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Original Article

# Irrational use of antibiotics and clinical outcomes in children with pneumonia

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## Abstract

***Background*** Pneumonia is a major cause of morbidity and mortality in children under five. Antibiotic treatment must be started immediately in children with pneumonia. The irrational use of antibiotics may increase morbidity and mortality in children with pneumonia.

***Obejctive*** To determine the prevalence of the irrational use of antibiotics and clinical outcomes in children with pneumonia.

***Methods*** We conducted a cross-sectional study in children with pneumonia who were admitted to the Pediatric Ward or PICU at Dr. Sardjito Hospital, Yogyakarta, from December 2010 to February 2013. Data were obtained from subjects' medical records. Children with malnutrition, congenital heart defects, sepsis, shock, central nervous system disorders, syndromes, or other concomitant infections were excluded.

***Results*** Of 46 children who fulfilled the inclusion criteria, 13 (28.3%) used antibiotics irrationally and 7 (15.2%) died. Most subjects were aged less than 1 year (25 subjects, 54.3%) and 1 - < 5 years (18 subjects, 39.1%). The female to male ratio was 1:1. Most cases were referred from other hospitals (23 subjects, 50%). Twenty-eight (60.9%) subjects stayed in hospital > 7 days. Ampicillin was the most common first-line, empirical antibiotic used (32 subjects, 69.6%). Blood cultures were obtained in 20 (43.5%) patients, yielding no growth in 16 subjects, coagulase-negative staphylococci (CONS) in 3 subjects, and *Pseudomonas aeruginosa* in 1 subject. The irrational use of antibiotics was significantly associated with mortality in a univariate analysis [PR 6.35; (95%CI 1.40 to 28.69); P=0.006].

***Conclusion*** The irrational use of antibiotics is common among children with pneumonia and is significantly associated with mortality. **[Paediatr Indones. 2017;57:211-5 ; doi: http://dx.doi.org/10.14238/pi57.4.2017.211-5 ]**.

***Keywords:*** *antibiotic; irrational; pneumonia*

Bacterial pneumonia is the main cause of morbidity and mortality in children below 5 years of age. The incidence and its mortality are higher in developing countries. The incidence of bacterial pneumonia in children below 5 years of age was estimated to be 0.29 episodes each year for children in developing countries, and 0.05 episodes for children in developed countries.[1] In 2013, there were 156 million new episodes for the year worldwide, with as many as 151 million in developing countries. Most cases were found in India (43 million), China (21 million), Pakistan (10 million), as well as Bangladesh, Indonesia, and Nigeria (6 million each).[2]

Antibiotic therapy must be started immediately in children with suspected community-acquired pneumonia (CAP) caused by bacteria.[3] Inappropriate antibiotic treatment may lead to greater expense, toxic side effects, antibiotic resistance, and superinfections that are difficult to treat. Thus, antibiotics should be

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used rationally for the treatment of pneumonia.[4,5] Irrational use of antibiotics significantly increased morbidity and mortality in children with infections, including pneumonia.[6] Although antibiotics have an important role in reducing mortality of pneumonia, research has been limited. We aimed to evaluate the irrational use of antibiotics and outcomes in children with pneumonia at Sardjito Hospital.

## Methods

This cross-sectional study was conducted in the Pediatric Ward and PICU of Sardjito Hospital, Yogyakarta, Central Java, in November 2016. Subjects were children with pneumonia treated according to standard medical procedures of Sardjito Hospital, aged 1 month - < 18 years, and hospitalized between December 2010 and February 2013. Data were obtained from patients' medical records. The exclusion criteria were children with malnutrition, congenital heart defects, sepsis, shock, central nervous system disorders, disease syndromes, or other concomitant infections. The minimum required number of subjects was calculated to be 46, with 0.05 confidence level and 80% power.

The subjects' basic characteristics were age, sex, and case classification. The outcomes were classified into primary (survived/died) and secondary (length of hospital stay, rational/irrational use of antibiotics, type of antibiotics used, first-line antibiotics, combination antibiotics, blood cultures, and types of microorganisms). The independent variable was the irrational use of antibiotics, while the dependent variables were primary outcomes (survived or died) and the secondary outcomes of hospital length of stay of 0-7 days or > 7 days.

Pneumonia was a diagnosis made by treating clinicians and was written in medical records as a final diagnosis based on ICD 10 of pneumonia which was J18. The diagnosis of pneumonia in Dr. Sardjito Hospital was made by clinical and radiological findings. The type of the pneumonia in this study was CAP. The irrational use of antibiotics was defined as antibiotic use that was not in accordance with that recommended for particular indications, dose, and/or length of treatment. Length of stay was defined to be the number of days hospitalization from the time of admission to the time of discharge, regardless of primary outcome and classified into two categories: 0-7 days or > 7 days. Type of case was classified as community, if patients had come directly to the hospital, referral, if patients were referred by another hospital, or transfer, if patients were initially treated in the PICU.

Data was described and analyzed with P values, prevalence ratio (PR), 95% confidence intervals. Bivariate analysis was done with Chi-square and Fisher's tests. Statistical analysis was performed with *SPSS* software. This study was approved by the Ethics Committee for Medical Research, Gadjah Mada University Medical School.

## Results

Fourty six children were fulfilled the inclusion criteria, of whom 13 (28.3%) received irrational use of antibiotics and 7 (15.2%) died. The characteristics of subjects are shown in **Table 1**.

**Table 1**. Characteristics of subjects

| Characteristics | N=46 |
|---|---|
| Gender, n(%) | |
| Male | 23 (50.0) |
| Female | 23 (50.0) |
| Age, n(%) | |
| < 1 year | 25 (54.3) |
| 1 - < 5 years | 18 (39.1) |
| 5 - < 10 years | 1 (2.2) |
| ≥ 10 years | 2 (4.3) |
| Type of case, n(%) | |
| Community | 21 (45.7) |
| Referral | 23 (50.0) |
| PICU transfer | 2 (4.3) |

Data on primary outcomes, rationality of antibiotics, type of irrational use, length of stay, blood culture results, types of microorganisms, and empirical therapy are shown in **Table 2**.

Univariate analysis of primary outcomes and rationality of antibiotic use is shown in **Table 3**. Univariate analysis of length of stay and rationality of antibiotic use is shown in **Table 4**.

**Table 2**. Clinical outcomes

| Outcomes | N=46 |
|---|---|
| Primary outcomes, n(%) | |
| Survived | 39 (84.8) |
| Died | 7 (15.2) |
| Rationality of antibiotic use, n(%) | |
| Irrational | 13 (28.3) |
| Spectrum/indication | 12 (92.3) |
| Length of treatment | 1 (7.0) |
| Dose | 0 |
| Rational | 33 (7.17) |
| Length of stay, n(%) | |
| 0-7 days | 18 (39.1) |
| > 7 days | 28 (60.9) |
| Blood culture, n(%) | |
| Culture | 20 (43.5) |
| No growth | 16 |
| Coagulase-negative staphylococcus (CONS) | 3 |
| | 1 |
| Pseudomonas aeruginosa | 26 (56.5) |
| No culture | |
| First-line antibiotics, n(%) | |
| Ampicillin | 32 (69.6) |
| Ceftriaxone | 5 (10.9) |
| Cefotaxime | 8 (17.4) |
| Imipenem | 1 (2.2) |
| Antibiotics combination, n(%) | |
| Cefotaxime | 1 (3.3) |
| Ceftazidime | 1 (3.3) |
| Cefixime | 1 (3.3) |
| Chloramphenicol | 14 (46.7) |
| Amikacin | 2 (6.7) |
| Gentamicin | 11 (36.7) |

Note: Antibiotics combination were given in 30 patients

**Table 3.** Univariate analysis of primary outcomes and rationality of antibiotic use

| Antibiotic use | Primary outcomes | | PR (95%CI) | P value |
|---|---|---|---|---|
| | Died | Survived | | |
| Irrational | 5 | 8 | 6.35 (1.40 to 28.69) | 0.006 |
| Rational | 2 | 31 | | |

**Table 4.** Univariate analysis of length of stay and rationality of antibiotic use

| Antibiotic use | Length of stay | | PR (95%CI) | P value |
|---|---|---|---|---|
| | More than 7 days | 0-7 days | | |
| Irrational | 10 | 3 | 1.41 (0.92 to 2.17) | 0.161 |
| Rational | 2 | 31 | | |

## Discussion

Of 46 children with pneumonia, 7 (15.2%) died, similar to that reported by Latumahina *et al.* (15%).1 Thirteen of our subjects (28.3%) received irrational antibiotic treatment for pneumonia. A previous study reported a similar 24% in Sardjito Hospital, although higher percentages were reported in Mongolia (56.6%), Turkey (56.5%), and India (56%). These differences may have been due to studying only children below 5 years of age or including adults.[4,7,8,9]

Most of our subjects were < 1 year of age (25; 54.3%) or 1 - < 5 years old (18; 39.1%), with a 1:1 ratio of males to females. Pneumonia was found to be the main cause of morbidity and mortality in children below 5 years by Latumahina *et al.* and the Indonesian Ministry of Health.[1,10]

Most pneumonia was caused by infectious agents, although non-infectious causes included food or gastric acid aspiration, foreign bodies, hydrocarbon and lipoid agents, hypersensitivity reactions, drugs, and radiation pneumonitis. Most of the time it was hard to find the cause of pneumonia, because invasive specimen collection was rarely, if ever, performed. Specimens from the upper respiratory tract or sputum are usually not accurate for determining the cause of lower respiratory tract disease.[11]

Treatment of pneumonia is based on the causative agent and clinical findings,[12] although, generally, clinical signs do not help to differentiate etiologies of pneumonia. Early identification of etiology is also difficult, so antibiotics are usually chosen by an empirical approach. All patients in this study received empirical antibiotic treatment. Ampicillin was the most common first-line, empirical antibiotic used (32; 69.6%), while the most common combination antibiotics used were chloramphenicol (14; 46.7%) and gentamicin (11; 36.7%). These findings were in agreement with the *World Health Organization* (WHO) and the Indonesian Pediatrics Society (IPS) recommendations that children with severe and very severe pneumonia be hospitalized, receive ampicillin as the first-line treatment, and be observed for next 24 to 72 hours. If the patient has a good response, treatment must be continue for 5 days. But if the patient becomes worse within 48 hours or experiences severe clinical conditions (unable to eat/drink, vomiting at all feedings, seizure, lethargy, unconsciousness, or cyanosis with respiratory distress), chloramphenicol must be added. Patients with severe clinical conditions should directly be given a combination of ampicillin-chloramphenicol or ampicillin-gentamicin. If the patient is unresponsive to the above antibiotics, amikacin or cephalosporin could be used.[13]

We noted that empirical therapy was not always given according to the recommended protocol, such as with the use of cefotaxime, imipenem, and ceftazidime. This finding may have been due to most cases (23; 50%) being referred from other hospitals or directly treated in the PICU (2; 4.3%). The antibiotics used in other hospitals also might have influenced the sensitivity of microorganisms to antibiotics, as increased antibiotic resistance among respiratory infectious agents might affect the choice of empirical treatment.[14]

From 13 subjects who used antibiotics irrationally, almost all were considered irrational based on spectrum of disease (12; 92.3%), while only 1 (7.7%) was based on duration. There was no irrational use based on dosage. However, these results were not subjected to a qualitative antibiotic evaluation using Gyssens pathway, that classifies antibiotic use into six categories: I. incorrect usage, IIa. incorrect dose, IIb. incorrect intervals, IIc. incorrect route, IIIa. incorrect due to long duration, IIIb. incorrect due to short duration, IVa. incorrect due to a more effective antibiotic, IVb. incorrect due to a closer spectrum, V. no indication for antibiotics, and VI. medical records not complete enough to evaluate. The antibiotic is correct if the evaluation matches with category I, but incorrect if it is IIa, IIb, IIc, IIIa, IIIb, IVa, IVb, IVc, IVd, V (II,III,IV,V).[15]

In developing countries, hospital microbiology data of that could be used to guide patient management is rare to non-existent. Specimen collection from the lungs to assess the pneumonia etiology is not possible, so specimens were taken from tracheal aspiration of intubated patients. This specimen is not sensitive enough to define the pneumonia etiology.[11] In addition, blood cultures from pneumonia patients are not routinely performed, except in cases of very severe pneumonia. In our study, 20 subjects had cultures started on the day of admission, but only 4/20 had positive findings: 3/20 coagulase-negative staphylococcus (CONS) and 1/20 Pseudomonas aeruginosa. This result differed from the reported pneumonia etiologies in children of Streptococcus pneumoniae, Haemophilus influenza, and respiratory syncytial virus.[16,17] Blood cultures in PICU patients at Cipto Mangunkusumo Hospital (CMH), Jakarta, were similar to our findings at Sardjito Hospital, as those CMH patients had mostly Pseudomonas (33.1%), coagulase-negative staphylococcus (19.5%), and Klebsiella pneumoniae (13.3%).[11] The most commonly found species in this study was coagulase-negative staphylococcus (15%), but blood culture was performed in only 20 patients, 4 of which grew bacteria. As such, these findings are too weak to be the basis of microorganism sensitivity data.

It has been shown that adequate antibiotic treatment shortens the length of stay and decreases mortality. The dilemma is that decreased antibiotic usage decreases resistance, but delayed or inadequate treatment increases the mortality and morbidity of pneumonia, especially that caused by Gram-negative bacteria.[18] We also found a significant association between irrational use of antibiotics and death (PR 6.35; 95%CI 1.40 to 28.69; P=0.006).

Antibiotic resistance and death outcome could not be analyzed because only 20 subjects underwent blood cultures. Those patients were the severe or very severe cases, so they did not reflect the general study population.

Athale et al. reported that inadequate empirical antibiotics for 30 days length of stay resulted in higher mortality (11.1%) than did a 7-day length of stay (3.7%). For delayed empirical therapy, there was no significant difference in mortality between 7 days or 30 days length of stay.[19]

We used a 7-day limit for the length of stay outcome based on the standard duration of pneumonia treatment of 5-7 days.[13] Eighteen subjects (39.1%) had a 0-7-day length of stay; 28 subjects (60.9%) had a > 7 day length of stay. No significant association was observed between irrational use of antibiotics and length of stay, indicating that the severity of the disease could influence the length of stay.

This study has several limitations. First, we used retrospective data, so risk factors and outcome were taken from one point of time. Second, there was no precise data on the severity of pneumonia or previous history of hospitalization, such as length of stay or previous antibiotics used. Third, a qualitative evaluation of antibiotic treatment was done with only 3 parameters: incorrect spectrum/indication, dose, and length of treatment, so the classification of irrational antibiotic use was weak.

In conclusion, irrational use of antibiotics in children with pneumonia at Dr. Sardjito Hospital is significantly associated with death, but we find no such relationship with length of stay. Irrational use of antibiotics was defined by simple clinical and laboratory data that were used to diagnose pneumonia. Further study using Gyssens pathway, the degree of pneumonia severity, previous hospitalization history (length of stay and antibiotic use), blood cultures for all subjects, and better study methods are needed.

## Conflict of Interest

None declared.

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