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Effect of pharmacist interventions on antibiotic use in the general pediatric ward

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Abstract: Antibiotics are widely prescribed and often used irrationally in Chinese hospitals. This study aimed to evaluate the pharmacist's influence on antibiotic use in the pediatric ward. We conducted this pre-to-post intervention study in the pediatrics of a Chinese tertiary hospital. The patients hospitalized from April to June 2018 were assigned to the pre-intervention group and those from April to June 2019 were distributed to post-intervention group. In the post-intervention stage, the pharmacist took measures to promote rational use of antibiotics and their effects were assessed. This study analyzed data of 1408 patients totally, 671 and 737 in the pre-intervention and post-intervention group respectively. The interventions of clinical pharmacist significantly reduced the rate of using antibiotics without indications (from 33.55% to 15.82%, $p<0.01$), percentage of inappropriate antibiotic choice (from 24.79% to 16.58%, $p<0.01$), dose (from 8.55% to 4.34%, $p<0.05$), combination (from 11.75% to 5.10%, $p<0.01$) and prolonged duration (from 14.53% to 10.46%, $p<0.05$). The mean antibiotic cost and cost/patient-day were also significantly reduced after the intervention. The ratio of average antibiotic cost saving to pharmacist time cost was 16.77:1. The pharmacist could play vital roles in optimizing antibiotic use, thus resulting in favorable clinical and economic outcomes in pediatric ward.

Keywords: Pharmacist interventions, pediatric, antibiotic use, medical cost, economic outcome.

INTRODUCTION

Antibiotics are among the drugs most widely prescribed in Chinese hospitals because their important roles in reducing mortality caused by bacterial infections. However, antibiotics are also often used unreasonably and this not only increases the risk of adverse effects but also contributes to the emergence of micro-organisms resistance (Goossens, 2009, Costelloe *et al*., 2010). In turn, resistance leads to treatment failure, prolonged hospitalization and increased costs (Principi and Esposito, 2019, Pinzone *et al*., 2014).

Pediatric patients get considerable attention in clinical treatment because of their special characteristics. Due to the immature organs and physiological functions, they are more sensitive to drugs compared with adults, inappropriate antibiotic administration may affect their whole life in some severe cases. So it is especially important to use antibiotics rationally based on the disease and physiological state of each pediatric patient.

Although guidelines on antibiotic use have been established in most Chinese urban tertiary hospitals, they can't be followed strictly due to multiple reasons (Wang *et al*., 2015). The unreasonable use of antibiotics in pediatric ward was still common according to an audit of prescription and medical advice organized by the medical department of our hospital. It was mainly manifested by non-indicated medications, improper selection of antibiotics, unnecessarily excessive dosage, long duration and unnecessary combination. Many pediatricians in China often prescribe antibiotics just based on their own experience or the orders of superior doctors, which may lack scientific evidence. For example, a proportion of acute respiratory tract infections or diarrhea is caused by viruses and should not be given antibiotics (Sharma *et al*., 2015), while doctors often prescribe antibiotics actually. Therefore, it is important to monitor the antibiotic prescription in hospitals to find out the areas needed to be improved (Sie *et al*., 2019). It is also urgent to take measures to prevent inappropriate antibiotic usage and slow down the development of bacterial resistance in pediatric ward.

As an important part of the medical team, the pharmacists play key roles in optimizing antibiotic use worldwide. An American study demonstrated that pharmacist intervention maximized the selection of antimicrobials and improved surrogate outcomes for mortality in patients with septic shock (Laine *et al*., 2018). In Europe, the existence of training pharmacists lowered antibiotic consumption significantly (Mueller and Ostergren, 2016). Due to imperfect pharmacist system in China, the role of

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pharmacists is relatively limited and they are mainly engaged in the physical work of dispensing medications in most hospitals (Zhu *et al*., 2010). China National Health and Family Planning Commission (NHFPC) launched a special rectification scheme to reorganize the rational use of antimicrobials in 2011 (Xiao *et al*., 2013) and it firstly required clinical pharmacists to participate in antimicrobial management (Wang *et al*., 2015). Since then the role of pharmacists in optimizing antibiotic use also becomes more and more prominent. For example, Zhang *et al*. found that clinical pharmacist intervention promoted reasonable use of prophylactic antibiotics in urological inpatients undergoing operations in a Chinese hospital (Zhang *et al*., 2014). Shen *et al*. confirmed that the proportion of inappropriate antibiotic use as well as the length of hospital stay of inpatients with respiratory tract infections decreased significantly after pharmacist interventions (Shen *et al*., 2011).

However, the effect of clinical pharmacists on inappropriate antibiotic use in pediatric ward has been few investigated. In our study, a clinical pharmacist was appointed to supervise and direct the antimicrobial therapy based on the established standard for antibiotics use in pediatric patients. The purpose of this research was to evaluate the effect of pharmacist intervention on the use of antibiotics in the general pediatric ward of a tertiary hospital.

MATERIALS AND METHODS

Study design and participants

This was a retrospective study conducted in Tang-du Hospital, which is a teaching hospital affiliated to the Fourth Military Medical University. Data about the characteristics of the inpatients were collected from the department of pediatrics. The study was divided into pre-intervention stage and post-intervention stage. The pre-intervention stage played the part of an observational period to identify issues related to antibiotic usage, and was performed from April 1, 2018 to June 30, 2018. In this stage, the medical treatment was conducted by the pediatricians without pharmacist involvement. In the post-intervention stage, an experienced clinical pharmacist worked as a part of the medical team and cooperated with the pediatricians closely. This intervention stage was from April 1, 2019 to June 30, 2019. Then the patients hospitalized during April-June 2018 were assigned to the pre-intervention group and those admitted during April-June 2019 were distributed to post-intervention group. To guarantee the comparability of statistics, patients were excluded if they met any one of the following: had been transferred from other medical departments; had already received antibiotics within the two weeks before admission.

Criteria

The standard for rational use of antibiotics in pediatric patients was established based on the official document issued by NHFPC in 2009 (National Health and Family Planning Commission of the People’s Republic of China, 2011) and “Guidelines for Antibacterial Use in Clinical Practice” published in 2015 (National Health and Family Planning Commission of the People’s Republic of China, 2015). The indications for rational antibiotics use were evaluated according to these criteria.

Interventions

According to the design of the study, a full-time clinical pharmacist worked as a part of medical team for three months in the pediatric ward from April 1, 2019. During this period, the role of the clinical pharmacist was to real-time monitor medical records and make sure that the criteria for rational use of antibiotics was carried out in the prescribing practices. Specifically, pharmacist developed the following interventions: (i) delivering lectures about antibiotic usage, especially the knowledge about antibiotics' indications, pharmacokinetics, pharmacodynamics and antibacterial spectrum. (ii) extracting the information of inpatients from hospital information system (HIS) and electronic medical records (EMR), and judging the suitability of antibiotic usage from the following aspects: indication, choice, dose, duration and combination. Once a potentially inappropriate antibiotic application was found, the pharmacist discussed with the pediatricians and gave advices on the next step of treatment (Shen *et al*., 2011) (iii) providing consultations and participating in the formulation of treatment plan on complicated cases. (iv) The inappropriate prescriptions of antibiotics were gathered and classified, and the identified problems were feedback to pediatricians every day so that recommendations for improvement could be discussed. The problems were presented to the hospital administrator every week. The clinical pharmacist worked four hours on average every weekday.

Data collection

At the end of the study, a specialist blinding to the patients' allocation status recorded the data of patients in both groups. It included patients’ baseline characteristics (age, gender, body mass), antibiotic use (dose, frequency, duration, combination and replacement), cost (total cost of hospitalization, total drug cost and cost of antibiotics) and length of hospitalization. All costs in were expressed as US dollars and the exchange rate was 6.7 Yuan =US$1. The economic effect of pharmacist interventions for antibiotic usage was assessed by cost-benefit analysis. The analysis was a way to compare the costs against the benefits of pharmacist interventions (Luo *et al*., 2017). The benefit-to-cost ratio was expressed as the results of the cost savings of antibiotic divided by human costs of clinical pharmacist (Chisholm *et al*., 2000). The mean cost saving of antibiotic was assessed via measuring difference of antibiotic cost between the two groups before and after the intervention. The mean pharmacist time cost was expressed as ratio of total cost of time spent in implementing the interventions and the number of patient cases in post-intervention group.

Ethical approval

This study was approved by the Ethical Committee of Tang-du Hospital. Information on all patients was provided by the hospital database. All data handled was kept anonymous so individuals were impossible to identify from the database.

STATISTICAL ANALYSIS

Data was analyzed by the software of SPSS 22.0 (SPSS Inc., USA). The comparisons for continuous variables with a normal distribution were performed by Student's t-test. For some continuous variables with non-normal distribution, Mann-Whitney U-tests were used. Categorical variable was presented as frequency and percentage. Rate was analyzed with chi-squared test. In all cases, p<0.05 was considered to be significant.

RESULTS

Overall characteristics of the patients

The number of admissions that met inclusion criteria was 1408 during the study period, with 671 patients and 737 patients in the pre-intervention group and post-intervention group. The characteristics of included patients were presented in table 1. No significant differences were observed regarding demographics characteristics, including sex, age, body weight, height and patients' age distribution (p>0.05) between the two groups. Infants and children under 6 years accounted for the majority of hospitalized patients in both groups.

General data of antibiotic usage

The general data of antibiotic use in both groups was summarized in table 2. The rate of antibiotic usage in pre-intervention group was 69.7% (n=468), and it dropped to 53.2% (n=392) after pharmacist intervention (p<0.01). Among the patients administrated with antibiotic, 47.2% of them in pre-intervention group and 78.3% in post-intervention group received drug sensitivity test, indicating a significant increase in the proportion of patients receiving drug sensitivity test after the intervention (p<0.01). On the other hand, the intervention also led to a remarkable reduction in rate of two or three kinds of antibiotics combination, with a reduction from 31.8% to 20.2% (p<0.01) and 16.5% to 7.9% (p<0.01) respectively.

Frequency of the antibiotics usage

The frequency of the antibiotics used in pediatric ward was shown in table 3. Because same patients administrated more than one type of antibiotics, so the frequency was higher than the patients' number in both the pre-intervention (n=771) and post-intervention (n=533) group. In the pre-intervention group, cefoperazone tazobactam (11.15%) was the most frequently administrated antibiotic, followed by ceftazidime (9.34%),

Table 1: Baseline characteristics of patients in pre-intervention and post-intervention groups

	Pre-intervention group (n =671)	Post-intervention group (n = 737)	*p*-value
Male/Female	348/323	386/351	NS†
Body weight (kg)	17(1.7-56.5)	18.5(2.1-61)	NS
Height (cm)	97(38-162.5)	101(40.5-167)	NS
Number of infants (%)	193 (28.8%)	219 (29.7%)	NS
Number of children aged 1–6 years (%)	391(58.2%)	413 (56%)	NS
Number of children aged >6 years (%)	87(13%)	105 (14.3%)	NS

† NS = not significant ($p > 0.05$). Body weight and height were expressed as median.

Table 2: General data of antibiotic usage in pre-intervention and post-intervention groups

	Pre-intervention group N (%)	Post-intervention group N (%)	*p*-value
Rate of antibiotic usage	468 (69.7%)	392 (53.2%)	< 0.01
Rate of drug sensitivity test	221 (47.2%)	307 (78.3%)	< 0.01
Two kind of antibiotic combination	149 (31.8%)	79 (20.2%)	< 0.01
Triple usage of antibiotic	77 (16.5%)	31 (7.9%)	< 0.01

piperacillin sulbactam (8.17%), meropenem (7.78%).

Third-generation cephalosporins and other antibiotics account for nearly 60% of all the antibiotics usage. However, the usage of penicillins, first and second-generation cephalosporins was significantly increased after pharmacist intervention. They accounted for nearly 70% of the antibiotics used in post-intervention group. Conversely, the intervention led to a significant reduction in the use of third-generation cephalosporins (17.07%, p<0.01), and the pediatricians tend to choose cephalosporins without enzyme inhibitors. In addition, the usage of other high-level antibiotics, including meropenem and vancomycin, also decreased obviously in post-intervention group. These results suggested that the intervention promoted the switch from higher level antibiotics to lower level antibiotics.

Rate of inappropriate antibiotic usage

The rate of improper antibiotic administration in the two groups was shown in table 4. The percentage was expressed as the results of incorrect cases number dividing by number of patients ever used antibiotics during the hospitalization (468 cases and 392 cases in the two groups respectively). In the pre-intervention group, 33.55% of the patients had no indications but used at least one type of antibiotics. This percentage decreased to 15.82% in post-intervention group, indicating that unnecessary antibiotic administration was significantly reduced after intervention (p<0.01). The rate of irrational antibiotic choice was 16.58% after the intervention, which was remarkably lower than that in pre-intervention group (p<0.01). Pharmacist intervention also markedly reduced the rate of irrational antibiotic combination (p<0.01), the percentage decreased from 11.75% in the pre-intervention group to 5.10% in post-intervention group. The intervention exerted similar effects regarding the inappropriate dose or prolonged duration of antibiotic administration. The patients receiving unnecessarily prolonged duration of antibiotics decreased from 14.53% to 10.46% (p= 0.043).

Table 3: Frequency of the used antibiotics in pre-intervention and post-intervention groups

	Pre-intervention group	Post-intervention group	*p*-value
Frequency of antibiotic usage†	771	533	-
Penicillins and 1st - generation cephalosporins N (%)	181 (23.48%)	166 (31.14%)	< 0.01
Amoxicillin	19 (2.46%)	27 (5.07%)	-
Amoxicillin-clavulanate potassium	51 (6.61%)	42 (7.88%)	-
Piperacillin sulbactam	63 (8.17%)	38 (7.13%)	-
Cefathiamidine	32 (4.15%)	35 (6.57%)	-
Cephradine	16 (2.08%)	24 (4.50%)	-
2nd-generation cephalosporins N (%)	145 (18.81%)	193 (36.21%)	< 0.01
Cefazolin	41 (5.32%)	64 (12.01%)	-
Cefuroxime	46 (5.97%)	70 (13.13%)	-
Cefotiam	33 (4.28%)	42 (7.88%)	-
Cefaclor	25 (3.24%)	17 (3.19%)	-
3rd-generation cephalosporins N (%)	243 (31.52%)	91 (17.07%)	< 0.01
Ceftazidime	72 (9.34%)	32 (6.00%)	-
Ceftriaxone tazobactam	49 (6.36%)	16 (3.00%)	-
Cefoperazone tazobactam	86 (11.15%)	19 (3.56%)	-
Cefixime	36 (4.67%)	26 (4.88%)	-
Other antibiotics N (%)	202 (26.20%)	83 (15.57%)	< 0.01
Cefminox	25 (3.24%)	10 (1.88%)	-
Latamoxef	22 (2.85%)	15 (2.81%)	-
Meropenem	60 (7.78%)	16 (3.00%)	-
Vancomycin	43 (5.58%)	11 (2.06%)	-
Azithromycin	32 (4.15%)	17 (3.19%)	-
Ornidazole	20 (2.59%)	14 (2.63%)	-

† There were combinations or replacements of antibiotics in some patients in the two groups, resulting in the frequency of antibiotic usage being higher than the number of patients.

Table 4: Rate of inappropriate antibiotic usage in pre-intervention and post-intervention groups

	Pre-intervention group N (%)	Post-intervention group N (%)	*p*-value
No indication	157 (33.55%)	62 (15.82%)	< 0.01
Irrational choice of antibiotics	116 (24.79%)	65 (16.58%)	< 0.01
Improper antibiotic combination	55 (11.75%)	20 (5.10%)	< 0.01
Inappropriate dose	40 (8.55%)	17 (4.34%)	0.039
Unnecessary replacement of drugs	32 (6.84%)	19 (4.85%)	NS†
Unnecessary prolonged duration	68 (14.53%)	41 (10.46%)	0.043

† NS = not significant ($p > 0.05$)

Table 5: The medical cost in pre- and post-intervention groups

	Pre-intervention group	Post-intervention group	*p*-value
Mean total hospitalization cost (USD)	1710.07	1603.73	NS†
Mean total drug cost (USD)	701.41	625.16	NS
Antibiotic cost/patient-day (USD)	10.25	4.83	< 0.01
Mean antibiotic cost (USD)	141.75	66.22	< 0.01
Mean hospitalization days	14.25	13.55	NS

† NS = not significant ($p > 0.05$)

Table 6: Cost-benefit analysis of clinical pharmacist intervention

Cost of clinical pharmacist time	
Hourly salary	$7.46
4 hours per day × 67 working days during intervention period	268 hours
Total cost of pharmacist time (268 hours × $7.46 per hour)	$1999.28
Mean cost of pharmacist time (total cost of pharmacist time /392 cases)	$5.10
Mean antibiotic cost reduction for 392 cases in the post-intervention group	
Mean antibiotic cost for 468 cases in the pre-intervention group-mean antibiotic cost for 392 cases in the post-intervention group	$85.53
Net cost benefit	
Mean antibiotic cost reduction – mean cost of pharmacist intervention	$80.43
Benefit-to-cost ratio	
Mean antibiotic cost reduction: mean cost of pharmacist time	16.77:1

The length of hospitalization and medical costs

There was no change in the prices of antibiotics and other drugs during the period of our study. After the intervention, the antibiotic cost/patient-day ($p<0.01$) and mean antibiotic cost ($p<0.01$) both significantly reduced in post-intervention group. There was a downward trend regarding the average total hospitalization cost, average total drug cost and length of hospitalization after the intervention, but with no significant difference compared to the pre-intervention group (all $p>0.05$) (table 5).

Cost-benefit analysis

The mean antibiotic cost reduction was calculated by the differences in average cost of antibiotics between the two groups, which was $85.53. The total working time of the pharmacist was 268 hours within the 3-month intervention period. Accordingly, the total cost of pharmacist's time was nearly $1999.28 over 3 months with the hourly salary of $7.46. The mean cost of the pharmacists' time was expressed as the result of dividing total cost of pharmacist's time by total number of cases in the post-intervention group, and the average value was $5.10. Then a conservative estimation of the pharmacist intervention led to a benefit-to-cost ratio of 16.77:1, which was obtained through dividing mean cost reduction of antibiotics by mean cost of pharmacist time (table 6).

DISCUSSION

Although some studies demonstrated the crucial role of clinical pharmacist in the rational use of antibiotics in departments of hospitals (von Gunten *et al*., 2007, Shi *et al*., 2013), few data was available regarding its influence on antibiotic use in pediatric patients in Chinese hospitals.

In this study, we evaluated the effectiveness of pharmacist intervention on antibiotic usage in the general pediatric ward at Tang-du Hospital and found that pharmacist intervention played key roles in antibiotic stewardship and resulted in favorable clinical and economic outcomes.

In China, antibiotic overuse is very common and they were even found to be used in some cases of non-bacterial infection. In this study, using antibiotics without indication significantly decreased in the post-intervention group, demonstrating the important role of pharmacists in promoting doctors to prescribe antibiotics based on indications. The other inappropriate usage in this study also included irrational choices of antibiotics, unnecessarily excessive dosage of antibiotics, unnecessarily replacement or combinations of antibiotics. And these improper medical practices have also been curbed in post-intervention group after the pharmacist's participation. These suggested that the clinical pharmacist was helpful in avoiding antibiotic misuse or overuse in some unnecessary cases.

In the post-intervention stage of this study, the pharmacist monitored the antibiotic use in a real-time manner based on the established criteria. The pharmacist-implemented antibiotic stewardship has been demonstrated to be reliable in supervising the use of antimicrobial agents in American and European hospitals (Laine *et al*., 2018, Mueller and Ostergren, 2016). In our study, the clinical pharmacist assessed the rationality of antibiotic usage by comprehensively analyzing the condition of each patient. Once the inappropriate antibiotic usage was identified, the pharmacist communicated with the pediatricians timely and gave suggestions on how to choose the right one (Wang *et al*., 2015). Due to various reasons, not every suggestion of pharmacist could be accepted by the pediatricians. However, the rate of acceptance was increased along with the advance of the stewardship. Only less than half of the recommendations were adopted by pediatricians during the first month of intervention, whereas this percentage was elevated to over 80% at the later stage. It was observed that some pediatricians even changed their prescribing habits after the intervention. They preferred to choose high level or broad-spectrum antibiotics before the intervention. In contrast, the penicillins or lower levels of cephalosporins were more frequently prescribed after intervention. Given the close relationship between antibiotics abuse and the emergence of resistant bacteria (Barlam *et al*., 2016), the intervention of pharmacist in antibiotic use was helpful in preventing the deterioration of antibacterial treatment situation.

Besides contributing to bacterial resistance, inappropriate antibiotic use also increased patients' burden and wasted medical resources. Study has shown that taking measures to manage antibiotic use could lead to considerable financial savings (Malani *et al*., 2013). In our study, substantial reduction of average antibiotic cost was also observed after the intervention, which decreased from \$141.75 to \$66.22 ($p<0.01$). The average cost of pharmacist's time in the post-intervention group was \$5.10. Then the benefit-cost ratio was 16.77:1, which meant the mean financial rewards (antibiotic savings) was 16.77 times more than the cost (mean pharmacist's time cost). These favorable results demonstrated that the pharmacist intervention brought considerable economic benefits and avoided the unnecessary waste of healthcare resources. It indicated that the pharmacist could positively affect the clinical practice in Chinese healthcare system.

Although the advantages of pharmacist intervention were obvious, the pediatricians could not totally accept their advices just as mentioned above. Several factors contributed to this special situation in Chinese hospitals. First, clinical pharmacists in China are not authorized to deny irrational prescriptions, the doctors can choose to accept or reject pharmacists' suggestions. Second, the tense doctor-patient relationship force doctors to practice defensive medicine to in order to avoid lawsuit (Zhang and Harvey, 2006). Third, a part of doctors have some misconceptions regarding antibiotic usage, such as "new antibiotics are stronger" (Zhang and Harvey, 2006), which promote the prescription of new or high-level antibiotics in some unnecessary cases. Based on this analysis, it is obvious that only pharmacists' intervention is not enough to eliminate the inappropriate antibiotic use completely in China. It is also urgent for hospital administrators to develop comprehensive antibiotic stewardship and further strengthen the intervention, such as educating pediatricians, monitoring their prescribing behaviors and giving punishment for improper medical treatment (Wang *et al*., 2015). Moreover, the clinical pharmacists should be granted supervising right over medication practices by Chinese health authority. Only in this way can the effectiveness of pharmacist interventions be maximized and rational usage of antibiotics be improved to the utmost extent.

This study also had some limitations. It was designed in a pre-to-post way, lacking the parallel control group, thus it was not as convincing as a prospective design. Second, the sample size was small, the effect of pharmacist intervention needs to be confirmed in further studies with larger sample size. Third, some other factors may also contribute to the results, therefore more rigorous design was needed in the future.

CONCLUSION

Our study found that the pharmacist intervention in general pediatric ward resulted in favorable clinical and economic outcomes. It obviously promoted rational usage of antibiotics and reduced the costs. These results indicated that clinical pharmacists could play important roles in the medical practice of Chinese hospitals.

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