ORIGINAL ARTICLE

National epidemiology of carbapenem-resistant and extensively drug-resistant Gram-negative bacteria isolated from blood samples in China in 2013

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Abstract

Although antimicrobial resistance poses a great challenge to clinicians in China, there are limited antimicrobial resistance data on Gram-negative bacteria nationwide. We investigated the phenotypic characteristics of carbapenem-resistant *Escherichia coli* (CREC) and *Klebsiella pneumoniae* (CRKP) as well as extensively drug-resistant strains of *Pseudomonas aeruginosa* (XDRPA) and *Acinetobacter baumannii* (XDRAB) isolated from blood cultures in China. Data were collected on 24 113 isolates from the China surveillance of antimicrobial resistance program in 2013, which comprised 208 hospitals located in all seven administrative regions of China. Minimum inhibitory concentrations (MICs) for common antimicrobials were determined by commercial automated systems available at local hospitals, and associations with geographic and clinical distributions was further studied. The overall prevalence of CREC, CRKP, XDRAB and XDRPA strains was 1.0, 5.5, 13.7 and 4.2%, respectively. Except for CREC, which did not differ greatly by region, the prevalence of the remaining three strains varied significantly across regions. The highest prevalence of CRKP (10.6%) and XDRAB (13.1%) were found in the pediatric group, and higher prevalence of all four target strains was found in the intensive care unit. For imipenem, 55.8% of CREC and 22.9% of CRKP strains had MICs of $\leq$4 μg/mL, while 97.4% XDRAB and 84% XDRPA isolates had MICs of $\geq$16 μg/mL. All CREC, CRKP and 81.2% of XDRAB strains were susceptible to tigecycline, with MIC_{90} values of 0.5, 2 and 4 μg/mL, respectively. In conclusion, a high prevalence of CRKP and XDRAB has emerged in China, especially in children and in the intensive care unit.

Keywords: Carbapenem, China, extensively, Gram-negative bacteria, resistance
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Introduction

Antimicrobial resistance is a major problem in China, with over 50% of Gram-negative bacilli exhibiting resistance to clinically important antimicrobial agents in many tertiary-care hospitals before 2010, including extended-spectrum β-lactamase-producing *Escherichia coli,* quinolone-resistant *E. coli,* and carbapenem-resistant *Acinetobacter baumannii* (CRAB) [1]. Furthermore, China had the world's most rapid average resistance growth rate, 22%, for the ten most commonly isolated bacteria from 1994 to 2000 [2]. The dominant clone of *K. pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* is ST11 and of carbapenem-resistant (CR) *A. baumannii* is CC92 in multiple provinces of China [3,4]. Consequently, in April 2012, China's Health Ministry enacted a policy on the management method for clinical use of antimicrobials to establish a hierarchical management system for clinical use of antibiotics [5]. The benefits of this policy included a significant improvement in the rational use of antibiotics and a subsequent stabilization [6].

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Infections caused by some superbugs such as CR and extensively drug-resistant (XDR) Gram-negative pathogens pose a great challenge to clinicians in regard to the choice of appropriate antimicrobial therapy, especially in resource-constrained settings without access to last-resort antibiotics such as colistin or tigecycline. Combination regimens involving carbapenems or aminoglycosides, the available antibiotics in many regions of China, have been proposed for the treatment of CR *Enterobacteriaceae* (CRE) infections because several CREs had minimum inhibitory concentrations (MICs) for carbapenems within the previously susceptible range of ≤4 mg/L and also are susceptible to aminoglycosides [7,8].

There are still limited national data on the epidemiologic characteristics of CR and XDR Gram-negative bacilli in China, which is essential for monitoring antimicrobial resistance rates as well as formulating relevant policies for control and management of these infections. For this purpose, the phenotypic characteristics of CR *E. coli* (CREC) and *Klebsiella pneumoniae* (CRKP), and XDR strains of *Pseudomonas aeruginosa* (XDRPA) and *A. baumannii* (XDRAB) isolates obtained from blood were studied. Antimicrobial susceptibility and MIC distribution for available drugs were determined and analysed in relation to geographic locale and clinical information.

Materials and Methods

Source of bacterial isolates

This study was based on isolates obtained from the China surveillance antimicrobial resistance program of 2013, which is a national laboratory-based multicenter study on antimicrobial resistance of several bacteria. A total of 208 hospitals were enrolled onto this surveillance study on the basis of the high quality of the laboratory testing and available surveillance information. The 208 hospitals comprised 193 tertiary-care and 15 secondary-care hospitals, which were located in all seven administrative regions of mainland China; these included 11 hospitals in the Northeast, 34 in the North, 48 in the East, 25 in the South, 33 in Central, 15 in the Northwest and 42 in the Southwest region of the country. All the surveillance information was reconfirmed (by checking for completeness, with any suspicious data rechecked and unconfirmed data removed), including MIC detection by microbroth diffusion assay and commercial automated systems, by Peking Union Medical College Hospital, the national quality control center of antimicrobial resistance. All the isolates were subcultured on blood agar and MacConkey agar plates at each laboratory for a purity check and to confirm species identification. The Vitek II GN card was used (bioMérieux, Marcy l'Etoile, France). Basic clinical information of the patients from whom the isolates originated was retrieved retrospectively and included age, gender and clinical ward to which the patient was admitted.

Antimicrobial susceptibility

MICs of different antimicrobial agents were determined by Vitek 2 (bioMérieux, Marcy l'Etoile, France) using software version 5.04 and the AST-GN13, AST-GN09 and AST-GN16 cards, according to the manufacturer's instructions. The Vitek 2 extended-spectrum β-lactamase test is included on the AST-GN13 card for *E. coli, K. pneumoniae* and *Klebsiella oxytoca*. The Advanced Expert System rules were not used for this study. Results were interpreted following the 2013 Clinical and Laboratory Standards Institute criteria [9]. The MIC interpretive breakpoints of tigecycline for *Enterobacteriaceae* as recommended by the US Food and Drug Administration (susceptible, ≤2 μg/mL; intermediate, 4 μg/mL; resistant, ≥8 μg/mL) was applied to *A. baumannii* [10].

CR and XDR Gram-negative definition

CR was defined as strains with ertapenem MICs ≥1 μg/mL, imipenem MICs ≥2 μg/mL and/or meropenem MICs ≥2 μg/mL. XDR was defined as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e. bacterial isolates remain susceptible to only one or two categories) according to European expert consensus [11].

Results

General distribution of isolates

A total of 33 028 isolates of Gram-negative bacteria from blood, 95.4% (23 029/33 028) from hospitalized patients, were studied, including screening for CR and XDR isolates. Overall, *E. coli, K. pneumoniae, Pseudomonas aeruginosa* and *A. baumannii* accounted for 73.1% (24 113/33 028) of the total pathogens isolated from blood (Table 1). Detailed distributions of CREC, CRKP, XDRPA, XDRAB and other strains are listed in Table 1.

TABLE 1. Distribution of Gram-negative bacteria isolated from blood in China in 2013

Organism	Total, *n* (%)	CR, *n* (%)	XDR, *n* (%)
Escherichia coli	14250 (43.1)	138 (1.0)	133 (0.9)
Klebsiella pneumoniae	6061 (18.5)	333 (5.5)	325 (5.4)
Pseudomonas aeruginosa	1940 (5.9)	317 (16.3)	82 (4.2)
Acinetobacter baumannii	1862 (5.6)	1001 (53.5)	256 (13.7)
Enterobacter cloacae	1296 (3.9)	81 (6.3)	70 (5.4)
Serratia marcescens	847 (2.6)	36 (4.3)	35 (4.1)
Stenotrophomonas maltophilia	842 (2.5)	ND	ND
Klebsiella oxytoca	486 (1.5)	41 (8.4)	34 (7)
Burkholderia cepacia	429 (1.3)	ND	ND
Enterobacter aerogenes	331 (1.0)	24 (7.3)	21 (6.3)
Other	4625 (14.0)	ND	ND
Total	33028 (100.0)	ND	ND

CR, carbapenem resistant; ND, no done; XDR, extensively drug resistant.