Original Article

Trends in Drug Resistance of *Acinetobacter baumannii* over a 10-year Period: Nationwide Data from the China Surveillance of Antimicrobial Resistance Program

Lei Gao, Yuan Lyu, Yun Li

Institute of Clinical Pharmacology, Peking University First Hospital, Beijing 100034, China

Abstract

Background: *Acinetobacter baumannii* has emerged as an important pathogen causing a variety of infections. Using data from the China Surveillance of Antimicrobial Resistance Program conducted biennially, we investigated the secular changes in the resistance of 2917 isolates of *A. baumannii* from 2004 to 2014 to differ antimicrobial agents.

Methods: Pathogen samples were collected from 17 to 20 hospitals located in the eastern, central, and western regions of China. Minimum inhibitory concentrations (MICs) were determined by a 2-fold agar dilution method, and antimicrobial susceptibility was established using the 2014 Clinical Laboratory Standards Institute-approved breakpoints. Isolates not susceptible to all the tested aminoglycosides, fluoroquinolones, β-lactams, β-lactam/β-lactam inhibitors and carbapenems were defined as extensively drug resistant.

Results: The rates of nonsusceptibility to common antimicrobial agents remained high (>65%) over the years with some fluctuations to certain agents. The prevalence of imipenem-resistant *A. baumannii* (IRAB) increased from 13.3% in 2004 to 70.5% in 2014 and that of extensively drug-resistant *A. baumannii* (XDRAB) increased from 11.1% in 2004 to 60.4% in 2014. The activity of tigecycline was stable with MIC_{90} ≤4 mg/L against *A. baumannii* from 2009 to 2014. Susceptibility to colistin remained high (97.0%) from 2009 to 2014. The prevalence of XDRAB increased in all the three surveillance regions over the years and was significantly higher in Intensive Care Unit (ICU) wards than non-ICU wards.

Conclusions: This longitudinal multicenter surveillance program revealed the nationwide emergence of *A. baumannii* in China and showed a significant increase in prevalence from 2004 to 2014. High levels of bacterial resistance were detected among samples collected from clinical settings in China, with IRAB and XDRAB being especially prevalent. This study will help to guide empirical therapy and identify at-risk groups requiring more intense interventional infection control measures, while also helping to focus surveillance efforts.

Key words: *Acinetobacter baumannii*; Nonsusceptibility; Extensive Drug Resistance

Introduction

Acinetobacter spp. are glucose-nonfermentative, nonmotile, nonfastidious, catalase-positive, oxidase-negative, aerobic Gram-negative coccobacilli. *Acinetobacter baumannii* has emerged as an important pathogen causing a variety of infections including pneumonia, bloodstream infections, skin and soft tissue infections, and urinary tract infections, resulting in high morbidity and mortality.[1] Among the bacterial species monitored by the China Surveillance Program of Antimicrobial Resistance, *A. baumannii* was the third most common Gram-negative bacteria, just behind *Escherichia coli* and *Klebsiella pneumoniae*.[2] *A. baumannii* was the fifth most common Gram-negative bacteria in the U.S. hospitals between 2006 and 2007.[3] In recent years, due to the widespread use of broad-spectrum antibiotics, the rapid increase of drug resistance of *A. baumannii* has become an urgent issue around the world. In addition to its intrinsic resistance to many commonly used antibiotics,

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Address for correspondence: Prof. Yuan Lyu, Institute of Clinical Pharmacology, Peking University First Hospital, Beijing 100034, China
E-Mail: lvyuan0901@sina.com

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this pathogen can gain additional resistance rapidly in response to new broad-spectrum antibiotics.[3] The emergence of multidrug resistance (MDR), extensive drug resistance (XDR), and even pan-drug resistance (PDR) is common among *A. baumannii* isolates.[4] As a consequence, MDR, XDR, and PDR now present a significant challenge in the management of bacterial infections. For infections caused by drug-resistant strains, efficacious treatment is limited and therefore *A. baumannii* has become an important cause of nosocomial infections over the past 10 years.

Methods

Study period and unit

Between 2004 and 2014, 17–20 tertiary hospitals (17 hospitals in 2004–2005; 20 in 2007–2008; 19 in 2009–2010; 19 in 2011–2012; and 19 in 2013–2014), in economically developed, densely populated major cities in mainland China, participated in the China Surveillance of Antimicrobial Resistance Program. These hospitals are located in three regions of China: 8–11 in the eastern, three in central, and 4–7 in the western regions. Each participating hospital had two to four research unit wards, but only one Intensive Care Unit (ICU) ward for these studies was selected. The selected wards performed annual monitoring of all bacterial infections, as one bacteriological examination per collection year. The study period spanned from 2004 to 2014. Bacterial samples were collected biennially from these tertiary hospitals, for every year except 2006.

Bacterial isolates and information

All samples were collected and identified in each tertiary hospital and forwarded to a central monitoring laboratory (Microbiology Laboratory, the Institute of Clinical Pharmacology, Peking University First Hospital, Beijing, China) for identification and susceptibility testing.

Any body site was considered an acceptable region to sample; however, sterile sites were sampled in preference, if possible (e.g., blood, pleural effusion, and cerebrospinal fluid). Only a single sample was permitted from each patient. Inclusion of any isolate in the study was independent of a patient's medical history, previous antimicrobial use, age, or gender. Ethics Committee approval was not required as the study does not collect patient-identifying information.

Antimicrobial susceptibility testing

Minimum inhibitory concentrations (MICs) for all pathogens were determined using the Clinical Laboratory Standards Institute (CLSI) 2-fold agar dilution method.[5] Piperacillin, piperacillin-tazobactam, ceftazidime, cefoperazone/sulbactam, cefepime, imipenem, amikacin, ciprofloxacin, levofloxacin, minocycline, tigecycline, and colistin were tested on all pathogen samples from each study year. Quality control strains were tested on each day of sample testing and included *E. coli* ATCC 25922 and ATCC 35218 and *Pseudomonas aeruginosa* ATCC 27853. Antimicrobial susceptibility phenotypes were established using CLSI-approved breakpoints. The CLSI 2014 version was used for all samples in this study.[5]

Identification of extensive drug resistance *Acinetobacter baumannii*

Bacterial isolates not susceptible to all the tested aminoglycosides, fluoroquinolones, β-lactams, β-lactam/β-lactam inhibitors, and carbapenems were defined as XDR. This is a modification of the European Centre for Disease Prevention and Control (ECDC) definition of XDR, which specified nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories.[4,6] According to the CLSI 2014 version-approved breakpoints, extensively drug-resistant *A. baumannii* (XDRAB) screened out from all clinical strains were not susceptible to all the above-described antimicrobial agents.[5]

Results

Bacterial isolates

Between 2004 and 2014, a total of 2917 *A. baumannii* samples were collected. Isolates were mostly recovered from respiratory samples (1834 isolates, 62.9%), followed by blood (343, 11.8%), pus/discharge (293, 10.0%), excreta of wounds (229, 7.9%), and urine (118, 4.0%). Of these samples, 1800 (61.7%) were from non-ICU wards and 1117 (38.4%) were from ICU. Samples from the eastern region of China comprised the largest proportion of the total samples collected (1489, 51.0%) [Table 1].

Changes in nonsusceptibility to different antimicrobial agents over the years

The rates of nonsusceptibility to different antimicrobial agents between 2004 and 2014 are shown in Table 2. The trend of nonsusceptibility to piperacillin/tazobactam, ceftazidime, cefepime, imipenem, amikacin, levofloxacin, minocycline, and colistin over the 10-year period is also shown in Figure 1 to highlight the rapid increase in imipenem (carbapenem) nonsusceptibility from 16.4% (MIC_{90} 8 mg/L) in 2004 to 71.4% (MIC_{90} 64 mg/L) in 2014. The rates of nonsusceptibility to other antimicrobial agents remained high (>56.4%) over this time period although slight fluctuations were observed with some agents [Table 2 and Figure 1]; nonsusceptibility to piperacillin/tazobactam, ceftazidime, cefepime, amikacin, and levofloxacin increased nonsignificantly, and then stayed at a plateau [Table 2]. In contrast, the rate of nonsusceptibility to minocycline increased significantly from 13.5% (MIC_{90} 8 mg/L) in 2004 to 64.5% (MIC_{90} 32 mg/L) in 2014. The rate of nonsusceptibility to colistin (not yet listed for sale in mainland China) increased slightly from 0.9% to 3.0% (MIC_{90} 1–2 mg/L) over a 6-year period.

Cefoperazone/sulbactam is one of the most commonly used antimicrobials for the treatment of *Acinetobacter* spp. infections and is routinely used in China. This study also investigated the *in vitro* activity of cefoperazone/sulbactam (2:1) and found it to be superior to that of other third-generation cephalosporins alone against clinical isolates of *A. baumannii* (MIC_{90} 64–128 mg/L),

Table 1: Sources of *Acinetobacter baumannii* isolates included in the China Surveillance Program of Antimicrobial Resistance by year

Strata	2004–2005	2007–2008	2009–2010	2011–2012	2013–2014	2004–2014
Hospital region						
Eastern (8–11)	254 (61.5)	243 (51.4)	459 (58.6)	264 (44.0)	269 (41.6)	1489 (51.0)
Central (3)	82 (19.9)	52 (11.0)	128 (16.3)	90 (15.0)	125 (19.3)	477 (16.4)
Western (4–7)	77 (18.6)	178 (37.6)	197 (25.1)	246 (41.0)	253 (39.1)	951 (32.6)
Patient location						
ICU	128 (31.0)	162 (34.2)	359 (45.8)	214 (35.7)	254 (39.3)	1117 (38.3)
Non-ICU	285 (69.0)	311 (65.8)	425 (54.2)	386 (64.3)	393 (60.7)	1800 (61.7)
Specimen type						
Respiratory	355 (86.0)	388 (82.0)	565 (72.1)	266 (44.3)	260 (40.2)	1834 (62.9)
Discharge	8 (1.9)	32 (6.8)	94 (12.0)	114 (19.0)	104 (16.1)	352 (12.1)
Blood	9 (2.2)	27 (5.7)	99 (12.6)	70 (11.7)	138 (21.3)	343 (11.8)
Excreta of wound	5 (1.2)	15 (3.2)	15 (1.9)	101 (16.8)	93 (14.4)	229 (7.8)
Urine	13 (3.1)	5 (1.0)	8 (1.0)	42 (7.0)	50 (7.7)	118 (4.0)
Others	23 (5.6)	6 (1.3)	3 (0.4)	7 (1.2)	2 (0.3)	41 (1.4)
Total	413 (100)	473 (100)	784 (100)	600 (100)	647 (100)	2917 (100)

All data were expressed as *n* (%). ICU: Intensive Care Unit.

Table 2: Antibacterial susceptibility of *Acinetobacter baumannii* between 2004 and 2014

Antibiotic	Year (isolates)																			
	2004–2005 (*n* = 413)				2007–2008 (*n* = 473)				2009–2010 (*n* = 784)				2011–2012 (*n* = 600)				2013–2014 (*n* = 647)			
	S (%)	I (%)	R (%)	MIC_{90} (mg/L)	S (%)	I (%)	R (%)	MIC_{90} (mg/L)	S (%)	I (%)	R (%)	MIC_{90} (mg/L)	S (%)	I (%)	R (%)	MIC_{90} (mg/L)	S (%)	I (%)	R (%)	MIC_{90} (mg/L)
Piperacillin	12.6	10.4	77.0	512	8.2	23.9	67.9	512	20.3	8.0	71.7	512	17.3	7.0	75.7	512	13.0	10.3	76.7	512
Pip/taz	25.9	30.3	43.8	256	29.6	29.2	41.2	512	27.2	9.8	63.0	512	24.2	4.3	71.5	512	24.3	0.9	74.8	512
Ceftazidime	30.7	1.5	67.8	512	35.9	4.2	59.8	512	28.3	0.6	71.0	512	25.7	0.7	73.7	512	25.5	0.6	73.9	512
Cfp/sub	–	–	–	64	–	–	–	32	–	–	–	64	–	–	–	128	–	–	–	128
Cefepime	30.8	8.5	60.8	512	39.1	14.2	46.7	256	27.9	15.6	56.5	128	26.0	11.7	62.3	256	24.0	3.5	72.5	256
Imipenem	83.5	3.1	13.3	8	63.2	4.2	32.6	64	42.2	2.0	55.7	64	33.2	1.5	65.3	64	28.6	0.9	70.5	64
Amikacin	42.6	1.2	56.2	512	43.6	0.8	55.6	512	31.8	0.9	67.3	512	33.2	0.7	66.2	512	33.7	0.3	66.0	512
Ciprofloxacin	38.5	0.5	61.0	64	33.8	1.7	64.5	64	28.2	0.6	71.2	128	23.8	0.2	76.0	64	24.7	0.0	75.3	128
Levofloxacin	41.4	19.9	38.7	16	39.7	24.3	35.9	16	34.3	25.1	40.6	16	25.8	19.8	54.3	16	25.8	10.7	63.5	16
Minocycline	86.5	8.2	5.3	8	87.5	7.8	4.7	8	73.3	17.5	9.2	8	58.7	18.7	22.7	16	35.5	23.8	40.7	32
Tigecycline	–	–	–	ND	–	–	–	ND	–	–	–	4	71.0	–	–	–	49.8	–	–	4
TMP/SMX	–	–	–	ND	–	–	–	ND	27.8	–	72.2	128	23.7	–	76.3	128	38.9	–	61.1	128
Colistin	–	–	–	ND	–	–	–	ND	99.1	–	0.9	1	96.7	–	3.3	2	97.0	–	3.0	1

MIC: Minimum inhibitory concentrations; Pip/taz: Piperacillin/tazobactam; Cfp/sub: Cefoperazone/sulbactam; TMP/SMX: Trimethoprim/sulfamethoxazole; ND: Not deducted; –: Not available; S: Susceptible; I: Intermediate; R: Resistant.

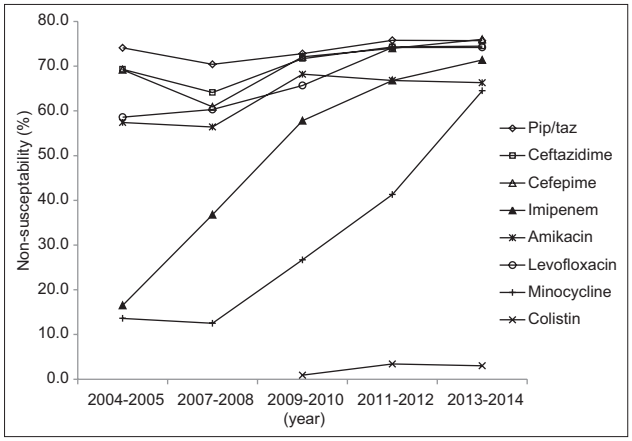

Figure 1: Trends in antimicrobial nonsusceptibility of *Acinetobacter baumannii* from 2004 to 2014.

in which activity is due to sulbactam alone [Table 2]. For the combination of cefoperazone/sulbactam, there are no standards specified by the CLSI or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for the sulbactam concentration to be used in agar dilution or disk diffusion tests, and interpretations usually take into account the MICs of cefoperazone.

There are no CLSI and EUCAST breakpoints available for tigecycline (2011 in listed). However, over the past 6 years, the MIC_{90} of tigecycline was 4 mg/L.

Emergence of drug-resistant *Acinetobacter baumannii*

The prevalence of XDRAB increased significantly from 11.1% in 2004 to 60.4% in 2014, with an overall prevalence rate of 43.7% (1276 samples) over the 10-year study period [Table 3]. The increase in XDRAB also occurred in

samples from different specimen types, in ICU as well as non-ICU patients, and in different geographical regions of China from 2004 to 2014 [Figures 2-4].

Discussion

This nationwide longitudinal study of 2917 *A. baumannii* samples over 10 years revealed the continuous increase of nonsusceptibility to antibiotics and the emergence of XDRAB. For most common antibiotics, the resistance rate of *A. baumannii* is maintained at a high level and increased slightly from 2004 to 2014. Minocycline is a derivative of tetracycline, but due to its toxicity, it is not a common antibiotic in hospitals in mainland China. However, the rate of nonsusceptibility to minocycline rapidly increased from 13.6% (with a resistance rate of 5.3%) to 64.5% (resistance rate of 40.7%) between 2004 and 2014, which was higher than that reported for the monitoring data between 2005 and 2011 (susceptible rate of 72.1%) by Denys *et al*.[7]

Carbapenems are the main antibacterial agents used to treat serious infections, especially MDR infections. The increasing rate of resistance to carbapenems has raised a wide concern. In most cases, samples that are resistant to carbapenems are also resistant to many other types of antibiotics, which cause difficulties in clinical therapy and infection control. The prevalence rates of imipenem-resistant *A. baumannii* (IRAB) were 14.1%, 39.4%, 11.4%, and 30.8% in Europe, Latin America, North America, and the Asia-Pacific region, respectively, according to surveillance data from 2004 to 2006 reported by Reinert *et al*.[8] Study data from Gales *et al*.[9] in 2009 showed that the prevalence of IRAB was 54.9%, 76.3%, 37.5%, and 62.6% in Europe, Latin America, North America, and the Asia-Pacific region, respectively, and up to 59.8% worldwide. A monitoring report by the ECDC in 2013 showed that the prevalence of carbapenem-resistant *A. baumannii* was 3.6%, and the nonsusceptibility rate was 81.2%.[9] Our research revealed

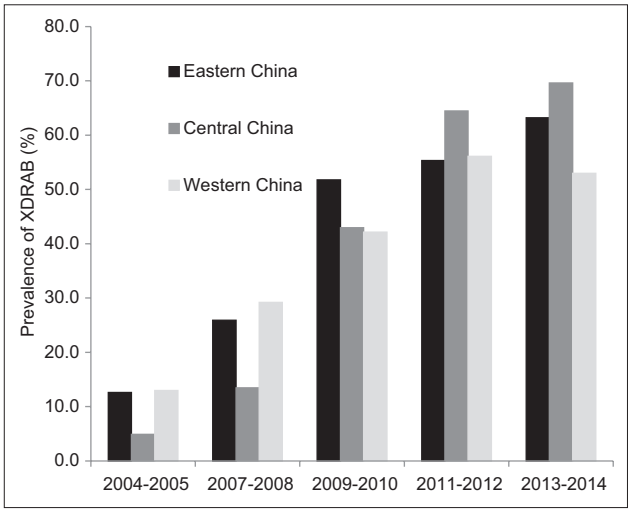

Figure 2: Trends of extensive drug resistance rates in *Acinetobacter baumannii* by geographic region of China from 2004 to 2014.

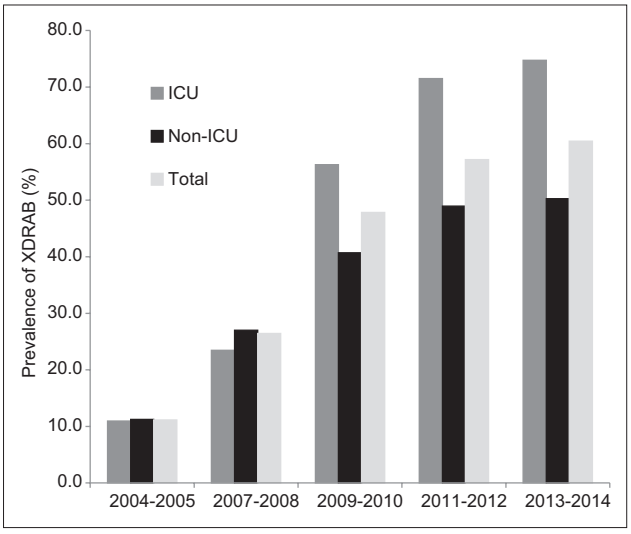

Figure 3: Trends of extensive drug resistance rates in *Acinetobacter baumannii* by health-care setting in China from 2004 to 2014.

Table 3: Relevant factors and prevalence of XDRAB from 2004 to 2014 in China

Strata	2004–2005 (*n* = 413)	2007–2008 (*n* = 473)	2009–2010 (*n* = 784)	2011–2012 (*n* = 600)	2013–2014 (*n* = 647)	2004–2014 (*n* = 2917)
Hospital region						
Eastern	32 (12.6)	63 (25.9)	234 (51.8)	146 (55.3)	170 (63.2)	645 (43.5)
Central	4 (4.9)	7 (13.5)	55 (43.0)	58 (64.4)	87 (69.6)	211 (44.2)
Western	10 (13.0)	52 (29.2)	86 (42.2)	138 (56.1)	134 (53.0)	420 (43.8)
Patient location						
ICU	14 (10.9)	38 (23.5)	202 (56.3)	153 (71.5)	201 (74.7)	608 (53.7)
Non-ICU	32 (11.2)	84 (27.0)	173 (40.7)	189 (49.0)	190 (50.3)	668 (37.4)
Specimens						
Respiratory	36 (10.1)	97 (25.0)	261 (46.2)	150 (56.4)	155 (59.6)	699 (38.1)
Blood	3 (33.3)	8 (29.6)	51 (51.5)	41 (58.6)	88 (63.8)	191 (55.7)
Discharge	2 (25.0)	13 (40.6)	55 (58.5)	79 (69.3)	66 (63.5)	215 (61.1)
Others	5 (12.2)	4 (15.4)	8 (30.8)	72 (48.0)	82 (56.6)	171 (44.1)
Total	46 (11.1)	122 (25.8)	375 (47.8)	342 (57.0)	391 (60.4)	1276 (43.7)

All data were expressed as *n* (%). *n*: Number of cases; XDRAB: Extensively drug-resistant *Acinetobacter baumannii*; ICU: Intensive Care Unit.

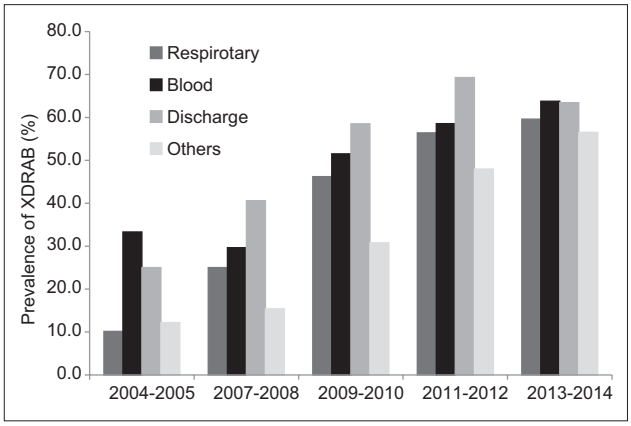

Figure 4: Trends of extensively drug resistance rates in *Acinetobacter baumannii* by sample origin from 2004 to 2014 in China. XDRAB: Extensively drug-resistant *Acinetobacter baumannii*.

that in mainland China, although the imipenem susceptibility rate was higher than that of other types of antibiotics, its nonsusceptibility rate had rapidly increased 4 folds during our 10-year study to an alarming 71.4% (resistance rate 70.5%), which was higher than the nonsusceptibility rate of amikacin (66.3%). Our survey data also revealed that the nonsusceptibility rate of IRAB was higher than that from other countries and similar to the imipenem resistance rates reported in China.[10,11]

In our study, the rate of resistance to colistin in 2009–2010, which has not been sold in mainland China yet, was only 0.9%, which was similar to that reported in samples from the Asia-Western Pacific region between 2006 and 2009.[9] In contrast, one study in Korea reported a resistance rate of 18.1%.[12] The rate of resistance to colistin in 2013–2014 had increased to 3.0% (MIC_{90} = 1 mg/L). Tigecycline has been used in mainland of China since 2011 but has not been included in the list of State Basic Drugs for Medical Insurance; however, clinical application is increasingly wide. Our data showed that the MIC_{90} value of tigecycline was 4 mg/L for *A. baumannii*, which was higher than that reported for the monitoring data in 2005–2011 by Denys *et al*. (MIC_{90} 1–2 mg/L).[7] The breakpoint of tigecycline has not been established.

Prolonged hospitalization, ICU stays, invasive medical procedures, and prior broad-spectrum antibiotic use, especially carbapenems, third-generation cephalosporins, and fluoroquinolones, have been shown to be risk factors for the acquisition of IRAB and MDR infections.[13-18] All these factors, as well as clonal dissemination, likely contributed to the increased prevalence of IRABC and XDRAB.[19-21] In the present study, among the 2917 *A. baumannii* strains isolated, 1276 (43.7%) XDRAB strains were detected. The prevalence of XDRAB significantly increased over our study period, reaching 60.4% by 2014. The prevalence of *A. baumannii* in the eastern region of mainland China was slightly higher than that in the central and western regions. The prevalence of *A. baumannii* among non-ICU patients was higher than that in ICU patients, but the prevalence of XDRAB among ICU patients was significantly higher than that in non-ICU patients, which might be related to the severity of patients' conditions and therefore the use of more broad-spectrum antibiotics, especially carbapenems in ICU patients. The prevalence of XDRAB in respiratory specimens accounts for more than 60% of the total, followed by chest and abdominal drainage fluids, cerebrospinal fluid, and blood specimens. The prevalence of XDRAB among different specimens also showed an increasing trend over the study period. It should be noted, however, that for pneumonia and infections of other nonsterile sites, it is often difficult to distinguish colonization from real *A. baumannii* infections and to determine to which type of pathogen therapy should be directed.[19] Therefore, some of the epidemiological source data may include isolates that were not responsible for the primary infections, but were simply colonizing ill patients, and the estimate of resistance may consequently show some bias.

In this study, samples were only collected from some of the tertiary hospitals in the eastern, central, and western regions of mainland China. Coverage is therefore limited, and our data may not therefore be completely representative of the overall state of bacterial resistance in mainland China. However, the MICs of all clinical isolates were determined in this study which more accurately reflects the sensitivity of bacteria to antimicrobial agents compared with the K-B method sensitivity test.

This longitudinal multicenter surveillance program revealed the significantly increased prevalence and nationwide emergence of IRAB and XDRAB in mainland China, despite the fact that nonsusceptibility to other antibiotics remained stable or declined over the past 10 years. Given the increase in carbapenem resistance over the last decade, this once-reliable drug class now offers only slightly better than 30% coverage of this pathogen. *a priori* prediction of resistance is difficult as *A. baumannii* has multiple related mechanisms of resistance. However, if carbapenem resistance continues to increase in *A. baumannii*, empiric coverage for carbapenem-resistant and XDR strains will likely require colistin-based combination therapy even prior to the determination of antimicrobial susceptibilities in critically ill patients.

In conclusion, we hope that this study provides insight into the situation regarding the antimicrobial resistance of *A. baumannii* as well as the currently available treatment options, thereby leading to new strategies to combat *A. baumannii*.

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Conflicts of interest

There are no conflicts of interest.

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