ORIGINAL ARTICLE

Evaluation of Antimicrobial Prescription in Empiric and Definitive Therapy Of Bloodstream Infections due to *Salmonella spp.* and *Salmonella typhi*

Muhammad Riko Dadiarta[1], Osman Sianipar[2], Arum Tri Wahyuningsih[2]

[1] Student of Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada
[2] Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada

ABSTRACT

Introduction: As the main cause of typhoid, *Salmonella spp.*, especially *Salmonella typhi* contribute to the incidence of community-acquired bloodstream infections in developing countries. Annually, there are around 20 million cases of typhoid fever and more than 150,000 deaths reported. However, several studies suggest *Salmonella spp.* have become resistant to some antimicrobials. This resistance to antibiotics may be caused by inappropriate antimicrobial prescriptions. **Methods:** This research was a descriptive observational study. Data of clinical isolates of *Salmonella spp.* from blood cultures and results of antimicrobial sensitivity tests were obtained from the Clinical Laboratory Installation of Dr. Sardjito General Hospital. The data were then processed and analyzed using descriptive statistics and proportion tests. **Results:** We obtained 14 isolates of Salmonella spp. and 11 isolates of Salmonella typhi. All of the *Salmonella spp.* isolates were resistant to cefazolin, but 100% of isolates were sensitive to aztreonam, ceftazidime, ciprofloxacin, etc. All of the *Salmonella typhi* isolates were resistant to tetracycline and cefazolin, but 100% of isolates were sensitive to aztreonam, ceftazidime, ciprofloxacin, etc. The number of inappropriate definitive antimicrobial prescriptions due to *Salmonella spp.* and *Salmonella typhi* infections at Dr. Sardjito General Hospital was 47.36% (p=0.0015;95%CI:0.2846-0.6614). The proportion of cephalosporin used as empiric therapy for bloodstream infection was 68% (95%CI:0.52-0.83). **Conclusions:** Significant number of inappropriate antimicrobial prescriptions in definitive treatment of bloodstream infections caused by *Salmonella typhi* and *Salmonella spp.* were found at Dr. Sardjito General Hospital in 2018. More efforts are needed to properly prescribe antimicrobials and prevent increases in antibiotic resistance microbes.

Keywords: Antimicrobial resistance, Definitive antimicrobial, Empirical antimicrobial, *Salmonella spp.*, *Salmonella typhi*.

Corresponding Author:
Arum Tri Wahyuningsih, PhD
Email: arumtriw@ugm.ac.id
Tel: +62-811-2655990

INTRODUCTION

Salmonella enterica is the main cause of community-acquired bloodstream infections in developing countries. One dangerous serovarian is *Salmonella typhi*. Systemic blood flow infection by this bacterium is a part of the pathophysiology of typhoid fever. The World Health Organization (WHO) reports every year there are over 20 million cases of typhoid fever with more than 150,000 deaths. Alarmingly, there were 216,500 deaths reported in 2004 (1, 2). In South Asia, the incidence of typhoid fever with positive blood cultures in children aged 5-15 years has reached up to 400-500 cases per 100,000 population, in Southeast Asia 100-200 cases per 100,000 population, and in East Asia less than 100 cases per 100,000 population (3). Without effective therapy, the Case Fatality Rate reaches 10-30%, which can be reduced to 1-4% if patients receive appropriate therapy (4).

Typhoid fever may even affect the economy of a country. Based on research involving five Asian countries (China, Indonesia, India, Pakistan, and Vietnam), inpatient care costs USD $432 in Indonesia, while outpatient care costs USD $57. It reported also that in Indonesia adult cases were more severe than children's cases, the public costs of treatment of inpatient treatment were higher for children than adults. In most cases costs were still a significant burden incurred by the patient's family, with out of pocket spending around 15% of total family income per year (5). Based on the results of *Riset Kesehatan Dasar* (Riskesdas) in 2007, typhoid fever prevalence in Indonesia reached 1.6%, with Nanggroe Aceh Darussalam having the highest prevalence rate (2.96%), Bengkulu (2.58%), West Papua (2.38%),

and East Nusa Tenggara (2.33%), while the highest prevalence distribution according to age group was the age of 5-14 years (1.9%), age 1-4 years (1.6%), age 15-24 years (1.5%), and age less than 1 year (0.8%) (6).

Systemic bloodstream infections can cause high morbidity and mortality and is one of the most common complications that occur in inpatients at health facilities. Research in Indonesia showed that about 8.6% of bloodstream infections are caused by *Salmonella typhi* (7). Another in Ghana showed that *Salmonella typhi* caused 36.5% of bloodstream infections (8). The high number of cases and accompanying mortality rates from *Salmonella typhi* infection, indicate the importance of providing effective therapy. The use of antimicrobial agents is still currently the main therapeutic choice for infections caused by *Salmonella typhi*. However, studies have pointed out *Salmonella typhi* has developed resistance towards several antimicrobial agents, particularly those categorized as first line treatments. Research in Bangladesh showed 43.1% isolates were resistant against amoxicillin; 33.65% were resistant against trimethoprim-sulfamethoxazole; 31.35% were resistant to chloramphenicol; and 26.4% were resistant against ciprofloxacin (9). Studies in Cambodia showed that 75% of *Salmonella typhi* isolates were Multidrug resistant (MDR), with resistance against ampicillin, chloramphenicol, and sulfamethoxazole-trimethoprim (10).

Antimicrobial resistance is one of the main problems in the health sector. More than 700,000 people die every year around the world due to infection by microorganisms resistant to antimicrobial (11). Antimicrobial resistance rates tend to increase along with the appearance of various deviations in using antimicrobials; one of which is inappropriate antimicrobial prescribing. A study in England showed that about 20% of antimicrobial prescribing at primary health centers are classified as inappropriate. Cephalosporins are broad spectrum antimicrobials widely used for the treatment of bloodstream infections caused by unknown pathogenic bacteria. A study in Indonesia showed the usage of cephalosporin as the most commonly used antimicrobial compared to other antimicrobials, reaching 45% of the total antimicrobial prescribing (12). Due to the growing number of MDR microbes, cephalosporins should be prescribed carefully to avoid the increase of antibiotic resistant bacteria.

Various attempts have been made to decrease antimicrobial resistance. One method is by evaluating the effectiveness of antimicrobials as a therapy for infection. Considering the number of cases and high mortality due to *Salmonella typhi* infection, as well as studies showing antimicrobial resistance in *Salmonella typhi*, the evaluation of antimicrobial prescribing in empirical and definitive treatment for systemic bloodstream infections due to *Salmonella spp*. and *Salmonella typhi* is vitally important.

MATERIALS AND METHODS

Design

This research was a descriptive observational preliminary study to determine the proportion of inappropriate antimicrobial prescriptions for the definitive therapy of bloodstream infections due to *Salmonella spp*. and *S. typhi* and to elaborate empirical cephalosporin prescriptions for bloodstream infections. The study was conducted from August to December 2018. Antimicrobial prescribing data for empirical and definitive therapy as well as patient clinical data, clinical isolates and antimicrobial sensitivity test results were all obtained from the Installation for Medical Records and also the Clinical Laboratory Installation, Dr. Sardjito General Hospital, which has been designated as a National Referral Hospital in the southern part of Yogyakarta and Central Java, Indonesia. The Medical and Health Research Ethics Committee (MHREC) of the Faculty of Medicine, Universitas Gadjah Mada – Dr. Sardjito General Hospital approved this study and confirmed that the protocol meets the ethical principles outlined in the Declaration of Helsinki 2013 (reference number: KE/FK/0833/EC/2018).

Study Population and Research Subjects

The minimum number of samples was calculated according to the Lemeshow formula for single proportions in one population. A number of 62 research subjects was obtained. The targeted population was patients with bloodstream infections due to *Salmonella spp*. and *Salmonella typhi* in any age range. The inclusion criteria were patients with bloodstream infections due to *Salmonella spp*. and *Salmonella typhi* in in any age group treated at Dr. Sardjito General Hospital.

Inappropriateness of antimicrobial prescribing was assessed by comparing between antimicrobial sensitivity test results with choice of antimicrobial that was provided by doctors to subjects. Proportionl of cephalosporin prescribing for empirical therapy was obtained by comparing cephalosporin prescriptions against total antimicrobial prescribing.

Data analysis

The Z test was used for single proportion in one population to analyze the inappropriateness of definitive antimicrobial prescribing and the proportions of empirical antimicrobial for bloodstream infections due to *Salmonella typhi* and *Salmonella spp*. Basic characteristics of the subject and antimicrobial sensitivity test results of *Salmonella typhi* and *Salmonella spp*. were analyzed with univariate analysis.

RESULTS

A total of 25 subjects was involved in the study, with

15 (60%) male subjects and 10 (40%) female subjects. The average age was 15.7 years (0.5 - 57.5 years), with most cases in the age groups of ≤ 5 years (36%) and 19-59 years (36%). As many as 3 subjects originated from the intensive care unit, while 17 subjects were from the adult non-intensive care and 5 were from the children non-intensive care (Table I).

Table I: Baseline demographic of research subjects

Variable	*N*	%
Sex		
• Male	15	60
• Female	10	40
Age (years old)		
• ≤ 5	9	36
• 6-18	7	28
• 19-59	9	36
• ≥ 60	0	0
Ward		
• Intensive		
○ ICU	0	0
○ PICU	3	12
• Non-intensive		
○ Adult	17	68
○ Children	5	20

N = subjects, % = percentage

From 25 blood cultures performed, 44% isolates were *Salmonella typhi* and 56% of isolates were *Salmonella spp*. Antimicrobial sensitivity test results of *Salmonella typhi* isolates are shown in Table II. Tetracycline and cephazolin were unable to kill *Salmonella typhi* isolates, with 100% showing resistant results. Isolates showing 100% susceptible results were that of aztreonam, ceftazidime, ciprofloxacin, ceftriaxone, ertapenem, cefepime and meropenem. Table III shows the antimicrobial sensitivity test results in *Salmonella spp*.

Table II: Antimicrobial sensitivity test results of *Salmonella typhi*

Antimicrobial	*N*	S, *N*(%)	I, *N*(%)	R, *N*(%)
Tetracycline	3	-	-	3 (100)
Trimethoprim-Sulfamethoxazole	11	8 (72.7)	-	3 (27.3)
Ampicillin	11	10 (90.9)	-	1 (9.1)
Amikacin	11	3 (27.3)	-	8 (72.7)
Aztreonam	11	11 (100)	-	-
Ceftazidime	11	11 (100)	-	-
Ciprofloxacin	11	11 (100)	-	-
Ceftriaxone	11	11 (100)	-	-
Cefazoline	3	-	-	3 (100)
Quinolone	3	-	3 (100)	-
Ertapenem	11	11 (100)	-	-
Cefepime	11	11 (100)	-	-
Nitrofurantoin	5	4 (80)	-	1 (20)
Gentamicin	11	3 (27.3)	-	8 (72.7)
Meropenem	8	8 (100)	-	-

N = isolate, S = Susceptible, I = Intermediate, R = Resistance

Table III: Antimicrobial sensitivity test results of *Salmonella* spp.

Antimicrobial	*N*	S, *N*(%)	I, *N*(%)	R, *N*(%)
Tetracycline	9	1 (9.1)	-	8 (90.9)
Trimethoprim-Sulfamethoxazole	11	3 (27.3)	-	8 (72.7)
Ampicillin	14	13 (92.9)	-	1 (7.1)
Amikacin	14	9 (64.3)	-	5 (35.7)
Aztreonam	13	13 (100)	-	-
Ceftazidime	14	14 (100)	-	-
Ciprofloxacin	14	14 (100)	-	-
Ceftriaxone	14	14 (100)	-	-
Cefazoline	8	-	-	8 (100)
Quinolone	8	-	8 (100)	-
Ertapenem	14	14 (100)	-	-
Cefepime	13	13 (100)	-	-
Nitrofurantoin	10	2 (20)	5 (50)	3 (30)
Gentamicin	14	9 (64.3)	-	5 (35.7)
Meropenem	5	5 (100)	-	-

N = isolate, S = Susceptible, I = Intermediate, R = Resistance

isolates. The use of cephazolin resulted in 100% isolates resistant. Those isolates were susceptible to aztreonam, ceftazidime, ciprofloxacin, ceftriaxone, ertapenem, cefepime, and meropenem.

Of the 25 study subjects, 6 subjects had no information of definitive antimicrobial in the medical record. Nineteen subjects who had information of definitive antimicrobial in the medical record, 52.63% of the subjects received appropriate definitive antimicrobial suitable with the antimicrobial sensitivity test. Meanwhile, 47.36% (p=0.0015, 95% CI = 0.2846 - 0.6614) of subjects received inappropriate definitive antimicrobials. This finding meant that either the given antimicrobial was not tested for the antimicrobial sensitivity test or either sensitivity of the antimicrobial had been tested but showed intermediate test results or resistance. The prescribing pattern of empirical antimicrobial is shown in Table IV. Subjects receiving cephalosporin as empirical antimicrobial therapy were 68% (95% CI = 0.52 - 0.83). Cephalosporins that were given as single therapy were 56% and as combination therapy as much as 12. The rest of subjects (32%) received empiric antimicrobial therapy of non-cephalosporins.

DISCUSSION

Salmonella types found in this study consisted of 44% of isolates as *Salmonella typhi* and 56% of isolates as *Salmonella spp*. Sensitivity tests showed that 100% of *Salmonella typhi* isolates were resistant against tetracycline and cephazolin, and 100% susceptible to aztreonam, ceftazidime, ciprofloxacin, ceftriaxone, ertapenem, cefepime, and meropenem. Alternately, *Salmonella spp*. isolates were 100% resistant to cephazolin, with a high level of resistance against tetracycline (72.72%) and trimethoprim-

Table IV: Empirical antimicrobial prescription

Antimicrobial	N	%	95% CI
Cephalosporin	17	68	52-83
• Single			
o Cefotaxime	7	28	
o Ceftriaxone	6	24	
o Ceftazidime	1	4	
• Combination			
o Cefotaxime and Metronidazole	1	4	
o Ceftazidime and Gentamicin	1	4	
o Ceftriaxone, Ampicillin and Gentamicin	1	4	
Non Cephalosporin	8	32	17-47
• Chloramphenicol	1	4	
• Azithromycin	1	4	
• Ampicillin and Gentamicin	1	4	
• Ampicillin	1	4	
• Ciprofloxacin	4	16	

N = subjects, % = percentage, 95% CI = 95% confidence interval

sulfamethoxazole (90.9%). Similar to *Salmonella typhi*, 100% isolates were still susceptible to aztreonam, ceftazidime, ciprofloxacin, ceftriaxone, ertapenem, cefepime and meropenem. Eliopoulos (2001) reported that resistance to trimethoprim-sulfamethoxazole is most possibly caused by efflux pumps which actively remove both molecules out from the cell (13). In addition, resistance to sulfonamides itself was announced due to the expression of genes *sul1* and *sul2* which synthesize variants of the dihydropteroate synthase enzyme. These variants could not be bound by sulfonamide molecules (14). On the other hand, investigation by Labar (2012) and Chiou (2014) mentioned that trimethoprim resistance is also strengthened by the *dfrA* gene which synthesizes variants of dihydrofolate reductase enzymes that are unable to be inhibited by the trimethoprim molecule. *Sul 1, sul 2*, and *dfrA* genes located inside the plasmids are able to be transferred to other bacteria thus gradually increasing the number of bacteria resistant to trimethoprim and sulfamethoxazole (15, 16). Similarly, resistance to tetracycline is due to the tetA and tetA (B) genes which synthesize the tetA (B) protein a tetracycline efflux pump (17). On the other hand, cephazolin resistance is caused by the *blaTEM-1* gene which synthesizes the penicillinase enzyme through hydrolyzation of cephazolin's antibiotic molecules. This gene is also found in the plasmids (18).

Antimicrobial resistance rate of *Salmonella typhi* varies in countries around the world. A study from Cambodia showed 75% of *Salmonella typhi* isolates were MDR against ampicillin, chloramphenicol, and sulfamethoxazole-trimethoprim (10). Studies performed at Tangerang Hospital, Indonesia, showed low resistance rate against ampicillin (5.4%), trimethoprim-sulfamethoxazole (8.6%), ceftriaxone (0.0%), imipenem (1.1%), meropenem (1.1%), ciprofloxacin (1.1%), and levofloxacin (3.2%) (19). Investigation in Ghana resulted in 62.7% of *Salmonella typhi* isolates were resistant to ampicillin, tetracycline (70.3%), chloramphenicol (61.4%), cefuroxime (17.4%), cotrimoxazole (13.8%); amoxicillin (8.3%), gentamicin (4.1%) amikacin (9.1%), while no bacteria were resistant to ciprofloxacin and cefotaxime (9). One study in Bangladesh showed *Salmonella typhi* isolates were resistant to ciprofloxacin (39.5%), ampicillin (68.4%), trimethoprim (57.9%), and sulfamethoxazole (68.4%). A study in Vietnam showed resistance to ampicillin, trimethoprim, and sulfamethoxazole (80.4%) and no bacteria were resistance to ciprofloxacin (16). There are various rates of antimicrobial resistance in different countries. These differences are due to the various strains of *Salmonella typhi* which have different chemo-resistance (19).

Inappropriateness in prescribing antimicrobial drugs is presently found in various types, for example prescribing unnecessary antibiotics, prescribing antimicrobial incompatible with the pathogens, inappropriate antibiotic doses and duration of therapy, or decision not to prescribe antibiotics even though the patient had indications of need to be given antibiotics (20). Our study found the percentage of inappropriate antimicrobial prescription in the bloodstream infections due to *Salmonella typhi* and *Salmonella spp*. in Dr. Sardjito General Hospital was 47.36% (p = 0.0015, 95% CI = 0.2846 - 0.6614). We found that antimicrobial prescriptions were not given in accordance with the bacteria that caused the disease. Possible causes of the inappropriateness were time consuming of the sensitivity test result led the physician to use the empirical therapy for live savings. As a comparison against other countries, the percentage of inappropriate antimicrobial prescription in Britain was 20% (11) and in Lebanon was 72.16%. Those numbers were an accumulation of inappropriate antibiotic prescribing (61.54%), inappropriate administration of antibiotic doses (52.01%), and inappropriate duration of antibiotics therapy (63.74%) (21).

Various causes can contribute to the inappropriateness of antimicrobial prescriptions in a hospital. These include lack of available guidelines for infection therapy and the absence of bacteriogram or antibiogram, lack of training in the use of antimicrobial therapy, absence of updates regarding antibiotic resistance or insufficient quality control. Several cases (45.5%) of non-bacterial infections with clinical manifestations of fever encouraged physicians to prescribe antibiotics especially on children, as mentioned by Ruvinsky (2011) (22). Bacterial infection that occur in the age group of children might develop progressively into serious complications if antibiotics are not given immediately. These concerns have led pediatricians to prescribe antibiotics more often compared to other specialists. The cause of inappropriate antimicrobial prescription was also investigated by Cadieux *et al.* (23) who reported that

lack of knowledge possessed by physicians can influence the decision of the use of antimicrobials. Clinical experience of physicians is also related to the decision of antimicrobial prescription, where senior physicians tend to prescribe antibiotics incorrectly. Increased antibiotics prescription was also caused by personal requests of the patient him/herself which was then obeyed by the physician though no indication requiring administration was found. In addition, physicians who are dealing with large numbers of patients tend to prescribe antibiotics incorrectly compared to physicians who are treating low numbers of patients (22).

Inappropriate antimicrobial prescription can also be burdensome financially. This is especially noteworthy in the era of National Health Coverage implementation (Jaminan Kesehatan Nasional) which started in 2014. It was known that the predicted expenditure for antibiotics was 93.52% at the highest, while the lowest was 0.57% of total expenditure in a hospital. Presuming that a patient's expense becomes larger than the claimable budget, the hospital will carry the burden of excess (24). Inaccuracy of antimicrobial prescribing can also be caused by limited stock in the hospital which may force the physician to use the available stock. Practically, some patients had an adequate clinical response due to inappropriate antimicrobial prescription. From the study of Geography *et al*. (25), the irrational antibiotics usage, however, still improved clinical outcomes in 75% of patients, even though those antibiotic prescriptions are still classified as inappropriate antimicrobial prescriptions.

Hospitals should manage the incidence of antimicrobial resistance, and one way is by reducing the number of inappropriate antimicrobial prescriptions. Improper administration of antimicrobials can lead to the increased resistance to antibiotics through genetic changes in bacteria (26). All cephalosporins used as empirical therapy in this study were the third generation employed as single or combined antimicrobial therapy. The advantages of third-generation cephalosporin compared to first and second generation are they have better antibacterial activities, are stable against β-lactamase, have broader spectrum especially to gram-negative, minimal side effects, longer half-life of the drug, lower levels peaks in serum, and lower price (27). The antibiotics combination has become the better choice in treating infectious patients, because of its advantages, namely: (1) increases the extent of eradication bacteria, (2) prevents resistance, and (3) the antibacterial effect could be mutually synergistic. Selection of the right antibiotic combinations is still crucial to increase the effectiveness of therapy. However, it also has several disadvantages, including: (1) the antibacterial effects might be antagonistic, (2) may increase possible toxicity, (3) increase costs, and (4) increase possibility of superinfection (24).

In addition to the small sample population, some limitations of this study were not all patients of bloodstream infections due to *Salmonella typhi* and *Salmonella spp*. underwent the blood culture and antimicrobial sensitivity tests at Dr. Sardjito General Hospital during the short time span of this study.

CONCLUSION

The proportion of inappropriate antimicrobial prescriptions in definitive therapy of bloodstream infections due to *Salmonella typhi* and *Salmonella spp*. was significantly high considering the small number of subjects in our study. We recommend to increase the sample size for future studies and to closely monitor the progress of the antimicrobial resistance of *Salmonella typhi* and *Salmonella spp*.

ACKNOWLEDGEMENTS

We extend our deepest gratitude to the Installation Medical Records and Clinical Laboratory Installation, Dr. Sardjito General Hospital and staff for their kind help. This publication has been funded by the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada

REFERENCES

1. Crump J, Sjulund-Karlsson M, Gordon M and Parry C. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive salmonella infections. Clin Microbiol Rev. 2015;28(4):901-937.
2. World Health Organization. Typhoid fever surveillance and vaccine use, South-East Asia and Western Pacific Regions, 2009–2013. World Health Organization. 2014.
3. Ochiai RL, Acosta CJ, Agtini M, Bhattacharya SK, Bhutta ZA, Do CG, *et al*. The use of typhoid vaccines in Asia: The DOMI experience. Clin Infect Dis. 2007;45(Suppl 1):34S-38S.
4. Buckle GC, Walker CLF and Black RE. Typhoid fever and paratyphoid fever: systematic review to estimate global morbidity and mortality for 2010. J Glob Health. 2012;2(1):1-9.
5. Poulos C, Riewpaiboon A, Stewart JF, Clemens J, Guh S, Agtini M, *et al*. Cost of illness due to typhoid fever in five Asian countries. Trop Med Int Health. 2011;16(3):314-323.
6. Depkes RI. Riset Kesehatan Dasar (RISKESDAS) 2007. Jakarta: Depkes RI 2007.
7. Vollaard AM, Ali S, Widjaja S, van Asten HAGH, Visser LG, Surjadi C, van Dissel JT. Identification of typhoid fever and paratyphoid fever cases at presentation in outpatient clinics in Jakarta, Indonesia. Trans R Soc Trop Med Hyg.

2004;99:440-450.
8. Labi A, Obeng-Nkrumah N, Addison NO and Donkor, ES. Salmonella blood stream infections in a tertiary care setting in Ghana. BMC Infect Dis. 2014;14(1):1-10.
9. Afroz H, Hossain MM and Fakruddin M. A 6-year retrospective study of bloodstream Salmonella infection and antibiotic susceptibility of Salmonella enterica serovar Typhi and Paratyphi in a tertiary care hospital in Dhaka, Bangladesh. Tzu Chi Med J. 2014;26(2):73-78.
10. Vlieghe ER, Phe T, De Smet B, Veng CH, Kham C, Bertrand S, *et al*. Azithromycin and ciprofloxacin resistance in salmonella bloodstream infections in Cambodian adults. PLoS Negl Trop Dis. 2012;6(12):1-7.
11. Davies S. Reducing inappropriate prescribing of antibiotics in English primary care: evidence and outlook. J Antimicrob Chemother. 2018;73(4):833-834.
12. Sari DPP. Kajian Penggunaan Antibiotik pada Terapi Empiris dengan Hasil Terapi Di Ruang ICU RSUD "X" Periode 2015. Universitas Muhammadiyah Surakarta. 2016:5.
13. Eliopoulos G, Huovinen P. Resistance to trimethoprim-sulfamethoxazole. Clin Infect Dis. 2001;32(11):1608-1614.
14. Skuld, O. Sulfonamide resistance: mechanisms and trends. Drug Resist. Update 2000;3(3):155-160.
15. Labar AS, Millman JS, Ruebush E, Opintan JA, Bishar R, Aboderin A, *et al*. Regional dissemination of a trimethoprim-resistance gene cassette via a successful transposable element. PLoS ONE. 2012;7(5):1-10.
16. Chiou C, Lauderdale T, Phung DC, Watanabe H, Kuo J, Wang P, *et al*. Antimicrobial resistance in Salmonella enterica serovar Typhi isolates from Bangladesh, Indonesia, Taiwan, and Vietnam. Antimicrob Agents Chemother. 2014;58(11):6501-6507.
17. Guay GG, Tuckman M and Rothstein DM. Mutations in the tetA(B) gene that cause a change in substrate specificity of the tetracycline efflux pump. Antimicrob Agents Chemother. 1994;38(4):857-860.
18. Kono M, Sasatsu M, O'Hara K, Shiomi Y, Hayasaka T. Mechanism of resistance to some cephalosporins in Staphylococcus aureus. Antimicrob Agents Chemother. 1983;23(6):938- 940.
19. Lugito NH and Cucunawangsih. Antimicrobial resistance of Salmonella enterica Serovars Typhi and Paratyphi Isolates from a general hospital in Karawaci, Tangerang, Indonesia: a five-year review. Int J Med Microbiol. 2017;2017:1-7.
20. Smieszek T, Pouwels KB, Dolk FCK, Smith DRM, Hopkins S, Sharland M, *et al*. Potential for reducing inappropriate antibiotic prescribing in English primary care. J Antimicrob Chemother. 2018;73(2 suppl):pp.36S-43S.
21. Saleh N, Awada S, Awwad R, Jibai S, Arfoul C, Zaiter L. Evaluation of antibiotic prescription in the Lebanese community: a pilot study. Infect Ecol Epidemiol. 2015;5(1):27094.
22. Ruvinsky S, Monaco A, Perez G, Taicz M, Inda L, Kijko I, *et al*. Reasons for inadequate prescription of antibiotics in a high complexity pediatric hospital. Rev Panam Salud Publica. 2011;30(6):580-585.
23. Cadieux G, Tamblyn R, Dauphinee D, Libman M. Predictors of inappropriate antibiotic prescribing among primary care physicians. Can Med Assoc J. 2007;177(8):877-883.
24. Hidayat F, Setiadi AP, Setiawan E. Analisis penggunaan dan biaya antibiotik di ruang rawat intensif sebuah Rumah Sakit di Surabaya. Pharmaciana. 2017;7(2):213-230.
25. Geografi L, Wahyono D, Yasin NM. Evaluasi Penggunaan Antibiotik untuk Terapi Infeksi Saluran Kemih pada Pasien Sindrom Nefrotik Pediatri. JMPF. 2014;4(1):1-6.
26. Ventola C. The antibiotic resistance crisis. Pharm Ther. 2015;40(4):277-283.
27. Chambers S, Murdoch D, Pearce M. Clinical and economic considerations in the use of third-generation oral cephalosporins. PharmacoEconomics. 1995;7(5):416-427.