonesia showed that *S. typhi* remained sensitive to first-line and second-line antibiotics in 95.7 - 100% of patients.[3]

The inappropriate use of antibiotics can lead to antimicrobial resistance. An audit of antibiotic use conducted by the *Antimicrobial Resistance Indonesia: Prevalence and Prevention* (AMRIN) task force in 2008 reported that appropriate antibiotic use for

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all infectious diseases in the Pediatrics Department of Dr. SoetomoHospital, was up to 24%.[4] Although the antibiotic sensitivity of *S. typhi* in Indonesian pediatric populations is good, the low proportion of appropriate antibiotic use raises concerns about the development of antimicrobial resistance. Resistance can lead to increased severity of patients' illness as well as treatment costs.[5] Therefore, we conducted an antimicrobial resistance control training program to prevent antimicrobial resistance. One such program was pediatric resident training on the proper use of antibiotics conducted in November 2012. Therefore, this study was conducted to evaluate the impact of rational, antibiotic-use training for pediatric residents on their antibiotic prescription performance.

Methods

This was a cross-sectional study included all children with typhoid fever who were hospitalized in Dr. Soetomo Hospital, Surabaya, East Java, from 1 January 2012 to 31 December 2013. In order to obtain a specific and valid evaluation of antibiotic use, we excluded patients with bacterial infections other than *S. typhi*, based on positive culture results. Patients with incomplete medical records or who were discharged on request were also excluded. Typhoid fever was diagnosed based upon clinical manifestation (fever >5 days and gastro-intestinal disturbance) with positive serological test (IgM salmonella Tubex ≥ 4 or Widal O/A/B ≥ 1/200). We collected data on patient characteristics, i.e., sex, age, length of hospital stay, laboratory diagnosis for typhoid fever, and severity (uncomplicated or complicated typhoid fever). We also collected data on antibiotic prescriptions, i.e.,name of antibiotic, duration of therapy, dosage, interval, route, and time of prescription.

The proper use of antibiotic training was held in November 2012, and all of the participants started having a duty to take care of hospitalized patients in the beginning of 2013. We divided in to 2 groups: pre-training (1 January -31 Desember 2012) and post-training (1 January -31 December 2013).

Some subjects received more than one antibiotic prescription. Using Gyssens algorithm,[6] we compared the prescriptions to the education module of the Pediatrics Department at Dr. Soetomo Hospital[7] and the *Indonesian Pediatrics Association* guidelines.[8] Gyssens algorithm was chosen because this algorithm was standardized and useful for evaluating the use of antibiotics in six categories: definitely appropriate (0), inappropriate indication (V), inappropriate choice (IV), inappropriate duration (III), inappropriate dose (II) and inappropriate timing (I). Inappropriate choice was divided into four subcategories: more effective antibiotic (IVa), antibiotic with lower toxicity (IVb), less expensive antibiotic (IVc), and narrower spectrum antibiotic (IVd). Inappropriate duration was divided in two subcategories: too long (IIIa) and too short (IIIb) durations. Inappropriate dose was divided in three subcategories: inappropriate dose (IIa), inappropriate interval (IIb), and inappropriate route (IIc). For the purposes of statistical comparative analysis, quality of antibiotic use was expressed as a percentage of 'appropriate' (including appropriate timing, dosage, duration, and choice) and 'inappropriate' (including inappropriate timing, dosage, duration or choice).

Data was processed and analyzed by Microsoft Excel 2007 and SPSS 17.0 software. We compared the quality between year 2012 (pre-training) and 2013 (post-training) using Chi-square test, with a $P<0.05$ level of significance.

Results

There were 128 children with typhoid fever in year 2012 and 2013, but only 83 patients fulfilled the inclusion criteria of the study, consisting of 49 patients with

Table 1. Characteristics of subjects with typhoid fever

Characteristics	Year 2012 (n=49)	Year 2013 (n=34)
Gender, n		
Male	28	14
Female	21	20
Age, n		
< 3 years	9	4
3 - 6 years	12	9
> 6 years	28	21
Typhoid test, n		
Widal	5	2
Tubex	44	32
Typhoid severity, n		
Uncomplicated	38	23
Complicated	11	11

Table 2. Quality of antibiotic use expressed as appropriate or inappropriate in 2012 and 2013

Year	Antibiotic-use quality		Total (N)
	Appropriate/Gyssens 0, n	Inappropriate/Gyssens I-V, n	
2012	41	26	67
2013	39	9	48

X2 = 4.408, df =1, P=0.036

Table 3. Quality of antibiotic use expressed in Gyssens categories in 2012 and 2013

Gyssens category	Year 2012 n(%)	Year 2013 n(%)
0	41(61.2)	39(81.3)
I	1(1.5)	0
II a	17(25.4)	8(16.7)
II b	0	0
II c	0	0
III a	0	0
III b	0	0
IV a	7(10.4)	1(2.1)
IV b	1(1.5)	0
IV c	0	0
IV d	0	0
V	0	0
Total	67(100)	48(100)

0: appropriate; I: inappropriate timing; IIa: inappropriate dose; IIb: inappropriate interval; IIc: inappropriate route; IIIa: too long duration; IIIb:too short duration; IVa: alternative agent more effective; IVb: alternative agent less toxic; IVc: alternative agent less expensive; IVd: alternative agent less broad spectrum; V: inappropriate indication

67 prescriptions in year 2012 and 34 patients with 48 prescriptions in year 2013. Patient characteristics are shown in **Table 1**. Severity of typhoid was divided into uncomplicated and complicated. The complications of typhoid fever were thrombocytopenia (6/83), pneumonia (3/83), pleural effusion (2/83), hemodynamic shock (3/83), hepatitis (1/83), severe anemia or gastrointestinal bleeding needing blood transfusion (2/83), cholecystitis (1/83), and ileus (1/83) or urinary tract infection (1/83). Antibioticsused in 2012 were ampicillin (21%), chloramphenicol (49%), thiamphenicol (7%), ceftriaxone (16%), and cefixime (6%). Those used in 2013 were ampicillin (17%), chloramphenicol (42%), thiamphenicol (6%), ceftriaxone (28%), and cefixime (6%).

Quality of antibiotic use expressed as "appropriate" or "inappropriate" is shown in **Table 2.** The 2013 quality of antibiotic use was significantly improved compared to that of 2012 (P=0.036). Quality of an-

Table 4. Quality of antibiotic use expressed in Gyssens category based on the type of antibiotic in 2012 and 2013

Gyssens Category	Ampicillin		Chloramphenicol		Thiamphenicol		Ceftriaxone		Cefixime	
	2012 (n=14)	2013 (n=8)	2012 (n=33)	2013 (n=20)	2012 (n=5)	2013 (n=3)	2012 (n=11)	2013 (n=14)	2012 (n=4)	2013 (n=3)
0	11	8	22	18	4	3	0	7	4	3
Appropriate	11	8	22	18	4	3	0	7	4	3
I	0	0	1	0	0	0	0	0	0	0
II a	2	0	4	2	1	0	10	6	0	0
II b	0	0	0	0	0	0	0	0	0	0
II c	0	0	0	0	0	0	0	0	0	0
III a	0	0	0	0	0	0	0	0	0	0
III b	0	0	0	0	0	0	0	0	0	0
IV a	1	0	4	0	0	0	1	1	0	0
IV b	0	0	2	0	0	0	0	0	0	0
IV c	0	0	0	0	0	0	0	0	0	0
IV d	0	0	0	0	0	0	0	0	0	0
V	0	0	0	0	0	0	0	0	0	0
Inappropriate	3	0	11	2	1	0	11	7	0	0

0, appropriate; I, Inappropriate timing; IIa, Inappropriate dose; IIb, Inappropriate interval; IIc, Inappropriate route; IIIa, duration too long; IIIb, duration too short; IVa, alternative agent more effective; IVb, alternative agent less toxic; IVc, Alternative agent less expensive; IVd, alternative agent less broad spectrum; V, Inappropriate indication

tibiotic use expressed as Gyssens categories is shown in **Table 3**. The most common type of error in 2012 was category IIa (inappropriate dosage), followed by category IVa (more effective antibiotic), category IVb (antibiotic with lower toxicity), and category I (inappropriate timing). Giving second line antibiotics for uncomplicated typhoid or giving first line antibiotics for complicated typhoid were categorized as IVa. Giving chloramphenicol to a patient with iron deficiency anemia was categorized as IVb. Antibiotic therapy that started more than three days after obtaining the serological test result was considered to becategory I. However, inappropriate use in categories I and IVb was not observed in 2013 subjects.

Inappropriate uses of antibiotics occurred for all antibiotic types except cefixime (**Table 4**). The most common inappropriate use was in the use of ceftriaxone.

Discussion

Multidrug resistant strains of *S. typhi* were reported inthe Indian subcontinent and other Asian countries. The WHO recommendations for fully sensitive and MDR typhoid fever are fluoroquinolone and 3rd generation cephalosporin.[2] However, we found that the most commonly used antibiotic to treat children with typhoid fever in our study was chloramphenicol. In Indonesia, chloramphenicol is the drug of choice for children with typhoid fever. A study conducted in the Pediatrics Department of Hasan Sadikin Hospital found the sensitivity of *S. typhi*to chloramphenicol to be 94.3-100%.[3]

One of several factors contributing to antimicrobial resistance is inappropriate use of antibiotics. As such, residents at Dr. Soetomo Hospital underwent training on the proper use of antibiotics. We found that the appropriate use of antibiotics was significantly improved after the training (2013) than before the training (2012) (P=0.036). Similarly, a systematic review by Roque*et al*. reported that quality of antibiotic use improved after clinician education (92% of the total studies).[9]

Training in Dr. Soetomo Hospital was provided in the form of seminars, workshops, and interactive problem solving in small groups. These methods were chosen in order to improve retention. The AMRIN study in 2008 reported that the appropriate use of antibiotics for all pediatric diseases was about 24%. Given this dismal result, efforts were made to improve the quality of prescribing antibiotics in the form of clinician training. Indeed, we observed an increase in the appropriate use of antibiotics in children with typhoid fever after the training (from 61% to 81%). Hence, we are on the right track for preventing antimicrobial resistance.

The errors found in our 2012 subjects were inappropriate dose, choice and timing. But in 2013, only inappropriate dose and choice were found (**Table 3**). The most common error in both 2012 and 2013 was improper dosage, (under- or over-dosing). An under dosed prescription can lead to resistance and therapeutic failure,[10] but in this study, there were seven cases (7/67) in 2012 and two cases (2/48) in 2013. Under-dosed prescription wa smostly found in the use of chloramphenicol (5/67).

Overdosed prescription also has negative effects.[12] Ceftriaxone was prescribed at 100 mg/kg/day with maximum doses of 2 g/day given twice a day, while the local guideline doses were 50 mg/kg/day given twice a day or 80 mg/kg/day given once a day. This use of a higher dose was based on clinical experience in previous years. According to Katzung (2010), ceftriaxone can be administered at 50-100mg/kg/day with maximum doses of 2g/day given once or twice a day for bacterial infections.[12] As such, 100mg/kg/day of ceftriaxone was categorized as an overdose because of dissonance between the guidelines and empiric experience. A review of the local guidelines to determine the correct dose range for ceftriaxone is needed.

Other errors found in this study were inappropriate timing and choice. Inappropriate choice was found in both 2012 and 2013 (**Table 3**). Prescribing second-line antibiotics for uncomplicated typhoid and first-line for complicated typhoid were categorized as IVa (7/67 in 2012 and 1/48 in 2013). This result suggests that the use of second line antibiotics was less common after training than before training. Prioritizing first line antibiotic use and using second line only in advanced disease, is one of the strategies to prevent resistance.[13] Therefore, emphasis on the appropriate use of first and second line antibioticsis needed in the next training session. Inappropriate choice in IVb category was also found, but in only

one case in 2012, i.e., prescribing chloramphenicol to a patient with iron deficiency anemia.

In some cases, replacement of the antibiotic type was needed. We found that 12 appropriate stepped-up antibiotic replacements (from first-line to the second-line) were made during 2012 and 2013. These antibiotic replacements were based on clinical and laboratory evaluations done during the first antibiotic therapy. Replacements were made for patients whose conditions worsened (7% cases in 2012 and 8% cases in 2013). Another reason of for replacement was the absence of fever defervescence after the expected time limit (3% cases in 2012 and 2% cases in 2013). The expected time limits for fever defervescence are: 3-7 days for chloramphenicol,[14,15] 7-10 days for ampicillin,[16] 4-5 days for ceftriaxone,[17] and 6 days for cefixime.[18] The need for replacement antibiotics may be related to the strain of *S. typhi* and its resistance to antibiotics. Ideally, cultures with antibiotic sensitivity tests help clinicians identify the most appropriate antibiotic. However, antibiotic sensitivity tests could not be done because of the difficulty in culturing *S. typhi* in children with typhoid fever.[19]

Route of antibiotic administration was changed for all subjects. Patients were switched from an injection route to an oral route after their conditions had improved and they were ready for discharge. Oral antibiotics are easier for caregivers to administer at home. Antibiotic therapy for typhoid patients should be continued for an adequate duration to avoid relapse or developing a carrier state. Therefore, switching from injection to oral route is very important.

In conclusion, a significant difference on the quality of antibiotic-use for treatment of pediatric typhoid fever was seen between 2012 and 2013. This improvement occurred after training on the proper use of antibiotics, as part of the antimicrobial resistance control program at Dr. Soetomo Hospital. The most frequent types of errors found in 2012 (before and during training) were inappropriate dose, choice, and timing. But in 2013 (after training), there were significantly fewer errors and the types observed were only inappropriate dose and choice.

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Conflict of interest

None declared.

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