Infection and Drug Resistance

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Appropriateness of Empirical Fluoroquinolones Therapy in Patients Infected with *Escherichia coli*, *Klebsiella pneumoniae*, or *Pseudomonas aeruginosa*: The Importance of the CLSI Breakpoints Revision

Ying Wang[1]
Xinping Zhang[1]
Xuemei Wang[1]
Xiaoquan Lai[2]

[1]School of Medicine and Health Management, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, HuBei, People's Republic of China; [2]Department of Nosocomial Infection Management, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, HuBei, People's Republic of China

Purpose: Empirical antibiotic therapy should follow the local bacterial susceptibility, and the breakpoints revisions of the antimicrobial susceptibility testing can reflect the changes in the antimicrobial susceptibility of bacteria. This study aimed to analyze whether the changes in the antimicrobial susceptibility to antibiotics caused by the breakpoint revision will affect the empirical antibiotic therapy and its appropriateness.

Patients and Methods: A retrospective study was conducted among 831 hospitalized patients infected by *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* from April 10, 2018, to April 11, 2020. We evaluated the appropriateness of empirical therapy based on the antimicrobial susceptibility testing results. The rate of empirical use and appropriateness of fluoroquinolones was calculated, and logistic regression was used to analyze influencing factors of empirical use of fluoroquinolones.

Results: The susceptibility rate of the three bacteria to levofloxacin (50.78% vs 32.06%) and ciprofloxacin (48.45% vs 21.90%) was decreased (P<0.001), while the resistance rate to levofloxacin (45.74% vs 58.73%) and ciprofloxacin (46.90% vs 66.67%) was increased (P<0.001) after the breakpoints revision. The empirical usage rate of fluoroquinolones in patients infected with *Escherichia coli*, *Klebsiella pneumoniae*, or *Pseudomonas aeruginosa* was 20.94%, which was influenced by the breakpoint revision (P=0.022), age (P=0.007), and the department (P=0.006); the appropriateness rate was 28.74%, affected by the pathogenic bacteria (P=0.001) and multidrug-resistant microorganism (P=0.001), department (P=0.024), and the length of stay before the empirical therapy (P=0.016).

Conclusion: The susceptibility of bacteria to antibiotics has changed significantly after the breakpoint revision while the clinicians' empirical therapy failure to change accordingly, which results in the decrease of the appropriateness of empirical use. It is enlightened that we should conduct more research to evaluate the rational use of antibiotics from the laboratory perspective and carry out interventions such as education and supervision to strengthen the collaboration between the microbiology laboratories and clinicians to improve the empirical antibiotic therapy and slow down the antimicrobial resistance.

Keywords: empirical antibiotic therapy, appropriateness, fluoroquinolones, antimicrobial resistance, breakpoint revision, antimicrobial susceptibility testing

Correspondence: Xinping Zhang
School of Medicine and Health Management, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China
Tel +86 133 4995 0095
Email xpzhang602@hust.edu.cn

Introduction

Antimicrobial resistance (AMR) is increasing, driven by widespread antibiotic use. As reported in the "Antimicrobial resistance: global report on surveillance" in 2014 by

Received: 15 July 2021
Accepted: 18 August 2021
Published: 31 August 2021

WHO, AMR is a global trend, which is closely associated with increased morbidity, length of stay, mortality, and healthcare costs.[1,2] The United Nations General Assembly also pointed out that AMR has become the fourth major health problem after AIDS, non-communicable diseases, and Ebola in June 2016.[3]

As one of the most commonly used antibiotic categories in clinical practice, Fluoroquinolones (FQs) are widely used in the treatment of various bacterial infections such as urinary system infections and respiratory system infections due to their good pharmacokinetics.[4,5] Between 1995 and 2002 in the United States, the number of prescriptions for FQs tripled, and the proportion of prescriptions for antibiotics increased from 10% to 24%.[6] Although the use of FQs decreased from 2006 to 2012, it was still the most commonly used antibiotic in US hospitals in 2012.[7] It was well-known that the overuse and abuse of antibiotics, especially the abuse of broad-spectrum antibiotics, are the most important factors leading to AMR.[8–11] With the overuse of FQs, the resistance of bacteria to FQs is gradually increasing. Data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) showed that between 2012 and 2015, the resistance rate of FQs to gram-negative bacteria was high and increasing,[12] Centers for Disease Control and Prevention (CDC) also found similar results through the monitoring of the National Surveillance System.[13,14] The increase in resistance will lead to the pressure of antibiotic selection and the difficulty of clinical treatment.

Doctors should use targeted antibiotics after clarifying the type of bacteria and the results of drug susceptibility. However, before the bacterial culture and antimicrobial susceptibility testing (AST) results are reported, the doctor will often prescribe antibiotics empirically based on the patient's infection site, primary disease, and other basic conditions.[15] Studies showed that timely and appropriate empirical medication can help reduce the hospital infection rate and mortality of patients,[16] while inappropriate empirical treatment can lead to a poorer prognosis such as infection and death.[17,18] Therefore, in the process of clinical treatment, the empirical use of antibiotics, especially broad-spectrum antibiotics, should be strictly controlled. However, most previous studies have evaluated medications based on relevant clinical practice guidelines, there is a lack of research on strengthening empirical antibiotic treatment management from a laboratory perspective. When deciding on an empirical antibiotic therapy, physicians should not only consider the relevant factors of the patient but also take the local bacterial distribution and bacteriologic susceptibilities as an important reference,[19] which is an important factor affecting the success of empiric therapy.[15]

To curb AMR, the World Health Organization and the European Commission require strengthening laboratory capacity building to regulate the use of antibiotics.[20,21] Studies have shown that the enhancement of laboratory capacity can reduce AMR.[22] AST is one of the most important functions of a clinical microbiology laboratory, and the AST breakpoint is used as a criterion that enables the laboratory to categorize the result as susceptible, intermediate, or resistant to a given antibiotic. The setting of AST breakpoints is a complex and dynamic process that integrates microbiological, pharmacokinetic (PK)/pharmacodynamic (PD), and clinical outcome data.[23] Therefore, changes in the breakpoints can reflect the changes in the antimicrobial susceptibility of bacteria and other characteristics of antibiotics, which should be used as an important reference for empirical antibiotic therapy.

The Clinical and Laboratory Standards Institute (CLSI) breakpoint guideline is updated yearly and is crucial to microbiology laboratories' capacity to provide quality results.[24] Recommendations and criteria provided by the guideline are now used in day-to-day patient care by physicians and pharmacists. However, if the change of breakpoint guideline is only understood by the laboratorians but not by the clinicians, it may lead to errors in interpretation and irrational use of antibiotics.[25] Therefore, interdisciplinary collaboration is essential in the implementation of the new breakpoint guidelines,[24,26] Clinicians should be announced in time for changes in methods that impact identification, susceptibility testing, or simply reporting.[25] The microbiology laboratories should collaborate with clinicians to guide the most appropriate therapeutic strategy and strengthen contributions to antimicrobial stewardship.

The CLSI published revisions to the breakpoints of ciprofloxacin and levofloxacin against Enterobacter (except Salmonella) and *Pseudomonas aeruginosa* in the CLSI M100 in 2019 (Table 1) after reviewing the data compiled and used by The European Committee on Antimicrobial Susceptibility Testing (EUCAST) because there was evidence that the breakpoints of ciprofloxacin and levofloxacin before 2019 were too high to detect low-level FQs resistance among Enterobacteriaceae and *Pseudomonas aeruginosa* strains.[23] We assume that the CLSI breakpoint revision could have an impact on susceptibility rates of FQs, with concomitant changes in antibiotic prescriptions by physicians.

Table 1 Ciprofloxacin and Levofloxacin Breakpoint Summary

		KB/MIC(2018)			KB/MIC(2019)		
		S	I	R	S	I	R
Enterobacteriaceae	Ciprofloxacin Levofloxacin	≥21/≤1 ≥17/≤2	16–20/2 14–16/4	≤15/≥4 ≤13/≥8	≥26/≤0.25 ≥21/≤0.5	22–25/0.5 17–20/1	≤21/≥1 ≤16/≥2
Pseudomonas aeruginosa	Ciprofloxacin Levofloxacin	≥21/≤1 ≥17/≤2	16–20/2 14–16/4	≤15/≥4 ≤13/≥8	≥25/≤0.5 ≥22/≤1	19–24/1 15–21/1	≤18/≥2 ≤14/≥4

Abbreviations: S, susceptible; I, intermediate; R, resistance.

This study explored whether the breakpoints revision on the change in the sensitivity of bacteria to antibiotics will affect the empirical therapy of FQs, this empirical therapy and its appropriateness was evaluated based on the AST results, which can provide sound evidence for the important role of microbiology laboratories in the antimicrobial stewardship programs and to improve the quality of empirical therapy.

Patients and Methods

Study Setting and Population

A retrospective study was conducted in a tertiary teaching hospital in Hubei province of China.

The hospital began to implement the new FQs breakpoint (CLSI 2019)[27] on April 11, 2019, so the study included two periods, period 1, from April 10, 2018, to April 10, 2019, with old breakpoint implemented (CLSI 2018);[28] period 2, from April 11, 2019, to April 11, 2020, with revised breakpoint implemented (CLSI 2019).

We identified patients admitted to the study hospital between April 10, 2018, and April 11, 2020, with a diagnosis of bacterial infection, and the pathogenic bacteria was one kind among *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), and *Pseudomonas aeruginosa* (*P. aeruginosa*). Patients who were only colonized by bacteria are excluded. To avoid over-representation of multiple isolates from individual patients we only included the first isolate per patient.

Levofloxacin and ciprofloxacin were selected in this study as the breakpoints revision we studied only for levofloxacin and ciprofloxacin against Enterobacter (except Salmonella) and *Pseudomonas aeruginosa*. And our study only included two Enterobacteriaceae, *Escherichia coli* and *Klebsiella pneumonia* as they were the main types of enterobacteria for clinical infection in the research hospital.

Bacterial Isolation and Testing

Strains were identified using VITEK2-compact microbial identification system (BioMérieux, France), duplicate strains isolated from the same part of the same patient were eliminated.

In vitro susceptibility testing was carried out by Kirby-Bauer disk diffusion, the interpretation standards and quality control requirements were following the CLSI guidelines.[29] The agents tested included two kinds of FQs, ciprofloxacin, and levofloxacin. Strain ATCC25922 (*E. coli*), ATCC700603 (*K. pneumoniae*), and ATCC27853 (*P. aeruginosa*) were used as reference strains.

Data Collection

The data extraction included three steps. Firstly, patients with *E. coli*, *K. pneumoniae*, or *P. aeruginosa* infections were identified, and then we selected patients who have empirically used levofloxacin and ciprofloxacin, the appropriateness of empirical therapy was judged based on the AST results of the patients finally. So, we collected the AST results of the patients with infection, and the antibiotics prescribed by doctors for empirical therapy. Demographic data included age, gender, department, infection type, length of stay (LOS) before empirical therapy, pathogenic bacteria, multidrug-resistant microorganism (MDRO), and surgery were also retrieved from the medical records.

All case information was manually extracted from the hospital infection monitoring system.

Definitions

Empirical antibiotic therapy is considered that the antibiotic prescribed by the doctor before AST result is reported.

Appropriate antibiotic therapy was defined when the isolated bacteria were susceptible in vitro to the antibiotic empirically prescribed.

The rate of empirical usage and appropriateness of FQs was calculated as follows:

$$\text{Usage rate} = \frac{Nu}{N} \times 100\%$$

$$\text{Appropriateness rate} = \frac{Na}{Nu} \times 100\%$$

N: total number of patients, Nu: number of patients used FQs, Na: number of patients used FQs appropriately, Nun: number of patients unused FQs, Nia: number of patients used FQs inappropriately.

Statistical Analysis

Continuous variables were described as mean and standard deviation, and compared using Student's *t*-test or Mann–Whitney *U*-test as appropriate; the categorical variable description was the number and percentage of empiric usage and appropriateness for each category, compared using a chi-square test or Fisher's exact test as appropriate. Univariate and multivariate analysis were used to identify influencing factors of empirical therapy. Variables with $P < 0.05$ in Univariate analysis were considered potential independent variables and included in a multivariate logistic regression analysis. The unordered multi-classification variable sets the dummy variable with "Others" as the reference group, the results were expressed as odds ratio (OR) and 95% confidence interval (95% CI). All tests were two-tailed, and significance was set at p-value <0.05 in multivariate analysis. All statistical analysis was performed using SPSS software (version 25.0).

Results

Characteristics of Patients and Empirical Use of FQs

A total of 831 patients infected with *E. coli*, *K. pneumoniae*, or *P. aeruginosa* were identified, 174 (20.94%) patients used FQs empirically, of which the empirical use of levofloxacin was in 173 (20.82%) patients, while only 2(0.24%) patients were prescribed ciprofloxacin empirically. Table 2 summarizes the characteristics of patients who used and unused FQs empirically. The percentage of patients infected by each type of pathogenic bacteria was presented as follows: *E. coli* (114,24.10%), *K. pneumoniae* (38,16.81%), *P. aeruginosa* (22,16.67%).

Compared the empirical use of FQs during the two periods according to the revision of breakpoints. In the second period, after the breakpoints were revised, the empirical use of FQs was higher (80,25.40%) than patients in the first period (94,18.22%). Patients between 18 to 44 years old (33,23.57%) were more likely to be used FQs empirically compared to other age groups. Those who admitted to Internal Medicine (54.27,69%) departments were also more likely to be used FQs empirically than those who were in the surgical department (56,16.33%) and other departments (64,21.84%). Meanwhile, the usage rate varied in different infection types, patients with bloodstream infection (BSI) (49,27.07%) were used FQs empirically most, followed by urinary tract infection (UTI) (88,21.67%), lower respiratory tract infection (LRTI) (26,14.13%) and other infections (11,13.75%) (Table 2).

Among 174 patients who had empirically used FQs, 50 (28.74%) were appropriate, of which the appropriateness rate of levofloxacin was 28.90% (50/173), while the 2 empirical use of ciprofloxacin were inappropriate. Table 3 summarizes the characteristics of patients appropriate and inappropriate used FQs empirically. From the different pathogenic bacteria, the appropriateness rate of patients infected by *P. aeruginosa* was the highest (10,54.55%), followed by *K. pneumoniae* (13,34.21%) and *E. coli* (25,21.93%).

Patients in the second period (17,21.25%) had a lower appropriateness rate than those in the first period (33,35.11%). Patients without a diagnosis of MDRO infection (49,31.82%) were significantly more likely to be used FQs appropriately compared to those who were infected by MDROs (1,5.00%). Patients who admitted to Internal Medicine (23.42.59%) departments were also more likely to be used FQs appropriately than those who were in the surgical department (16,28.57%) and other departments (11,17.19%). Meanwhile, those who had a shorter LOS (<7 days) (33,42.31%) were also more likely to be used FQs appropriately than those who had a longer LOS,18.60% for 7–30 days and 10.00% for >30 days (Table 3).

The Impact of CLSI Levofloxacin and Ciprofloxacin Breakpoints Revision on the Susceptibility Reporting for *E. coli, K. pneumoniae and P. aeruginosa*

We analyzed the impact of the revised breakpoints on the antimicrobial susceptibility to FQs in *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. The overall detected susceptibility rate to levofloxacin was 43.68% (363/831), the intermediary rate was 5.66% (47/831), and the resistance rate was 50.66% (421/831); the overall detected susceptibility rate of ciprofloxacin was 38.39% (319/831), the intermediary rate was 7.22% (60/831), and the resistance rate was 54.39% (452/831).

Table 2 Characteristics of Patients Used and Unused FQs Empirically (n, %)

Characteristics	Total N=831	Used Nu=174	Unused Nun=657	Usage Rate (%)	P value
Gender					
Male	410(49.34)	83(47.70)	338(51.45)	20.24	0.380
Female	421(50.66)	91(52.30)	319(48.55)	21.62	
Age					
Mean ± SD	51.30±20.16	55.30±16.01	50.24±21.01		0.001
< 18	76(9.15)	3(1.72)	73(11.11)	3.95	0.002
18–44	140(16.85)	33(18.97)	107(16.27)	23.57	
45–60	324(38.99)	74(42.53)	250(38.05)	22.84	
>60	291(35.01)	64(36.78)	227(34.55)	21.99	
Period					
1	516(62.09)	94(54.02)	422(64.23)	18.22	0.014
2	315(37.91)	80(45.98)	235(35.77)	25.40	
MDRO					
Yes	116(13.96)	20(11.49)	96(14.61)	17.24	0.291
No	715(86.04)	154(88.51)	561(85.39)	21.54	
Department					
Internal Medicine	195(23.47)	54(31.03)	141(21.46)	27.69	0.007
Surgical	343(41.28)	56(32.18)	287(43.68)	16.33	
Others	293(35.26)	64(36.78)	229(34.86)	21.84	
Infection type					
UTI	406(48.86)	88(50.57)	318(48.40)	21.67	0.026
BSI	181(21.78)	49(28.16)	132(20.09)	27.07	
LRTI	184(22.14)	26(14.94)	138(21.00)	14.13	
Others	80(9.63)	11(6.32)	69(10.50)	13.75	
Pathogenic bacteria					
Escherichia coli	473(56.92)	114(65.52)	359(54.64)	24.10	0.036
Klebsiella pneumoniae	226(27.20)	38(21.84)	188(28.61)	16.81	
Pseudomonas aeruginosa	132(15.88)	22(12.64)	110(16.74)	16.67	
LOS before empirical therapy					
Mean ± SD	11.24±10.95	12.25±10.76	10.97±10.99		0.170
<7 days	433(52.11)	78(44.83)	355(54.03)	18.01	0.085
7–30 days	351(42.24)	86(49.43)	265(40.33)	24.50	
>30	47(5.66)	10(5.75)	37(5.63)	21.28	
Surgery					
Yes	282(33.94)	55(31.61)	227(34.55)	19.50	0.466
No	549(66.06)	119(68.39)	430(65.45)	21.68	

Abbreviations: UTI, urinary tract infection; BSI, bloodstream infection; LRTI, lower respiratory tract infection; LOS, length of stay; N, total number of patients; Nu, number of patients used FQs; Nun, number of patients unused FQs.

After the breakpoints were revised, the susceptibility rate of the three bacteria to levofloxacin (50.78% vs 32.06) and ciprofloxacin (48.45% vs 21.90%) was decreased, while the intermediary rate was increased (4.65% vs 11.43%), as well as the resistance rate (46.90% vs 66.67%).

Among the different pathogenic bacteria, the resistance rate of *E. coli* to FQs was the highest and the lowest was *P. aeruginosa*; the intermediary rate of P. aeruginosa to FQs was the highest and the lowest is *K. pneumoniae*; the susceptibility rate of P. aeruginosa to FQs was the highest, and *E. coli* is the lowest (Table 4).

Table 3 Characteristics of Patients Appropriate and Inappropriate Used FQs Empirically (n, %)

Characteristics	Appropriate Na=50	Inappropriate Nia=124	Appropriateness Rate (%)	P value
Gender				
Male	22(44.00)	61(49.2)	26.51	0.535
Female	28(56.00)	63(50.8)	30.77	
Age				
Mean ± SD	58.56±16.00	53.98±15.89		0.088
< 18	1(2.00)	2(1.6)	33.33	0.117
18–44	8(16.00)	25(20.16)	24.24	
45–60	16(32.00)	58(46.77)	21.62	
>60	25(50.00)	39(31.45)	39.06	
Period				
1	33(66.00)	61(49.19)	35.11	0.044
2	17(34.00)	63(50.81)	21.25	
MDRO				
Yes	1(2.00)	19(15.32)	5.00	0.013
No	49(98.00)	105(84.68)	31.82	
Department				
Internal Medicine	23(46.00)	31(25.00)	42.59	0.010
Surgical	16(32.00)	40(32.26)	28.57	
Others	11(22.00)	53(42.74)	17.19	
Infection type				
UTI	23(46.00)	65(52.42)	26.14	0.358
BSI	14(28.00)	35(28.23)	28.57	
LRTI	11(22.00)	15(12.10)	42.31	
Others	2(4.00)	9(7.26)	18.18	
Pathogenic bacteria				
Escherichia coli	25(50.00)	89(71.78)	21.93	0.006
Klebsiella pneumoniae	13(26.00)	25(20.16)	34.21	
Pseudomonas aeruginosa	12(24.00)	10(8.06)	54.55	
LOS before empirical therapy				
Mean ± SD	8.14±7.63	13.91±11.40		<0.001
<7 days	33(66.00)	45(36.29)	42.31	0.001
7–30 days	16(32.00)	70(56.45)	18.60	
>30	1(2.00)	9(7.26)	10.00	
Surgery				
Yes	14(28.00)	41(33.06)	25.45	0.516
No	36(72.00)	83(66.94)	30.25	

Abbreviations: UTI, urinary tract infection; BSI, bloodstream infection; LRTI, lower respiratory tract infection; LOS, length of stay; Na, number of patients used FQs appropriately; Nia, number of patients used FQs inappropriately.

Multivariate Analysis of the Influencing Factors of FQs Empirical Use and Appropriateness

Table 2 showed that age, breakpoint revision, LOS before empirical therapy, department, infection type, pathogenic bacteria have significant impact on the empirical use of FQs in patients infected with *E. coli*, *K. pneumoniae*, or *P. aeruginosa*. Introduce these variables into the logistic regression model. The results showed that breakpoint revision (P=0.022), age (P=0.007), department (P=0.006) were independent influencing factors of the empirical use of FQs in patients infected with *E. coli*, *K. pneumoniae*, or *P. aeruginosa* (Table 5).

Table 3 showed that breakpoint, MDRO, department, pathogenic bacteria, LOS before empirical therapy have

Table 4 Susceptibilities of *E. coli*, *K. pneumoniae* and *P. aeruginosa* Clinical Isolates According to CLSI 2018–2019 (n, %)

Pathogenic Bacteria	Drug	Breakpoint	Patients	S	I	R	P value
E. coli	Levofloxacin	CLSI 2018 CLSI 2019	302 171	116(38.41) 47(27.49)	9(2.98) 8(4.68)	177(58.61) 116(67.84)	0.046
	Ciprofloxacin	CLSI 2018 CLSI 2019	302 171	105(34.77) 22(12.87)	11(3.64) 22(12.87)	186(61.59) 127(74.27)	<0.001
K. pneumoniae	Levofloxacin	CLSI 2018 CLSI 2019	126 100	77(61.11) 30(30.00)	3(2.38) 11(11.00)	46(36.51) 59(59.00)	<0.001
	Ciprofloxacin	CLSI 2018 CLSI 2019	126 100	69(54.76) 16(16.00)	9(7.14) 9(9.00)	48(38.10) 75(75.00)	<0.001
P. aeruginosa	Levofloxacin	CLSI 2018 CLSI 2019	88 44	69(78.41) 24(54.55)	6(6.82) 10(22.73)	13(14.77) 10(22.73)	0.008
	Ciprofloxacin	CLSI 2018 CLSI 2019	88 44	76(86.36) 31(70.45)	4(4.55) 5(11.36)	8(9.09) 8(18.18)	0.086
Total	Levofloxacin	CLSI 2018 CLSI 2019	516 315	262(50.78) 101(32.06)	18(3.49) 29(9.21)	23(45.74) 185(58.73)	<0.001
	Ciprofloxacin	CLSI 2018 CLSI 2019	516 315	250(48.45) 69(21.90)	24(4.65) 36(11.43)	242(46.90) 210(66.67)	<0.001

Abbreviations: S, susceptible; I, intermediate; R, resistance.

Table 5 Logistic Regression of Empirical Use of FQs

	P value	OR	OR95% C.I.	
Breakpoint revision	0.022	1.503	1.060	2.131
Age	0.007	1.013	1.003	1.022
Department(reference)	0.006			
Internal Medicine	0.093	1.458	0.939	2.263
Surgical	0.103	0.711	0.472	1.072
Infection type(reference)	0.245			
UTI	0.365	1.383	0.686	2.788
BSI	0.107	1.831	0.877	3.822
LRTI	0.778	1.123	0.501	2.519
Pathogenic bacteria(reference)	0.144			
Escherichia coli	0.234	0.693	0.379	1.268
Klebsiella pneumoniae	0.057	0.640	0.405	1.014
Constant	<0.001	0.100		

Abbreviations: UTI, urinary tract infection; BSI, bloodstream infection; LRTI, lower respiratory tract infection.

a significant impact on the appropriate empirical use of FQs. Introduce these variables into the logistic regression model. The results showed that MDRO (P=0.001), department (P=0.024), Pathogenic bacteria (P=0.001) were independent influencing factors of the appropriate empirical use of FQs (Table 6).

Discussion

Empirical Usage and Appropriateness Rate of FQs

In our study, the total empirical usage rate of FQs was 20.94% in patients infected with *E. coli*, *K. pneumoniae*, or *P. aeruginosa*, patients with BSI (27.07%), UTI (21.67%), and LRTI (14.13%). The previous studies often analyzed empirical use of FQs with only one type of infection. A study found that 43 cases (56%) used FQs empirically among 77 patients with severe community-acquired pneumonia (CAP) and requiring intensive care,[30] which is higher than which in our study, especially higher than LRTI (56% vs 14.13%). Similarly, a study on the resistance of pathogens and empiric medication in urinary tract infections (UTI)

Table 6 Logistic Regression of Appropriate Empirical Use of FQs

	P value	OR	OR95% C.I.	
MDRO	0.001	0.025	0.003	0.232
Department(reference)	0.024			
Internal Medicine	0.007	3.877	1.445	10.401
Surgical	0.257	1.755	0.664	4.640
Pathogenic bacteria(reference)	0.001			
Escherichia coli	0.004	5.596	1.722	18.186
Klebsiella pneumoniae	0.002	4.874	1.789	13.277
LOS before empirical therapy	0.016	0.935	0.885	0.987
Breakpoint revision	0.204	0.594	0.266	1.327
Constant	0.051	0.376		

Abbreviations: UTI, urinary tract infection; BSI, bloodstream infection; LRTI, lower respiratory tract infection; LOS, length of stay.

analysis found that 71/139 (62.8%) patients used FQs empirically,[31] which is also higher than the empirical usage rate of FQs in UTI than our results (62.8% vs 21.67%). The Infectious Diseases Society of America (IDSA) recommended that 10% to 20% is an appropriate benchmark for FQs as initial empirical therapy for UTI,[32] although it acknowledged no specific data support this recommendation, we can still refer to the benchmark to delay the development of resistance to these drugs. The empirical use rate of FQs in our study is lower compared to other studies, but according to the bacterial resistance after the breakpoints revision, measures still need to be taken to control the use of FQs.

The appropriate rate of empirical use of FQs was only 28.74%. Grossman defined appropriate antibiotic therapy as when the isolated bacteria were susceptible in vitro to at least one of the antibiotics empirically administrated at the first dose, the appropriate antibiotic therapy rate was 79.8%,[33] Estela used a similar definition, and the appropriate usage rate was 61%.[17] Chen analyzed the empirical antibiotic therapy based on the final AST results, and the coincidence rate was 46.9%.[31] These rates are higher than those in our studies and the reason may be that these studies not only considered FQs but also included other antibiotics; And the appropriate for empirical use is sensitivity to at least one drug in the empirical antibiotic therapy in these researches, rather than just considering a single drug. In addition, studies have shown that fluoroquinolone-resistant P. aeruginosa harms the prognosis of patients,[34] but our study found that the appropriate rate of fluoroquinolone empirical use of patients with *Pseudomonas aeruginosa* is only 52.17%, although it is higher than that of patients with *E. coli* and *K. pneumoniae*.

The Impact of Breakpoint Revision on the Empirical Use of FQs

Empiric antibiotic therapy should sufficiently cover all the suspected pathogens, and be guided by the bacteriologic susceptibilities of the medical center.[15] Previous studies have analyzed the significant changes in the susceptibility rates of bacteria to antibiotics after the breakpoint changes,[35,36] but few studies have analyzed the impact of changes in antimicrobial resistance on the empirical use of antibiotics caused by the breakpoint revisions. Our results found that in the second period, the revision of the breakpoint led to a significant decrease in FQs-susceptible isolates and a significant increase in FQs-resistant isolates. At the same time, the empirical use rate of FQs increased significantly in the second period, resulting in a significant decrease in the appropriate rate of FQs empirical use. This may be because although the susceptibility of bacteria to antibiotics has changed significantly after the breakpoint changed, the clinicians' empirical therapy habits and methods have not adjusted accordingly, resulting in the empirical therapy that should have been evaluated as appropriate was evaluated as inappropriate after the breakpoint revised. And the reason why the doctor's empirical therapy did not adjust in time with the change in the susceptibility of bacteria to antibiotics may be that the clinicians are not informed about this CLSI revised breakpoints and the change in the susceptibility rate in bacteria after applying them, they were unaware of the changes in local antimicrobial resistance epidemiology, which may aggravate the fluoroquinolone resistance. It may also be that clinicians were confused about the changes in the breakpoint and chose not to change their therapy because some researchers have made relevant explanations that the revised breakpoints can prove challenging for laboratories to implement and can be confusing for clinicians to interpret.[36] It is indicated that we need to strengthen the communication between the microbiology laboratory and the clinicians, and take actions that can improve the empirical antibiotic prescription such as a periodical reports of local resistance

data, education, and training of clinicians, leaflets elaboration and distribution, etc.

Factors Affecting the Empirical Use of FQs

The results indicated that the breakpoint revision can significantly affect the empirical use of FQs in patients infected with *E. coli*, *K. pneumoniae*, or *P. aeruginosa*, the main reason may be that in the second period, the revision of breakpoint leads to a significant change in the susceptibility of the bacteria to the antibiotics, which has been discussed above. Moreover, many studies have proved that the consumption of antibiotics demonstrated a significant positive correlation with antimicrobial resistance. Results of 10 published case-control studies of risk for fluoroquinolone resistance in isolates of Enterobacteriaceae were pooled by using a random-effects model, it found that exposure to FQs was significantly positively associated with fluoroquinolone resistance (OR=3.17) and negatively associated with fluoroquinolone susceptibility (OR=0.18).[37] A study on the relationship between fluoroquinolone usage and resistance in *Escherichia coli* found the same result.[38]

The patient's age and the department are also factors affecting the empirical use of FQs. The older the patient, the more likely it is to be empirically used FQs; Compared with "other" departments, internal medicine patients are more likely to be used empirically, while surgical patients are less likely to be used. Effective empirical treatment should be based on the discovery of patients who are at risk of antibiotic resistance,[39] and the age and department of the patient are important risk factors for antibiotic resistance.[40–42] The relevant guidelines point out that most of the clinical applications of FQs are safe, but the safety and effectiveness in minors have not been established and should be avoided to use as much as possible, elderly patients should be prescribed according to the renal function.[43] Different departments reflect the different disease conditions of the patients. Doctors need to understand the adverse reactions of FQs to patients with different diseases and prescribe after weighing the risks. For example, FQs can lead to prolonged QTc, patients with cardiovascular diseases should be prescribed carefully; FQs can also increase the risk of tendon injury, especially in patients over 60 years old, using glucocorticoids, and receiving heart, lung, or kidney transplants.[44]

Factors Affecting the Appropriate Empirical Use of FQs

The pathogenic bacteria and Patients infected by MDROs or not can affect the appropriateness of the empirical use of FQs, which may be because that when the results of bacterial culture and antimicrobial susceptibility are not reported, doctors often predict the possible pathogens based on the patient's infection site and other situations to prescribe antibiotic empirically.[45] Therefore, whether the bacteria detected by antimicrobial culture is consistent with the doctor's prediction will affect the appropriateness of the empirical therapy. And then, if the pathogen is an MDRO, more bacteria-resistant antibiotics will be reported in the AST results than those non-multi-drug-resistant microorganisms, so that the appropriateness of empirical use of antibiotics will be lower as our standard for evaluating the appropriateness is the result of the AST.

Other factors which can affect the appropriateness of the empirical use of FQs included the LOS before empirical therapy and department. Studies have shown that inappropriate empirical therapy is associated with higher morbidity of healthcare-related infections and mortality.[46,47] Patients who were admitted to surgical departments and with a longer LOS have a more complicated diseases and more trauma than those in other departments, which will not only increase the infection morbidity but also the mortality.[48,49] Some researchers suggested that doctors should consider empirical combination therapy to improve the appropriateness of treatment for patients with longer LOS and severe infections.[34]

Our study has some limitations. First, this study was conducted in a single tertiary hospital, and there are restrictions on the types of drugs and bacteria because of the range of breakpoint revision, the empirical use rate in this study was limited among patients infected with *E. coli*, *K. pneumoniae*, or *P. aeruginosa*, so the results can only be applied to patients in settings with similar local susceptibilities rate for those microorganisms, and our next step is to verify the results in a future multicenter study. Despite this, the low appropriate rate of the empirical use in this study still reflected the inadequacy in medication of clinicians. Second, although the changes in empirical therapy are statistically significant, the consumption of certain antibiotic drugs may not be directly correlated with antimicrobial resistance, the relationship with the breakpoint revision may also be affected by other factors. In addition, we did not analyze the association

between the appropriateness of therapy and clinical outcome in patients, however, previous studies have shown that inappropriate empiric therapy increases the risk of poor prognosis, this will be the content of our further researches. Finally, we did not consider the influence of doctor's characteristics on the appropriateness of empirical therapy as relevant data were not available.

Conclusion

In conclusion, our research is to find evidence to promote the rational use of antibacterial drugs from the perspective of the laboratory. The role of microbiology laboratories in antimicrobial stewardship is increasingly emphasized, but clinical-based evidence is less. We found that the change of breakpoint guideline is only understood by the laboratorians but not by the clinicians, and there is a lack of communication between the microbiology laboratory and the clinicians. It is necessary to take interventions such as periodical reports of local resistance data, education, and training of clinicians to strengthen the collaboration between microbiology laboratories and clinicians and play the important role of laboratories in antimicrobial stewardship to help facilitate the appropriate use of antimicrobials and slow down the AMR.

Ethics Statement

The study was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (2020-S252). As the study used anonymous, pooled, and retrospective data, the Ethics Committee waived the need for participants to provide written informed consent. The study complies with the Declaration of Helsinki.

Acknowledgments

The authors would like to thank the National Natural Science Foundation of China for providing research funding and Tongji Hospital for providing the research data.

Funding

This work was supported by the National Natural Science Foundation of China (71974062, http://www.nsfc.gov.cn/). The funders played no role in the process of manuscript preparation.

Disclosure

The authors report no conflicts of interest in this work.

References

1. World Health Organization. *Antimicrobial Resistance: Global Report on Surveillance 2014*. Geneva, Switzerland: World Health Organization; 2014.
2. Zeng S, Xu Z, Wang X, et al. Time series analysis of antibacterial usage and bacterial resistance in China: observations from a tertiary hospital from 2014 to 2018. *Infect Drug Resist*. 2019;12:2683–2691. doi:10.2147/IDR.S220183
3. Roope LSJ, Smith RD, Pouwels KB, et al. The challenge of antimicrobial resistance: what economics can contribute. *Science*. 2019;364(6435):eaau4679. doi:10.1126/science.aau4679
4. Bolon MK. The newer fluoroquinolones. *Infect Dis Clin North Am*. 2009;23(4):1027–x. doi:10.1016/j.idc.2009.06.003
5. Ezelarab HAA, Abbas SH, Hassan HA, Abuo-Rahma GEA. Recent updates of fluoroquinolones as antibacterial agents. *Arch Pharm (Weinheim)*. 2018;351(9):e1800141. doi:10.1002/ardp.201800141
6. Linder JA, Huang ES, Steinman MA, Gonzales R, Stafford RS. Fluoroquinolone prescribing in the United States: 1995 to 2002. *Am J Med*. 2005;118(3):259–268. doi:10.1016/j.amjmed.2004.09.015
7. Baggs J, Fridkin SK, Pollack LA, Srinivasan A, Jernigan JA. Estimating national trends in inpatient antibiotic use among US hospitals from 2006 to 2012. *JAMA Intern Med*. 2016;176(11):1639–1648. doi:10.1001/jamainternmed.2016.5651
8. Centers for Disease Control and Prevention, US Department of Health and Human Services [Website on the Internet]. Antibiotic resistance threats in the United States. US; 2013. Available from: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf. Accessed August 20, 2021.
9. Yang P, Chen Y, Jiang S, Shen P, Lu X, Xiao Y. Association between the rate of fluoroquinolones-resistant gram-negative bacteria and antibiotic consumption from China based on 145 tertiary hospitals data in 2014. *BMC Infect Dis*. 2020;20(1):269. doi:10.1186/s12879-020-04981-0
10. Mutnick AH, Rhomberg PR, Sader HS, Jones RN. Antimicrobial usage and resistance trend relationships from the MYSTIC programme in North America (1999–2001). *J Antimicrob Chemother*. 2004;53(2):290–296. doi:10.1093/jac/dkh039
11. Kim B, Kim Y, Hwang H, et al. Trends and correlation between antibiotic usage and resistance pattern among hospitalized patients at university hospitals in Korea, 2004 to 2012: a Nationwide Multicenter Study. *Medicine (Baltimore)*. 2018;97(51):e13719. doi:10.1097/MD.0000000000013719
12. Weist K, Högberg LD. ECDC publishes 2015 surveillance data on antimicrobial resistance and antimicrobial consumption in Europe. *Euro Surveill*. 2016;21(46):30401. doi:10.2807/1560-7917.ES.2016.21.46.30399
13. U.S. Department of Health and Human Services. *Antibiotic Resistance Threats in the United States, 2013*. Centers for Disease Control and Prevention. 2013.
14. Rhomberg PR, Jones RN. Summary trends for the meropenem yearly susceptibility test information collection program: a 10-year experience in the United States (1999–2008). *Diagn Microbiol Infect Dis*. 2009;65(4):414–426. doi:10.1016/j.diagmicrobio.2009.08.020
15. Reddy P. Empiric antibiotic therapy of nosocomial bacterial infections. *Am J Ther*. 2016;23(4):e982–e994. doi:10.1097/MJT.0000000000000042
16. Muscedere JG, Shorr AF, Jiang X, Day A, Heyland DK; Canadian Critical Care Trials Group. The adequacy of timely empiric antibiotic therapy for ventilator-associated pneumonia: an important determinant of outcome. *J Crit Care*. 2012;27(3):322.e7–322.e14. doi:10.1016/j.jcrc.2011.09.004

17. Membrilla-Fernández E, Sancho-Insenser JJ, Girvent-Montllor M, Álvarez-lerma F, Sitges-Serra A; Secondary Peritonitis Spanish Study Group. Effect of initial empiric antibiotic therapy combined with control of the infection focus on the prognosis of patients with secondary peritonitis. *Surg Infect (Larchmt)*. 2014;15(6):806–814. doi:10.1089/sur.2013.240
18. Fitzpatrick JM, Biswas JS, Edgeworth JD, et al. Gram-negative bacteraemia; a multi-centre prospective evaluation of empiric antibiotic therapy and outcome in English acute hospitals. *Clin Microbiol Infect*. 2016;22(3):244–251. doi:10.1016/j.cmi.2015.10.034
19. Aypak C, Altunsoy A, Düzgün N. Empiric antibiotic therapy in acute uncomplicated urinary tract infections and fluoroquinolone resistance: a Prospective Observational Study. *Ann Clin Microbiol Antimicrob*. 2009;8:27. doi:10.1186/1476-0711-8-27
20. Castro-Sánchez E, Bennasar-Veny M, Smith M, et al. European commission guidelines for the prudent use of antimicrobials in human health: a missed opportunity to embrace nursing participation in stewardship. *Clin Microbiol Infect*. 2018;24(8):914–915. doi:10.1016/j.cmi.2018.02.030
21. World Health Organization. Laboratory leadership competency framework; 2019. Available from: https://apps.who.int/iris/handle/10665/311445. Accessed August 20, 2021.
22. Cui Y, Liu J, Zhang X. Effects of laboratory capabilities on combating antimicrobial resistance, 2013–2016: a static model panel data analysis. *J Glob Antimicrob Resist*. 2019;19:116–121. doi:10.1016/j.jgar.2019.03.007
23. Van TT, Minejima E, Chiu CA, Butler-Wu SM. Don't get wound up: revised fluoroquinolone breakpoints for Enterobacteriaceae and Pseudomonas aeruginosa. *J Clin Microbiol*. 2019;57(7):e02072–18. doi:10.1128/JCM.02072-18
24. Morency-Potvin P, Schwartz DN, Weinstein RA. Antimicrobial stewardship: how the microbiology laboratory can right the ship. *Clin Microbiol Rev*. 2016;30(1):381–407. doi:10.1128/CMR.00066-16
25. Heil EL, Johnson JK. Impact of CLSI breakpoint changes on microbiology laboratories and antimicrobial stewardship programs. *J Clin Microbiol*. 2016;54(4):840–844. doi:10.1128/JCM.02424-15
26. Ginocchio CC. Role of NCCLS in antimicrobial susceptibility testing and monitoring. *Am J Health Syst Pharm*. 2002;59(8 Suppl 3):S7–S11. doi:10.1093/ajhp/59.suppl_3.S7
27. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Ninth Informational Supplement*. CLSI document M100-S29. Wayne: Clinical and Laboratory Standards Institute; 2019.
28. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing; 28th Informational Supplement*. CLSI document M100-S28. Wayne: Clinical and Laboratory Standards Institute; 2018.
29. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*. 27th informational supplement M100-S27. Wayne: Clinical and Laboratory Standards Institute. 2017.
30. Tseng YT, Chuang YC, Shu CC, Hung CC, Hsu CF, Wang JY. Empirical use of fluoroquinolones improves the survival of critically ill patients with tuberculosis mimicking severe pneumonia. *Crit Care*. 2012;16(5):R207. doi:10.1186/cc11839
31. Chen CH, Wu B, Tong HC. Analysis on drug resistance of pathogens and empiric medication in urinary tract infections. *Mod Med J*. 2015;43(2):173–176. In Chinese.
32. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin Infect Dis*. 1999;29(4):745–758. doi:10.1086/520427
33. Grossman C, Keller N, Bornstein G, Ben-Zvi I, Koren-Morag N, Rahav G. Factors associated with suitability of empiric antibiotic therapy in hospitalized patients with bloodstream infections. *J Chemother*. 2017;29(3):159–163. doi:10.1080/1120009X.2016.1182770
34. Hsu DI, Okamoto MP, Murthy R, Wong-Beringer A. Fluoroquinolone-resistant Pseudomonas aeruginosa: risk factors for acquisition and impact on outcomes. *J Antimicrob Chemother*. 2005;55(4):535–541. doi:10.1093/jac/dki026
35. Liu PY, Shi ZY, Tung KC, et al. Antimicrobial resistance to cefotaxime and ertapenem in Enterobacteriaceae: the effects of altering clinical breakpoints. *J Infect Dev Ctries*. 2014;8(3):289–296. doi:10.3855/jidc.3335
36. Chu YW, Tse H, Tsang D. Adoption of the new CLSI fluoroquinolone breakpoints for Enterobacteriaceae. *J Clin Microbiol*. 2019;57(11):e01176–19. doi:10.1128/JCM.01176-19
37. Bolon MK, Wright SB, Gold HS, Carmeli Y. The magnitude of the association between fluoroquinolone use and quinolone-resistant Escherichia coli and Klebsiella pneumoniae may be lower than previously reported. *Antimicrob Agents Chemother*. 2004;48(6):1934–1940. doi:10.1128/AAC.48.6.1934-1940.2004
38. Durham LK, Ge M, Cuccia AJ, Quinn JP. Modeling antibiotic resistance to project future rates: quinolone resistance in Escherichia coli. *Eur J Clin Microbiol Infect Dis*. 2010;29(3):353–356. doi:10.1007/s10096-009-0862-x
39. Bischoff S, Walter T, Gerigk M, Ebert M, Vogelmann R. Empiric antibiotic therapy in urinary tract infection in patients with risk factors for antibiotic resistance in a German emergency department. *BMC Infect Dis*. 2018;18(1):56. doi:10.1186/s12879-018-2960-9
40. Arslan H, Azap OK, Ergönül O, Timurkaynak F; Urinary Tract Infection Study Group. Risk factors for ciprofloxacin resistance among Escherichia coli strains isolated from community-acquired urinary tract infections in Turkey. *J Antimicrob Chemother*. 2005;56(5):914–918. doi:10.1093/jac/dki344
41. Azap OK, Arslan H, Serefhanoğlu K, et al. Risk factors for extended-spectrum beta-lactamase positivity in uropathogenic Escherichia coli isolated from community-acquired urinary tract infections. *Clin Microbiol Infect*. 2010;16(2):147–151. doi:10.1111/j.1469-0691.2009.02941.x
42. Al-Zahrani J, Al Dossari K, Gabr AH, Ahmed AF, Al Shahrani SA, Al-Ghamdi S. Antimicrobial resistance patterns of Uropathogens isolated from adult women with acute uncomplicated cystitis. *BMC Microbiol*. 2019;19(1):237. doi:10.1186/s12866-019-1612-6
43. Zhang YY, Wang F, Wang ZM, et al. The indications and rational use of quinolones in the treatment of infectious diseases: a consensus. *Chin J Infect Chemother*. 2009;9(02):81–88. (In Chinese.)
44. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. *Clin Infect Dis*. 2003;36(11):1404–1410. doi:10.1086/375078
45. Zhong NS, Wan XR, Ma XJ, et al.Guidelines for the clinical application of antibacterial drugs. National health commission of the People's Republic of China, national administration of traditional Chinese medicine, medical department of general logistics department. 2015. (In Chinese).
46. Diamantis S, Rioux C, Bonnal C, et al. Suitability of initial antibiotic therapy for the treatment of bloodstream infections and the potential role of antibiotic management teams in improving it. *Eur J Clin Microbiol Infect Dis*. 2012;31(7):1667–1671. doi:10.1007/s10096-011-1491-8
47. Lee CC, Lee CH, Chuang MC, Hong MY, Hsu HC, Ko WC. Impact of inappropriate empirical antibiotic therapy on outcome of bacteremic adults visiting the ED. *Am J Emerg Med*. 2012;30(8):1447–1456. doi:10.1016/j.ajem.2011.11.010
48. Mosdell DM, Morris DM, Voltura A, et al. Antibiotic treatment for surgical peritonitis. *Ann Surg*. 1991;214(5):543–549. doi:10.1097/00000658-199111000-00001
49. Guo N, Xue W, Tang D, Ding J, Zhao B. Risk factors and outcomes of hospitalized patients with blood infections caused by multidrug-resistant Acinetobacter baumannii complex in a hospital of Northern China. *Am J Infect Control*. 2016;44(4):e37–e39. doi:10.1016/j.ajic.2015.11.019