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Original Article

Risk factors for cefotaxime resistance in children with pneumonia

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Abstract

Background Pneumonia is a health problem in developing countries, often caused by bacterial agents. The widespread use of cefotaxime, a third-generation of cephalosporin, may lead to increased incidence of resistance to this antibiotic. Several studies have reported on risk factors associated with resistance to cefotaxime.

Objective To identify risk factors for cefotaxime resistance in children with pneumonia.

Methods We performed a case-control study at Sanglah Hospital between January 2006-December 2010. The case group included children with blood culture-positive pneumonia and resistance to cefotaxime by sensitivity test. The control group was selected from the same population as the case group, but the bacteria isolated from these subjects were sensitive to cefotaxime. We tested the following risk factors for resistance to cefotaxime: age ≤3 years, microorganism species, history of antimicrobial use, and history of hospitalization within the prior 3 months. Chi square test and logistic regression analysis were performed to determine any associations between the four potential risk factors and resistance to cefotaxime. A P<0.05 was considered to be statistically significant.

Results Univariate analysis showed that the risk factors for resistance to cefotaxime were history of antimicrobial use in the prior 3 months (OR 2.79; 95%CI 1.40 to 5.55; P=0.001) and history of hospitalization within the prior 3 months (OR 5.57; 95%CI 1.95 to 15.87; P=<0.0001). By multivariate analysis, risk factors associated with resistance to cefotaxime were history of antimicrobial use in the prior 3 months (OR 2.4; 95%CI 1.18 to 4.86; P=0.015), history of hospitalization within the prior 3 months (OR 4.7; 95%CI 1.62 to 13.85; P=0.004), and history of breastfeeding for less than 2 months (OR 2.3; 95%CI 1.0 to 5.4; P=0.042).

Conclusion History of antimicrobial use and history of hospitalization within the prior 3 months were significant risk factors for resistance to cefotaxime in children with pneumonia. **[Paediatr Indones. 2012;52:255-9]**.

Keywords: *pneumonia, antibiotic, resistance, microorganism*

Pneumonia is an acute infection of lung parenchyma, including alveoli and interstitial tissues. In the United States, the incidence of pneumonia is high, with 6-12 cases per 1000 children aged > 9 years, and 30-45 cases per 1000 children aged < 5 years.[1] In Indonesia, according to the General Directorate of Medical Services, Ministry of Health in 2005, respiratory tract infection comprised the most common diagnosis of 10 major illnesses in outpatient clinics of Indonesian hospitals (15.1%).[2]

Resistance is deemed to be a protective factor for bacteria against antimicrobials produced by

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microorganisms or other antimicrobial products that they manufacture on their own.[3] Multi-center studies on microbial resistance conducted in 2000 in the United States reported an increase in resistance rates of *Streptococcus pneumoniae* to various antimicrobials.[4] Samore *et al.* [5] reported that a history of cephalosporin use in the prior 3 months increased the risk of resistance of *Streptococcus pneumoniae* by 2.7 times. A Brazilian study reported that age ≤3 years had a 3.5 times relative risk of resistance to penicillin in *Streptococcus pneumoniae*.[6] A study in Massachusetts reported an increased risk of *Streptococcus pneumoniae* resistance to penicillin due to history of hospitalization within the prior 3 months at about 2.9 times.[7] The widespread use of cefotaxime, a third-generation of cephalosporin, may increase resistance incidence in the next few years.[8]

Data on bacterial resistance patterns in Sanglah Hospital is limited. We aimed to identify risk factors for resistance to cefotaxime in children with pneumonia.

Methods

This case-control study was conducted at the Division of Pulmonology, Department of Child Health, Udayana University Medical School/Sanglah Hospital, Bali between January 2006 to December 2010.

A sample size formula was used to test the relationship between 2 variables. We included children aged 0-12 years, who were diagnosed with pneumonia clinically and radiologically. We excluded children with severe disease such as kidney failure, heart failure, or liver failure; those with congenital abnormalities such as Down syndrome, cleft lip, or heart defects; those with immune system disorders such as HIV infection; and those with incomplete data. Case group subjects showed cefotaxime resistance by sensitivity test. Control group subjects did not show cefotaxime resistance by sensitivity test. Risk factors tested that were potentially capable of increasing the risk of resistance to cefotaxime included age ≤ 3 years, type/strain of microorganisms, history of antimicrobial use, and history of hospitalization within the prior 3 months.

The study was conducted by collecting data from medical records in Sanglah Hospital Denpasar. This study was approved by the Research Ethics Committee of Udayana University Medical School / Sanglah Hospital, Denpasar.

Data were analyzed by SPSS version 14.0. Categorical independent variables to identify risk factors for resistance to cefotaxime were analyzed using odds ratio (OR) and 95% confidence interval. Chi square test and logistic regression analysis were performed to determine an association between the four potential risk factors and resistance to cefotaxime. A result was considered significant if P value was less than 0.05.

Results

During the study period, 890 patients with pneumonia were admitted to the Department of Child Health, Udayana University Medical School /Sanglah Hospital, Denpasar. Of these, 229 patients had positive blood culture, but 73 children were excluded due congenital heart disease with heart failure (4 cases), congenital heart disease without heart failure (4 cases), kidney failure (2 cases), Down syndrome (5 cases), HIV infection (2 cases), or incomplete data (56 cases). From the remaining 156 eligible subjects, 78 subjects were cefotaxime resistant (case group), and 78 subjects were cefotaxime sensitive (control group). In the case group, 53 patients were male (68%), 75 patients (96%) had a history of birth weight ≥ 2500 grams, 49 patients (63%) had good nutritional status, 62 patients (79%) had severe pneumonia, 26 patients (33%) had 5 family members and 46 patients (59%) had a history of breastfeeding for more than 2 months. Baseline characteristics of subjects are shown in **Table 1**.

Staphylococcus was the most common cause of pneumonia (75%). The relationship between microorganism species and cefotaxime resistance is shown in **Table 2**.

Several possible risk factors for resistance to cefotaxime were evaluated (**Table 3**). Those that significantly affected the occurrence of resistance to cefotaxime were history of antimicrobial use within the prior 3 months (OR 2.7; 95% CI 1.4 to 5.5; P=0.001) and history of hospital admission within the prior 3 months (OR 5.5; 95% CI 1.9 to 15.8; P=<0.0001).

Multivariate analysis showed significant relationships between cefotaxime resistance and the use

Table 1. Baseline characteristics of subjects

Characteristics	Cefotaxime resistant (n=78)	Cefotaxime sensitive (n=78)
Sex, n (%)		
Male	53 (68)	41 (53)
Female	25 (32)	37 (47)
Birth weight, n (%)		
≤1500 grams	0 (0)	1 (1)
>1500-<2500 grams	3 (4)	2 (3)
≥2500 grams	75 (96)	75 (97)
Nutritional status, n (%)		
Severely undernourished	1 (1)	1 (1)
Mild-moderately undernourished	26 (33)	31 (40)
Well-nourished	49 (63)	41 (53)
Overweight	2 (3)	5 (6)
Grade of pneumonia, n (%)		
Very severe pneumonia	6 (8)	1 (1)
Severe pneumonia	62 (79)	57 (73)
Pneumonia	10 (13)	20 (26)
Number of family members, n (%)		
3	18 (23)	14 (18)
4	25 (32)	40 (51)
5	26 (33)	18 (23)
≥6	9 (12)	6 (8)
History of breast feeding, n (%)		
< 2 months	32 (41)	12 (15)
≥2 months	46 (59)	66 (85)

Table 2. Relationship between type of microorganisms and resistance to cefotaxime

	Cefotaxime resistant	Cefotaxime sensitive	Total	P
Staphylococcus, n (%)	56 (72)	61 (78)	117 (75)	
Pseudomonas, n (%)	2 (3)	4 (5)	6 (4)	0.08
Klebsiella pneumoniae, n (%)	5 (6)	2 (3)	7 (4)	
Others, n (%)	15 (19)	11 (14)	26 (17)	

Table 3. Univariate analysis of risk factors for cefotaxime resistance

	Cefotaxime resistant	Cefotaxime sensitive	OR	95% CI	P
Age ≤ 3 years, n	72	69	1.2	0.3 to 4.1	0.588
History of antibiotics use in the last 3 months (+), n	53	31	2.7	1.4 to 5.5	0.001
History of hospital admission in the last 3 months (+), n	24	5	5.5	1.9 to 15.8	<0.0001

Table 4. Logistic regression analysis of risk factors for cefotaxime resistance

Variabel	OR	95% CI	P
History of antibiotics use in the prior 3 months	2.4	1.1 to 4.8	0.015
History of hospital admission in the prior 3 months	4.7	1.6 to 13.8	0.004
History of breastfeeding < 2 months	2.3	1.0 to 5.4	0.042
Grade of pneumonia	0.4	0.2 to 1.0	0.068

of antimicrobials within the prior 3 months (OR 2.4; 95% CI 1.1 to 4.8; P=0.015), hospital admission within the prior 3 months (OR 4.7; 95% CI 1.6 to 13.8; P=0.004), as well as breastfeeding for less than 2 months (OR 2.3; 95% CI 1.0 to 5.4; P=0.042). Logistic regression analysis results are shown in **Table 4**.

Discussion

A previous study from Utah reported that resistance to various antimicrobials occurred in 36% of male subjects.[5] In our study, male subjects were more commonly resistant to cefotaxime (68%) than females.

This difference may be due to geographical, microbial (*Streptococcus pneumoniae* in the Utah study) or antimicrobial differences (differing cephalosporins i.e., cefixime, carbapenem, ceftibuten).

In pneumonia, transmission of microorganisms occurs from person to person through droplet spread. The disease can progress rapidly in densely populated areas.[8] The Utah study reported that the emergence of resistance to various antimicrobials occurred in 41% of residences occupied by 4 or more people.[5] We found that the highest rates of cefotaxime resistance were in residences occupied by 5 people (33%), followed by those occupied by 4 people (32%).

In Bangladesh, Baqui *et al*. showed that *Staphylococcus aureus* was the most common Gram-positive bacteria causing lower respiratory tract infections (4.5%), followed by *Streptococcus pneumonia*e (0.8%) and *Haemophilus influenzae* (0.4%). Other microorganisms, such as coagulase-negative staphylococci (16.7%), *Micrococcus sp* (6.4%), and *Streptococcus viridans* (0.7%) were also isolated, but were excluded because they were considered to be contaminants.[9] In our study, *Staphylococcus* was the most common bacteria causing pneumonia in our subjects (75%).

A 2000 CDC report shows *Streptococcus pneumonia*e resistance to penicillin to be 27.4%.[9] We observed *Staphylococcus* resistance to cefotaxime to be 71.8%. Other studies have reported that widespread usage of antimicrobials may increase the risk of resistance to these medications.[9-11]

The use of antimicrobials may lead to selection of resistant mutant species during administration or to a shift in the genetic determinants of resistance.[12] Cephalosporin resistance may be due to a bacterial mechanism in which β-lactamase enzymes render the drug inactive.[13] A Spanish study reported a 2.8 times increased risk of resistance to the penicillin group due to betalactam use within the prior 3 months (95%CI 0.97 to 8.42).[14] Also, a Toronto study reported a 2.15 times risk of resistance to the penicillin group in subjects with penicillin use in the previous months (95%CI 1.3 to 3.54).[15] Similarly, we found a statistically significant relationship between the history of antimicrobial use within the prior 3 months and cefotaxime resistance with an odds ratio of 2.4 times (95% CI 1.1 to 4.8).

History of recent hospitalization was also included as a risk factor for resistance to antimicrobials, although this mechanism is still unclear. An epidemiological study in Massachusetts of risk factors for resistance reported that children hospitalized within a preceding 3 month period of time had 2.9 times the risk for resistance (95% CI 1.8 to 4.6).[7] We found a significant association between history of hospitalization within the prior 3 months and cefotaxime resistance with an odds ratio of 4.7 times (95% CI 1.6 to 13.8).

Breast milk contains a variety of immune components such as sIgA, leukocytes, oligosaccharides, lysozymes, lactoferrin, interferon-γ, nucleotides, and cytokines. These substances provide passive protection against severe gastrointestinal and respiratory tract infections.[16] A meta-analysis from seven cohort studies found that exclusive breastfeeding for 4 months in term infants could reduce the risk of hospitalization due to respiratory tract infection by 72% (RR 0.28; 95% CI 0.14 to 0.54).[17] In our study, we found that a history of breastfeeding for less than 2 months was a risk factor for cefotaxime resistance with an odds ratio of 2.3 times (95% CI 1.0 to 5.4).

Severe pneumonia is often caused by *Streptococcus pneumoniae* with resistance to penicillin.[18] Panton-Valentine leukocidin (PVL) causes lysis of neutrophil membranes which facilitates infection by resistant microbes.[19] A Colombian study reported that grades of pneumonia were not risk factors for *Streptococcus pneumoniae* resistance to penicillin (OR 3.8; 95% CI 0.9 to 15.4).[20] Similarly, we found that grade of pneumonia was not a risk factor for cefotaxime resistance with an odds ratio of 0.4 times (95% CI 0.2 to 1.0).

There were several limitations in this study. This study was conducted retrospectively, which may lead to biased information, such as information about antibiotic usage. Also, we did not analyze the types of antibiotics or their duration of use.

In conclusion, we found that a history of antimicrobial therapy within the prior 3 months, history of hospitalization within the prior 3 months, and history of breastfeeding for less than 2 months were the risk factors for resistance to cefotaxime.

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