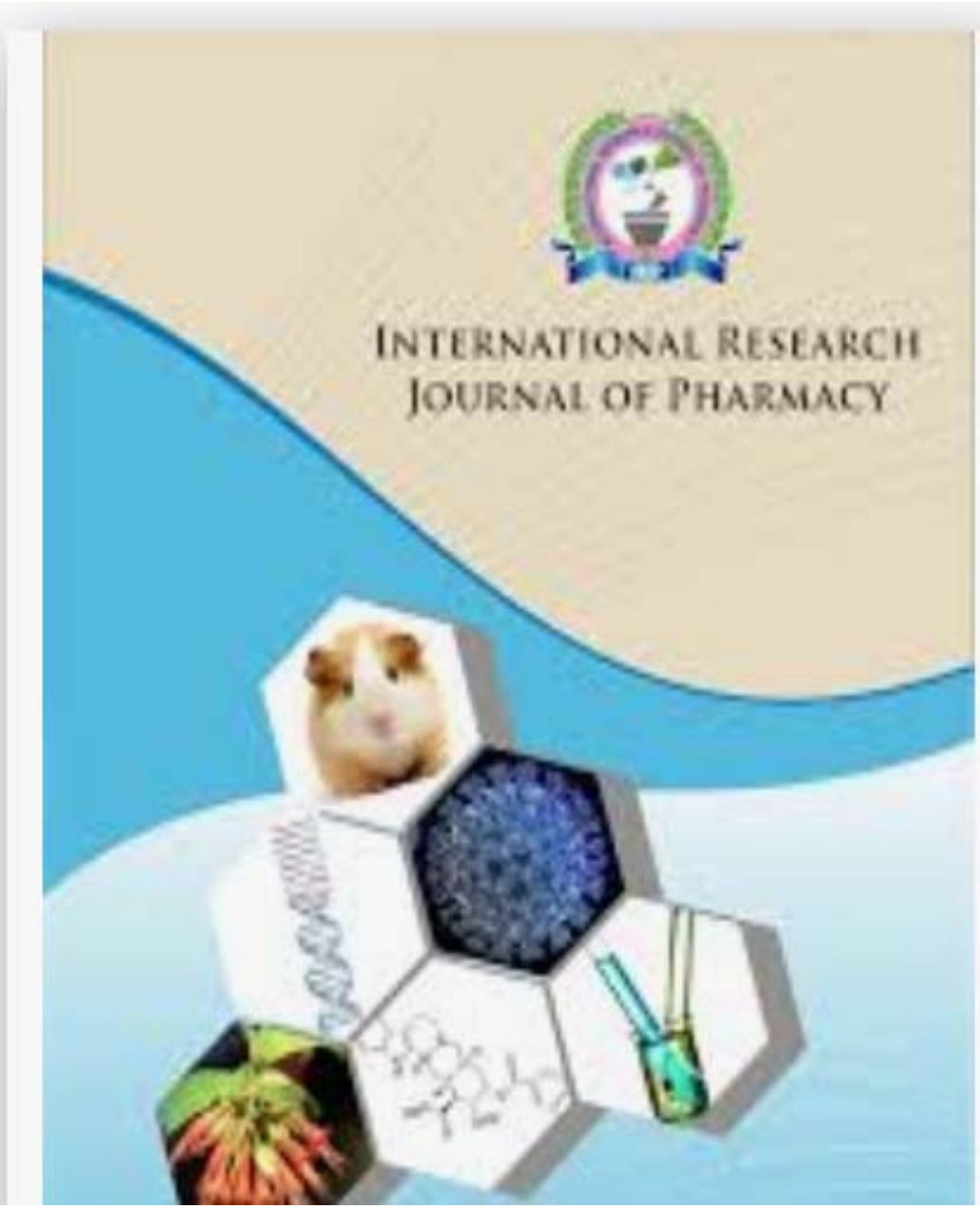
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INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

THE THIRD-GENERATION CEPHALOSPORIN USE IN A REGIONAL GENERAL HOSPITAL IN INDONESIA

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Article Received on: 23/08/18 Approved for publication: 12/09/18

DOI: 10.7897/2230-8407.099185

ABSTRACT

Antibiotic is used abundantly over time. This study aimed to determine the profile of the use of antibiotics in units of DDD/100 bed-days, types of bacteria as well as the sensitivity of bacteria in the Surgery, Obstetrics and Gynecology, and Medical Ward of Bangil Regional General Hospital, Pasuruan in 2016. The study was conducted using a descriptive, cross-sectional study design and data collection was done retrospectively. The results showed that the most-used antibiotics in surgery and medical wards are the third-generation cephalosporins, whereas in Obstetrics and Gynecology is the first-generation cephalosporins. The total DDD per bed-days of the medical ward (53.76 DDD per bed-days) is higher than surgery ward (45.83 DDD per bed-days) and Obstetrics and Gynecology ward (28.78 DDD per 100 bed-days). Only limited microbial culture perform during the study period. The most bacteria came from the isolates were *Staphylococcus aureus* and *Escherichia coli*. Antibiotic stewardship programme is urgently needed due to a high antibiotic use in the hospital.

Keywords: Antibiotic, ATC/DDD, DU 90%, bacteria sensitivity test

INTRODUCTION

The healthcare-associated infection (HAI) is one of the causes of high morbidity and mortality in the hospital. A prevalence survey in 10 geographically diverse states the USA, 183 hospitals, determine that the prevalence of HAI in acute care hospitals was 4.0% (452 of 11,282 patients, had 1 or more healthcare-associated infection).[1] The HAI prevalence in Southeast Asia was 5-10%.[2] A survey at two hospitals in Indonesia in 2001-2002 showed that the overall prevalence of HAI in hospital A was 5.9% and in hospital B 8.3%.[3] The preventable aetiological factors for HAIs were controlled the infection transmission between patients by health workers and practice a rational antibiotic use.[4]

Antibiotic indicated for bacterial infection. However, the growing population of bacteria being resistant to antibiotics threatens the success of antibiotics against infections. Inappropriate use of antibiotics will result in bacteria or microbes becoming resistant to the antibiotic, thus it causes the antibiotics losing their activity.[5-7] A study about antibiotic use qualitatively with Gyssen method showed that in Dr. Soetomo General Hospital (Surabaya city) and Dr. Kariadi General Hospital Medical Center (Semarang city), among 84% patients in those hospitals who received an antibiotic, 32% of the antibiotics used were unclear indications.[8]

Controlling the use of antibiotics is considered necessary in order to reduce the incidence of antibiotic resistance. One way of doing so is through the implementation of an Antibiotic Stewardship Program, which is an institutional or healthcare system approach to promote and monitor the use of antibiotics appropriately in order to maintain its effectiveness. The Ministry of Health in Indonesia has established an Antimicrobial Resistance Control Program (ARCP) team to support and oversee the running of Antibiotic Stewardship Program, which is recommended by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC). The Regulation of the Minister of Health No. 8 Year 2015 states that every hospital in Indonesia must implement an Antimicrobial Resistance Control Program optimally.[9-11]

MATERIALS AND METHODS

This research is conducted at Bangil Regional General Hospital. This hospital is a secondary care hospital with 272 bed. This retrospective, descriptive, observational cross-sectional study research material was data on antibiotic usage in the Surgery, Obstetrics and Gynecology, and Medical Ward of Bangil Regional General Hospital in 2016 obtained from the Pharmacy Installation and microbiology laboratory of Bangil Regional General Hospital; does not contain any studies with human participants. The study has an ethical clearance from the Health Research Ethics Committee of Politeknik Kesehatan Kemenkes Surabaya, Kementerian Kesehatan. Antibiotic usage was calculated and expressed in DDD units (defined daily dose) per 100 bed-days, as well as calculated using Drug Utilization 90% (DU 90%) method to discover the most widely used antibiotics and percentage positive isolate. In addition, data on bacterial culture obtained from the microbiology laboratory of Bangil Regional General Hospital were also used in order to find out the types of bacteria and the percentage of bacterial sensitivity in the Surgery ward during the period of January – June 2016;

Obstetrics and Gynecology, and Medical ward during the period of July – December 2016.

The equation to calculate DDD per 100 bed-days is modified from DDD/1000 population/day as follow:[11-13]

$$DDD/1000\ population/day = \frac{Amount\ used\ in\ 1\ year\ (mg) * 1000}{DDD\ (mg) x\ population\ x\ 365\ (days)}$$

…. Equation 1

Several adjustments to the equation are i. the specific period of a month, ii. bed-days derived from the total length of stays of the patient. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The calculation results of antibiotic use and percentage of bacterial sensitivity to antibiotics presented in tables.

RESULTS

There are 9679 patients in six-month periods; their average length of stay was 2.9 days, 2.5 days, 3.3 days in surgical, obstetrics and gynecology, medical ward respectively (Table 1). From a total of 3016 patients in the surgical wards of Regional General Hospital Bangil, 572 patients received antibiotic therapy. In this research, more than 50% antibiotic use in the surgical and medical ward is third-generation cephalosporins and fluoroquinolones, whereas more than 70% antibiotic use in obstetrics and gynecology ward is first-generation cephalosporins and penicillins with extended spectrum (Table 2). The total number of DDD/100 bed-days was 45.83, 28.78, 53.76 in surgical, obstetrics and gynecology, medical ward respectively, the detailed data could be seen in Table 3. According to these data, the most commonly used antibiotics in the surgical wards were ciprofloxacin (11.78 DDD/100 bed-days); in obstetrics and gynecology was cefadroxil (11.64 DDD/100 bed-days); in the medical ward was ceftriaxone (12.99 DDD/100 bed-days). From the microbiology laboratory data, there are 124 isolates which were 48 Gram-negative bacteria and 76 Gram-positive bacteria, as shown in Table 4. These bacteria are Gram-negative bacteria, such as *Escherichia coli* (12), *Acinetobacter sp.* (8), *Stenotrophomonas maltophilia* (6); and Gram-positive bacteria, such as *Staphylococcus aureus* (16).

DISCUSSION

The number of DDD/100 bed-days was 45.83. This number is similar to the number of antibiotics used in the surgical wards of Dr. Karjadi Hospital in Semarang in 2008, which was 51.8 DDD/100 patient-days and higher than the DDD/100 bed-days in other hospitals in Indonesia.[14-17] The number of antibiotics used was a combined data from all patients in the surgical wards who used antibiotics, unnoticed the diagnosis, thus the value of DDD cannot describe its appropriateness to every indication. It is necessary to conduct further research that considers the patient diagnosis during antibiotic therapy and other factors influencing the use of antibiotics.

In the calculation result regarding the number of DDD/100 bed-days, the major parenteral antibiotics used during the months of January to June 2016 were also reported, i.e ceftazidime (6.66 DDD/100 bed-days). The increase in the use of ceftazidime may be due to a shortage of ceftriaxone injection in the Pharmacy Department of Bangil Regional General Hospital in early 2016, which was most widely used in the surgical wards of Bangil Regional General Hospital. A research conducted at Dr. Kariadi Hospital in Semarang and other hospitals in Indonesia also suggested that the most widely used antibiotics were ceftriaxone.[14-17] Ceftazidime and ceftriaxone are a third-generation cephalosporin. Further research regarding the use of the third generation cephalosporin in surgical wards is needed.

From the data on DDD/100 bed-days of each antibiotic, the 90% DU segment was then calculated to identify the most commonly used antibiotics in the hospital. Antibiotics in the 90% DU segment in order from largest to smallest were cefadroxil (13.8%), ciprofloxacin (12.9%), ceftriaxone (12.2%), metronidazole (11.7%), amoxicillin (9.4%), ceftazidime (6.7%), cefixime (6.2%), ampicillin/sulbactam (5.4%), levofloxacin (5.4%), gentamicin (3.1%), cefuroxime (2.8%). Ceftriaxone, ceftazidime, and cefixime are the third-generation cephalosporins (25.1%). The third-generation cephalosporins active against Gram-positive and Gram-negative bacteria, therefore widely used in the hospital.

The use of antibiotics as therapy in patient care greatly affects the growth of bacteria, in which they could become resistant to antibiotics which shown at the local resistance patterns. In the surgical wards of Bangil Regional General Hospital, the culture test performed not for every SSI patient and patient who diagnosed open fracture. The types of bacteria isolated in the surgical wards of Bangil Regional General Hospital, *Staphylococcus aureus*, *Acinetobacter* sp., *Stenotrophomonas maltophilia*, and *Klebsiella pneumoniae* are similar to the results of a study carried out at a hospital in Yogyakarta during August 2013-August 2015.[18,19]

From microbiology data, we can't obtain microbial patterns because the number of isolates of each bacterium was insufficient and not all specimens gave positive isolate in the culture test; therefore, it was not possible to calculate the sensitivity percentages of several antibiotics due to the small number of isolates. These sensitivity test bacteria to antibiotics are classified into 3 (three) categories, i.e.: usually effective clinically, if the antibiotic sensitivity test result is more than 60% of all examinations; intermediate effective clinically, if the antibiotic sensitivity test result is between 30-60% of all examinations; and not effective clinically, if the antibiotic sensitivity test result is less than 30% based on the Sanford Guide to Antimicrobial Therapy 46th ed, 2016.[20] Further research needs a sufficient number of isolates and a standard protocol for antibiotic susceptibility tests.

Table 1: Patient's area characteristic

	Surgical ward	Obstetrics and gynecology ward	Medical ward
Number of bed	5[b]	43	104
Beds Occupancy Rate (BOR)	–	73.3%	74.3%
Number of patient[a]	3016	2360	4303
Length of stay[a]	8805	–	–
Bed-days	8805	5802	14218

[a] number of patients or patient's length of stay in six months period, [b] operating theatre

Table 2: The DDD percentage antibiotic use in hospital

Antibiotic class	Surgical ward	Obstetrics and gynecology ward	Medical ward
Third-generation cephalosporins	29%	2%	38%
Fluoroquinolones	26%	1%	21%
Other aminoglycosides	11%	2%	1%
Imidazole derivatives	9%	4%	11%
Penicillins with extended spectrum	7%	33%	1%
First-generation cephalosporins	7%	46%	6%
Carbapenems	4%	0%	2%
Nitroimidazole derivatives	4%	1%	4%
Second-generation cephalosporins	2%	5%	2%
Combinations of penicillins, incl. beta-lactamase inhibitors	1%	6%	11%
Macrolides	0%	0%	1%
Lincosamides	0%	0%	0%
Tetracyclines	0%	0%	0%
Amphenicols	0%	0%	0%
Streptomycins	0%	0%	1%
Other quinolones	0%	0%	1%

Table 3: Types antibiotics use in the hospital

No	Anatomical Therapeutic Chemical Classification	Generic Name	Surgical wards		Obstetrics and gynecology ward		Medical ward	
			DDD/100 Patient-Days	Drug Utilization	DDD/100 Patient-Days	Drug Utilization	DDD/100 Patient-Days	Drug Utilization
	Tetracyclines							
1	J01AA02	Doxycycline (O)	–	–	0.13	0.44%	–	–
	Amphenicols							
2	J01BA02	Thiamphenicol	–	–	0.04	0.13%	–	–
3	J01BA01	Chloramphenicol (P)	–	–	–	–	0.04	0.07%
	Beta-lactam antibacterials, penicillins							
4	J01CA01	Ampicilin (P)	1.09	2.38%	0.03	0.12%	0.05	0.09%
5	J01CA04	Amoxicillin (O/P)	2.08	4.53%	9.45	32.84%	0.51	0.96%
6	J01CR01	Ampicillin/Sulbactam (P)	0.40	0.87%	1.30	4.52%	5.23	9.72%
7	J01CR02	Amoxicilin/Clavulanic Acid (O)	0.12	0.26%	0.32	1.09%	0.54	1.01%
	Other beta-lactam antibacterials: cephalosporins							
8	J01DB04	Cefazolin (P)	–	–	1.56	5.41%	0.38	0.71%
9	J01DB05	Cefadroxil (O)	3.00	6.55%	11.64	40.43%	3.07	5.72%
10	J01DC02	Cefuroxime (P)	0.92	2.00%	1.46	5.08%	1.18	2.19%
11	J01DD01	Cefotaxime (P)	0.25	0.54%	0.05	0.18%	1.85	3.44%
12	J01DD02	Ceftazidime (P)	6.66	14.53%	0.08	0.28%	1.89	3.52%
13	J01DD04	Ceftriaxone (P)	2.19	4.79%	0.51	1.78%	12.99	24.16%
14	J01DD08	Cefixime (O)	4.27	9.32%	0.02	0.07%	3.68	6.84%
	Other beta-lactam antibacterials: carbapenems							
15	J01DH02	Meropenem (P)	1.76	3.83%	0.10	0.35%	1.33	2.47%
	Macrolides							
16	J01FA01	Erythromycin (O)	0.01	0.02%	–	–	0.00	0.01%
17	J01FA10	Azithromycin (O)	0.19	0.42%	0.01	0.05%	0.35	0.64%
	Lincosamides							
18	J01FF01	Clindamycin (O)	0.06	0.13%	0.03	0.09%	0.22	0.41%
	Aminoglycoside antibacterials							
19	J01GA01	Streptomycin (P)	–	–	–	–	0.64	1.18%
20	J01GB03	Gentamicin (P)	3.32	7.25%	0.48	1.68%	0.24	0.44%
21	J01GB06	Amikacin (P)	1.83	4.00%	–	–	0.06	0.12%
	Quinolone antibacterials							
22	J01MA02	Ciprofloxacin (O/P)	11.78	25.70%	0.15	0.50%	4.60	8.55%
23	J01MA12	Levofloxacin (P)	0.30	0.66%	0.03	0.12%	6.58	12.24%
24	J01MB04	Pipemidic acid (O)	–	–	–	–	0.37	0.68%
	Imidazole derivatives							
25	J01XD01	Metronidazole (P)	3.93	8.57%	1.18	4.11%	6.00	11.14%
26	P01AB01	Metronidazole (O)	1.67	3.64%	0.21	0.74%	2.00	3.71%
TOTAL			**45.83**	**100.00%**	**28.78**	**100.00%**	**53.76**	**100.00%**

O, oral; P, parenteral

Table 4: Total Isolates Bacterial in the hospital

Gram of bacteria	Type of bacteria	Surgery ward	Obstetrics and gynecology ward	Medical ward
Gram Negative	*Acinetobacter Sp.*	7	–	1
	Stenotrophomonas maltophilia	4	–	2
	Klebsiella pneumoniae	3	–	–
	Escherichia coli	2	4	6
	Enterobacter agglomerans	2	–	1
	Enterobacter aerogenes	1	–	–
	Enterobacter cloacae	1	1	1
	Klebsiella ozaenae	1	1	–
	Pragia fontium	1	–	–
	Shigella dysenterid	1	–	–
	Burkholderia cepacia	–	1	–
	Hafnia alvei	–	1	–
	Morganella morganii	–	1	1
	Serratia odorifera	–	1	1
	Enterobacter sp	–	–	1
	Salmonella sp	–	–	1
	Total Gram Negative Bacteria	**23**	**10**	**15**
Gram Positive	*Staphylococcus aureus*	9	5	2
	Staphylococcus haemolyticus	–	2	–
	Staphylococcus intermedius	–	2	1
	Staphylococcus simulans	1	–	–
	Streptococcus mitis	1	–	–
	Streptococcus pyogenes	1	1	–
	Staphylococcus xylosus	–	1	–
	Staphylococcus schleiferi	–	1	–
	Streptococcus suis	–	1	–
	Total Gram Positive Bacteria	**12**	**13**	**3**
	TOTAL	**35**	**23**	**18**

CONCLUSION

The number of DDD/100 bed-days from three wards of Bangil Regional General Hospital was 128.4. The most antibiotics use was the third-generation cephalosporins. There were 124 bacteria growing during a cultural test carried out on 35 antibiotics, the number of Gram-positive bacteria higher than the number of Gram-negative bacteria.

Impact on practice: The research will urge the organization to obtain sufficient cultural isolates to determine the microbial patterns in the Surgery, Obstetrics and Gynecology, and Medical Ward of Bangil Regional General Hospital, i.e. to perform a bacterial culture on patients who take antibiotics after 3 days, who use prophylactic antibiotics and undergo a surgical site infection; to evaluate the use of antibiotics regarding patient diagnosis; to update the antibiotic therapeutic guideline considering to the microbial pattern in the hospital.

ACKNOWLEDGMENT

This study was conducted in the collaboration framework agreement between the Faculty of Pharmacy University of Surabaya, Surabaya, and the Bangil Regional General Hospital, Pasuruan. The authors would like to thank the hospital management and staffs for their cooperation to collect the data from the patient files and to use them for the evaluation.

REFERENCES

1. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care–associated infections. N Engl J Med. 2014;370(13):1198-1208. doi:10.1056/NEJMoa1306801.
2. Ling ML, Apisarnthanarak A, Madriaga G. The burden of healthcare-associated infections in Southeast Asia: a systematic literature review and meta-analysis. Clin Infect Dis. 2015;60(11):1690-9. doi: 10.1093/cid/civ095. Epub 2015 Feb 12.
3. Duerink DO, Roeshadi D, Wahjono H, Lestari ES, Hadi U, Wille JC, et al. Surveillance of healthcare-associated infections in Indonesian hospitals. J Hosp Infect. 2006;62(2):219-29. Epub 2005 Nov 22.
4. Murni IK, Duke T, Kinney S, Daley AJ, Soenarto Y. Reducing hospital-acquired infections and improving the rational use of antibiotics in a developing country: an effectiveness study. Arch Dis Child. 2015;100(5):454-9. doi: 10.1136/archdischild-2014-307297. Epub 2014 Dec 10.
5. World Health Organization. Antimicrobial resistance: global report on surveillance [Internet]. Geneva: World Health Organization; 2014. Available from: http://www.who.int/iris/handle/10665/112642.
6. World Health Organization. World health report 2013: research for universal health coverage [Internet]. Geneva: World Health Organization; 2013. Available from: http://www.who.int/iris/handle/10665/85761.
7. Centers for Disease Control and Prevention Office of Infectious Disease. Antibiotic resistance threats in the United States, 2013. 2013. Available from: http://www.cdc.gov/drugresistance/threat-report-2013. Accessed January 28, 2015.
8. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T. 2015;40(4):277-283.
9. Hadi U, Duerink DO, Lestari ES, Nagelkerke NJ, Keuter M, Huis In't Veld D, et al. Audit of antibiotic prescribing in two governmental teaching hospitals in Indonesia. Clin Microbiol Infect. 2008 Jul;14(7):698-707. doi: 10.1111/j.1469-0691.2008.02014.x.
10. Doron S, Davidson LE. Antimicrobial stewardship. Mayo Clin Proc. 2011;86(11):1113-23. doi: 10.4065/mcp.2011.0358.
11. Indonesian Ministry of Health (IMOH). Peraturan Menteri Kesehatan Republik Indonesia Nomor 8 tahun 2015 tentang program pengendalian resistensi antimikroba di rumah sakit. Jakarta, Indonesia; 2015. Available from:

https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&cad=rja&uact=8&ved=2ahUKEwjQu6eWl63dAhUKuo8KHXM2COYQFjABegQICBAB&url=http%3A%2F%2Fperaturan.go.id%2Fpermen%2Fkemenkes-nomor-8-tahun-2015.html&usg=AOvVaw3Je9LBJhw8zJiBC1es7TNO.

12. Indonesian Ministry of Health (IMOH). Pedoman Umum Penggunaan Antibiotik. Jakarta, Indonesia; 2011. Available from: http://www.binfar.depkes.go.id/dat/Permenkes_Antibiotik.pdf. Accessed July 26, 2018.
13. ATC/DDD Index 2017 [Internet]. Date unknown. Available from: https://www.whocc.no/atc_ddd_index/. Accessed July 26, 2018.
14. WHO International Working Group for Drug Statistics Methodology, WHO Collaborating Centre for Drug Statistics Methodology & WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services. Introduction to drug utilization research. Geneva: World Health Organization; 2003.
15. Laras NW, Farida H. Kuantitas penggunaan antibiotik di bangsal bedah dan obstetri-ginekologi RSUP Dr. Kariadi setelah kampanye PP-PRA. Fakultas Kedokteran Universitas Diponegoro. Jurnal Media Medika Muda. 2012. Available from: http://download.portalgaruda.org/article.php?article=73679&val=4695.
16. Rahayuningsih N, Mulyadi Y. Evaluasi penggunaan antibiotik sefalosporin di ruang perawatan bedah salah satu rumah sakit di Kabupaten Tasikmalaya. Jurnal Kesehatan Bakti Tunas Husada. 2017; 17(1): 139-147. Available from: http://download.portalgaruda.org/article.php?article=529877&val=10872&title=EVALUASI%20PENGGUNAAN%20ANTIBIOTIK%20SEFALOSPORIN%20%20DI%20RUANG%20PERAWATAN%20BEDAH%20SALAH%20SATU%20RUMAH%20SAKIT%20DI%20KABUPATEN%20TASIKMALAYA.
17. Herawati F, Yulia R, Hak E, Hartono AH, Michiels T, Woerdenbag HJ, et al. A retrospective surveillance of the antibiotics prophylactic use of surgical procedures in private hospitals in Indonesia. Hospital Pharmacy. 2018; 00(0): 1-7. First Published August 21, 2018. https://doi.org/10.1177/0018578718792804.
18. Yezli S, Barbut F, Otter JA. Surface contamination in operating rooms: a risk for transmission of pathogens?. Surg Infect (Larchmt). 2014;15(6):694-9. doi: 10.1089/sur.2014.011.
19. Wiguna DS. Pola resistensi bakteri terhadap antibiotik pada penderita infeksi luka operasi (ILO) Di Rumah Sakit X periode Agustus 2013-Agustus 2015 [Skripsi]. Fakultas Farmasi Universitas Muhammadiyah Surakarta. 2016. Available from: http://download.portalgaruda.org/article.php?article=73679&val=4695.
20. Gilbert DN, Chambers HF, Eliopoulos GM, Saag MS, Pavia AT, Black D, et al.. The Sanford guide to antimicrobial therapy. 46th ed. Sperryville, VA: Antimicrobial Therapy, Inc.; 2016.

Cite this article as:

Rika Yulia *et al*. The third-generation cephalosporin use in a regional general hospital in Indonesia. Int. Res. J. Pharm. 2018;9(9):41-45 http://dx.doi.org/10.7897/2230-8407.099185

Source of support: Nil, Conflict of interest: None Declared