

Effectiveness Analysis of Clinical Pharmacists-led Medication Therapy of Refined Management Mode: Antibiotics Administration

Yue Li^{1*}, Yue Liu^{1,2*}, Riran Zhu¹, Jianfeng Ju¹, Ying Wang¹, Chao Huang¹, Chuanjiang Ma¹, Jingyi Wang¹, Li Guo³, Zhijie Chu¹, Xiaoqian Liu^{1#} and Qun Liu^{1#}

¹Affiliated Hospital of Shandong University of Traditional Chinese Medicine (TCM), Jinan, 250014, PR China

²Shandong University of Traditional Chinese Medicine (TCM), Jinan, 250014, PR China

³Shaanxi Provincial Hospital of Chinese Medicine, Xi'an, 710000, PR China

*These authors contributed equally to this work and should be considered co-first authors

#These authors contributed equally to this work and should be considered co-corresponding authors

*Corresponding author: Yue Li, Affiliated Hospital of Shandong University of Traditional Chinese Medicine (TCM), Jinan, 250014, PR China.

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Abstract

Objective: The effectiveness of clinical pharmacists was explored in regulating the application of antibiotics, promoting rational drug use and reducing antibiotics use density (AUD) by the refined management strategy of antibiotics.

Methods: We compared and analyzed the improvement of related indexes of antibiotics and the unreasonable application of antibiotics before and after the implementation of the program, with the help of the refined management mode

Results: From 2018 to 2021, the clinical indicators of antibiotics use at our hospital showed an overall downward trend. The utilization rate of antibiotics and the AUD in inpatients gradually decreased by 12.88% and 22.44% respectively, and the rate of microbial examination increased by 39.81%. Compared the changes in indicators, it was found that the antibiotics cost /total drug cost decreased from 1.79% to 1.02%. PDCA was used to improve the reasonable rate of antibiotics prophylactic use in orthopedic cases from 72.22% to 89.71%.

Conclusion: The participation of clinical pharmacists in the refined management of antibiotics can reduce AUD and the drug costs of patients, and promote the rational application of antibiotics simultaneously.

Keywords: Refined Management of Antibiotics, Clinical Pharmacists, Interrupted time Series, Antibiotics Use Density (AUD), Pharmacy Services

Introduction

At present, antimicrobial resistance (AMR) has become a serious global public health event [1, 2]. Inappropriate antibiotic use is one of the main reasons for accelerating AMR, which leads to treatment failure and healthcare cost escalation in countries around the world [3, 4]. It is expected that AMR may cause 10 million deaths a year by 2050, and meanwhile, economic output will be reduced by \$100 trillion, unless there is a global response to the problem of AMR [5, 6]. As a result, both the WHO and several countries have developed strategies to tackle AMR, and the rational use of

antibiotics has become a research hotspot worldwide [7, 8]. In a university hospital in Taiwan, the inpatient antibiotic consumption was reduced 13% by an AMS programme that aimed to educate physicians [9]. A systematic review and meta-analysis of AMS programmes in Asia also reported reductions in antibiotic usage, healthcare costs and mortality rates associated with the implementation of the programmes [10].

Until 2018, the AUD at our hospital had been steadily increasing every year. In 2018, it was much higher than the target value

40DDDs stipulated by the state. How to promote rational clinical application of antibiotics and reduce the AUD has become a critical problem for pharmaceutical management at our hospital. In February 2019, the refined management of antibiotics was conducted jointly by the Department of Pharmacy and other departments. Numerous management measures were simultaneously undertaken to strengthen the clinical application management of antibiotics, with continuous optimization of various indicators and standardization of clinical use. The experience and shortcomings are summarized below for reference.

Management Measures

The working group on the refined management of antibiotics was established in our hospital. The Faculty of Pharmacy played a dominant role in this working group, in collaboration with the Medical Department, Infection Management Department, Microbiology Department, Information Center and other departments, with a clear division of responsibilities (Figure 1). Relying on the antibiotics management working group, clinical pharmacists were assigned to 70 wards of the hospital to participate in the whole process of clinical antibiotics application, promote the refined management of antibiotics and ensure rational antibiotics use.

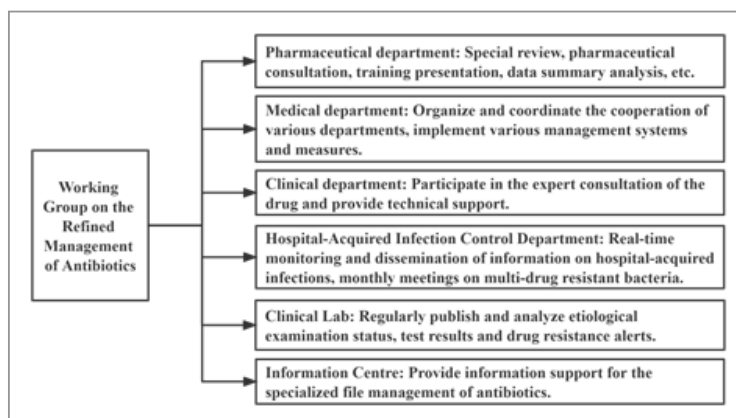


Figure 1: Management work group division of labor

Develop Antibiotics-related System

The working group on the refined management of antibiotics formulated and distributed a series of management systems to all wards providing tools and standards for application of the refined management of antibiotics. The antibiotics-related systems involved “Regulations on the Administration of Perioperative

Prophylactic Application of Antibiotics”, “Implementation Rules of Clinical Application Management of Antibiotics”, “Training and Assessment System of Rational Use Knowledge and Standardized Management of Antibiotics”, “Classification Management System for Antibiotics”.

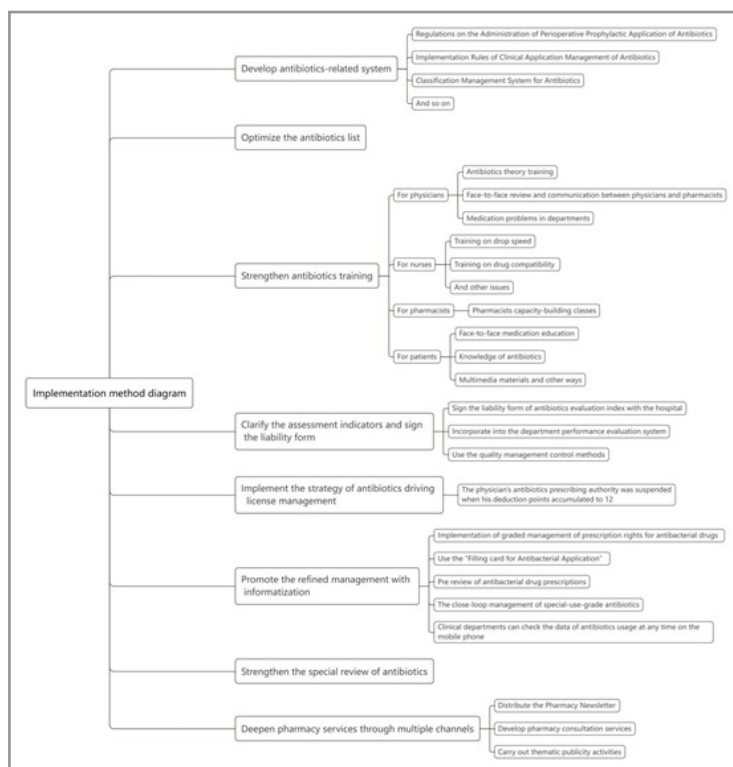


Figure 2: Implementation Method Diagram for the Fined Management of Antibiotics

Optimize the Antibiotics List

The antibiotics supply list was adjusted every two years. Clinical pharmacists submitted the adjustment plan to the Pharmacy and Therapeutics Committee. To ensure the antibiotics varieties reasonable, our adjustment principle referred to disease spectrum, clinical application requirements, antimicrobial resistance monitoring results, adverse drug reactions, evidence-based medicine, China's National Essential Medicines List, the National Centralized Drug Procurement and so on.

Strengthen Antibiotics Training

Clinical pharmacists use flexible and diverse approaches to conduct special training on antibiotics. For physicians, routine training (antibiotics theory training), participatory training (face-to-face review and communication between physicians and pharmacists), and targeted training (medication problems in departments) were adopted. For nurses, targeted training was conducted on drop speed, drug compatibility and other issues. For pharmacists, training was performed on pharmacist's capacity-building classes which was named "Pharmacists need do something different" to enhance the ability of pharmacist's prescription review. For patients, face-to-face medication education, knowledge of antibiotics, multimedia materials and other ways were adopted to improve their understanding of antibiotics. For physicians, nurses, pharmacists, and patients, their overall awareness of antibiotics was improved through standardized, normalized, and scientific training, which regulated the use of antibiotics.

Clarify the Assessment Indicators and Sign the Liability form

According to the requirements of the national "Measures for the administration of clinical use of Antibacterial", the AUD in tertiary general hospitals is less than 40DDD, and the rate of antibiotics use in inpatients is less than 60%. Based on the total control of hospital-wide data, combined with professional characteristics, disease distribution and other factors, the defined daily dose method was utilized to establish the target value of antibiotics use in each ward [11]. According to the target value, every ward signed the liability form of antibiotics evaluation index with the hospital, which was incorporated into the department performance evaluation system to ensure the effective implementation of antibiotics management measures. With the help of PDCA, quality control circle and other quality management control methods, clinical pharmacists assist each ward to control their indicators within the target value [12].

Implement the Strategy of Antibiotics Driving License Management

The antibiotics examination was organized every year and only doctors who passed the examination were authorized to prescribe antibiotics. Based on the scoring and deduction method of motor vehicle driving license, clinical pharmacists set reasonable drug use rules, unified the caliber of deduction points, and conducted quantitative management on the unreasonable use of antibiotics by physicians. When a physician's deduction points accumulated to 12, the physician's antibiotics prescribing authority was suspended, and the authority could be granted only after passing another examination.

Promote the Refined Management with Informatization

1. With the support of rational medication software, the grading management of physicians' right to prescribe antibiotics was conducted. When the physician oversteps his or her

prescribing authority, the system will display a reminder of "no corresponding prescription right" and will refuse to perform. For key monitoring drugs such as polymyxin B, all physicians had no prescription authority. If physicians want to be granted with the temporary right, they should first apply for Multi-Disciplinary Treatment and obtain the approval of the clinical pharmacist.

2. Use the "Filling card for Antibacterial Application". When prescribing antibiotics, physicians should select the purpose of antibiotics, infection-related diagnosis, whether to submit microorganism's examination and other items, to standardize the rational use of antibiotics.
3. Clinical pharmacists optimized prescription rules through rational drug use intelligent management system to achieve risk early warning, intelligent reminder, real-time intervention.
4. The close-loop management of special-use-grade antibiotics was carried out. Many links (such as etiological examination before application of antibiotics, consultation of infectious disease experts and establishment of doctor's orders) were supervised and traced to ensure the safety of patients' medication.
5. The BI pharmaceutical information management system had been improved. Clinical departments could check the data of antibiotics usage at any time on the mobile phone, know the current status of the management indicators of antibiotics, and effectively promote the control and continuous improvement of the indicators.

Strengthen the Special Review of Antibiotics

Clinical pharmacists conducted special reviews of antibiotics, constantly increased the depth and breadth of the reviews. Irrational drug use problems found in prescription reviews were discussed with medical department, hospital-acquired infection control department, microbiology room and other disciplines, and then gave feedback to physicians. Clinical pharmacists participated in clinical consultation, difficult and complex case discussion, and assisted clinical departments to continuously improve the rational use of antibiotics.

Deepen Pharmacy Services Through Multiple Channels

Clinical pharmacists regularly distributed the Pharmacy Newsletter to the whole hospital, and conducted statistics and analyzed on the use of antibiotics at our hospital. We also developed pharmacy consultation services online and offline. We used WeChat official accounts, videos and other new media forms to actively promote rational drugs use. We carried out thematic publicity activities on world pharmacist's Day and antibacterial drug publicity week, and put four-way services (popular science lectures in schools, communities, enterprises and villages) into practice.

The Results of the Refined Management Mode of Antibiotics at Our Hospital

Sources and Methods

Three indicators including inpatient antibiotics use rate, AUD, and inpatient microbial examination rate were retrieved from our hospital information system (HIS) between January 2017 and December 2021. The trend of relevant usage data of the hospital before and after the refined antibiotics management was studied using interrupted time series (ITS) analysis. Taking June 2019 as the time node, the statistical model of ITS analysis was

constructed: $Y_t = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \varepsilon$. Y_t represented the data of antibiotics use in month t , and X_1 represented the continuous time variable from the observation period. X_2 represented the intervening variable and was assigned 0 before taking management measures and 1 after taking management measures. X_3 represented the count variable after the intervening time and was assigned 0 before taking management measures, and the value is 0 before management and counts by time after management. β_0 was the estimated value of the initial level. β_1 was the slope before management. β_2 was the level change after management compared with before management. β_3 was the amount of slope change. ε was the error term.

Before ITS analysis, Durbin-Watson test (DW) should be used to determine whether autocorrelation exists. When DW is 2 or close to 2, it means that there is no first-order autocorrelation in the data, and the ITS model level is included for fitting [13]. The

data were entered in computer software MS Excel. Computer software SPSS, version 27.0 (Microsoft, Redmond, Washington, United States) was used for the analysis. The data have been expressed as mean \pm standard deviation (range). For continuous variables, unpaired Student's t-test was used. The categorical variables were compared using Chi-square test. A value of $P < 0.05$ was considered statistically significant.

Results

Antibiotics Use

Through the gradual development of refined management of antibiotics over the past two years, the clinical use indicators of antibiotics were improved significantly. The rate of inpatient antibiotics uses decreased by 12.88%, and AUD decreased by 22.44%. The rate of microbial examination in inpatients was increased by 39.81% (Figure 2).

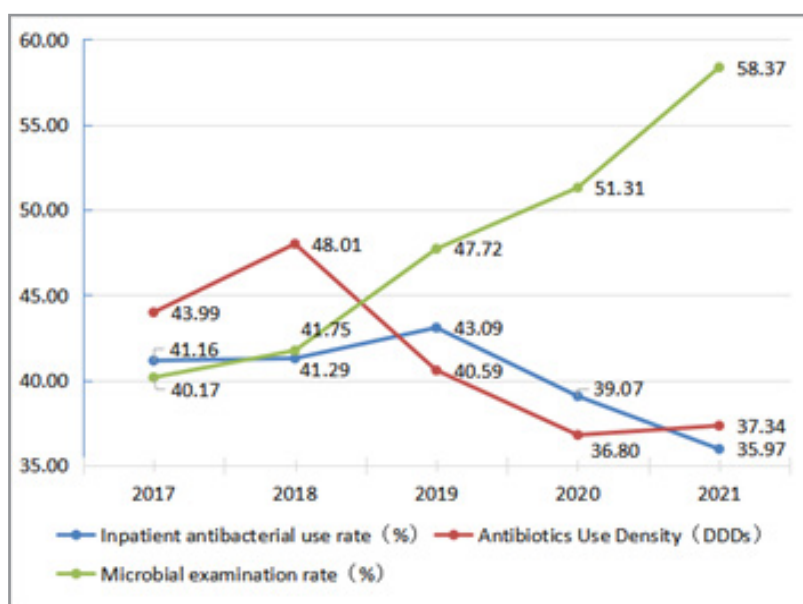


Figure 2.a : Trend chart of clinical application indicators management of antibiotics at our hospital from 2017 to 2021.

Results of Interrupted Time Series Analysis of Antibiotics Management

As shown in Table 1, the monthly data of AUD and use rate of antibiotics in hospitals showed a linear trend without autocorrelation, which met the requirements of ITS analysis. As shown in Figure 3, AUD changed from an upward trend to a downward

trend after management, indicating that the management of antibiotics had achieved positive effects ($P < 0.05$) and had a long-term trend ($P < 0.05$). As shown in Figure 4, after management, the use rate of antibiotics showed a downward trend, and the P value of the trend coefficient after intervention was approximately equal to 0.05.

Table 1: Results of interrupted time series analysis of antibiotics use before and after management

Variable	Antibiotics use density	Antibiotics use rate
DW test adjustment value	1.9552	1.7112
β_0 Pre-intervention level coefficient	41.4643*	0.4176*
β_1 Pre-intervention trend coefficient	0.2802	-0.0001
β_2 Intervention immediate effect coefficient	-1.8863	0.0096
β_3 Trend difference coefficient before and after the intervention	-0.9459*	-0.0023
$\beta_1 + \beta_3$ Post-intervention trend coefficient	-0.6657*	-0.0024

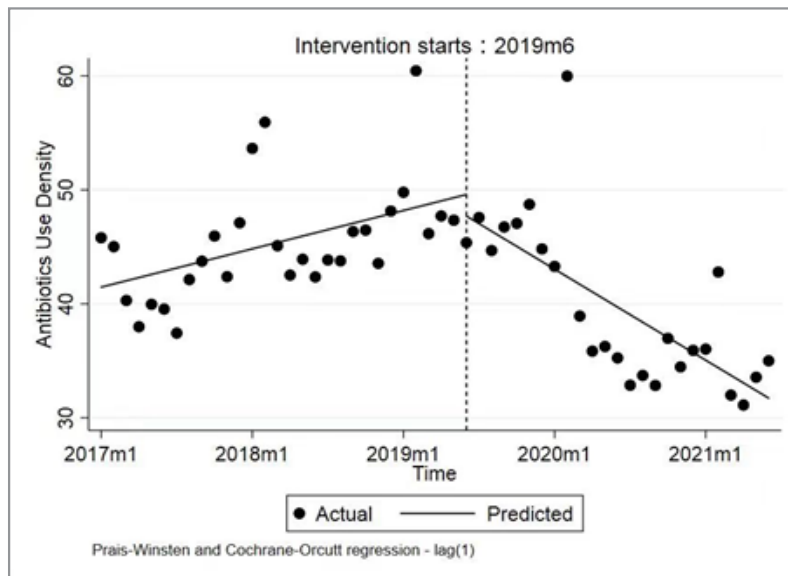


Figure 3: Interrupted time series analysis of antibiotics use density.

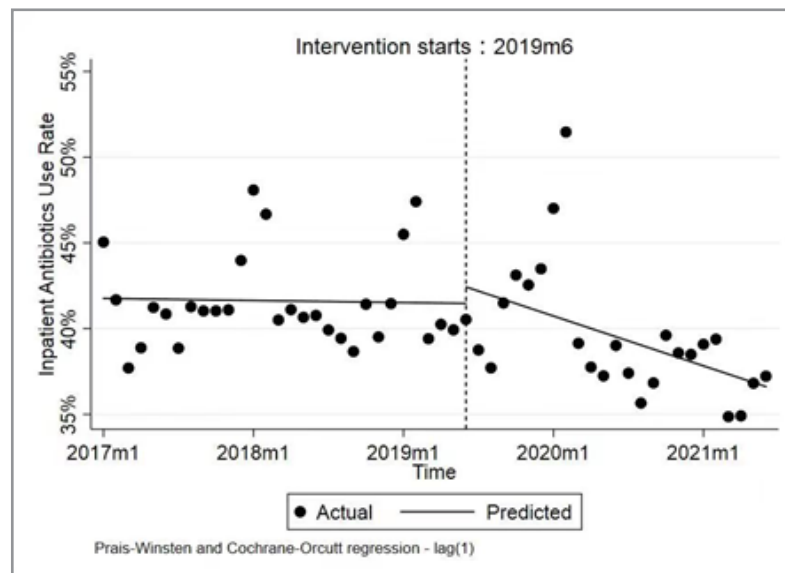


Figure 4: Interrupted time series analysis of antibiotics use rate.

The Proportion of Hospitalization Antibiotics Cost

Through the refined management of antibiotics, the proportion of antibiotics cost after the implementation of measures was significantly lower than the data in 2018 (Table 2).

Table 2: Proportion of hospitalization antibiotics cost in 2017-2021

Indicator	2017	2018	2019	2020	2021
Proportion of hospitalization antibiotics cost (%)	9.35	11.17	10.57	10.64	10.19

Statistics of Rational Drug Use in Clinic

Taking orthopedics as an example, PDCA method was applied to refined management of antibiotics, and the preventive use and cost of antibiotics in Class I incisions before and after management were compared. The results were shown in Table 3. The

reasonable rate of variety selection and administration time of antibiotics were significantly higher than before management. The proportion of prophylactic antibiotics decreased. The cost of antibiotics for inpatients decreased compared with that before management, as shown in Table 4.

Table 3: Comparison of application of prophylactic antibiotics before and after intervention

Indicator	Before intervention (n=126)	After intervention (n=136)
Number of antibacterial prophylaxis use	99	76**
Number of rational antibacterial prophylaxis use	91	122**
Number of antibiotics use as indicated	79	72*
Number of rational timing of administration	83	75*
Number of rational antibiotics course	69	68**
Number of rational antibiotics dosage	79	72*
Number of rational antibiotics varieties	90	75

*P<0.05. **P<0.01

Table 4: Comparison of cost indicators before and after intervention

Indicator	Before intervention median (IQR)	After intervention median (IQR)
Hospitalization antibiotics cost	8.15 (2.55-24.65)	4.25 (2.55-16.04)
Antibiotics cost / Total drug cost	0.23% (0.10%-0.68%)	0.19% (0.09%-0.62%)

Discussion

Antimicrobial resistance has become one of the most serious public health threats in the twenty-first century, because it reduces the efficacy of antibiotics. According to a systematic analysis, there were an estimated 4.95 million deaths associated with bacterial AMR in 2019 [14]. Antimicrobial management aims to optimize programs and interventions for antibiotics use. Antimicrobial management programs range from hospitals and communities to veterinary application management, and also to the WHO global management framework. It is a hotspot worldwide [15-19]. In order to further strengthen the work of curbing antimicrobial resistance, National Health Commission of the People's Republic of China launched the National Action Plan based on the evaluation and summary of the work effect in the past few years, initiating the National Action Plan to Curb Antimicrobial Resistance (2022-2025) [20]. Antimicrobial stewardship (AMS) is an important strategy for the decrease of antimicrobial resistance and is widely used in antimicrobial management [21]. Clinical pharmacists are identified as key members of the AMS team [22]. They participate in the whole process of antimicrobial use and management, and play a more prominent role.

Effect of Refined Management of Antibiotics led by Clinical Pharmacists

Based on the experience of AMS, clinical pharmacists at our hospital have been strengthening multi-departmental collaboration and improving the top-level design of cross-departmental coordination mechanism to fully utilize their professional advantages. Through the development of appropriate work plans, pre-training, in-process monitoring, and post-supervision, the refined management of antibiotics was sufficiently performed from multiple perspectives. ITS was an analysis of the outcome variables of time series, which was used to retrospectively analyze the effect of an intervention. By analyzing the two indicators of slope change and immediate level change, the actual effect of the intervention was determined. It was especially important for evaluating the change in group-level outcomes caused by the intervention over a specific period of time. ITS enriches the traditional intervention evaluation model and has a wide range of applications in intervention effectiveness evaluation. The present study confirmed that the AUD at our hospital showed a down-

ward trend after management using the ITS method, indicating that antibiotics management achieved positive effects, reduced the cost of antibiotics and promoted maximization of the value of medical services.

Review of Clinical Pharmacists' Participation in the Refined Management of Antibiotics

Clinical pharmacists play a role in participating in multiple processes such as antibiotics supply catalog adjustment, prescription pre-review, clinical case consultation, prescription and medical order review, and monitoring of drug safety [23].

The varieties of antibiotics in medical institutions has an important impact on the actual selection and application in clinical practice. Clinical pharmacists should evaluate the rationality of the antibiotics supply catalog in medical institutions and formulate optimization plans. Shaoqiang Cong et al [24]. confirmed that pharmacist-led optimization of the antibiotics supply list was an important measure to reduce the AUD. Fuchang Que et al [25]. removed four antibiotics with high antimicrobial resistance rate, many adverse drug reactions and insufficient evidence-based medicine from the hospital supply list to ensure that the varieties of antibiotics were reasonable and consistent with the latest clinical treatment guidelines.

Clinical pharmacists should implement antimicrobial drug management under the concept of "patient-centered" rational drug use. They play an important role in the development of antibiotics treatment plans according to the PK/PD theory of antimicrobial drugs [26]. Other factors needed to be considered include the severity of the patient's condition, site of infection, tissue penetration, antimicrobial drug selection, clinical efficacy, safety, possible pathogenic bacteria, assessment of antimicrobial resistance, protein binding rate, and liver and kidney function. Clinical pharmacist intervention can reduce the rate of unreasonable drug application, shorten the length of hospital stay of patients, lower the incidence of adverse drug reactions, and improve the effect of anti-infection treatment. Daijing Dong et al [27-30]. found the rational rate of prophylactic use of antibiotics in class I incisions was significantly improved, and the course of medication was obviously reduced before and after the interven-

tion of clinical pharmacists. Meanwhile, other studies also pointed out that the participation of clinical pharmacists in the consultation and individualized adjustment of medication regimens can ensure that patients receive more economic and effective treatment, and have a positive impact on reducing the in-hospital mortality of patients with multi-drug resistant infection. Our research further affirmed the value of clinical pharmacists in the rational use of antibiotics [31, 32].

Consideration on the Participation of Clinical Pharmacists in the Refined Management of Antibiotics

Although the health systems of many countries have recognized the important value of pharmacists in the rational use of antibiotics, the coverage of clinical pharmacists' participation in rational drug use needs to be strengthened [33-36]. At present, there is no unified system for clinical pharmacists to participate in consultation, and clear standard for clinical pharmacist consultation. The most common obstacle to the implementation of clinical pharmacist consultation, one is the lack of support from hospital managers and relevant policies of health management departments; the other is professional ability and clinical thinking ability of clinical pharmacists needed to be further improved [37]. On the other hand, pharmacists are responsible for prescription review, so all medical orders are dispensed after pharmacists reviewed. However, real-time review is unavailable, and post-event sampling reviews as an alternative supplement, which lead to a certain lag in the rational use of antibiotics. How to combine with information management to better achieve the real-time review, is the goal that need to be gradually improved in the future [38, 39].

Antimicrobial management cannot be achieved instantaneously, and there is a long way to go for clinical pharmacists in the refined management of antibiotics. As the next step, we will learn from the management experience of advanced hospitals at home and abroad, and incorporate antibiotics management into the clinical pathway of infectious diseases and treatment specifications. We will strengthen the construction of multidisciplinary management teams, enhance feedback to clinical departments, and continue to provide patients with better pharmaceutical services.

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