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Comparative effectiveness of empiric antibiotics in pediatric community acquired pneumonia patient

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Abstract. Community-acquired pneumonia (CAP) is one of the leading caused of death in pediatrics. Immediately after infection diagnosed, the empiric antibiotic should be given. The goal of this research was to compare the effectiveness of empirical antibiotics for hospitalized children with CAP. This research was retrospective observational study by collecting data from patient medical record. Study conducted in one of a government hospital in Central Java, Indonesia in period of January-December 2017. This research involved 77 patient whose met inclusion criteria, divided into an ampicillin-gentamicin group (53) and 3rd generation cephalosporine group (24). There was no significant difference on clinical response in mild and moderate (p=0.485) condition in two group, but significantly different in severe condition (p=0.035). The effectiveness based on length of stay (LOS) in test analysis by Mann-Whitney showed that there was a significant difference in mild (p=0.028) and severe condition (P=0.000), but shown the same effectiveness in moderate condition (p=0.077). The effectiveness based on the rehospitalization showed that there was no significant difference in mild, moderate and severe condition (P = 1,000; p=0.051; p=0.0469). The effectiveness of ampicillin-gentamicin was better than 3rd generation cephalosporine in terms of LOS in children with mild and severe condition.

Keywords:Community-acquired pneumonia, Pediatric, Empiric antibiotics, Effectiveness

1. Introduction

In developing countries like Indonesia, pneumonia is one of the leading causes of death in infants. The number of children suffering from pneumonia in Central Java in 2017 (52,033 patient) was higher than in 2016 (28,590 patient). Escalation of the case also increases mortality due to pneumonia [1]. Most pneumonia patients are diagnosed with community-acquired pneumonia (CAP), and more than 50% of children with CAP need to be hospitalised [2].

Empirical antibiotic therapy was usually selected in CAP because the microorganisms have not been known at diagnosis. The World Health Organization (WHO) recommended ampicillin combined with gentamicin as first-line therapy for pneumonia in infant and toddlers [3]. The effectiveness of antibiotics is indicated by the improvement of clinical signs and symptoms in 48–72 hours. The rate of treatment failure and mortality is higher when prescribing antibiotic regimens in patients pneumonia not meet the guidelines therapy. Inappropriate use of antibiotics can also lead to the development of antibiotic resistance [4]. An effectiveness comparison study is considered important to determine the appropriate recommendations for empirical therapy in community-acquired pneumonia (CAP). This research aimed to compare the effectiveness of empirical antibiotics therapy between the third generation cephalosporine and ampicillin-gentamicin in pediatric with CAP.

2. Material and methods

2.1 Study design, data source and research subject

The study was approved by the Health Research Ethics Committee Dr. Moewardi General Hospital School of

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Medicine Sebelas Maret University No. 179/II/HREC/2018. Reseacher conducted a retrospective observational study in one of Government Hospital in Klaten, Central Java, Indonesia. Patient characteristic, empirical antibiotics used, patient clinical response, length of stay, and rehospitalisation were extracted from the medical record. The population of this study was pediatric patient with CAP hospitalized in January until December 2017. Sample size determined by consecutive sampling. Patient that first diagnosed with CAP, at least used antibiotic for three days, had complete medical record data were eligible.

2.2 Measured Outcome

The primary outcome was a clinical response that classified into clinical cured and failure. Clinical cured defined as an improved clinical response or not found at the end of therapy in 12-24 hours. Failure, if there were one of the following signs: respiratory rate is more than the normal value according to the patient's age, inability to eat and drink, and oxygen saturation <90% for some time in 12-24 hours after therapy [5,6]. The secondary outcome was the length of stay and rehospitalisation period. Re-hospitalization was the number of patients being hospitalized again in the same hospital with the same diagnosis for 90 days after discharged.

2.3 Data Analysis

2.3.1. Patient assessment using pediatric respiratory severity score (PRESS) consists of :

1) Respiratory rate was defined as the average rate of breathing at rest if the patient was categorised as tachypnea then given point 1, but if it was classified as normal then given a point 0.
2) Wheezing was the result of auscultation examination if the patient had wheezing then given point 1, but if they didn't have to wheeze, they were given 0 points.
3) Retraction is defined as the pull of the chest wall which can be in the form of sternomastoid/ suprasternal, intercostal, and subcostal, if the patient has retraction then given point 1, but if the patient does not have retraction then given 0 points.
4) The oxygen saturation evaluated was above or below 95%, if the patient's oxygen saturation value was ≥95%, then it was given 0 points, but if the patient's oxygen saturation value was <95%, then it was given point 1.
5) Difficulty in eating was the inability to eat or decreased appetite if the patient had difficulty eating then given point 1, but if the patient didn't have difficulty eating then given 0 points.

The total score was used to classify the patient into three categories that are mild (0-1), moderate (2-3) and severe (4-5) [7].

2.3.2. Statistical Analysis

The primary outcome was analyzed by the Chi-squared test or Fisher test. Secondary parameters analyzed by paired t-test or Mann Whitney depend on normality and homogeneity tests.

3. Result and Discussion

3.1. Patient characteristic

The antibiotics evaluated in this study were the last antibiotics used before patients discharge. The last use of antibiotics because these antibiotics affect the outcome of the patient's final response which determines the length of stay (LOS). This study enrolled 77 patients who've met the criteria. The Patient was grouped into 2 group that was monotherapy 3rd generation cephalosporin and combination therapy penicillin-gentamycin group. The 3rd generation cephalosporin that used as an empirical antibiotic in this studied were ceftriaxone and ceftazidime, while penicillin that combined with gentamycin was ampicillin. The patient characteristic can be seen in table 1.

Based on the study, the highest prevalence of pneumonia occurred in the infant age group compared to others. Pneumonia can affect people of all ages. However, infant were one of age groups that at greater risk of developing pneumonia and having more severe pneumonia. The immune systems of the infant are still developing during the first few years of life [8]. The incidence of CAP is relatively high in the infant age and tends to decrease until adulthood and will increase again in the elderly, such as forming a U shape diagram [9].

The most of the studied patients were male (63.64%). Some other study also showed that the incidence of pneumonia is higher in males than in females in all age groups studied. In general, females respond better to vaccination with higher immunoglobulin levels. Other study indicated that sex-specific differences in host immunity, such as differences in neutrophil apoptosis and cytokine secretion patterns, were linked to the presence of female sex hormones [10].

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Table 1. Characteristic of studied patient

Characteristic	3rd generation cephalosporin (n=24)		ampicillin + gentamisin (n=53)		Total patient per category (N=77)	Percentage**
	Patient number	Percentage *	Patient number	Percentage*		
Age						
Infant (1-12 month)	10	41.67%	22	41.51%	32	41.56 %
Toddler (1-3 years old)	7	29.16%	15	28.30%	22	28.57 %
Pre school (3-5 years old)	4	16.67%	10	18.87%	14	18.18 %
School age (5-18 years old)	3	12.5%	6	11.32%	9	11.69 %
Sex						
Male	15	62.5%	34	64.15%	49	63.64 %
Female	9	37.5%	19	35.85%	28	36.36 %

*** Percentages were calculated from the number of patients divided by each group of antibiotics multiplied by 100**
**** Percentages were calculated from the total number of patients per category divided by the total number of subjects multiplied by 100**

3.2. Severity Assessment

The equivalent severity of the initial patient's condition required to evaluate the effectiveness of antibiotics. Assessment of the severity of community-acquired pneumonia (CAP) can be obtained from wheezing, respiratory rate, retraction, oxygen saturation, and difficulty in eating. These components are important to determine the status of respiratory conditions in community-acquired pneumonia (CAP). Components of body temperature, heart rate, and blood pressure data are not included in the assessment criteria because these parameters are difficult to evaluate in crying children [7]. Among studied patient, moderate severity was the most patient condition. Patient severity condition could be seen in table 2.

Table 2. Baseline of patient severity condition

Severity categories (PRESS)	3rd generation cephalosporin (n=24)	Ampicillin + Gentamicin (n=53)
Mild	6	7
Moderate	15	37
Severe	3	9

PRESS: *pediatric respiratory severity score,* mild (0-1), moderate (2-3) and severe (4-5)

3.3. Effectiveness evaluation

Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or ceftazidime) should be prescribed for hospitalised infants and children who are not fully immunised, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection [6]. Unfortunately, in this study, we couldn't get information about immunisation and also etiological microorganism didn't check. Although some guideline recommended third-generation cephalosporin and combination penicillin-gentamicin for the severe CAP, in fact, both of antibiotics therapy used for hospitalised CAP patient whether with mild or moderate severity. A study said that third-generation cephalosporin accounted for about 90% of prescribing for hospitalised CAP patient at 29 U.S. children's hospitals between 2005 and 2010 [11]. A study in Bangladesh showed that third-generation cephalosporins such as cefixime, cefuroxime, and ceftriaxone were highly used for respiratory or other infections, and 83% prescriptions were used irrationally without any positive microbial test [12]. Proper management of selection and duration of antibiotics was one of the major management of pneumonia case management [13].

In this study, the minimum duration of antibiotics use in two group was three days. Three days course of antibiotics was as effective as five days course [5]. Short-term duration (≤7 days) of antibiotic use in patients with community-acquired pneumonia (CAP)

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showed equivalent results for long-term use (≥2 weeks) [14].

3.3.1 Effectiveness based on the primary outcome

Effectiveness based on clinical response divided into two groups, clinical cured and failure. If symptoms of fever, cough, and shortness of breath improved or not found at the end of therapy for approximately 12-24 hours then said to clinical cured. It categorised in failure if there were one sign of tachypnea, inability to eat and drink, and oxygen saturation value <90% [15] . Figure 1 showed a comparison of clinical responses in both antibiotics group with mild, moderate and severe severity

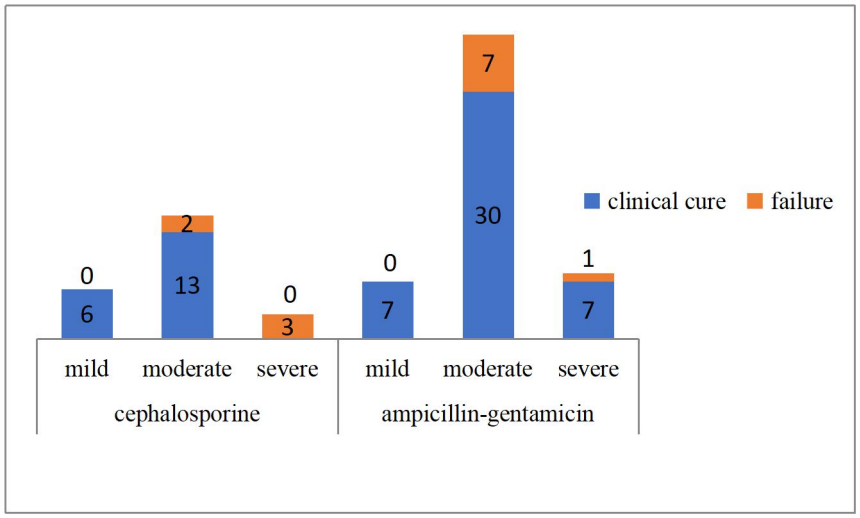

Figure 1. clinical responses in both antibiotics group

The primary outcome data were tested for normality and homogeneity test. Normality test using the Shapiro-Wilk test due to the number of samples <50 patients. Shapiro-will test results in third-generation parenteral cephalosporin antibiotics and ampicillin-gentamicin antibiotic combination groups showed P = 0.000 (P <0.05) which means that the data were not normally distributed. The homogeneity test using the Levene test showed P = 0.327 (P> 0.05) which means that the data variant is not statistically homogeneous. Chi-square test results didn't meet the requirements because there was one cell that has an expected count value less than five so that the effectiveness was analysed using Fisher's test (table 3).

Table 3. The result of the Fisher test based on clinical response

Antibiotics	p		
	Mild	Moderate	Severe
Third-generation cephalosporin (n=24)	a	0.485	0.035*
Ampicillin-Gentamycin (53)			

a. No statistics are computed because the clinical response was constant
*** significantly different on clinical response**

Based on figure 1, we could see that all patient in mild condition clinical cured. In moderate severity condition, most of them clinical cured so that it showed equal or no significant effectiveness (p>0.05). But, in severe condition, all patient in the cephalosporine group was a failure, in contrast with the ampicillin-gentamicin group. So, the result of the statistical test shown that effectiveness based on clinical response in two group was significantly different (p<0.05). It means that combination therapy ampicillin-gentamicin was superior than ceftriaxone to treat severe CAP. WHO guideline recommended parenteral penicillin (ampicillin)-gentamicin as first-line therapy for pediatric with severe CAP [3].

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3.3.2. Effectiveness based on the secondary outcome

The secondary outcome of this study was the length of stay (LOS) and rehospitalisation. Table 4 shown the comparison LOS in two antibiotics therapy group.

Table 4. Comparison length of stay (LOS) in two group

Antibiotics	Mean	Median	Interval	Result of Mann-Whitney		
				Mild	Moderate	Severe
third generation cephalosporine	6.9	6	4-10	p = 0.028*	p =0.077	p = 0.000*
ampicillin + gentamicin	4.6	4	3-8			

***significantly different (p<0.05)**

Effectiveness based on length of stay (LOS) showed a significant difference in study subjects with mild and moderate respiratory conditions, but not significantly different in subjects with severe respiratory conditions. The median duration of hospitalisation was about 4-6 days. It is similar to another study in some country in Europe [9].

The third generation cephalosporine group with mild and moderate respiratory conditions had longer LOS than the ampicillin-gentamicin combination group. Another study in one hospital in Bandung, Indonesia showed that combination gentamicin and ampicillin had a better effect on LOS in pneumonia patients under five years old. This is due to the synergistic effect between ampicillin and gentamicin [4].

In this study, etiological bacteria data not available, so that the accuracy of antibiotic related to eradication ability couldn't be analysed. Study in some country showed that S. Pneumoniae was the most caused by bacteria [16.] Ampicillin can eradicate penicillin-susceptible S. pneumoniae (PSSP) with an average ability of 83% for three days of used [17]. The proper use of antibiotics due to the ability to eradicate pathogenic bacteria can affect the patient's clinical response. The faster improve of clinical response, the shorter patient's length of stay (LOS) becomes.

Rehospitalization parameter only analysed the number of hospitalised patients after discharge. Patients are considered to re-hospitalisation if during the 90 days patient returns to hospitalisation in the same hospital with the same diagnose

Table 5. The statistical test result of rehospitalisation in two group

Antibiotics	Mild		Moderate		Severe	
	Rehospitalization (number of the subject)	Mann Witney test	Rehospitalization (number of subject)	Mann Witney test	Rehospitalization (number of subject)	Mann Witney test
third generation cephalosporine	0	p = 1.000	4	p = 0.051	0	p = 0.469
ampicillin + gentamicin	0		2		2	

The subjects in the two antibiotic groups mostly not needed re-hospitalisation. Based on table 5, the effectiveness based on rehospitalisation in studied subjects with mild, moderate, and severe conditions wasn't significantly different in the two group. Even, patient Community-acquired pneumonia (CAP) patient should be evaluated clinical for 30 days after hospitalisation because some patients may require rehospitalisation. As many as 20% of patients with a diagnosis of community-acquired pneumonia (cap) required rehospitalisation even after ambulatory care.

Patients who were re-hospitalised in both groups of antibiotics were clinical cured when they were discharged. however, it hasn't checked the criteria of microbiology cured. microbiology failure criteria were patient have recurrent or persistent bacteremia or persistent infection of the organism in sputum. organisms that persist in large numbers consistently show the failure of antibiotic therapy[16]. in this study, bacterial culture wasn't done so we couldn't know the argument need of re-hospitalisation were due to recurrent bacteremia or persistent infection of organisms in sputum. Therefore, it is important to get

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bacterial culture data to determine the cause of microbiology failure.

Conclusion

The effectiveness based on the primary outcome, no significant differences in clinical response between the third generation cephalosporine group and ampicillin-gentamicin group response in mild and moderate conditions. Whereas in severe conditions, the ampicillin-gentamicin combination is superior. Based on secondary parameters, rehospitalisation there is no significant difference between the two groups. The effectiveness of ampicillin-gentamicin was better than 3rd generation cephalosporine in terms of LOS in children with mild and severe condition.

Conflict of interest

All the author declared there is no conflict of interest.

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