Five-year Surveillance of Antimicrobial use in Chinese Pediatric Intensive Care Units

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Summary

In order to demonstrate antibiotic usage in Chinese Pediatric Intensive Care Units (PICUs), and provide some data to further study on relation of antimicrobial use and resistance. We reviewed the use of antibiotics in Chinese PICUs from 2002 to 2006. All data, including general data and antibiotic use data, were obtained from five PICUs of pediatric teaching hospitals in China. The results of antibiotic use were expressed as defined daily doses (DDDs) per 100 patient-days by WHO in this study. All 12,743 patients were included from the five PICUs in this study. Length of stay in PICUs was essentially unchanged, but the percentage of antimicrobial costs vs. drug costs dramatically decreased in this study period (p < 0.01). The percentage of empiric treatment decreased by year (from 82.2% to 70.2%), while the percentage of therapeutic treatment increased by year (from 11.2% to 24.2%) from 2002 to 2006. Total antibiotic usage decreased from 72.1 DDDs per 100 patient-days to 35.5 DDDs per 100 patient-days from 2002 to 2006 (p < 0.05). The significant increase was found in the DDDs per 100 patient-days of second generation cephalosporins in this study (p < 0.05). While usages of the some antibiotics decreased, for example penicillins, third-generation cephalosporins, and macrolides in this study period. The data of antimicrobial use were obtained from five PICUs of biggest pediatric teaching hospital in this 5-year period, which could serve as a basis of antibiotic treatment and a benchmark in future study of antibiotic use.

Key words: Antimicrobial use, pediatric intensive care units (PICUs), China.

Introduction

The pediatric intensive care unit (PICU) represents a distinctive population with distinctly variable underlying disease processes and unique microbiology [1]. Infections are common problem in the PICU, and antibiotics are therefore commonly used in this unit [2, 3].

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It is accepted that there is a relationship between resistance and the antibiotic usage because of the frequent use of broad-spectrum antibiotics, the acute or chronic suppression of the immune system in PICU patients, and the increased likelihood of cross transmission of resistant pathogens. Antimicrobial-resistant bacteria become a significant problem in PICU [4]. In addition, inappropriate antibiotic usage has resulted in greater patient morbidity, higher mortality rates, increased healthcare costs, and multi-antimicrobial resistance strains for patients of PICU [5–7], so appropriate usage of antibiotics in PICU is important to ensure an optimal clinical outcome and prevent the emergence and spread of antimicrobial-resistant pathogens [8]. However, only very few studies have obtained data of antibiotic use from PICU in China.

The aim of this study is to demonstrate the use of antibiotics in PICUs of five tertiary children’s teaching hospitals from 2002 to 2006 in China. This 5-year surveillance may provide information that...
can help pediatricians for appropriate usage of antibiotics, and prevent the emergence of resistance in PICU.

Materials and Methods

Participating hospital

Data were collected from PICUs of five tertiary teaching children’s hospitals, including Beijing children’s hospital, representing north part of China, Chongqing Children’s Hospital, representing west part of China, Guangzhou Children’s Hospital, representing south part of China, Shanghai Children’s Hospital and Fudan Children’s Hospital of Fudan University representing east part of China from 2002 to 2006, respectively. These pediatric hospitals are distributed geographically in four biggest cities throughout the country, representing a wide spectrum of socioeconomic levels, and are the largest pediatric teaching hospitals in China, with more than 750 hospital beds, including 12–18 PICU beds. There are more than 500 patients of admissions to each PICU per year. All patients of admission to PICUs were included in this study period.

Study design and data collection

Data included general data and antibiotic use data, the following general data of the patient was included: age, gender, weight, length of admission to the PICU, and principal diagnosis in this 5-year surveillance. Antibiotic data were collected for systemic antibiotic use in number of grams in PICU from each hospital’s central computer database for the entire year from 2002 to 2006. The quantity of antibiotic agents was standardized by conversion to defined daily doses (DDDs) according to the Anatomical Therapeutic Chemical (ATC) classification employed by the WHO. DDD is the presumptive average maintenance daily dose of a drug used for its main indication in adults. The use of antimicrobial agents was expressed as the number of DDDs per 100 patient-days for each antibiotic agent. To derive the number of DDDs per 100 patient-days, the pooled number of grams of each antimicrobial applied in the PICUs per year was divided by the number of grams per DDD for a specified antimicrobial; this result was then divided by the number of patient-days in the respective PICU and multiplied by 100.

Definition of indication for antibiotic usage

The indication for antibiotic use included prophylactic, empiric and therapeutic treatment. Prophylactic antimicrobial treatment was defined as any antimicrobial agent administered by injection in an operation or invasive procedure to prevent infection. Empirical treatment was considered to be present when antimicrobials were prescribed for fever or other systemic signs of infection without identifying a specific localized source of infection. Therapeutic treatment was defined as the administration of antimicrobials for a specific clinically pathogens of infection, which based on laboratory results.

Statistical analysis

All data were analyzed by SPSS10.0. Statistical analysis of the data of antibiotic use was performed by t-test. Chi-squared test was used for categorical variables, p-value of <0.05 was considered to be statistically significant.

Results

The general clinical characteristics of patients in PICUs

The general clinical characteristics of patients in the PICUs were shown in Table 1. All 12,743 patients were included from the five PICUs in this study. The mean number of admissions to PICUs remained almost constant each year. There were no significant difference in sex ratio (male/female) and age distribution of children for admission to PICUs from 2002
to 2006 ($p > 0.05$). Two-third of patients were aged younger than 3 years in the five PICUs. Length of stay in PICUs was essentially unchanged (2002, 11.3 days; 2003, 10.8 days; 2004, 10.3 days; 2005, 12.1 days; 2006, 12.9 days, respectively, $p > 0.05$). In addition, there were no significant differences among five PICUs (data not shown).

In this survey, the principal diagnoses of all selected patients were respiratory tract infections (including pneumonia and other respiratory tract infection), diarrhea, central nervous system infection and drug poison in three PICUs.

**Characteristics of antimicrobial use**

As can be seen in Fig. 1, antibiotic costs per patient decreased slightly from 2002 to 2006, especially in 2004, while the percentage of antimicrobial costs vs. drug costs dramatically decreased in this period ($p < 0.001$).

As shown in Table 2, $>70\%$ of all prescriptions were started empirically, $8\%$ as prophylaxis and $16\%$ for a therapeutic treatment. The percentage of empiric treatment decreased by year (from $82.2\%$ to $70.2\%$), while the percentage of therapeutic treatment increased by year (from $11.2\%$ to $24.2\%$) from 2002 to 2006.

As shown in the Table 2, total antibiotic usage, which included all intravenous and oral antibiotics in the five PICUs, decreased from 72.1 DDDs per 100 patient-days to 35.5 DDDs per 100 patient-days ($p < 0.05$). There were statistically significant reductions in the use of penicillins, which decreased more than 5-fold from 31.5 to 5.9 DDDs per 100 patient-days ($p < 0.01$), followed by macrolides, including erythromycin and azithromycin, their use decreased more than 4-fold from 9.6 to 2.3 DDDs per 100 patient-days ($p < 0.05$). The use of cephalosporins remained fairly constant during the study period, but there were changes in the relative use of the different generations. The use of second-generation cephalosporins (cefaclor, cefuroxime, cefazolin) slightly increased ($p < 0.05$), whereas the use of third-generation cephalosporins, including cefotaxime, ceftazidime, ceftriaxone, dramatically increased between 2002 and 2006 ($p < 0.05$). First-generation cephalosporins and fourth-generation cephalosporins were seldom used in this study.

Restricted antibiotics were included carbapenems, glycopeptides, fourth-generation cephalosporins, and $\beta$-lactam/$\beta$-lactamase inhibitor [13]. From our study, the use of restricted antibiotics was shown in Table 2. The usage of glycopeptides slightly decreased during the study period, but remained relatively low. Carbapenems, including imipenem/cilastatin and meropenem, were used equally from

![Fig. 1. Antimicrobial costs and percentage of antimicrobial costs vs. drug costs in this five-year period.](https://academic.oup.com/tropej/article-abstract/54/4/238/1649498)

**Table 2**

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<td>Empiric treatment</td>
<td>83.9</td>
<td>85.6</td>
<td>80.6</td>
<td>66.1</td>
<td>67.0</td>
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<tr>
<td>Therapeutic treatment</td>
<td>11.7</td>
<td>11.5</td>
<td>16.1</td>
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<td>30.1</td>
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<tr>
<td>Prophylactic treatment</td>
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<td>3.0</td>
<td>3.3</td>
<td>7.8</td>
<td>2.9</td>
<td></td>
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<tr>
<td>Antibiotics (DDDs/100 patient days)</td>
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<tr>
<td>Penicillins</td>
<td>31.5</td>
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<td>12.4</td>
<td>4.9</td>
<td>5.9</td>
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<td>$\beta$-lactam/$\beta$-lactamase inhibitor</td>
<td>4.7</td>
<td>6.0</td>
<td>4.9</td>
<td>5.2</td>
<td>3.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
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<td>0.2</td>
<td>0.8</td>
<td>0.5</td>
<td>NS</td>
</tr>
<tr>
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<td>1.9</td>
<td>3.3</td>
<td>5.6</td>
<td>6.9</td>
<td>4.6</td>
<td>&lt;0.05</td>
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<tr>
<td>3rd-generation cephalosporins</td>
<td>14.5</td>
<td>11.9</td>
<td>12.1</td>
<td>14.0</td>
<td>12.1</td>
<td>&lt;0.05</td>
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<tr>
<td>4th-generation cephalosporins</td>
<td>0.9</td>
<td>1.6</td>
<td>1.6</td>
<td>1.1</td>
<td>1.2</td>
<td>NS</td>
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<tr>
<td>Aminoglycosides</td>
<td>2.4</td>
<td>2.4</td>
<td>2.5</td>
<td>2.4</td>
<td>1.2</td>
<td>&lt;0.05</td>
</tr>
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<td>Macrolides</td>
<td>9.6</td>
<td>5.0</td>
<td>2.9</td>
<td>7.1</td>
<td>2.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Glycopeptide</td>
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<td>1.1</td>
<td>1.3</td>
<td>2.1</td>
<td>1.6</td>
<td>&lt;0.05</td>
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<tr>
<td>Carbapenems</td>
<td>2.3</td>
<td>3.4</td>
<td>3.4</td>
<td>1.5</td>
<td>2.6</td>
<td>NS</td>
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<tr>
<td>Total</td>
<td>72.1</td>
<td>66.8</td>
<td>46.9</td>
<td>46</td>
<td>35.5</td>
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2002, 2.3 DDDs per 100 patient-days to 2006, 2.6 DDDs per 100 patient days (p > 0.05). The use of β-lactam/β-lactamase inhibitor decreased during this 5-year period (from 4.7 to 3.5 DDDs per 100 patient-days, p < 0.05). No significant differences were found in density of antibiotic use among the five PICUs.

Discussion

Despite growing concern about antibiotic usage in pediatric patients, the data on antibiotic use in the PICUs of China are limited. We present the first data collected on antibiotic usage in Chinese PICUs in five of the largest tertiary teaching children’s hospitals during a 5-year period. These may serve as reference data and can be of service in understanding the relationship between antimicrobial use and the emergence of resistance in future study.

Antimicrobial use is frequently measured using the DDD system assigned by WHO to every antimicrobial drug. DDD is the presumptive average maintenance daily dose of a drug used for its main indication in adults [9]. DDD may be difficult to calculate in PICU patients, given the wide range of weights among pediatric patients and the fact that many antibiotics are dosed on a milligram per kilogram basis. Special categories of patients may have an atypical antimicrobial dosing pattern and assessment of the WHO DDDs may not be the best method to characterize antimicrobial use in such specialized patient populations, especially patients in PICUs. In our study, two-thirds of patients were aged younger than 3 years, the weights of children were limited to small variation, so we select DDDs per 100 patient-days to express the antibiotic use in PICUs during the study period. In addition, some studies had reported the results by DDD in children [14–16].

Though length of stay in PICUs was essentially unchanged, the use of antibiotics in Chinese PICUs gradually decreased from 72.1 DDDs per 100 patient-days to 35.5 DDDs per 100 patient-days. In addition, antibiotic costs decreased slightly from 2002 to 2006, but the percentage of antimicrobial costs vs. drug costs dramatically decreased in this period. All data shows that there was a reduction in total antibiotic use. It is important to decrease antimicrobial resistant by decreasing use of antibiotics to our PICUs. The change could contribute to several factors, such as education of pediatricians, or the development of guidelines of antibiotic usage [17].

Our results showed that a marked decrease was observed in the use of third-generation cephalosporins and penicillins in the DDDs per 100 patient-days of and the significant increase in the DDDs per 100 patient-days of second generation cephalosporins in this study period. Some factors could contribute to the category change in antimicrobials used. First, the spectrum of diseases had changed in this 5-year study period. Secondly, the rate of pathogens isolated had improved in our PICUs. Thirdly, education of pediatrician, and guideline of antibiotic usage were implemented [17]. In addition, the impact of economic factors should also be considered. This may explain the significant decrease in the use of β-lactam/β-lactamase inhibitor, aminoglycosides, macrolides, and glycopeptides in this period. As we know, antibiotics provide enormous selection pressure for the development of antibiotic-resistant bacteria [18]. A study had shown that over prescription of broad-spectrum antibiotics, such as third-generation cephalosporins, would contribute to the emergence of antimicrobial resistance in most species, especially for methicillin-resistant Staphylococcus aureus (MRSA) and extended spectrum β-lactamases (ESBLs) [19]. Another study had also shown that a restrictive policy targeting ceftazidime, which was effective in reducing the incidence of ESBLs producing bacteria [20]. The reducing the use of third-generation cephalosporins and broad-spectrum penicillins in this study may have an impact on decreasing selection pressure to resistance in Chinese PICUs. So it is important to decrease use of broad-spectrum antibiotics to the patients in PICUs.

From our study, more than two-third antibiotics were prescribed on an empirical basis without pathogen identification or antibiotic susceptibility test. Many factors may contribute to inappropriate empirical antibiotic choice on PICU [21], such as no evidence of pathogens, or low rate of bacterial organisms isolated. Pediatricians were probably affected by the idea that low rate of bacterial organisms isolated could not protect against infections [22]. In this condition, pediatricians usually prescribed empiric instead of therapeutic treatment. In this survey, we found that there was a shift from empirical treatment to therapeutic one. This result probably contributed to the published guideline of antibiotic usage, which may avoid inappropriate prescribing in PICU, and prevent further selection and dissemination of antibiotic resistant strains.

There are several limitations to our study. One is that evaluating use of antibiotics in PICU is a very complex subject to assess accurately on a retrospective basis, and prospective studies are robust more in this field [23]. Another limitation is that definitions of empiric, therapeutic and prophylactic were provided to personnel collecting the data, but it is not feasible to assess whether these definitions were accurately applied [24].

In conclusion, we present the data of antimicrobial use from five PICUs of the biggest pediatric teaching hospitals in this 5-year period, which could serve as a basis of antibiotic treatment and a benchmark in future study of antibiotic use. In addition, further research is needed to determine the relationship between antibiotic use, selection pressure and the emergence of resistance in our PICUs. To maintain
efficacy and safety of antibiotic use, continuous surveillance of antibiotic use and resistance is necessary.

References