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

Rongrong Wang1,* Qing Yang2,* Shaojun Zhang1 Yun Hong1 MeiHua Zhang1 Saiping Jiang1

1Department of Pharmacy, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, People’s Republic of China; 2Department of Clinical Laboratory, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, People’s Republic of China

*These authors contributed equally to this work

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-generation cephalosporins (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

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. 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. 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). 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. Similarly, antibiotic resistance has been a considerable burden on People’s Republic of China, 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.

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. For instance, polymyxin B was rarely used clinically for decades due to its toxicity. However, it has been gradually employed as a first-line agent against extensively drug-resistant pathogens because of its consistently high sensitivity rate. WHO and Centers for Disease Control and Prevention of the United States have managed several programs, such as GLASS and Get Smart program, 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. 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, 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; 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 or the VITEK 2 compact system. The results were then interpreted uniformly in accordance with the Clinical and Laboratory Standards Institute criteria. 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 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.

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, carbenapens, 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.
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
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. 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...
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. 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. 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. Given that fluoroquinolones may also contribute to the prevalence of ESBL-producing pathogens in FAHZU and in other settings, 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 2 Correlation between antibiotic consumption that increased remarkably and the corresponding antibiotic susceptibility

| Pathogens                  | Antibiotics | Trend for susceptibility | Correlation analysis |
|----------------------------|-------------|--------------------------|----------------------|
| *Escherichia coli*         | Imipenem    | 0.073 0.840 Stable       | Carbapenems          |
|                            | SCF         | −0.530 0.115 Stable      | 3GCs/b-lactamase inhibitors a |
|                            | Ceftazidime | 0.665 0.051 Stable       | 3GC sensitive to pae b |
| *Klebsiella pneumoniae*    | Imipenem    | −0.642 0.046 Decreasing  | Carbapenems          |
|                            | SCF         | −0.740 0.014 Decreasing  | 3GCs/b-lactamase inhibitors a |
|                            | Ceftazidime | 0.347 0.360 Stable       | 3GC sensitive to pae b |
| *Acinetobacter baumannii*  | Imipenem    | −0.056 0.878 Stable      | Carbapenems          |
|                            | SCF         | −0.783 0.007 Stable      | 3GCs/b-lactamase inhibitors a |
|                            | Ceftazidime | −0.267 0.488 Stable      | 3GC sensitive to pae b |
| *Pseudomonas aeruginosa*   | Imipenem    | 0.167 0.644 Stable       | Carbapenems          |
|                            | SCF         | 0.387 0.269 Stable       | 3GCs/b-lactamase inhibitors a |
|                            | Ceftazidime | −0.488 0.152 Stable      | 3GC sensitive to pae b |
| *Staphylococcus aureus*    | Linezolid   | 0.410 0.274 Stable       | Linezolid            |
|                            | Vancomycin  | Maintained 100% Glycopeptides | / / No correlation |
| *Coagulase-negative staphylococcus* | Linezolid | −0.275 0.473 Stable | Linezolid |
|                            | Vancomycin  | Maintained 100% Glycopeptides | / / No correlation |
| *Enterococcus faecium*     | Linezolid   | −0.320 0.401 Stable      | Linezolid            |
|                            | Vancomycin  | 0.925 <0.001 Increasing  | Glycopeptides        |
| *Enterococcus faecalis*    | Linezolid   | 0.483 0.188 Stable       | Linezolid            |
|                            | Vancomycin  | 0.735 0.015 Increasing   | Glycopeptides        |

**Note:** aSince the consumption of 3GCs/b-lactamase inhibitors increased remarkably among 3GCs and SCF belongs to 3GCs/b-lactamase inhibitors, the correlation was conducted between the corresponding susceptibility and consumption. bSince 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. aeruginosa*; SCF, cefoperazone/sulbactam.
monitoring, the concentration of vancomycin could exceed the mutant prevention concentration, thereby decreasing the prevalence of resistance. 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. 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.

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. Other risk factors that related with CRKP were invasive mechanical ventilation, parenteral nutrition, high APACHE II score, and so on. 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. The epidemics of CRE have gradually been challenging worldwide. In Europe, the resistance to carbapenem in *K. pneumoniae* increased in 5 of 24 countries from 2009 to 2012. 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. 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.

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

| Pathogens            | Trend for susceptibility | Correlation analysis |
|----------------------|--------------------------|----------------------|
|                      | r p                       | Antibiotic in consumption | r p Correlation |
|                      |                           | 3GCs | 0.270 0.452 No correlation |
|                      |                           | PCs  | 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 |
| Escherichia coli ESBL | −0.745 0.013 Decreasing | 3GCs | −0.134 0.712 No correlation |
|                      |                           | PCs  | −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 |
| Klebsiella pneumoniae ESBL | −0.789 0.007 Decreasing | 3GCs | −0.134 0.712 No correlation |
|                      |                           | PCs  | −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*.
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.

References
1. World Health Organization. Antimicrobial Resistance: Global Report on Surveillance. Switzerland, Geneva; 2014. Available from: https://www.who.int/drugresistance/documents/surveillance_report/en/. Accessed July 1, 2018.
2. U.S. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States. United States; 2013. Available from: http://www.cdc.gov/drugresistance/threat-report-2013/index.html. Accessed July 1, 2018.
3. World Health Organization. High levels of antibiotic resistance found worldwide, new data shows; 2018. Available from: http://www.who.int/news-room/detail/29-01-2018-high-levels-of-antibiotic-resistant-fou... Accessed July 1, 2018.
4. Hu FP, Guo Y, Zhu DM, et al. Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005-2014. Clin Microbiol Infect. 2016;22(Suppl 1):S9–S14. doi:10.1016/j.cmi.2016.01.001
5. Xiao YH, Giscke CG, Wei ZQ, Shen P, Hedinni A, Li LJ. Epidemiology and characteristics of antimicrobial resistance in China. Drug Resist Updat. 2011;14(4–5):236–250. doi:10.1016/j.drup.2011.07.001
6. U.S. Centers for Disease Control and Prevention. Antibiotic Use in the United States, 2017: Progress and Opportunities. United States, U.S.: Atlanta; 2017.
7. Falagas ME, Michalopoulos A. Polymyxins: old antibiotics are back. Lancet. 2006;367(9511):633–634. doi:10.1016/S0140-6736(06)68241-X
8. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61–e111. doi:10.1093/cid/ciw504
9. Bao L, Peng R, Wang Y, et al. Significant reduction of antibiotic consumption and patients’ costs after an action plan in China, 2010-2014. PLoS One. 2015;10(3):e0118868. doi:10.1371/journal.pone.0118868
10. Sun J, Shen X, Li M, et al. Changes in patterns of antibiotic use in Chinese public hospitals (2005-2012) and a benchmark comparison with Sweden in 2012. J Glob Antimicrob Resist. 2015;3(2):95–102. doi:10.1016/j.jgar.2015.03.001
11. Hu F, Chen S, Xu X, et al. Emergence of carbapenem-resistant clinical Enterobacteriaceae isolates from a teaching hospital in Shanghai, China. J Med Microbiol. 2012;61(Pt 1):132–136. doi:10.1099/jmm.0.036483-0
12. Xu J, Duan X, Wu H, Zhou Q. Surveillance and correlation of antimicrobial usage and resistance of Pseudomonas aeruginosa: a hospital population-based study. PLoS One. 2013;8(11):e78604. doi:10.1371/journal.pone.0078604
13. Zhou T, Zhang X, Guo M, et al. Phenotypic and molecular characteristics of carbapenem-non-susceptible Enterobacteriaceae from a teaching hospital in Wenzhou, southern China. Jpn J Infect Dis. 2013;66(2):96–102.
14. Zou YM, Ma Y, Liu JH, et al. Trends and correlation of antibacterial usage and bacterial resistance: time series analysis for antibacterial stewardship in a Chinese teaching hospital (2009-2013). Eur J Clin Microbiol Infect Dis. 2015;34(4):795–803. doi:10.1007/s10096-014-2293-6
15. Chen S, Hu F, Liu Y, Zhu D, Wang H, Zhang Y. Detection and spread of carbapenem-resistant Citrobacter freundii in a teaching hospital in China. Am J Infect Control. 2011;39(9):e55–e60. doi:10.1016/j.ajic.2011.02.009
16. Tan CK, Tang HJ, Lai CC, Chen YY, Chang PC, Liu WL. Correlation between antibiotic consumption and carbapenem-resistant Acinetobacter baumannii causing health care-associated infections at a hospital from 2005 to 2010. J Microbiol Immunol Infect. 2015;48(5):540–544. doi:10.1016/j.jmii.2014.02.004
17. Yang P, Jiang SP, Lu XY. Effectiveness of continuous improvement by a clinical pharmacist-led guidance team on the prophylactic antibiotic usage rationality in intervention procedure at a Chinese tertiary teaching hospital. Ther Clin Risk Manag. 2017;13:469–476. doi:10.2147/TCRM.S131937
18. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. 27th. CLSI supplement M100. United States, U.S.: Wayne; 2017
19. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment 2018. Norway: Oslo; 2017.
20. Versporten A, Zarb P, Caniaux I, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health. 2018;6(6):e619–e629. doi:10.1016/S2214-109X(18)30186-4
21. Perez F, El Chakhtoura NG, Papp-Wallace KM, Wilson BM, Bonomo RA. Treatment options for infections caused by carbapenem-resistant Enterobacteriaceae: can we apply “precision medicine” to antimicrobial chemotherapy? Expert Opin Pharmacother. 2016;17(6):761–781. doi:10.1517/14656566.2016.1145658
22. Rafailidis PI, Falagas ME. Options for treating carbapenem-resistant Enterobacteriaceae. Curr Opin Infect Dis. 2014;27(6):479–483. doi:10.1097/QCO.0000000000000109
23. Melynk AH, Wong A, Kassen R. The fitness costs of antibiotic resistance mutations. Evol Appl. 2015;8(3):273–283. doi:10.1111/eva.12196
24. Andersson DI, Hughes D. Antibiotic resistance and its cost: is it possible to reverse resistance? Nat Rev Microbiol. 2010;8(4):260–271. doi:10.1038/nrmicro2319
25. Epstein L, Mu Y, Belflower R, et al. Risk factors for invasive methicillin-resistant staphylococcus aureus infection after recent discharge from an acute-care hospitalization, 2011-2013. Clin Infect Dis. 2016;62(1):45–52. doi:10.1093/cid/civ777
26. Lee AS, de Lencastre H, Garau J, et al. Methicillin-resistant Staphylococcus aureus. Nat Rev Dis Primers. 2018;4:18033. doi:10.1038/nrdp.2018.33
27. Bassetti M, Peghin M, Pecori D. The management of multidrug-resistant Enterobacteriaceae. *Curr Opin Infect Dis*. 2016;29(6):583–594. doi:10.1097/QCO.0000000000000314

28. Ye ZK, Chen YL, Chen K, et al. Therapeutic drug monitoring of vancomycin: a guideline of the division of therapeutic drug monitoring, Chinese pharmacological society. *J Antimicrob Chemother*. 2016;71(11):3020–3025. doi:10.1093/jac/dkw254

29. Matsumoto K, Takesue Y, Ohmagari N, et al. Practice guidelines for therapeutic drug monitoring of vancomycin: a consensus review of the Japanese society of chemotherapy and the Japanese society of therapeutic drug monitoring. *J Infect Chemother*. 2013;19(3):365–380. doi:10.1007/s10156-013-0599-4

30. Zhu YL, Hu LF, Mei Q, et al. Testing the mutant selection window in rabbits infected with methicillin-resistant Staphylococcus aureus exposed to vancomycin. *J Antimicrob Chemother*. 2012;67(11):2700–2706. doi:10.1093/jac/dks280

31. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2016. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017. Available from: https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2016. Accessed July 1, 2018.

32. Holmes AH, Moore LS, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet*. 2016;387(10014):176–187. doi:10.1016/S0140-6736(15)00473-0

33. Yang P, Chen Y, Jiang S, Shen P, Lu X, Xiao Y. Association between antibiotic consumption and the rate of carbapenem-resistant Gram-negative bacteria from China based on 153 tertiary hospitals data in 2014. *Antimicrob Resist Infect Control*. 2018;7:137. doi:10.1186/s13756-018-0430-1

34. Li Y, Shen H, Zhu C, Yu Y. Carbapenem-resistant klebsiella pneumoniae infections among ICU admission patients in Central China: prevalence and prediction model. *Biomed Res Int*. 2019;2019:9767313.

35. Liu P, Li X, Luo M, et al. Risk factors for carbapenem-resistant klebsiella pneumoniae infection: a meta-analysis. *Microb Drug Resist*. 2018;24(2):190–198. doi:10.1089/mdr.2017.0061

36. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*. 2017;2:CD003543.

37. European Centre for Disease Prevention and Control. Annual Epidemiological Report. Antimicrobial Resistance and Healthcare-associated Infections. Stockholm: ECDC; 2015.