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ORIGINAL RESEARCH

Trends and correlation of antibiotic susceptibility and antibiotic consumption at a large teaching hospital in China (2007–2016): a surveillance study

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Purpose: To evaluate the trends and correlation between the antibiotic consumption and susceptibility of eight most frequent isolates in the First Affiliated Hospital of Zhejiang University (2007–2016).

Method: This study was based on the yearly surveillance data in a 2500-bed capacity tertiary-care teaching hospital. Trends and correlation were, respectively, analyzed by linear regression and Pearson's correlation coefficient.

Results: The consumption of all antibiotics decreased by 10.8% over time, especially first-generation cephalosporins (p=0.001), fourth-generation cephalosporins (p=0.01), aminoglycosides (p<0.001), and fluoroquinolones (p<0.001), but increased remarkably in linezolid, carbapenems, glycopeptides, and third-generationcephalosporins (3GCs). 72.7% of trend analyses indicated increased susceptibility to antibiotics with remarkably decreased consumption. In particular, susceptibility to aminoglycosides and fluoroquinolones remarkably increased in seven of eight pathogens and negatively correlated with the corresponding antibiotic consumption (p<0.05). Isolation density significantly declined in methicillin-resistant *Staphylococcus aureus* (54.9–41.3%, p=0.009) and in extended-spectrum β-lactamase producing *Klebsiella pneumoniae* (42.4–15.6%, p=0.007), which positively correlated with the consumption of fluoroquinolones. The susceptibility to antibiotics with increased consumption was almost stable. Decreased trends were only found in *K. pneumoniae* to imipenem (81–71.3%, p=0.046) and cefoperazone/sulbactam (70.8–61.0%, p=0.014) and in *Acinetobacter baumannii* to cefoperazone/sulbactam (59–28%, p=0.007), which negatively correlated with the consumption of carbapenems (r=−0.649, p=0.042) and 3GCs/β-lactamase inhibitors (p<0.05), respectively. The consumption of glycopeptides even positively correlated with the growing susceptibility to vancomycin in *Enterococcus faecium* (r=0.633, p=0.049) and *Enterococcus faecalis* (r=0.752, p=0.012).

Conclusion: The susceptibility to antibiotics with decreased consumption increased remarkably, but maintained stable to those with growing consumption. The stricter management of carbapenems and 3GCs is necessary.

Keywords: antibiotic susceptibility, antibiotic consumption, surveillance, correlation, People's Republic of China

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Introduction

Since the first antibiotic penicillin was discovered in the 1940s, illnesses and deaths from infectious diseases have remarkably reduced.[1] However, the war between pathogens and antibiotics continues because pathogens gradually adapt to their external environment, including various antibiotics. Misuse or widespread use of

antibiotics accelerates antibiotic resistance, which is one of the most serious health threats.[2,3] The appearance of methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), vancomycin-resistant *Enterococcus*, and other drug-resistant pathogens has not only compromised the treatment of infectious diseases but also undermined many achievements from different health fields.[2] The widespread of antibiotic resistance is found among 500,000 people with suspected bacterial infections from 22 countries by the WHO's Global Antimicrobial Surveillance System (GLASS).[3] In the United States, more than 2 million people were infected with drug-resistant pathogens, causing the death of at least 23,000 people annually.[2] Similarly, antibiotic resistance has been a considerable burden on People's Republic of China,[4,5] given that the ration of MRSA, extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, and carbapenem-resistant *Acinetobacter baumannii* was over 50% of the corresponding isolates nationwide in 2009.[5]

The way antibiotics are used needs to be changed, as it may be the single most important strategy to effectively slowdown the spread and development of antibiotic resistance.[2,6] For instance, polymyxin B was rarely used clinically for decades due to its toxicity.[7] However, it has been gradually employed as a first-line agent against extensively drug-resistant pathogens because of its consistently high sensitivity rate.[8] WHO and Centers for Disease Control and Prevention of the United States have managed several programs, such as GLASS[1] and Get Smart program,[6] to address antimicrobial resistance, emphasizing the importance of appropriate antibiotic usage and surveillance of antibiotic resistance. The Chinese Ministry of Health also launched the national antibiotic stewardship program, People's Republic of China antimicrobial resistance surveillance system, and other policies to control antibiotic resistance.[5,9,10] Based on this background, the First Affiliated Hospital of Zhejiang University (FAHZU), ranking one of the first-class hospitals in People's Republic of China, has implemented multifaceted interventions, including pharmacist-led antibiotic stewardship, surveillance and regular proclamation of antibiotic resistance data, financial penalties, and so on. Although the antibiotic consumption and resistance in People's Republic of China were characterized in previous studies,[4,11–16] few studies focused on the correlation between these two elements during a relatively long period. Furthermore, several important pathogens, such as *Enterococcus faecalis* and *Enterococcus faecium*, were seldom reported. Therefore, this study described the improvements and shortcomings of drug resistance status and provided an overview on the trends and correlation between the antibiotic consumption and sensitivity rates in FAHZU from 2007 to 2016.

Methods

Setting and study design

This observational and retrospective study was based on the yearly data of antibiotic susceptibility and consumption in FAHZU from 2007 to 2016. Located in the east of People's Republic of China, FAHZU is a 2500-bed capacity tertiary-care teaching hospital founded in 1947. It is now ranked as the top 10 medical facility in People's Republic of China and has been the best hospital in Zhejiang Province.

Antimicrobial stewardships in the FAHZU

From 2007 to 2016, the FAHZU implemented multifaceted interventions to combat antibiotic resistance, mainly including: 1) surveillance and regular proclamation of antibiotic resistance data and proportion of patient receiving antibiotic prescriptions; 2) structured antibiotic use policy;. a structured antibiotic use policy (Table S1) has been established in FAHZU to improve the usage of antibiotics. According to this policy, antibiotics were classified as nonrestricted, restricted, and very-restricted types on the basis of their safety, efficacy, resistance rate, and cost. The prescribing requirements were also different for each type; 3) the infectious disease department in the FAHZU kept collaboration with physicians and pharmacists to improve the practice in health care workers; 4) pharmacist-led antibiotic stewardship, including prescription evaluation program, consultation for very-restricted antibiotics, and therapeutic drug monitoring for a series of antibiotics; 5) financial penalties and point-based system that prescribing privileges are revoked if the cumulative score is 12 points; 6) regular Plan–Do–Check–Action programs involving improvement of the rationality to use prophylactic antibiotics in surgical site infection and intervention procedure;[17] 7) education programs.

Bacterial identification and antibiotic susceptibility tests

Data on pathogens isolated from patients admitted to the hospital were retrospectively obtained from FAHZU. The isolates were identified by the VITEK 2 compact system (bioMérieux), and antibiotic susceptibility was determined

by either the disc diffusion method[18] or the VITEK 2 compact system. The results were then interpreted uniformly in accordance with the Clinical and Laboratory Standards Institute criteria.[18] To guarantee the reproducibility of testing methodologies, we used *E. faecalis* ATCC 29212, *S. aureus* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853, and *Escherichia coli* ATCC 25922 as reference strains.

The pathogens included in this study were *Klebsiella pneumoniae, E. coli, A. baumannii, P. aeruginosa, S. aureus*, coagulase-negative *Staphylococcus* (CNS), *E. faecalis*, and *E. faecium*, which were the most frequent isolates in our hospital for the past 10 years. The isolation density for each species was the number of isolates per 10,000 patient-days (10,000-pd). The susceptibility rate of each antibiotic was calculated as the number of susceptible isolates divided by the total isolation number.

Antibiotic consumption

The data of antibiotic consumption from 2007 to 2016 were obtained from the database of the Pharmacy Department. Antibiotic consumption[19] in this study was measured based on the number of defined daily dose (DDD) normalized per 1000-pd. The DDD is the assumed average maintenance dose per day of the corresponding antibiotic used for its main indication in adults and was obtained from the ATC/DDD Index 2018.[19]

Statistical analyses

Trends of isolation density, antibiotic consumption, and susceptibility were determined by linear regression. Pearson's correlation coefficient was calculated to identify the relationship between antibiotic consumption and susceptibility. Statistical significance was considered at $p<0.05$, and IBM SPSS Statistics (version 23) was used for all the analyses.

Results

Bacterial isolates

Of the 732.5/10,000-pd isolates, 14.91% was *E. coli*, 10.16% was *K. pneumoniae*, 11.15% was *A. baumannii*, and 9.21% was *P. aeruginosa*. The most frequently isolated Gram-positive pathogens were CNS (16.80%), *S. aureus* (5.49%), *E. faecium* (4.08%), and *E. faecalis* (3.89%). All of them accounted for 75.70% of the isolated pathogens during the study period.

Antimicrobial susceptibility

As shown in Figure 1, susceptibility to many antibiotics increased markedly in different pathogens from 2007 to 2016. Consistent with the overall variation, the susceptibility to majority of the antibiotics rose remarkably in *E. coli*. In addition, the proportion of ESBL-producing isolates significantly decreased in *E. coli* (r=−0.745, $p=0.013$, Figure 1A) and *K. pneumoniae* (r=−0.789, $p=0.007$, Figure 1A). However, the susceptibility to imipenem and cefoperazone/sulbactam decreased in *K. pneumoniae* during the surveillance period. The susceptibility to ciprofloxacin (r=0.713, $p=0.031$) and amikacin (r=0.749, $p=0.013$) in *A. baumannii* has improved remarkably during the past 10 years. Whereas its susceptibility to cefoperazone/sulbactam, which is an important option for infections caused by *A. baumannii* (Figure 1A and C), decreased significantly from 59% in 2007 to 28% in 2016 (r=−0.783, $p=0.007$).

The results for Gram-positive pathogens showed that the ratio of MRSA (Figure 1B) decreased significantly from 2007 to 2016 (r=−0.769, $p=0.009$). However, the proportion of methicillin-resistant CNS remained unchanged (Figure 1B). During the study years, *S. aureus* and CNS became more sensitive to gentamicin, ciprofloxacin, erythromycin, clindamycin, and rifampicin (Figure 1C). The susceptibility in *E. faecium* was almost stable but increased to vancomycin (r=0.907, $p=0.001$) and gentamicin with a high concentration (r=0.921, $p<0.001$). Different from that in *E. faecium*, the susceptibility in *E. faecalis* to different antibiotics improved remarkably (Figure 1C).

Trends of antibiotic consumption

The overall antibiotic consumption decreased by 10.8% during the study period (r=−0.671, $p=0.034$). As shown in Figure 2A, consumption of first-generation cephalosporins (1GC, r=−0.882, $p=0.001$), fourth-generation cephalosporins (4GC, r=−0.762, $p=0.010$), aminoglycosides (r=−0.896, $p<0.001$), and fluoroquinolones (r=−0.938, $p<0.001$) fell by a wide margin, whereas the use of linezolid, carbapenems, glycopeptides, and third-generation cephalosporins (3GCs) grew substantially (Figure 2B), all increasing over 50%. A marked rise occurred after the introduction of linezolid in 2007, which was rarely used at the beginning, but the use grew from 0.13 DDD/1000-pd in 2007 to 14.64 DDD/1000-pd in 2016.

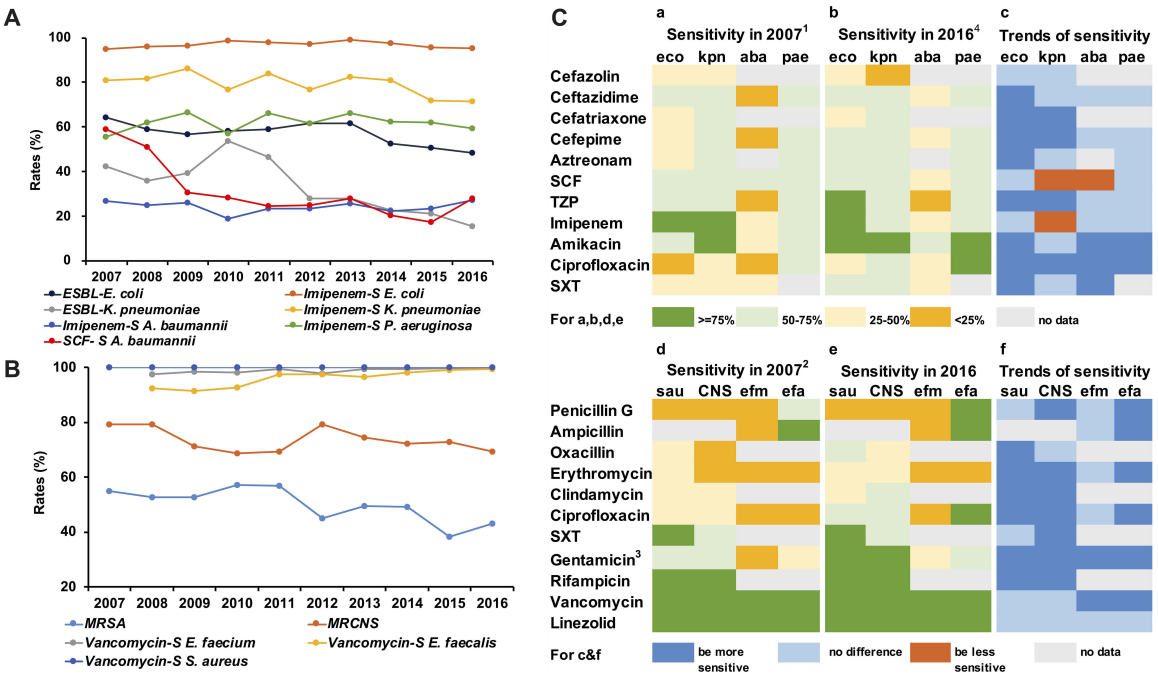

Figure 1 Trends of antibiotic susceptibility in FAHZU, 2007–2016.

Notes: Rates of important Gram-negative pathogens (**A**) and Gram-positive pathogens (**B**). The susceptibility of Gram-negative pathogens (**C:** a and b) and Gram-positive pathogens (**C:** d and e), and the trends of susceptibility from 2007 to 2016 (**C:** c and f). [1,2,4]The study period of susceptibility: aztreonam and SXT (2008–2016), cefazolin (2010–2016), piperacillin / tazobactam in *A. baumannii* (2007–2015), ciprofloxacin in *A. baumannii* (2008–2016). [3]Gentamicin with a high concentration.

Abbreviations: S, sensitive; eco, *E. coli*; kpn, *K. pneumoniae*; aba, *A. baumannii*; pae, *P. aeruginos*; sau, *S. aureus*; CNS, coagulase-negative *Staphylococcus*; efm, *E. faecium*; efa, *E. faecalis*; SCF, cefoperazone/sulbactam; TZP, piperacillin/tazobactam; SXT, sulfamethoxazole/trimethoprim; ESBL, extended-spectrum β-lactamase; FAHZU, First Affiliated Hospital of Zhejiang University.

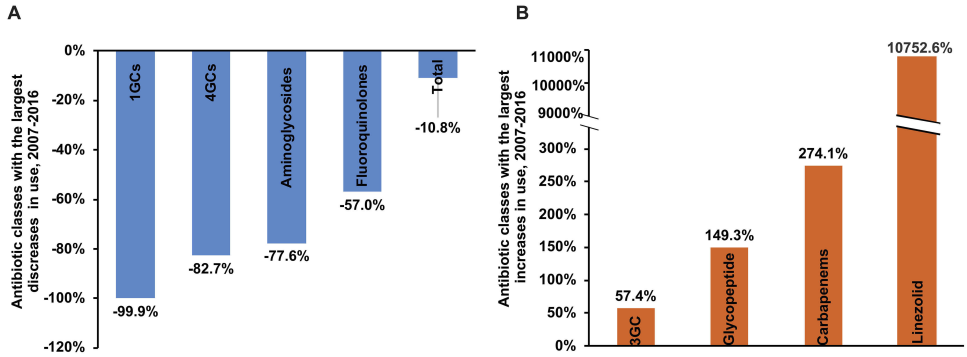

Figure 2 Trends of antibiotic consumption in FAHZU, 2007–2016 (**A**) and with the largest decreases in use (**B**).

Abbreviations: GC, cephalosporin; 1GCs, first-generation cephalosporins; 3GC, third-generation cephalosporins; 4GCs, fourth-generation cephalosporins; FAHZU, First Affiliated Hospital of Zhejiang University.

Correlation between antibiotic susceptibility and consumption

The correlation between the consumption of these antibiotics with most significant changes (Figure 2) and the corresponding susceptibility is shown in Tables 1 and 2, respectively.

For 1GCs, 4GCs, fluoroquinolones, and aminoglycosides, 16 of the total 22 (72.7%) trend analyses suggested increasing susceptibility, which was well correlated with the decreased consumption of the corresponding antibiotics (Table 1). In particular, susceptibility to aminoglycosides and fluoroquinolones rose markedly in seven of eight pathogens and was negatively related to the corresponding antibiotic consumption. However, the susceptibility of different pathogens to 1GCs remained unchanged. The correlation between consumption and susceptibility to antibiotics with

Table 1 Correlation between antibiotic consumption that decreased remarkably and the corresponding antibiotic susceptibility

Pathogens	Antibiotics	Trend for susceptibility			Correlation analysis			
		r	*p*	Trend	Antibiotic in consumption	r	*p*	Correlation
Klebsiella pneumoniae	Cefazolin	−0.457	0.362	Stable	1GCs	0.404	0.427	No correlation
	Cefepime	0.744	0.014	Increasing	4GCs	−0.763	0.010	Negative
	Ciprofloxacin	0.833	0.003	Increasing	Fluoroquinolones	−0.849	0.002	Negative
	Amikacin	0.607	0.063	Stable	Glycopeptides	−0.627	0.052	No correlation
Escherichia coli	Cefazolin	−0.097	0.855	Stable	1GCs	−0.335	0.516	No correlation
	Cefepime	0.963	0.000	Increasing	4GCs	−0.763	0.010	Negative
	Ciprofloxacin	0.953	0.000	Increasing	Fluoroquinolones	−0.857	0.002	Negative
	Amikacin	0.918	0.000	Increasing	Glycopeptides	−0.784	0.007	Negative
Acinetobacter baumannii	Cefepime	−0.110	0.762	Stable	4GCs	0.156	0.667	No correlation
	Ciprofloxacin	0.713	0.031	Increasing	Fluoroquinolones	−0.772	0.015	Negative
	Amikacin	0.749	0.013	Increasing	Glycopeptides	−0.871	0.001	Negative
Pseudomonas aeruginosa	Cefepime	−0.110	0.762	Stable	4GCs	0.219	0.543	No correlation
	Ciprofloxacin	0.800	0.005	Increasing	Fluoroquinolones	−0.647	0.043	Negative
	Amikacin	0.895	0.000	Increasing	Glycopeptides	−0.861	0.001	Negative
Staphylococcus aureus	Ciprofloxacin	0.915	0.000	Increasing	Fluoroquinolones	−0.867	0.001	Negative
	Gentamicin	0.902	<0.001	Increasing	Glycopeptides	−0.818	0.004	Negative
Coagulase- negative *staphylococcus*	Ciprofloxacin	0.800	0.005	Increasing	Fluoroquinolones	−0.686	0.028	Negative
	Gentamicin	0.968	<0.001	Increasing	Glycopeptides	−0.886	<0.001	Negative
Enterococcus faecium	Ciprofloxacin	0.394	0.260	Stable	Fluoroquinolones	−0.598	0.068	No correlation
	Gentamicin[a]	0.921	<0.001	Increasing	Glycopeptides	−0.827	0.003	Negative
Enterococcus faecalis	Ciprofloxacin	0.940	<0.001	Increasing	Fluoroquinolones	−0.968	<0.001	Negative
	Gentamicin[a]	0.898	<0.001	Increasing	Glycopeptides	−0.800	0.005	Negative

Note: [a]Gentamicin with a high concentration.
Abbreviations: 1GCs, first-generation cephalosporins; 4GCs, fourth-generation cephalosporins.

increased consumption was not as remarkable as those with decreased consumption. As shown in Table 2, only 4 of 12 (25%) trend analyses indicated decreasing susceptibility in Gram-negative pathogens to those with increased consumption. In terms of Gram-positive pathogens, the consumption of glycopeptides even positively correlated with the growing susceptibility to vancomycin in *E. faecium* (r=0.633, p=0.049) and *E. faecalis* (r=0.752, p=0.012).

Considering that the isolations of ESBL-producing pathogens and MRSA varied significantly (p<0.5), we conducted a correlation analysis to investigate the factors behind these variations. As shown in Table 3, the isolation density of ESBL-producing *E. coli* negatively correlated with the consumption of carbapenems and cephalosporins/β-lactamase inhibitors. The isolation density of ESBL-producing *K. pneumoniae* was positively related to the use of fluoroquinolones but not correlated with the use of either carbapenems or cephalosporins/β-lactamase inhibitors. As for MRSA, the isolation density negatively correlated with the use of fluoroquinolones but not with other antibiotics.

Discussion

The drug resistance status between People's Republic of China and some developed counties had a wide gap.[5,6,10,18,20] To improve the serious situation, Chinese government launched a series of policies and guidelines. As one of the best and largest comprehensive hospitals in People's Republic of China, FAHZU has also implemented multifaceted interventions and measures. Several improvements were observed, including the following: 1) the overall antibiotic consumption decreased; 2) susceptibility markedly rose to many antibiotics in different pathogens; 3) isolation density of serious drug-resistant pathogens, such as MRSA

Table 2 Correlation between antibiotic consumption that increased remarkably and the corresponding antibiotic susceptibility

Pathogens	Antibiotics	Trend for susceptibility			Correlation analysis			
		r	p	Trend	Antibiotic in consumption	r	p	Correlation
Escherichia coli	Imipenem	0.073	0.840	Stable	Carbapenems	−0.216	0.549	No correlation
	SCF	−0.530	0.115	Stable	3GCs/β-lactamase inhibitors[a]	−0.639	0.064	No correlation
	Ceftazidime	0.665	0.051	Stable	3GC sensitive to pae[b]	0.488	0.182	No correlation
Klebsiella pneumoniae	Imipenem	−0.642	0.046	Decreasing	Carbapenems	−0.649	0.042	Negative
	SCF	−0.740	0.014	Decreasing	3GCs/β-lactamase inhibitors[a]	−0.708	0.033	Negative
	Ceftazidime	0.347	0.360	Stable	3GC sensitive to pae[b]	0.511	0.160	No correlation
Acinetobacter baumannii	Imipenem	−0.056	0.878	Stable	Carbapenems	0.077	0.832	No correlation
	SCF	−0.783	0.007	Decreasing	3GCs/β-lactamase inhibitors[a]	−0.775	0.014	Negative
	Ceftazidime	−0.267	0.488	Stable	3GC sensitive to pae[b]	−0.322	0.398	No correlation
Pseudomonas aeruginosa	Imipenem	0.167	0.644	Stable	Carbapenems	−0.045	0.901	No correlation
	SCF	0.387	0.269	Stable	3GCs/β-lactamase inhibitors[a]	−0.064	0.870	No correlation
	Ceftazidime	−0.488	0.152	Stable	3GC sensitive to pae[b]	−0.477	0.163	No correlation
Staphylococcus aureus	Linezolid	0.410	0.274	Stable	Linezolid	0.228	0.555	No correlation
	Vancomycin	Maintained 100%			Glycopeptides	/	/	No correlation
Coagulase-negative *staphylococcus*	Linezolid	−0.275	0.473	Stable	Linezolid	−0.281	0.464	No correlation
	Vancomycin	Maintained 100%			Glycopeptides	/	/	No correlation
Enterococcus faecium	Linezolid	−0.320	0.401	Stable	Linezolid	0.098	0.802	No correlation
	Vancomycin	0.925	<0.001	Increasing	Glycopeptides	0.633	0.049	Positive
Enterococcus faecalis	Linezolid	0.483	0.188	Stable	Linezolid	0.122	0.754	No correlation
	Vancomycin	0.735	0.015	Increasing	Glycopeptides	0.752	0.012	Positive

Note: [a]Since the consumption of 3GCs/β-lactamase inhibitors increased remarkably among 3GCs and SCF belongs to 3GCs/β-lactamase inhibitors, the correlation was conducted between the corresponding susceptibility and consumption. [b]Since the consumption of 3GCs sensitive to pae increased remarkably among 3GCs and ceftazidime belongs to this antibiotic type, the correlation was conducted between the corresponding susceptibility and consumption.
Abbreviations: 3GCs, third-generation cephalosporins; pae, *P. aerugino*; SCF, cefoperazone/sulbactam.

and ESBL-producing isolates, remarkably declined and the well control of fluoroquinolones possibly contribute to these improvements.

The current result confirms that proper management of antibiotics can decelerate or even reverse bacterial resistance. The most successful example was that seven of eight (87.5%) investigated pathogens became more sensitive to both aminoglycosides and fluoroquinolones, which well correlated with the corresponding drug consumption. At present, these antibiotics have become an option against CRE and many other multidrug-resistant pathogens.[21,22] Thus, discontinuing or strictly controlling antibiotics with a high resistance rate for a certain period, similar to the "fallow cropping system", can be considered an effective way to reduce the selection pressure from antibiotics.[23,24] The results also demonstrated the development of resistance against antibiotics seems considerably slower than the recovery rate of susceptibility, given that 72.7% trend analyses suggested increasing susceptibility in antibiotics with remarkably decreased consumption, whereas only 15.0% trend analyses indicated declined susceptibility in antibiotics with increased consumption during the study time, strengthening our confidence to improve the usage of antibiotics.

The isolation density of MRSA was decreased with time and positively correlated with the consumption of fluoroquinolones, which are also recognized as the risk factor for MRSA in previous studies.[25,26] Given that fluoroquinolones may also contribute to the prevalence of ESBL-producing pathogens in FAHZU and in other settings,[27] strict control of the use of fluoroquinolones should be insisted on in the future. The susceptibility of *E. faecium* and *E. faecalis* to vancomycin increased but positively correlated with its consumption. One possible explanation is that with more experience to use vancomycin, such as PK/PD thesis and therapeutic drug

Table 3 Correlation between isolations of important pathogens (ESBL-producing *Enterobacteriaceae* and MRSA) and antibiotic consumption

Pathogens		Trend for susceptibility			Correlation analysis			
		r	p	Trend	Antibiotic in consumption	r	p	Correlation
Escherichia coli	ESBL	−0.745	0.013	Decreasing	3GCs	0.270	0.452	No correlation
					PCs with extended spectrum	0.430	0.215	No correlation
					Carbapenems	−0.877	0.001	Negative
					Cephalosporins/β-lactamase inhibitors	−0.730	0.017	Negative
					Fluoroquinolones	0.545	0.104	No correlation
Klebsiella pneumoniae	ESBL	−0.789	0.007	Decreasing	3GCs	−0.134	0.712	No correlation
					PCs with extended spectrum	−0.576	0.081	No correlation
					Carbapenems	0.136	0.708	No correlation
					Cephalosporins/β-lactamase inhibitors	−0.521	0.123	No correlation
					Fluoroquinolones	0.865	0.001	Positive
Staphylococcus aureus	MRSA	−0.767	0.009	Decreasing	Penicillins	0.615	0.059	No correlation
					Cephalosporins	0.198	0.584	No correlation
					β-lactamase antibiotics	0.233	0.518	No correlation
					Carbapenems	−0.524	0.120	No correlation
					Fluoroquinolones	0.781	0.008	Positive
					Glycopeptides	−0.142	0.695	No correlation

Abbreviations: 3GCs, third-generation cephalosporins; PCs, penicillins; ESBL, extended-spectrum β-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*.

monitoring,[28,29] the concentration of vancomycin could exceed the mutant prevention concentration, thereby decreasing the prevalence of resistance.[28–30] In fact, the isolation density of vancomycin-resistant *E. faecium* and *E. faecalis* were 0% and 0.5%, respectively, in our hospital in 2016, which are lower than the national level (0.4% in *E. faecium* and 1.9% in *E. faecalis*), and less than that in many counties worldwide.[2,31] This result illuminates that developing a comprehensive strategy that not only limits the consumption but also involves administering the proper dose, duration, and time to use antibiotics is necessary.[32]

However, some shortcomings still existed. Firstly, the susceptibility to carbapenems in *K. pneumoniae* decreased. In our study, the correlation analysis indicated that the increasing consumption of carbapenems may contribute to the burden of carbapenem-resistant *K. pneumoniae* (CRKP). The effect from carbapenems on the resistance of *K. pneumonia* was also found in other studies both in People's Republic of China and worldwide.[3,4,11,21,33] Other risk factors that related with CRKP were invasive mechanical ventilation, parenteral nutrition, high APACHE II score, and so on.[34,35] As a tertiary-care teaching hospital, the number of hospitalizations in the FAHZU increased markedly, and many critical patients who were easily exposure to CRKP-related factors would be transferred to the FAHZU from other hospitals (such as secondary-care teaching hospitals), therefore may result in the increasing trends of CRKP.[33] The epidemics of CRE have gradually been challenging worldwide.[1,2,36] In Europe, the resistance to carbapenem in *K. pneumoniae* increased in 5 of 24 countries from 2009 to 2012.[37] However, the CRE isolation density in some countries retained a low level. For example, the CRE isolation density in Germany was 0% from 2011 to 2013 and was <6% in Egypt from 2002 to 2010.[6] Therefore, opportunities are available to control the prevalence of CRE. The strict management of carbapenems has been included in the latest strategy in our hospital, introducing pharmacy consultation before prescribing carbapenems. Another limitation was that the lack of epidemiological analyses and subsequent data, such as the circulation of a clone of ESBL-producing *E. coli* with patients' cross infections, may affect the statistical significance. Finally, the correlation between antibiotics and consumption is well displayed but cannot confirm causal relationship due to the study design. However, this study was based on 10-year data from 63,711 isolated pathogens in a large comprehensive hospital, covering the most important pathogens in hospital-acquired infections and a full range of antibiotics that are frequently used worldwide. Therefore, the results can illuminate ways to combat drug resistance in other hospitals with a similar situation.

Conclusion

With the multifaceted interventions to improve the appropriate use of antibiotics and combat antibiotic resistance, the susceptibility of different pathogens to many antibiotics considerably increased. Despite the improvements, the decreasing trend of carbapenem-sensitive *Enterobacteriaceae* necessitates the strict management of carbapenems.

Abbreviations

1GCs, first-generation cephalosporins; 3GCs, third-generation cephalosporins; 4GCs, fourth-generation cephalosporins; FAHZU, First Affiliated Hospital of Zhejiang University; CNS, coagulase-negative *Staphylococcus.*

Ethical approval

Given that this study was performed without accessing patient information, approval of the ethics committee was not required.

Disclosure

The authors report no conflicts of interest in this work.

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