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Original Article

Etiological characteristics of pediatric pulmonary infection and rational use of antibiotics

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Abstract: Objective: To explore the etiological characteristics of pulmonary infection in pediatrics and the rational use of antibiotics. Methods: We retrospectively analyzed 768 of 2658 children with community-acquired pneumonia (CAP) and pathogen detection admitted from January 2018 to December 2019, and observed the irrational use of antibiotics. Results: The highest number of CAP cases was among children aged 0-1 year and the lowest in children aged 5-14 years (P<0.001). The morbidity of CAP was higher in winter than in the other three seasons (P<0.05). Pathogens were detected in 477 of 768 children (62.11%), and 188 of 477 children were coinfected with the two pathogens. Besides, the top three pathogens detected were respiratory syncytial virus, mycoplasma, and Haemophilus influenzae. The pathogen detection rate was higher in 5- to 14-year age group than in the other age groups (P<0.05). Antibiotics were used in 458 of 477 children with CAP (96.02%), with 43 (9.01%) cases of irrational drug use. Conclusion: We demonstrated the highest incidence of CAP in the winter, comparatively high detection rates of Haemophilus influenzae and respiratory syncytial virus, and high rate of irrational use of antibiotics. Therefore, it is necessary to strengthen the management and control of antibacterial agents in children with CAP.

Keywords: Children, community-acquired pneumonia, etiology, antibiotic, rational use of drugs

Introduction

Undeveloped immune system of children results in decreased resistance to exogenous pathogens, making them more vulnerable to infection which has an adverse impact on the prognosis [1]. Respiratory tract infections are among the most common infectious diseases in children [2, 3]. In pediatric clinical practice in China, community-acquired pneumonia (CAP) is the most common infection acquired outside of hospitals or extended-care facilities, accounting for about 40% of all pediatric infectious diseases [4]. In the treatment of pediatric CAP, antibiotics are the most widely used drugs [5].

With the aid of antibiotics, the mortality rate of CAP in children under 5 years old showed a downward trend [6]. However, CAP was still the main cause of death among the children <5 years old [7]. This may be due to a lack of rapid etiological diagnosis and targeted anti-infective treatment [8]. Although antibiotics can be used for infection control and treatment, irrational drug use or abuse leads to multi-drug resistance [9, 10]. Currently, antibiotics are still abused in China, especially in primary hospitals [11]. It is reported that there are high rates of antibiotic use and irrational use of antibiotics [12]. Due to antibiotic abuse, CAP and the economic burden are exacerbated and total mortality is increased [13]. As a result, it is required that the use rate of antibiotics in hospitalized patients with CAP in China should not exceed 60% [14].

Moreover, a previous study identified that children with CAP of different ages were susceptible to different types of pathogens. Virus and bacteria were commonly detected in children of similar ages, while mycoplasma was in children aged over 3 years old [15].

Definite indications for antibiotics should be advocated in the treatment of CAP, and the initial empirical treatment and combination of antibacterial agents are not recommended [14]. According to the 2011 CAP guideline in the United States, it was strongly recommended for preschool-age children without systemic toxic symptoms to avoid routine antimicrobial agents, which were supported by high-quality evidence [16].

In addition, antibiotic abuse is particularly serious in China, with high incidence of drug-resistant bacteria caused by irrational antibiotic use [11, 12]. Therefore, etiological detection in children with pulmonary infection and targeted antibiotic treatment have guiding significance for reducing the irrational antibiotic use. Herein, we analyzed retrospectively the distribution characteristics of pathogens and the antibiotic use in hospitalized children with CAP in The Second Affiliated Hospital of Hainan Medical University.

Materials and methods

Clinical data

This study was approved by the Ethics Committee of The Second Affiliated Hospital of Hainan Medical University. A total of 2658 children admitted to the department of pediatrics from January 2018 to December 2019 were selected from the information system. Their basic data, onset time, antibiotic use, pathogen detection, etc. were checked and 768 children with confirmed CAP and pathogen detection were retrospectively analyzed. Among them, there were 402 boys and 366 girls with a mean age of 4.02±1.78 years.

Inclusion and exclusion criteria

The included children, aged 0 to 14 years old, were diagnosed with CAP according to the criteria issued by the Respiratory Branch of Chinese Pediatric Society of Chinese Medical Association in 2013 [14]. Formal pathogen detection was performed (see below for details) for all the children. Children with chronic respiratory diseases, allergic cough or asthma, congenital heart disease, or other systemic diseases (e.g., liver and kidney dysfunctions or autoimmune diseases) were excluded. Children with an unclear diagnosis or incomplete medical data were also excluded.

Formal methods for pathogen detection

Before giving antibiotics, sputum specimens or respiratory specimens obtained from nasopharyngeal swabs, nasopharyngeal aspirates or bronchoalveolar lavage fluid were collected from all CAP children. After obtaining the specimens, the pathogen strains were isolated and detected according to the manual for clinical detection using New ATB automatic microorganism identification and drug sensitivity analyzer (BioMérieux, France) [17]. Subsequently, the virus antibody was detected by a reverse transcription polymerase chain reaction (RT-PCR) assay (SimpliAmp PCR instrument; Applied Biosystems, USA). Besides, 2 mL of venous blood was collected from each individual for the detection of IgM antibody to mycoplasma and chlamydia pneumoniae using enzyme-linked immunosorbent assay kits (Shanghai Generay Biotech Co., Ltd.).

Irrational antibiotic use

Irrational antibiotic use was mainly referred to drug use without indications, preferential use of late-generation antibiotics, insufficient or excessive dosage, and unreasonable combined use. In this study, drug use without indications and unreasonable combined use were observed.

Drug use without indications: According to the clinical practice guidelines for CAP, antibiotic treatment was necessary for children with bacterial, mycoplasma, chlamydia and fungal infections, but not in children with viral infection alone [16].

Unreasonable combined use: No or only one antibiotic was required for children with bacterial infection alone. Combined use of antibiotics was suitable for immunodeficient children with severe infections or children with mixed infections (e.g., aerobic and anaerobic infections). Besides, all combination therapies performed without the indications above were referred to irrational use [17].

Outcome measures

The detection rate, pathogen distribution and irrational antibiotic use among children with CAP were the main outcome measures.

The rates of CAP-related hospitalizations in children of different ages and children admit-

Table 1. Comparison of hospitalization rate among three age groups

Items	Hospitalized children (n=2658)	Children with CAP (n=768)
0-1 year	892	432 (48.43)
1-5 years	912	214 (23.46)***
5-14 years	854	122 (14.28)***,###
χ^2	274.350	
P	<0.001	

Note: Compared with age group 0-1 year, ***P<0.001; compared with age group 1-5 years, ###P<0.001. CAP, community-acquired pneumonia.

Table 2. Comparison of morbidity in different seasons

Items	Hospitalized children (n=2658)	Children with CAP (n=768)
Spring	671	201 (29.96)*
Summer	645	165 (25.58)**
Autumn	653	172 (26.34)**
Winter	689	230 (33.38)
χ^2	11.376	
P	0.01	

Note: Compared with morbidity in the winter, *P<0.05, **P<0.01. CAP, community-acquired pneumonia.

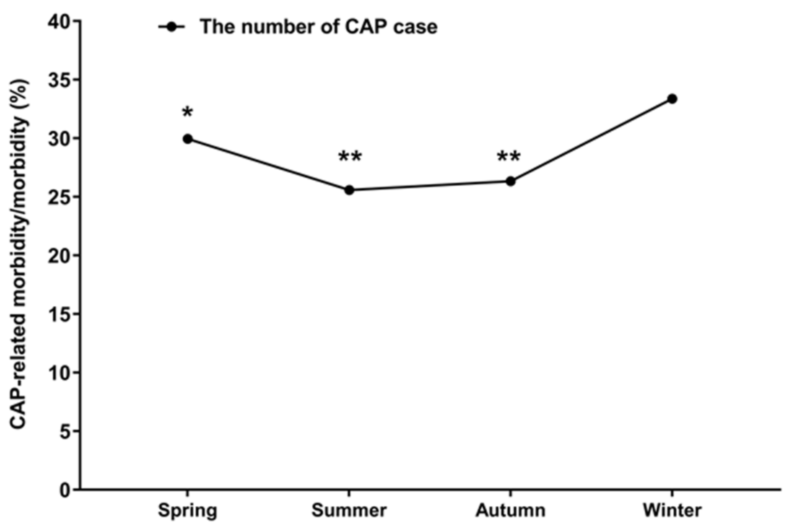

Figure 1. Comparison of morbidity of CAP in different seasons. Compared with morbidity in the winter, *P<0.05, **P<0.01. CAP, community-acquired pneumonia.

ted in different seasons as well as antibiotic use in children of different ages were the secondary outcome measures. The children were divided into three groups according to their age: 0-1 year, 1-5 years and 5-14 years.

Statistical analysis

Data analyses were performed with the SPSS 22.0 software. Continuous variables were expressed as mean ± standard deviation ($\bar{x}$ ± sd). One-way analysis of variance was used if the data were accorded with normal distribution and homogeneity of variance, and rank sum test was adopted if not. Besides, Pearson's chi-square test and Fisher's exact probability were applied for the comparison of enumeration data expressed as percentages. P<0.05 was considered statistically different.

Results

Comparison of hospitalization rate among three age groups

The rate of CAP-related hospitalizations was higher in age group 0-1 year than in age group 1-5 and 5-14 years, and higher in age group 1-5 years than in age group 5-14 years (P<0.001). See **Table 1**.

Comparison of morbidity in different seasons

The morbidity of CAP in winter was significantly higher than that in the other three seasons (P<0.05). See **Table 2** and **Figure 1**.

Comparison of pathogen distribution

One or more pathogens were detected in 477 of 768 children (62.11%), and 188 of 477 children were coinfected with two pathogens. The predominant pathogens were respiratory syncytial virus (RSV), mycoplasma infection, and Haemophilus influenzae. See **Table 3**.

Comparison of pathogen detection rate among three age groups

The pathogen detection rate was the highest in children aged 5-14 years (P<0.05). In terms of

Table 3. Comparison of pathogen distribution

Items	Detected cases (n)	Detection rate (%)
Bacterial infection		
Streptococcus pneumoniae	43	5.60
Haemophilus influenzae	98	12.76
Staphylococcus aureus	75	9.76
Moraxella catarrhalis	49	6.38
Escherichia coli	14	1.82
Mycoplasma/chlamydia infection		
Mycoplasma infection	124	16.14
Trachomatis infection	68	8.85
Viral infection		
Serum adenovirus	11	1.43
Respiratory syncytial virus	146	19.01
Influenza virus	15	1.95
Parainfluenza virus	22	2.86

specific pathogens, the detection rates of Haemophilus influenzae and RSV were higher in age group 0-1 year than those in age group 1-5 and 5-14 years (P<0.05); the detection rates of Staphylococcus aureus and Moraxella catarrhalis were higher in age group 1-5 and 5-14 years than those in age group 0-1 year (P<0.05); the detection rates of mycoplasma and chlamydia were higher in age group 5-14 years than those in age group 0-1 year and 1-5 years (P<0.05). See **Table 4**.

Comparison of antibiotic use among three age groups

Among the three groups, children aged 0-1 year treated with cephalosporins had the highest proportion, while those treated with macrolides showed the lowest proportion. With increasing age, the use of cephalosporins gradually decreased, while the use of macrolides increased (P<0.001). See **Table 5**.

Analysis of rational antibiotic use in 477 children with detected pathogens

Among the 477 children with detected pathogens, two antibiotics were used in 17 children with bacterial infection alone or mycoplasma and/or chlamydia infection alone, and five children with mixed infections (i.e., mixed viral, mycoplasma and/or chlamydia infection, bacterial and viral co-infection). Irrational antibiotic use was found in 21 children with viral infection alone. There were 43 cases (9.01%, 43/477) of irrational antibiotic use in total. See **Table 6**.

Discussion

CAP is a common infectious disease associated with high morbidity and rapid progression in infants and young children, which is prone to develop into severe life-threatening pneumonia [18, 19]. In China, there are 30,000-50,000 pneumonia deaths every year, most of which are in children aged 1-7 years (with infants and young children as the main part) [20]. Previous studies have unveiled that children under 5 years old have an average of 0.26 episodes of pneumonia per year worldwide [21, 22]. In this study, we found a decreasing trend in the incidence of CAP with increasing age, which is consistent with previous findings. Furthermore, our result was in line with the study, stating that the incidence of CAP was higher in winter than the other three seasons, which may be due to the increased risk of infection caused by low temperature in winter [23].

In terms of pathogen detection, the detection rate of bacteria was low while detection rates of viruses, mycoplasma and chlamydia were relatively high owning to the influence of storage, transportation, pathogen detection or antibiotic use [24]. In this study, one or more pathogens (i.e., bacteria, viruses, mycoplasma or chlamydia) were found in 477 of 768 (62.11%) children, which may be related to the low detection rate of bacteria. Additionally, a relatively high incidence of Haemophilus influenzae, which ranked second among all pathogens detected, was reported abroad [25]. The most common virus agent was found to be RSV in pediatric pneumonia [26]. Similarly, our study demonstrated that the highest bacterial detection rate was Haemophilus influenzae and the highest viral detection rate was RSV. Besides, mycoplasma and chlamydia infections accounted for about 10-40% of CAP cases and showed an upward tendency over bacterial infection with a shift towards onset at a younger age [27, 28]. In keeping with the results above, our study revealed a high incidence of mycoplasma and

Table 4. Comparison of the detection rate among three age groups

Items	0-1 year	1-5 years	5-14 years	χ^2	P
Detected cases/CAP cases	58.56 (253/432)	64.48 (138/214)	70.49 (86/122)$^{*,\#}$	6.463	0.040
Bacterial infection					
Streptococcus pneumoniae	5.56 (24/432)	5.61 (12/214)	5.74 (7/122)	0.006	0.997
Haemophilus influenzae	15.97 (69/432)	8.88 (19/214)*	8.20 (10/122)*	9.183	0.010
Staphylococcus aureus	7.41 (32/432)	11.68 (25/214)*	14.75 (18/122)*	7.064	0.029
Moraxella catarrhalis	4.86 (21/432)	7.48 (16/214)*	9.84 (12/122)*	7.451	0.024
Escherichia coli	1.85 (8/432)	1.87 (4/214)	1.64 (2/122)	0.028	0.986
Mycoplasma/chlamydia infection					
Mycoplasma infection	12.96 (56/432)	18.69 (40/214)*	22.95 (28/122)$^{*,\#}$	8.430	0.015
Chlamydia infection	6.94 (30/432)	10.28 (22/214)*	13.11 (16/122)$^{*,\#}$	7.866	0.020
Viral infection					
Serum adenovirus	1.16 (5/432)	1.87 (4/214)	1.64 (2/122)	0.558	0.757
Respiratory syncytial virus	21.76 (94/432)	17.28 (37/214)*	12.30 (15/122)*	6.240	0.044
Influenza virus	1.62 (7/432)	2.24 (5/214)	2.46 (3/122)	0.577	0.749
Parainfluenza virus	3.47 (15/432)	2.24 (5/214)	1.64 (2/122)	1.446	0.485

Note: Compared with age group 0-1 year, $^{*}P<0.05$; compared with age group 1-5 years, $^{\#}P<0.05$. CAP, community-acquired pneumonia.

Table 5. Comparison of antibiotic use among three age groups

Items	0-1 year	1-5 years	5-14 years	χ^2	P
Cephalosporins	302 (69.91)	118 (55.14)*	60 (49.18)$^{*,\#}$	24.924	<0.001
Macrolides	87 (20.14)	77 (21.03)*	45 (36.88)$^{*,\#}$	24.983	<0.001
Compound preparations of β-lactam antibiotics	26 (6.02)	12 (5.61)	3 (2.46)	2.482	0.297
Other β-lactam antibiotics	12 (2.78)	5 (2.34)	3 (2.46)	0.122	0.942
Polyphosphoric broad-spectrum antibiotics	5 (1.16)	2 (0.93)	1 (0.82)	0.128	0.933

Note: Compared with age group 0-1 year, $^{*}P<0.05$; compared with age group 1-5 years, $^{\#}P<0.05$. CAP, community-acquired pneumonia.

Table 6. Analysis of rational antibiotic use in 477 children with detected pathogens

Items	Use of one antibiotic	Use of two antibiotics	Non-use of antibiotics	Irrational use of antibiotics
Bacterial infection (n=169)	159	10	0	5.92 (10/169)
Mycoplasma and/or trachomatis infection (n=80)	73	7	0	8.75 (7/80)
Viral infection (n=40)	19	2	19	52.50 (21/40)
Mixed bacterial, and mycoplasma and/or chlamydia infection (n=89)	4	85	0	0 (0/89)
Mixed viral, and mycoplasma and/or chlamydia infection (n=38)	36	2	0	5.26 (2/38)
Bacterial and viral co-infection (n=61)	58	3	0	4.92 (3/61)

chlamydia infections though it was mainly in children over 5 years.

Antibiotics have a positive effect mainly on infectious diseases caused by bacteria. Therefore, the drugs are ineffective against virus though the symptoms of viral infection are similar to those of bacterial infection [29, 30]. Studies have identified that the irrational use and abuse of antibacterial agents exist in many countries, especially in China [17, 31]. Besides, the abuse of antibiotics leads to an increased incidence of multi-drug resistance, making the management and control of antibiotics urgent [32]. In this study, the use of cephalosporins gradually decreased while the use of macrolides increased with increasing age, which may be due to the high incidence of mycoplasma and chlamydia infection with advancing age. As to the irrational use of antibiotics, definite indications were advocated and initial empirical treatment was suggested to be avoided in guideline for management of community-acquired pneumonia in children (2013 revised version). Moreover, it was emphasized that the combination therapy was not recommended even if there were multiple infections with pathogens [14].

The irrational use of antibiotics was mainly referred to drug use without indications, preferential use of late-generation antibiotics, and excessive combined use. As stressed in the 2013 guideline, antibiotic therapy should be applied in cases of bacterial, mycoplasma, chlamydia and fungal pneumonias rather than in cases of viral pneumonia alone [14]. In our study, antibacterial agents were used in 21 children with viral infection alone; two antibiotics were used in combination in 17 cases of simple infection and in five cases of mixed infections (i.e., mixed viral, mycoplasma and/or chlamydia infection, bacterial and viral co-infection); the irrational use rate of antibiotics was 9.01%. According to the statistical results, most of the antibacterial treatments for CAP children in China are rational, but there is still a high proportion of irrational use.

With the small sample size in this single-center retrospective study, we are aware of that prospective multicenter studies with a larger sample size are needed in the future because of potential biased results.

In summary, we reported the highest incidence of CAP in the winter, comparatively high detection rates in Haemophilus influenzae and RSV, an increasing trend in detection rates of mycoplasma and chlamydia, and high rates of the use and irrational use of antibiotics. Hence, it is necessary to strengthen the management and control of antibiotics in CAP children.

Disclosure of conflict of interest

None.

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