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Appropriate Use of Antibiotics for the Treatment of Community Acquired Pneumonia in Children at Tertiary Hospital in Vietnam

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ABSTRACT

Objective: *To describe and analyse the use of appropriate antibiotics for the treatment of community-acquired pneumonia (CAP) in children aged 2 months to 5 years in a tertiary hospital in Vietnam.*

Methods: *A cross-sectional descriptive study was carried out based on retrospective data and information collected from 154 inpatient medical records for community-acquired pneumonia (CAP) at the Paediatric Department of Bach Mai Hospital, Hanoi, Vietnam in 2021.*

Results: *Clinical and laboratory information, antibiotic use was collected in order to describe and analyse appropriate use of antibiotics for community-acquired pneumonia in children aged 2 months to 5 years. There were 12 initial antibiotic regimens selected for the treatment of CAP. Of those, four regimens used a single antibiotic and eight regimens used a combination of antibiotics. The proportion of combination regimens increased with the severity of the disease, with 22.3%; 38.5% and 50% for mild pneumonia, severe pneumonia and very severe pneumonia, respectively. The most commonly used antibiotic groups in the initial regimen are penicillin/β-lactamase inhibitor (alone regimen) and penicillin/β-lactamase inhibitor in combination with macrolides (combination regimen). The rate of initial treatment regimens not following recommendations was up to 99.4%. There were 83/154 cases where patients were prescribed antibiotics with inappropriate dosages.*

Conclusion: *The rate of inappropriate use of antibiotics in the treatment of CAP in children in a tertiary hospital was still high. It is necessary to develop a system of assessment and monitoring of antibiotic use in order to reduce inappropriate use of antibiotics and drug resistance of bacteria.*

Keywords: *antibiotic, pneumonia, children.*

Introduction

Pneumonia is one of the leading causes of death in children, especially in developing countries. According to the World Health Organization (WHO), about 15% of children under 5 years of age died from pneumonia in 2017 and every 39 seconds a child dies from pneumonia [1, 2].

Vietnam is one of the 15 countries with the highest number of annual pneumonia cases in the world, estimated at about 2.9 million cases/year and the pneumonia incidence rate is about 0.35 cases/child/year [3]. According to statistics from Vietnamese medical facilities, pneumonia is the leading cause of children coming to the hospital for examination and treatment and is also the leading cause of death in children under 5 years of age [4].

The causes of pneumonia are diverse, including bacteria, viruses, parasites, fungi, etc. According to WHO, these groups of causes

change with age. Mycoplasma pneumonia is a atypical bacteria that causes community-acquired pneumonia (CAP) in children over 5 years old, while Streptococcus pneumoniae is the leading cause of (CAP) in children under 5 years old. Bacteria are the most common cause of CAP in developing countries. Of those, S. pneumoniae and H. influenzae are the two most common bacteria [1]. Therefore, antibiotics play an important role in the treatment of CAP. However, the inappropriate use of antibiotics has increased drug-resistant bacteria and reduced treatment effectiveness. This study was conducted to describe and analyse the use of appropriate antibiotics for CAP in children aged 2 months to 5 years in a tertiary hospital in Vietnam.

Methods

Data collection

A cross-sectional descriptive study was conducted based on retrospective data from inpatient medical records of children with community-acquired pneumonia aged 2 months to 5 years at the Pediatric Department of Bach Mai Hospital, Hanoi, Vietnam in 2021. The inclusion criteria for the study were that the medical records of these pneumonia patients must have been prescribed antibiotics for at least 3 days or more.

Data collected in the study included: initial treatment regimen, antibiotic regimen changes, antibiotic regimen change patterns. Assessment of appropriateness of antibiotic use based on the Antibiotic Use Guidelines of the Ministry of Health of Vietnam 2015 [5], the Vietnam National Pharmacopoeia 2018 [7] and the British National Pharmacopoeia for Children 2021 [6].

Analysis of appropriateness of dosage compared to recommendations in patients with normal renal function and patients with renal failure. A regimen is considered appropriate when the antibiotics in the regimen used for the patient are within the regimen stated in the Treatment Guidelines. A regimen is considered inappropriate when there is an excess or deficiency of at least 1 antibiotic in the regimen compared to the recommended regimen. Drug dosage is assessed in two groups of patients: patients with normal renal function and patients with renal failure.

Statistical analysis

Data was entered and processed on Microsoft Office Excel 2016 and SPSS 23.0. Qualitative variables were described by frequency and percentage. Continuous variables were described by mean ± standard deviation if the data followed a normal distribution, or represented by the median and interquartile range if the data were not normally distributed.

Results

Sociodemographic and Clinical Characteristics

Overall, 154 children were admitted with CAP; 52.6 % were males 53.2% were infants aged 2-12 months old. Most of the patients had mild pneumonia (61%) and severe pneumonia (33.8%). The proportion of patients with very severe pneumonia was low (5.2%). There were 31(20.1%) patients with 1-2 comorbidities, mainly ear-nose-throat diseases such as acute rhinitis (51.6%), and otitis media (38.7%). Some of them have severe underlying diseases such as immunodeficiency or myeloproliferative disorder (Table 1).

Table 1. Sociodemographic and clinical features, severity of pneumonia, comorbidities and underlying disease.

Characteristics	Number	Percent (%)
Age (months)		
2-11	82	53.2
12-23	45	29.2
24-35	17	11.0
36-47	6	3.9
48-59	4	2.6
Gender		
Female	73	47.4
Male	81	52.6
Severity of pneumonia		
Mild	94	61.0
Severe	52	33.8
Very severe	8	5.2
Comorbidities		
Acute rhinitis	16	10.4
Acute otitis media	12	7.8
Malnutrition	3	1.9
Diarrhea	2	1.3
Underlying disease		
Immunodeficiency	4	2.6
Myeloproliferative disorder	1	0.6

Bacterial and antibiotic sensitivity results

Of the 154 patients, 146 (94.8%) had been tested for bacteria. Of those, 74(50.7%) patients had positive results. The specimen used mainly nasopharyngeal swab (97.9%). Bacterial culture results showed that 3 out of 6 bacteria found in the study sample with the highest frequency were H. influenzae (63.5%), S. pneumoniae (29.7%), M. catarrhalis (12.2%). In addition, some rare strains of bacteria such as E. coli and multi-drug resistant K. pneumoniae were found with a very low frequency. There were 17 out of 154 patients assigned to test for Mycoplasma pneumoniae by Real-time Poly-chain Reaction technique, of which 1(5.9%) case was positive.

Of the 74 cases with positive bacterial cultures, 60 cases underwent antibiotic susceptibility testing. Quinolones remained susceptible to most of bacteria. Amoxicillin/clavulanate was susceptible to M. catarrhalis. H. influenzae was highly susceptible to third-generation cephalosporins. S. pneumoniae was highly resistant to macrolides such as erythromycin and azithromycin. S. aureus was also susceptible to doxycycline, linezolid and trimethoprim/sulfame-

thoxazole. K. pneumoniae and E. coli were resistant to most of antibiotics and were only susceptible to carbapenem and fosfomycin.

Initial antibiotic use results

The antibiotic regimens used as first-line treatment after hospital admission is depicted in Table 2.

There were 12 kinds of antibiotics selected as first-line treatment of community-acquired pneumonia. Of these, 4 antibiotics were used as monotherapy and 8 kinds of antibiotics were used in combination. The proportion of antibiotic combination regimens increased with the severity of pneumonia, respectively: mild pneumonia (22.3%); severe pneumonia (38.5%) and very severe pneumonia (50%). The most commonly used antibiotics in the initial regimen were penicillin/β-lactamase inhibitor (monotherapy) and penicillin/β-lactamase inhibitor combined with macrolide (combination regimen).

Table 2. Initial antibiotic regimens when the patient was admitted to hospital.

Initial antibiotic regimens	Mild Pneumonia		Severe Pneumonia		Very severe Pneumonia		Total N (%)
	N	%	N	%	N	%	
Monotherapy	**73**	**77.7**	**32**	**61.5**	**4**	**50**	**109 (70.8)**
Penicillin/ β-lactamase inhibitor	45	47.9	21	40.4	3	37.5	69 (44.8)
C2G	1	1.1	-	-	-	-	1 (0.006)
C3G	27	28.7	10	19.2	1	12.5	38 (24.7)
Macrolides	-	-	1	1.9	-	-	1 (0.006)
Combination	**21**	**22.3**	**20**	**38.5**	**4**	**50**	**45 (29.2)**
Penicilin/ β-lactamase inhibitor + macrolides	9	9.6	5	9.8	1	12.5	15 (9.7)
Penicilin/ β-lactamase inhibitor + aminoglycosides	3	3.2	2	3.8	-	-	5 (0.03)
Penicilin/ β-lactamase inhibitor + macrolides + aminoglycosides	-	-	1	1.9	-	-	1 (0.006)
C2G + macrolides	1	1.1	-	-	-	-	1 (0.006)
C2G + aminoglycosides + macrolides	-	-	1	1.9	-	-	1 (0.006)
C3G + aminoglycosides	4	4.2	1	1.9	1	12.5	6 (0.039)
C3G + macrolides	4	4.2	6	11.5	1	12.5	11 (7.1)
C3G + aminoglycosides + macrolides			4	7.7	1	12.5	5 (0.03)
Total	**94**	**100**	**52**	**100**	**8**	**100**	**154 (100)**

C2G - Second-generation cephalosporins, C3G - Third-generation cephalosporins.

Change of antibiotic regimen

The number of patients who maintained the initial antibiotic was 100 patients (64.9%). There were 54 antibiotic changes, mainly due to lack of clinical improvement (53.7%). Cases of antibiotic changes due to slow clinical improvement accounted for 29.6%. There were 16.7% of cases of antibiotic changes based on microbiological and antibiogram results. The two most common types of antibiotic changes were from penicillin/beta-lactamase inhibitor plus macrolide to penicillin/beta-lactamase inhibitor alone (16.7%) and from penicillin/beta-lactamase inhibitor to C3G (9.3%) (Table 3).

Table 3. Number of times of change of antibiotic regimen and reasons for change

Characteristics	Number	Percent (%)
No change antibiotics	100	64.9
Change antibiotics	54	35.1
Total	154	100
Reasons for change of antibiotics		
No clinical improvement	29	53.7
Clinical symptoms improved slowly	16	29.6
Based on microbiological and antibiogram results	9	16.7
Total	54	100

Appropriate in the selection of initial antibiotic regimens and dose

Table 4 shows that the rate of inappropriate initial treatment regimens compared to recommendations was very high, reaching 99.4%. Only 1 case of mild pneumonia was selected for the recommended initial treatment regimen. There were 93 patients with mild and severe pneumonia who were treated with inappropriate initial antibiotics, mainly using ampicillin/sulbactam and ceftriaxone. In cases of very severe pneumonia, the rate of inappropriate antibiotics prescribed was 100%. Among them, ampicillin/sulbactam was mainly used (37.5%).

Table 4. Appropriateness in the selection of initial antibiotic regimens.

Regime	Mild pneumonia		Severe pneumonia		Very severe pneumonia		Total	
	N	%	N	%	N	%	N	%
Appropriate	**1**	**1.1**	**-**	**-**	**-**	**-**	**1**	**0.6**
Amoxicillin/clavulanate	1	1.1	-	-	-	-	1	0.6
Inappropriate	**93**	**98.9**	**52**	**100**	**8**	**100**	**153**	**99.4**
Ampicillin/sulbactam	44	46.8	21	40.4	3	37.5	68	44.2
Ampicillin/sulbactam + aminoglycosides	3	3.2	2	3.8	-	-	5	3.3
Ampicillin/sulbactam + macrolides	9	9.6	5	9.6	1	12.5	15	9.8
Ampicillin/sulbactam + aminoglycosides + macrolides	-	-	1	1.9	-	-	1	0.6
Cefuroxime	1	1.1	-	-	-	-	1	0.6
Ceftriaxone	20	21.3	7	13.5	-	-	27	17.5
Cefoperazone/sulbactam	4	4.2	3	5.8	1	12.5	8	5.2
Cefotaxime	3	3.2	-	-	-	-	3	2
Macrolides	-	-	1	1.9	-	-	1	0.6
C2G + macrolides	1	1.1	-	-	-	-	1	0.6
C2G + aminoglycosides + macrolides	-	-	1	1.9	-	-	1	0.6
C3G + aminoglycosides	4	4.2	1	1.9	1	12.5	6	3.9
C3G + macrolides	4	4.2	6	11.6	1	12.5	11	7.2
C3G + aminoglycosides + macrolides	-	-	4	7.7	1	12.5	5	3.3
Total	**94**	**100**	**52**	**100**	**8**	**100**	**154**	**100**

There were 83/233 (35.6%) cases of antibiotics were used at inappropriate doses for patients with normal renal function. Of those, 75/83 (90.4%) cases used higher doses of antibiotics, the rest used lower doses. There were 57/83 (68.7%) cases used ceftriaxone at doses higher than recommended. The rate of use ceftriaxone with higher dose than recommended dose to be highest (68.7%), followed by azithromycin (13.3%) and ampicillin/sulbactam (3.6%). The rate of use amikacin with lower dose than recommended dose to be highest (3.6%), followed by azithromycin (2.4%) and clarithromycin (2.4%) (Table 5).

Table 5. Antibiotic dosage for patients with normal renal function.

Dosage of antibiotics	Number	Percent (%)
Appropriate dosage	150	64.4
Inappropriate dosage	83	35.6
Total of Appropriate and Inappropriate Dosage	233	100
Higher than recommended (mg/kg/24h)	75	90.4
Ampicillin/sulbactam	3	3.6
Azithromycin	11	13.3
Ceftriaxone	57	68.7
Amikacin	1	1.2
Clarithromycin	1	1.2
Cefixime	2	2.4
Lower than recommended (mg/kg/24h)	8	9.6
Ampicillin/sulbactam	1	1.2
Azithromycin	2	2.4
Amikacin	3	3.6
Clarithromycin	2	2.4
Total of Inappropriate Dosage	83	100

Discussion

In Vietnam, the use of antibiotics without prescription has become widespread and difficult to control. Although antibiotics are on the list of prescription drugs, patients can still buy them at pharmacies without a doctor's prescription. The arbitrary use of antibiotics can cause serious consequences for patients such as side effects, and increase antibiotic-resistant bacteria, affecting treatment results [8]. Ngocho JS et al found high rates of home treatment, particularly with antibiotics. Efforts are needed at the community level to improve awareness of antimicrobial resistance [9].

The use of ampicillin/sulbactam (38.8%) was the highest for the treatment of inpatients with community-acquired pneumonia in our study. Although there is a difference in the order of priority between penicillin and cephalosporins, our research and many other studies show that these two groups were most indicated when treating community-acquired pneumonia in children. Specifically, in our study, ampicillin/sulbactam and ceftriaxone are most commonly used. Ampicillin/sulbactam is a broad-spectrum antibiotic that is active against many strains of bacteria, including H. influenzae, S. pneumoniae, and M. catarrhalis [10]. These bacteria are the leading cause of community-acquired pneumonia in children. Ceftriaxone also has a good effect on S. pneumoniae and shows absolute sensitivity against H. influenzae. This is also the reason why these two antibiotics were used with the highest frequency in our study. Lodha R et al concluded that penicillin/ampicillin plus gentamycin is superior to chloramphenicol for children hospitalised with severe and very severe CAP. The other alternative drugs for such patients are co-amoxyclavulanic acid and cefuroxime, these can be used as second-line therapies [11].

The third most common antibiotic group used in our study were a macrolide (17.8%). In Vietnam, the incidence of macrolide-resistant respiratory tract bacteria is increasing, so macrolides are often used in combination with beta-lactams to treat suspected cases of atypical pneumonia [9]. The antibiotic used with the lowest rate in our study was aminoglycoside (9.3%). The drugs used in this group are mainly amikacin and gentamicin. Amikacin has a rapid bactericidal effect but is toxic to the kidneys and inner ear, so the drug should only be used in the treatment of severe or life-threatening pneumonia [12,13]. The majority of patients 109/154 (70.8%) were prescribed initial monotherapy after admission. The proportion of patients using combination antibiotics was 29.2%. The most commonly used antibiotics were penicillin/β-lactamase inhibitors (44.8%), followed by C3G (24.7%). Le Thi Tuong Vi et al studied antibiotic use for children with CAP in southern Vietnam and found that monotherapy was 66%, twice as high as combination therapy (34%). Amoxicillin/clavulanic acid (50.77%) and azithromycin (30.74%) were the most commonly prescribed drugs in both monotherapy and combination therapy [14]. In Nepal, Pokhrel B et al found that nearly seven in ten under-five children hospitalized with pneumonia in a tertiary care hospital in Nepal were managed with ampicillin monotherapy with good treatment outcomes [15].

According to the Ministry of Health's guidelines for the treatment of community-acquired pneumonia in children, the recommended initial antibiotics are ampicillin and penicillin G, not C3G. Due to the high prevalence of β-lactamase-producing strains of H. influenzae and M. catarrhalis in Vietnam, the use of penicillin in combination with a β-lactamase inhibitor may be an alternative [5, 9]. According to the 2015 Antibiotic Guidelines, aminoglycosides should only be used in combination in very severe cases of pneumonia [5]. However, in our study, 7.4% of mild pneumonia cases and 15.3% of severe pneumonia cases were prescribed aminoglycoside combination.

In this study, the rate of beta-lactam combination with macrolide in the treatment of mild, severe and very severe pneumonia was 9.6%, 9.8% and 12.5%, respectively, and the rate of cephalosporin and macrolide combination in mild, severe and very severe pneumonia was 5.2%, 11.5% and 12.5%, respectively. However, according to the guidelines of the Vietnamese Ministry of Health in 2015 and the British Thoracic Society (BTS) in 2011, adding a macrolide is only recommended if there is no response to initial treatment or Mycoplasma or Chlamydia pneumonia is suspected or very severe pneumonia.

More than one-third of patients had to change their initial treatment regimen, mainly because their clinical symptoms did not improve (53.7%) or improved slowly (29.6%). There were only 9 (16.7%) patients changed antibiotics according to the results of microbiological and antibiogram tests (Table 3). The reason for the high rate of initial antibiotic regimen changes in this study may be due to the high rate of severe and very severe pneumonia and the high rate of self-prescription of antibiotics by families, which may increase the rate of antibiotic resistance of pathogenic bacteria. This explains why doctors have to use broad-spectrum antibiotics or combinations of antibiotics, such as penicillin/beta-lactam inhibitors or ceftriaxone combined with amikacin or macrolide. Kok HC et al commented that this is especially important as concerns mount over rising antibiotic resistance in respiratory bacterial pathogens, which increases the risk of treatment failure [16].

The study also showed a high rate of inappropriate use of penicillin/β-lactamase inhibitors. In the mild pneumonia group, only 1 (0.6%) case of penicillin/β-lactamase inhibitor use was in accordance with the guidelines, the remaining (46.7%) were inconsistent with the guidelines. In the severe pneumonia group, 21/52 children were prescribed injectable ampicillin/sulbactam instead of ampicillin alone according to the guidelines. However, some authors have suggested that penicillins should be used in combination with β-lactamase inhibitors because of the high prevalence of β-lactamase-producing strains of H. influenzae and M. catarrhalis in Vietnam. Yusuf et al and Abeja et al concluded that the irrational use of antibiotics is common among children with pneumonia and is significantly associated with treatment outcomes and mortality [17, 18]. Phuong NTK et al noted that encouraging the rational use of antibiotics requires education of healthcare professionals, use of a simple evidence-based management algorithm, facilitation of cultural change, improved clinical guidance and the establishment of functional microbiology laboratories to monitor disease

etiology and drug resistance patterns, together with the removal of inappropriate incentives and effective enforcement of national regulations to restrict antibiotic use in health care [19, 20].

Regarding dosage, 57 patients were given ceftriaxone at a higher dose than recommended. Four patients were given amikacin at an incorrect dose. Of these, one patient received a higher dose and three patients received a lower dose than recommended. The use of high doses of aminoglycosides, even in patients with normal renal function, can cause adverse effects on the kidneys and hearing. Aminoglycosides are concentration-dependent antibiotics and the Cpeak/MIC ratio is a factor in assessing the therapeutic effect. Therefore, the use of amikacin at a lower dose than recommended does not achieve the therapeutic effect [21].

Conclusions

The rate of inappropriate use of antibiotics in the treatment of community-acquired pneumonia in children in a tertiary hospital was high. It is necessary to develop a system of assessment and monitoring of antibiotic use, from which timely adjustments and control can be made, to limit the ability of bacteria to develop drug resistance.

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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