



## Research Article

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

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#### 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).<sup>1</sup> The HAI prevalence in Southeast Asia was 5-10%.<sup>2</sup> 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%.<sup>3</sup> The preventable aetiological factors for HAIs were controlled the infection transmission between patients by health workers and practice a rational antibiotic use.<sup>4</sup>

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.<sup>5-7</sup> 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.<sup>8</sup>

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.<sup>9-11</sup>

#### 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:<sup>11-13</sup>

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

.... 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.<sup>14-17</sup> 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.<sup>14-17</sup> 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.<sup>18,19</sup>

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 46<sup>th</sup> ed, 2016.<sup>20</sup> 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 <sup>b</sup> | 43                             | 104          |
| Beds Occupancy Rate (BOR)      | –              | 73.3%                          | 74.3%        |
| Number of patient <sup>a</sup> | 3016           | 2360                           | 4303         |
| Length of stay <sup>a</sup>    | 8805           | –                              | –            |
| Bed-days                       | 8805           | 5802                           | 14218        |

<sup>a</sup> number of patients or patient's length of stay in six months period, <sup>b</sup> 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 |
|    |  | <b>Tetracyclines</b>                                    |                      |                  |                                |                  |                      |                  |
| 1  | J01AA02  | Doxycycline (O)   | –                    | –                | 0.13                           | 0.44%            | –                    | –                |
|    |  | Amphenicols   |                      |                  |                                |                  |                      |                  |
| 2  | J01BA02  | Thiamphenicol   | –                    | –                | 0.04                           | 0.13%            | –                    | –                |
| 3  | J01BA01  | Chloramphenicol (P)                                     | –                    | –                | –                              | –                | 0.04                 | 0.07%            |
|    |  | <b>Beta-lactam antibacterials, penicillins</b>          |                      |                  |                                |                  |                      |                  |
| 4  | J01CA01  | Ampicillin (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  | Amoxicillin/Clavulanic Acid (O)                         | 0.12                 | 0.26%            | 0.32                           | 1.09%            | 0.54                 | 1.01%            |
|    |  | <b>Other beta-lactam antibacterials: cephalosporins</b> |                      |                  |                                |                  |                      |                  |
| 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%            |
|    |  | <b>Other beta-lactam antibacterials: carbapenems</b>    |                      |                  |                                |                  |                      |                  |
| 15 | J01DH02  | Meropenem (P)   | 1.76                 | 3.83%            | 0.10                           | 0.35%            | 1.33                 | 2.47%            |
|    |  | <b>Macrolides</b>                                       |                      |                  |                                |                  |                      |                  |
| 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%            |
|    |  | <b>Lincosamides</b>                                     |                      |                  |                                |                  |                      |                  |
| 18 | J01FF01  | Clindamycin (O)   | 0.06                 | 0.13%            | 0.03                           | 0.09%            | 0.22                 | 0.41%            |
|    |  | <b>Aminoglycoside antibacterials</b>                    |                      |                  |                                |                  |                      |                  |
| 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%            |
|    |  | <b>Quinolone antibacterials</b>                         |                      |                  |                                |                  |                      |                  |
| 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%            |
|    |  | <b>Imidazole derivatives</b>                            |                      |                  |                                |                  |                      |                  |
| 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%            |
|    |  | <b>TOTAL</b>  | <b>45.83</b>         | <b>100.00%</b>   | <b>28.78</b>                   | <b>100.00%</b>   | <b>53.76</b>         | <b>100.00%</b>   |

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 |
|----------------------|-------------------------------------|-------------------------------------|--------------------------------|--------------|
| <b>Gram Negative</b> | <i>Acinetobacter Sp.</i>            | 7                                   | –                              | 1            |
|                      | <i>Stenotrophomonas maltophilia</i> | 4                                   | –                              | 2            |
|                      | <i>Klebsiella pneumoniae</i>        | 3                                   | –                              | –            |
|                      | <i>Escherichia coli</i>             | 2                                   | 4                              | 6            |
|                      | <i>Enterobacter agglomerans</i>     | 2                                   | –                              | 1            |
|                      | <i>Enterobacter aerogenes</i>       | 1                                   | –                              | –            |
|                      | <i>Enterobacter cloacae</i>         | 1                                   | 1                              | 1            |
|                      | <i>Klebsiella ozaenae</i>           | 1                                   | 1                              | –            |
|                      | <i>Pragia fontium</i>               | 1                                   | –                              | –            |
|                      | <i>Shigella dysenterid</i>          | 1                                   | –                              | –            |
|                      | <i>Burkholderia cepacia</i>         | –                                   | 1                              | –            |
|                      | <i>Hafnia alvei</i>                 | –                                   | 1                              | –            |
|                      | <i>Morganella morganii</i>          | –                                   | 1                              | 1            |
|                      | <i>Serratia odorifera</i>           | –                                   | 1                              | 1            |
|                      | <i>Enterobacter sp</i>              | –                                   | –                              | 1            |
|                      | <i>Salmonella sp</i>                | –                                   | –                              | 1            |
|                      | <b>Total Gram Negative Bacteria</b> | <b>23</b>                           | <b>10</b>                      | <b>15</b>    |
| <b>Gram Positive</b> | <i>Staphylococcus aureus</i>        | 9                                   | 5                              | 2            |
|                      | <i>Staphylococcus haemolyticus</i>  | –                                   | 2                              | –            |
|                      | <i>Staphylococcus intermedius</i>   | –                                   | 2                              | 1            |
|                      | <i>Staphylococcus simulans</i>      | 1                                   | –                              | –            |
|                      | <i>Streptococcus mitis</i>          | 1                                   | –                              | –            |
|                      | <i>Streptococcus pyogenes</i>       | 1                                   | 1                              | –            |
|                      | <i>Staphylococcus xylosus</i>       | –                                   | 1                              | –            |
|                      | <i>Staphylococcus schleiferi</i>    | –                                   | 1                              | –            |
|                      | <i>Streptococcus suis</i>           | –                                   | 1                              | –            |
|                      |                                     | <b>Total Gram Positive Bacteria</b> | <b>12</b>                      | <b>13</b>    |
|                      | <b>TOTAL</b>                        | <b>35</b>                           | <b>23</b>                      | <b>18</b>    |

## 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.

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