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Research Article

Influence of historical use of antibiotics toward antibiotic resistance

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ABSTRACT

A WHO's Global Surveillance of Antibiotic Resistance showed there is an increase of antimicrobial resistance in Asia between 2013 until 2014. Many studies showed that there is a correlation between prior antibiotic use with antimicrobial resistance case. The primary objective of this study is to analyze the relationship between prior antibiotic use with antimicrobial resistance. İt was a retrospective and descriptive study conducted at Bangil Regional General Hospital. The data collected from the medical record and microbiological test from the patient at the internal ward. Chi-square analysis used for the statistic. This study showed that prior antibiotic use increased 0,399 bigger for antimicrobial resistance rate (p=0,001).

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INTRODUCTION

Global Surveillance of Antibiotic Resistance conducted by the World Health Organization (WHO) shows an increase in the incidence of antibiotic resistance from 2013 to 2014 on the Asian continent. Southeast Asia is one region that has a high prevalence of antibiotic resistance and occurs in almost all classes of antibiotics (World Health Organization, 2013). Antibiotic resistance is the ability of a microorganism to fight or resist the effects of one or more antibiotics (World Health Organization, 2015). Resistance can occur in cases of different infectious diseases or bacteria.

Research conducted in Indonesia in the period 1998-1999 showed for *Salmonella spp*. experience resistance to several antibiotics such as ampicillin (7%), chloramphenicol (15%), tetracycline (20%), cotrimoxazole (10%), ceftriaxone (2%), kanamycin (10%), norfloxacin (1%), cephalothin (7%), neomycin (3%) (Lestari, Severin & Verbrugh, 2012). Several factors are thought to be the cause of resistance, including bacterial gene mutations, horizontal gene transfer between bacterial species, and inappropriate use of antibiotics.

In addition to the things mentioned above, several studies show that there is a relationship between

antibiotic resistance and antibiotic use over a certain period (prior antibiotic use) before the patient diagnosed with resistance. Research conducted by Kuster et al. (2014) showed that prior antibiotic use has a relationship with the occurrence of resistance in a patient at three months after the last time using the antibiotic in question.

Research on this subject is very little, so the authors are interested in observing this because knowing the presence or absence of the influence of prior antibiotic use on the occurrence of resistance can help the clinician in determining which therapy is more appropriate for the patient. The use of 3 months as a reference from the time of last antibiotic use was due to a study conducted by Kuster et al. (2014), which showed that the possibility of resistance from an antibiotic to return to baseline level was 90 days after the last dose gave to patients.

RESEARCH METHODS

This study is retrospective and descriptive. Data obtained from medical records and bacterial culture results of all internal medicine patients in Bangil Regional General Hospital in July to December 2016.

Based on medical records obtained and then traced to patients diagnosed with an infection and using antibiotics so that patients who had infections but did not get antibiotics and outpatients included in the exclusion criteria in this study. Patients who are known to have an infection and get antibiotics will then be traced to a history of antibiotic use for three months before the patient is admitted to the hospital and observed the occurrence of resistance in these patients based on the results of the culture.

The analytical method for proving the relationship between antibiotic use after patients hospitalized with resistance was tested statistically using the chi-square method. The results of processing the next data will show in tables and diagrams.

RESULT AND DISCUSSIONS

Patients who were hospitalized in the internal hospital ward Bangil in July to December 2016 reached 4303 people with the highest number of patients, namely 846 people in November and the lowest as many as 600 people in July. The total patients through BPJS funding were 2348 patients (54.57%), private insurance as many as 4 patients (0.093%), GAKIN APBD 90 patients (2.1%), Jamkesmas 2 patients (0.046%), SPM 1247 patients (28 , 98%), and general as many as 612 patients (14.22%).

The value of 54.57% of patients whose funding through BPJS resembles the coverage of BPJS in East Java Province which amounted to 59.16% in 2016 (Kementrian Kesehatan Republik Indonesia [Kemenkes RI], 2017). The number of patients whose funding through BPJS on inpatient wards also resembled the coverage of BPJS participation in 2015 in East Java Province which amounted to 55.95% (Kemenkes RI, 2017).

The most common diagnosis of the cause of culture is Complication of procedures, not elsewhere classified as many as 33 patients followed by infection in the surgical wound which also includes cesarean surgery as many as 30 patients then pneumonia as many as 19 patients.

Table 1. Antibiotic sensitivity profile in the group of patients with a history of antibiotic use over the past three months.

Culture Diagnosis	Total
The complication of procedures, not elsewhere classified	33
Infection of obstetric surgical wound	30
Pneumonia	23
Osteomyelitis	12
Cutaneous abscess	9
Type 2 diabetic with gangrene	7
Bacteremia	2
Vulvovaginitis	2
Rheumatic heart disease	2
Abses submandibular	1
Acute pharyngitis	1
Burn of an unspecified body region	1
Corneal ulcer	1
Diare and gastroenteritis presume infectious origin	1
Fracture	2
skin ulcer	1
Urine tract infection, site not specified	1
Staphylococcal arthritis elbow	1
Sepsis due to E.coli	1
Cellulitis	2
Nontoxic goiter	1
Meningitis	1
Laryngeal diphtheria	1
Intracranial injury, unspecified	1
Impetigo bullous	1
Generalized skin eruption due to drugs and medicaments taken internally	1
Total	**140**

Table 2. Antibiotic sensitivity profiles in the group of patients with a history of antibiotic use over the past three months.

Antibiotics	Sensitivity	
	Sensitive	Resistent
Amikacin	1	-
Amoxicillin	-	-
Ampisillin	-	-
Azythromycine	-	-
Benzathine Penicillin	-	-
Metronidazole	-	-
Cefadroxil	-	-
Cefazolin	1	-
Cefixime	-	-
Ceftazidime	6	3
Ceftriaxone	2	-
Cefuroxime	1	-
Ciprofloxacine	1	1
Doxycline	-	1
Gentamicin	3	-
Total	**15**	**5**

Table 3. Antibiotic sensitivity profile in the patient group without a history of antibiotic use in the last three months.

Antibiotic Class	**Sensitivity**	
	Sensitive	**Resistent**
Penicillin	203	352
Cephalosporin	146	336
Aminoglycoside	76	117
Macrolide	34	40
Amphenicol	20	18
Carbapenem	59	37
Lincosamide	25	20
Streptomycin	-	-
Imidazole	-	-
Anti TBC	18	6
Quinolon	155	257
Others	170	118
Total	**906**	**1301**

Observations were made regarding the history of antibiotic use by patients over the past three months. Of the 140 samples, there were 78 samples where the patient had a history of antibiotic use in the last three months before the culture was carried out and the remaining 62 patients had no history of antibiotic use. Patients who have a history of antibiotic use in the last three months have observed sensitivity. From the results of these observations for ceftazidime, antibiotics had the highest number of sensitive results (6 samples) while for antibiotics that had the highest resistance level was cefazolin (14 samples). Cefadroxil is the most commonly found antibiotic in the history of antibiotic use with as many as 35 samples, but there is no sensitivity data from the antibiotic.

From patients who did not have a history of antibiotic use, meropenem became an antibiotic with the highest number of sensitive samples as many as 59 samples then followed by piperacillin + tazobactam and norfloxacin (52 samples) and cotrimoxazole (44 samples)

Based on observations in groups with a history of use, antibiotics that showed sensitive results found in 15 samples and 54 samples showed resistance. The antibiotics that have the most number of sensitive samples are ceftazidime with six samples while for antibiotics, which show that the most resistant amount is cefazolin with 14 samples. Sensitivity for groups that do not have history is as many as 906 antibiotic samples tested showing 1301 sensitive and resistant results. The antibiotics that showed the most sensitive results were meropenem with 59 samples and Ampicillin, showing the most resistant results as many as 87 samples. Antibiotic sensitivity from history groups with no history showed significantly different results where the likelihood of antibiotic resistance was higher in the history group compared to the group without history. It indicated by the calculation of OR from the sensitivity of the two groups where the possibility of antibiotic resistance in patients who have a history of antibiotic use is 0.399 times greater than patients without a history of antibiotics (p = 0.001).

It supported by research conducted by Kuster et al. (2014), which showed that antibiotic resistance in patients was caused more by patients having a history of antibiotic use before being hospitalized. Penicillin, cephalosporins, and quinolones decreased their resistance faster than with macrolide. Antibiotic resistance other than the macrolide can reach the baseline level after 90 days after the last antibiotic administration. Cephalosporin antibiotics mentioned in the study took 17 to 65 days after the last administration to return to sensitivity in pneumonia patients, whereas macrolide such as azithromycin require a longer time of 49-78 days to reach back to painful conditions. It needs between

each antibiotic to reach the half-life of the plasma (Bolon, 2009; Ferrero et al., 1990; Foulds, Shepard & Johnson, 1990; Humbert, Spyker, Fillastre & Leroy, 1979; Maholtra et al., 2007) influences the baseline.

Other studies that support this idea include the results of a study conducted by Chung et al., (2007), wherein the bacterium *Haemophilus influenza*, the resistance level of new amoxicillin will approach the baseline after > 12 weeks. In other research, the old, low dose and the last time used for amoxicillin in urinary tract infections can affect the level of resistance, which will only return at baseline after 1-3 months (Hillier et al., 2007). Other studies say that considering the last time given antibiotics themselves with what antibiotics will give next referring to antibiotics requires time to replenish the mucous membrane of the bacteria so that the amount will exceed the number of resistant strains of the bacteria (Levin & Rozen, 2006).

CONCLUSION

This study does have limitations related to the lack of data in the medical record related to the history of antibiotic use in hospitalized patients but based on calculations comparing the antibiotic profile in patients with and without a history of antibiotic use for the last 3 months shows that patients who have a history of antibiotic use over the past 3 months has been shown to increase the likelihood of higher resistance compared to patients without a history of antibiotic use over the past 3 months

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