

## Current and Future Landscape of the Antimicrobial Resistance of Nosocomial Infections in China

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### ABSTRACT

The rapid increase in antimicrobial resistance driven by the widespread use, abuse, and misuse of antibiotics constitutes one of China's most challenging healthcare problems. In particular, nosocomial infections caused by multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant Enterobacterales (CRE), which exhibit resistance to most available antibiotics, lead to high mortality and enormous economic and human costs. Here, we summarize the current patterns of the antimicrobial resistance of nosocomial infections in China and address possible interventions to combat antimicrobial resistance.

### ANTIMICROBIAL RESISTANCE PATTERNS AMONG SIGNIFICANT CLINICAL PATHOGENS IN CHINA

China's most common hospital-acquired infections are bloodstream infections (BSIs) and hospital-acquired pneumonia (HAP). The proportion of gram-negative isolates was higher than that of gram-positive isolates for both BSIs and HAP, according to data from the Chinese Antimicrobial Resistance Surveillance of Nosocomial Infections (CARES), a national surveillance program monitoring the antibiotic resistance profiles of pathogens causing hospital-acquired infections in China (1–2). Overall, *Escherichia coli* (29.21%) and *Klebsiella pneumoniae* (12.70%) were the most common BSI-causing pathogens, followed by *Staphylococcus aureus* (9.79%), *Acinetobacter baumannii* (7.03%), and *Pseudomonas aeruginosa* (6.33%) (1). For HAP, the most prevalent pathogens were *A. baumannii* (25.6%), *P. aeruginosa* (20.1%), *K. pneumoniae* (15.4%), *S. aureus* (12.6%), and *E. coli* (7.5%) (2).

Multidrug resistance of gram-negative bacteria, such

as CRAB, carbapenem-resistant *P. aeruginosa* (CRPA), and CRE, presents a particularly critical problem in China. *A. baumannii* has a higher carbapenem resistance rate than *P. aeruginosa* and Enterobacterales, with a proportion of more than 50% among isolates in 2020 (3). Furthermore, the rates of resistance to imipenem and meropenem differed by region, with the highest in Henan Province (78.5%), Liaoning Province (69.1%), and Hubei Province (64.1%) (3). The carbapenem-resistant proportion of *P. aeruginosa* was relatively stable and the resistance rate was 18.3% in 2020 (3).

CRE is an emerging critical public health threat worldwide. Although the overall rates of resistance to carbapenems in Enterobacterales remain at approximately 10%, they continue to rise significantly. Carbapenem resistance rates in *E. coli* and *K. pneumoniae* were 1.6% and 10.9% in 2020, respectively (3). A wide variation in the prevalence of carbapenem-resistant *K. pneumoniae* (CRKP) was reported among different regions, with the highest proportion in Henan Province, Shanghai, and Beijing (more than 25%) (3). Most CRE strains produce carbapenemase, and *Klebsiella pneumoniae* carbapenemase-2 (KPC-2) is the most common carbapenemase, followed by New Delhi metallo- $\beta$ -lactamase (NDM).

In China, methicillin-resistant *Staphylococcus aureus* (MRSA) is the main cause of nosocomial infections that increase hospitalization costs and length of stay. The proportion of MRSA in 2005 was 69%, which represented a very high prevalence. The prevalence, however, had steadily declined each year, reaching 29.4% in 2020 (3). Between 2005 and 2011, *S. aureus* ST239 was the predominant lineage in hospital infections in China, accounting for 50%–80.8% of MRSA isolates, but has subsequently been declining due to the replacement by ST59. ST59 is more virulent and has been increasing in prevalence since 2013 (4). Furthermore, vancomycin-resistant *Enterococcus* (VRE) was observed, with an isolation rate of 1% in 2020 (3).

## EMERGING RESISTANCE TO LAST-RESORT ANTIMICROBIALS IN GRAM-NEGATIVE BACTERIA IN CHINA

Multidrug resistance has recently increased in prevalence, with novel and complex resistance mechanisms emerging. The increased prevalence of CRKP coproducing KPC-2 and NDM-1 is an example (5). Carbapenem-resistant hypervirulent *K. pneumoniae* has been reported worldwide in current statistics. Notably, this novel *K. pneumoniae* clone was more prevalent than previously assumed, especially among KPC-2-producing ST11, exhibiting an isolation rate rising from 2.1% in 2015 to 7.0% in 2017 (6).

Colistin and tigecycline, as well as the latest drugs ceftazidime-avibactam and cefiderocol, are considered the last-line antimicrobials against carbapenem-resistant gram-negative pathogens. The mechanism of colistin resistance mainly involves the modification of lipid A, and most of these modifications are chromosomally mediated by the inactivation of *mgrB*. The plasmid-mediated colistin resistance gene *mcr-1*, which has a prevalence of 10%–20% in animals and 1%–2% in clinical isolates, was discovered for the first time in China (7). Clinical settings have also shown the presence of *mcr* and carbapenemase genes, including *bla*<sub>NDM</sub> and *bla*<sub>KPC</sub>. Furthermore, clinical isolates have been reported to exhibit tigecycline resistance mediated by the *tmexCD1-toprJ1* or *tet(X)* plasmid. More seriously, the “super plasmids” carrying *tmexCD1-toprJ1* and *mcr-8* can cause resistance to both tigecycline and colistin (8). Before ceftazidime-avibactam and cefiderocol were clinically available in China, the resistance had already developed in Enterobacterales. Ceftazidime-avibactam resistance was largely attributed to the production of metallo- $\beta$ -lactamases, the *bla*<sub>KPC-2</sub> mutation, or high expression, whereas carbapenem-resistant *E. coli* exhibits cefiderocol resistance through the *cirA* inactivation combined with PBP3 mutation (9–10).

## INTERVENTIONS AND STRATEGIES TO COMBAT ANTIMICROBIAL RESISTANCE

### Diagnosis and Management of Infections Caused by Multidrug-Resistant Bacteria

The antibiotic resistance crisis is expected to be alleviated with the integration of advanced

multidisciplinary technologies, including genome sequencing and metagenomics, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, spectroscopy, microfluidic technology, biosensing technology, and artificial intelligence. Metagenomic next-generation sequencing (mNGS) is used increasingly frequently in clinical laboratories for culture-independent diagnosis, particularly for identifying uncommon, novel, challenging-to-culture, and coinfecting pathogens. It also has excellent potential for resistance prediction by analyzing antibiotic resistance genes. In addition to mNGS being considered a last resort to address clinical infection issues by some physicians, several obstacles, such as workflow validation, quality control, method standardization, and data interpretation, still need to be overcome (11); otherwise, mNGS results can mislead the diagnosis and management of infections in clinical settings. Utilizing the “Five Rights” — the Right patient, the Right drug, the Right dose, the Right route, and the Right time — is one of the recommendations made to reduce medication errors, harm, antimicrobial resistance, and hospital expenses.

Furthermore, to combat antimicrobial resistance in China, the National Health Commission (NHC), as well as academic committees and associations, have published a series of Regulations, Notices, Standards, Guidelines, and Consensus to strengthen the prevention and control of multidrug-resistant organism (MDRO) infections in hospitals. Namely, handwash protocols, environment management, patient isolation, aseptic techniques, and rational use of antimicrobial agents. Over the past three decades, China has made significant strides in infection control for MDROs with the help of the antimicrobial stewardship program.

### Establishment of the Surveillance System for Antimicrobial Resistance in Hospitals

Several multicenter surveillance systems, mainly based on the susceptibility patterns of clinical bacterial and fungal strains, have been established to monitor the resistance profiles and dynamics of clinical strains, especially MDROs of concern in China. A national surveillance network, the China Antimicrobial Resistance Surveillance System (CARSS), was established by the former Ministry of Health (now known as the National Health Commission, NHC) in 2005 for hospital antimicrobial resistance surveillance, and until recently, over 1,400 centers in 31 provincial-

level administrative divisions (PLADs) throughout China have participated. However, most surveillance systems are strain- and laboratory-based and focus on the microbiological features of MDROs in China, and few have examined the patient-based disease burden in China.

In addition to conventional approaches for resistance phenotype surveillance, novel technologies, such as whole-genome sequencing (WGS) and culture-independent diagnostic tests (CIDTs), are providing new ideas for the surveillance of antimicrobial resistance. WGS can quickly screen for basic information, such as bacterial genus, species, and serotypes, and trace and screen resistance genes. Moreover, WGS can be used to find new drug resistance genes after testing for phenotypic susceptibility of some isolates or even genes conferring resistance to drugs that are not under surveillance.

### **'One Health' Approach to Combating Antimicrobial Resistance in China**

Antibiotic abuse and misuse in humans, animals, and environmental reservoirs are the main triggers of the emergence of antimicrobial resistance. The overuse of antimicrobials in agriculture has made China one of the hotspots of antimicrobial resistance in the world (12). Colistin was one of the first effective antibiotics against gram-negative bacteria, and it was replaced due to its nephrotoxicity and neurotoxicity in the 1970s. However, the quantity of colistin used in agriculture was high in China. To combat the spread of resistance to colistin, particularly plasmid-mediated resistance by *mcr-1*, China banned the use of colistin as an animal feed additive. It has been demonstrated that complete reductions in colistin use significantly reduced the *mcr-1* prevalence, suggesting the effectiveness of colistin stewardship in reducing colistin resistance in both livestock and humans (13).

Furthermore, in recent years, an increasing number of investigators have recognized the mutual transmission of resistant bacteria and resistance genes among humans, animal host populations, and the environment (i.e., soil, water, and air). When anthropogenic factors cause a significant increase in antibiotic content in the environment, a large decrease in the population of susceptible bacteria results, and this unintended artificial selection simultaneously facilitates the survival of bacteria with antibiotic resistance genes and mutations. Considering the tight and interconnected association among human, animal,

and environmental elements, it is essential to take the 'One Health' approach to integrate multisectoral and multidisciplinary efforts to address the serious problem of antimicrobial resistance.

### **Basic Research on Resistance and Transmission Mechanisms**

China is challenged by the rapid dissemination of antimicrobial resistance genes (ARGs) and the remarkable development of multidrug-resistant bacteria. It is crucial to examine the mechanisms of resistance transmission to prevent, control, and eradicate the spread of antimicrobial resistance. Mobile genetic elements (MGEs), which include insertion sequences (IS), transposons (Tn), integrons (In) as well as genetic elements such as plasmids and integrated conjugative elements that can move between bacterial cells, cooperate in causing drug resistance. These components are essential for promoting horizontal genetic exchange, which aids in spreading and acquiring resistance genes in these strains (14). Furthermore, phages can transfer genetic material without the requirement for direct contact with bacteria, facilitating the development of bacterial resistance and the transfer of resistance genes. The prevalence of numerous ARG-carrying phages in the environment has been demonstrated, indicating that phages can act as environmental carriers for the horizontal transfer of ARGs. Gene transfer agents (GTAs) are phage-like particles containing DNA produced by particular bacteria and archaea (15). GTAs are a novel strategy for HGT and seem to be a cross between phage transduction and organic transformation. The distribution of virulence and resistance genes is one way that GTAs may influence bacterial evolution and genome plasticity.

### **New Antibacterial Therapy Strategies**

Peptide treatment, immunotherapy, and phage therapy are emerging therapeutics for antimicrobial resistance. Antimicrobial peptides primarily act to suppress or kill pathogenic microorganisms by processes such as cell wall and membrane destruction, induction of changes in metabolic enzyme activity, and host immunological control (16). The current issue, in which the progress of antibiotic development cannot keep pace with the increase in resistance to new antibiotics, may be resolved by the development of immunotherapy (17). The most commonly explored bacterial vaccines are whole-bacteria-inactivated or

attenuated vaccines, outer membrane vesicles, recombinant DNA, and capsular polysaccharide vaccines. The first recombinant *S. aureus* vaccine has been approved by China's State Food and Drug Administration for phase III clinical research (18). Furthermore, the phage can self-replicate and, when used therapeutically, improve the effectiveness of antibiotics. To increase clinical efficacy, several researchers in China have used phage cocktail therapy, the combination of phage with antibiotics, phage lyase, and antibacterial medications. Additionally, new antibacterial approaches include probiotic therapy, antibacterial nanotechnology, antibacterial photodynamic therapy, and gene editing technologies.

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