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ORIGINAL ARTICLE

Resistance traits and molecular characterization of multidrug-resistant *Acinetobacter baumannii* isolates from an intensive care unit of a tertiary hospital in Guangdong, southern China

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Abstract

Purpose This study aims to characterize antimicrobial resistance (AMR) of all the non-duplicated *Acinetobacter baumannii* strains isolated from an intensive care unit in a tertiary hospital during the period of January 1 to December 31, 2015.

Methods *A. baumannii* ($n = 95$ strains) isolated from patients was subjected to antimicrobial susceptibility test (AST) by Vitek 2 Compact system to determine minimum inhibitory concentrations, followed by genotyping by enterobacterial repetitive intergenic consensus-PCR (ERIC-PCR). Resistance genes of interest were PCR amplified and sequenced.

Results All isolates were qualified as MDR, with a resistance rate of > 80% to 8 antimicrobials tested. In terms of beta-lactamase detection, the bla_{OXA23}, $bla_{\text{TEM-1}}$, and *armA* genes were detected frequently at 92.63%, 9 1.58%, and 88.42%, respectively. The metallo-β-lactamase genes bla_{IMP} and bla_{VIM} were undetected. *Aph (3')-I* was detected in 82 isolates (86.32%), making it the most prevalent aminoglycoside-modifying enzyme (AMEs) encoding gene. In addition, *ant (3")-I* was detected at 30.53%, while 26.32% of the strains harbored an *aac (6')-Ib* gene. ERIC-PCR typing suggested moderate genetic diversity among the isolates, which might be organized into 10 distinct clusters, with cluster A ($n = 86$ isolates or 90.53%) being the dominant cluster.

Conclusions All of the *A. baumannii* strains detected in the ICU were MDR clones exhibiting extremely high resistance to carbapenems and aminoglycosides as monitored throughout the study period. They principally belonged to a single cluster of isolates carrying bla_{OXA23} and *armA* co-producing different AMEs genes.

Keywords *Acinetobacter baumannii* · Antimicrobial resistance · Resistance genes · Healthcare-associated infection · Intensive care unit

Introduction

Acinetobacter baumannii (*A. baumannii*) is an opportunistic pathogen adept at colonizing and thriving in the hospital environment. In the recent decade, carbapenemase-producing multidrug-resistant (MDR) *A. baumannii* has emerged as a prominent cause of healthcare-associated infections (HAIs) notably at intensive care units (ICUs), and its incidence seems to be ascending alarmingly in parts of China (He et al. 2011; Li et al. 2018; Bitrian et al. 2012; Behdad et al. 2020). Patients undergoing invasive procedures, immunosuppressive therapy, or treatment with broad-spectrum antibiotics are vulnerable to HAIs caused by *A. baumannii*, particularly in the contexts of ventilator-associated pneumonia, bacteremia, septicemia, urinary tract, and wound

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infections (Bitrian et al. 2012; del Mar et al. 2005; Freire et al. 2016; Gomez-Arrebola et al. 2021).

By virtue of its extraordinary aptitude to survive in the hospital environment and to develop extremely high resistance to an array of common antibiotics including aminoglycoside and carbapenem classes of antibiotics, *A. baumannii* has become a major challenge to medical care at the ICU (Shimose et al. 2016; Molter et al. 2016; Shamsizadeh et al. 2017). One of the most prevalent sequence types (ST) of epidemic clones in China is ST208, which has gained notoriety for causing outbreaks in local ICUs (Bahador et al. 2015). Analysis on genomic relatedness among clinical isolates can help detect an epidemic strain, which can also offer information on infection diagnosis and anti-infection treatment.

Although substantial efforts have been made over the years in monitoring the epidemicity and AMR trends of *A. baumannii* in China, the scope of previous studies tends to be limited to highly populous urban centers in northern and eastern China (Ning et al. 2017; Zhou et al. 2018). In southern China including Guangdong province (population 108.5 million), where the humid subtropical climate indeed favors microbial growth, epidemiological surveys on *A. baumannii* in HAIs were only with moderate frequencies and again covered only very large urban centers such as Guangzhou (population 14.9 million) (Zhou et al. 2015; Li et al. 2013). In contrast, studies on HAIs by *A. baumannii* and underlying mechanisms of AMR are otherwise scant in other Chinese regions overlooked in epidemiological survey. In this regard, we undertook the current study to examine the AMR traits, molecular determinants of AMR, and clonal relationship of *A. baumannii* strains isolated from an ICU of a teaching tertiary hospital in the Chaoshan metropolitan area (13.93 million residents) in Guangdong province, southern China. We found that the isolates ($n = 95$) generally exhibited very high resistance to most of the commonly used clinical antibiotics including aminoglycosides and carbapenems, carried bla_{OXA23}, $bla_{\text{TEM-1}}$, and *aph (3')-I* as the most frequently detected resistance genes, and consisted mostly of strains belonging to a single dominant cluster (cluster A in ERIC-PCR analysis).

Materials and methods

Research settings and bacterial isolates

This study was conducted at the ICU of a tertiary-level teaching hospital affiliated to the Shantou University Medical College (SUMC) in Shantou City in Guangdong, a populous province in southern China. The hospital (1816 inpatient beds) serves the Chaoshan metropolitan area in eastern Guangdong. A total of 95 non-duplicated *A. baumannii* isolates were systematically collected from patients' samples during the period of January 1 to December 31, 2015. This study had been reviewed and approved by the Research Ethics Committee of the First Affiliated Hospital of Shantou University Medical College. The study was given a waiver of informed consent on the ground that it focuses only on characterizing bacterial isolates and involves no patient's information.

Antimicrobial susceptibility

All isolates were first identified by using Vitek 2 Compact system (bioMérieux, France) and their antimicrobial susceptibility profiles obtained by using the Gram negative susceptibility cards (GN16 cards), according to the manufacturer's instructions. Antimicrobial susceptibility test (AST) results for MICs (minimum inhibitory concentrations) were interpreted according to the criteria recommended by the Clinical and Laboratory Standards Institute (CLSI 2015). Confirmed *A. baumannii* isolates were stored at − 80 °C for subsequent experiments.

Detection of antimicrobial resistance genes

Whole genomic DNA was extracted by using TIANamp Bacteria DNA kit (Tiangen Biotech, China), according to the manufacturer's instructions. Detection of antimicrobial resistance (AMR) genes by PCR amplification was carried out with specific primers (Lin et al. 2015; Chen et al. 2010) (see details in Table 1) to screen for the following genes of interest: extended-spectrum β-lactamases (ESBLs) encoding gene ($bla_{\text{TEM-1}}$, bla_{SHV}), metallo-β-lactamases encoding genes (bla_{IMP}, $bla_{\text{VIM-2}}$, $bla_{\text{NDM-1}}$), OXA carbapenemases encoding genes (bla_{OXA23}, bla_{OXA24}, bla_{OXA58}), aminoglycoside-modifying enzyme (AME) encoding genes (*aac(6')-Ib*, *ant(3'')-I*, *aph(3')-I*), and 16 s rRNA methylase encoding gene (*armA*) were detected. For PCR amplification, the following thermal cycling conditions were adopted: initial denaturation at 94 °C for 3 min, followed by 30 cycles (94 °C for 1 min, 58–62 °C for 1 min, and 72 °C for 1 min), and a final extension step of 8 min at 72 °C. PCR products were separated by electrophoresis (at 100 V through a 1% agarose gel in 0.5 × TBE running buffer), stained with ethidium bromide, and observed under ultraviolet light. Identity of all PCR products was confirmed by DNA sequencing (Beijing Genomics Institute, BGI).

Table 1 Primer sequences used in this study for detecting resistance genes

Target gene	Sequence 5′→3′	Annealing temp. (°C)	Amplicon size (bp)
$bla_{\text{TEM-1}}$	ACCCAGAAACGCTGGTGAAA TGACTCCCCGTCGTGTAGAT	57	724
Bla_{SHV}	TTATCTCCCTGTTAGCCACC GATTTGCTGATTTCGCTCGG	55	795
bla_{IMP}	AATTGAGAAGCTTGAAGAAGGCG TTAACAGCCTGCTCCCATGT	56	621
$bla_{\text{VIM-2}}$	AGTCTCCACGCACTTTCAT CACAACCACCATAGAGCACA	57	505
$bla_{\text{NDM-1}}$	GGTTTGGCGATCTGGTTTTC CGGAATGGCTCATCACGATC	55	621
bla_{OXA23}	TTTCTGGTTGTACGGTTCAGCA AACCAGCCCACTTGTGGTTTT	57	646
bla_{OXA24}	GTTTCTCTCAGTGCATGTTCATCT CCCAACCAGTCAACCAACCT	55	664
bla_{OXA58}	CCAATCGGCTTTTTCTTCAGCA TCATCACCAGCTTTCATTTGCAT	56	837
aac(6′)-Ib	TTGCGATGCTCTATGAGTGGCTA CTCGAATGCCTGGCGTGTTT	57	482
ant(3″)-I	GCCATACAGCGATATTGATTTG AAGGCAACGCTATGTTCTCTTG	58	306
aph(3′)-I	CGTTGCCAATGATGTTACAGAT TTACGCTCGTCATCAAAATCAC	58	333
armA	TGAAAAGGTTGTTTCCATTTCTGA TCATTCCCTATAACCTTCGAATCA	57	669

Genotyping of isolates

For determination of genetic relatedness of the isolates, enterobacterial repetitive intergenic consensus-PCR (ERIC-PCR) was performed with primer ERIC2 (5′-AAG TAAGTGACTGGGGTGAGCG-3′) (Bahador et al. 2015) to amplify the conserved sequences of bacterial strains, by using the following thermal cycling conditions: initial denaturation at 94 °C for 5 min, 4 cycles (94 °C for 1 min, 26 °C for 1 min, 72 °C for 1 min), then 40 cycles (94 °C for 30 s, 40 °C for 30 s, and 72 °C for 1 min), and extension at 72 °C for 5 min. To resolve the PCR products, each PCR product was analyzed by electrophoresis in a 1.5% agarose gel stained with ethidium bromide. Results for ERIC-PCR banding patterns were appraised by the software Quantity One (version 4.6.2) and scored as absent (0) or present (1) to construct a dendrogram according to the unweighted pair group (UPGMA) method, using the software NTSYS-pc (version 2.10e). Isolates with more than 90% similarity were considered as belonging to the same cluster.

Statistics analysis

Statistical analysis on antimicrobial susceptibility rates was analyzed by WHONET 5.6 software.

Results

Isolate characteristics and resistance rates

In this study, a total of 95 non-duplicative *A. baumannii* strains were isolated from ICU patients. Strains from male patients evidently outnumbered those from females at a ratio of 65 (68.42%) to 30 (31.58%). Affected patients had a mean age of 61.93 ± 1.87 years (range of 7 to 89 years old). The major isolation sites were sputum ($n = 91$), puncture fluid ($n = 2$), and stool ($n = 2$). As shown in Table 2, AST results suggested that all isolates could be qualified as multidrug-resistant (MDR) *A. baumannii*, which were highly resistant to 8 antibiotics including cefepime (FEP), ceftriaxone (CRO), imipenem (IPM), gentamycin (GEN), tobramycin

Table 2 Antimicrobial susceptibility profiles of *A. baumannii* isolates

Antibiotics	Resistance		Intermediate		Susceptible		MIC range	MIC_{50}	MIC_{90}
	n	Rate (%)	*n*	Rate (%)	*n*	Rate (%)			
FEP	89	93.68	0	0.00	6	6.32	1–64	64	64
CRO	88	92.63	7	7.37	0	0.00	1–64	64	64
IPM	89	93.68	0	0.00	6	6.32	1–16	16	16
GEN	85	89.47	2	2.11	8	8.42	1–16	16	16
TOB	82	86.32	0	0.00	13	13.68	1–16	16	16
LVX	51	53.68	36	37.90	8	8.42	0.25–8	4	8
CIP	90	94.74	0	0.00	5	5.26	0.25–4	4	4
SXT	77	81.05	0	0.00	18	18.95	1–16	16	16
TZP	79	83.16	4	4.21	12	12.63	4–28	128	128

FEP cefepime, *CRO* ceftriaxone, *IPM* imipenem, *GEN* gentamycin, *TOB* tobramycin, *CIP* ciprofloxacin, *SXT* trimethoprim/sulfamethoxazole, *TZP* piperacillin/tazobactam

(TOB), ciprofloxacin (CIP), trimethoprim/sulfamethoxazole (SXT), and piperacillin/tazobactam (TZP) while levofloxacin (LVX) might not be deemed any more efficient than the abovementioned agents against *A. baumannii*, as it had a notable rate of intermediate-level resistance (37.90%) as shown in Fig. 1.

Genotypic patterns in ERIC-PCR analysis

ERIC-PCR was used to compare the genetic relatedness among the *A. baumannii* isolates. All PCR banding patterns ranging from 550 to 2000 bp were analyzed by the NTSYS software to construct a dendrogram, as shown in Fig. 2. In general, 86 (or 90.53%) of the analyzed *A. baumannii* strains belonged to a major cluster A, while the remaining 9 isolates exhibited substantially different banding patterns, additionally designated as isolates B, C, D, E, F, G, H, J, and K. In a longitudinal analysis, strains belonging to cluster A were detectable throughout the study period in 2015, indicating that members of this cluster correspond to the major clone causing the epidemic of MDR *A. baumannii* at our hospital.

Determination of antimicrobial resistance genes

Analysis on AMR genes suggests that the *A. baumannii* isolates included in this study had high carriage rates for some specific AMR genes. Among the 95 strains, 87 (91.58%) were tested positive for the ESBL encoding gene $bla_{\text{TEM-1}}$. In terms of detection of carbapenemase genes, 88 strains (92.63%) were found to harbor the bla_{OXA23} gene. Gene *armA*, a member of 16S rRNA methylases, was detected in 84 isolates (88.42%), while the most prevalent AME encoding gene *aph (3')-I* was found in 82 isolates (86.32%). In comparison, 29 (30.53%) and 25 (26.32%) of the isolates harbored the *ant (3")-I* and *aac (6')-Ib* genes, respectively. In further analysis, the genes bla_{SHV}, bla_{IMP}, $bl_{\text{aVIM-2}}$, $bla_{\text{NDM-1}}$, bla_{OXA24}, and bla_{OXA58} were undetected in any of the *A. baumannii* strains (Table 3).

Through genotyping and detection of resistance genes, we classified the 95 isolates of *A. baumannii* in this study, as shown in Table 3. Cluster A could be categorized into 9 subtypes on the basis of different AMR gene combinations. The most prevalent subtype in cluster A was subtype Ai, comprising 55 (63.95%) isolates expressing the genes bla_{OXA23}, $bla_{\text{TEM-1}}$, *armA*, and *aph (3')-I*. Among subtype Ai isolates, 38 (44.19%) were non-susceptible to all of the antibiotics tested. Twenty-two (25.58%) isolates in group Aii harbored 6 different genes, non-susceptible to cefepime and ceftriaxone. The aminoglycoside resistance genes *aph (3')-I* and *ant (3")-I* were only detected in subtypes Aviii and Aix, but surprisingly they were susceptible to gentamycin and tobramycin. The rest of the isolates showed various combinations of AMR genes, presumably giving rise to different resistance patterns.

Discussion

ERIC-PCR, a genotyping method premised on amplification of conserved regions of genomic DNA, has the advantage of facile instrumentation and reliability comparable to pulsed field gel electrophoresis (PFGE). It has been proven useful for determining genomic relationship across strains with heterogeneous backgrounds (Cartelle Gestal et al. 2016; Ece et al. 2015). In the present study, a dendrogram based on ERIC-PCR results identifies 1 cluster (cluster A) and other 9 distinct isolates, suggesting that a single dominant clone of MDR *A. baumannii* prevailed in the ICU in 2015 (Jan. to Dec.). In terms of resistance phenotype, strains in cluster A were consistently more non-susceptible to all tested antibiotics than other strains. By using ERIC-PCR as a genotyping method, Ning and coworkers reported carbapenem-resistant clones of *A. baumannii* spreading at an ICU in western China (Ning et al. 2017). Chen and coworkers also described

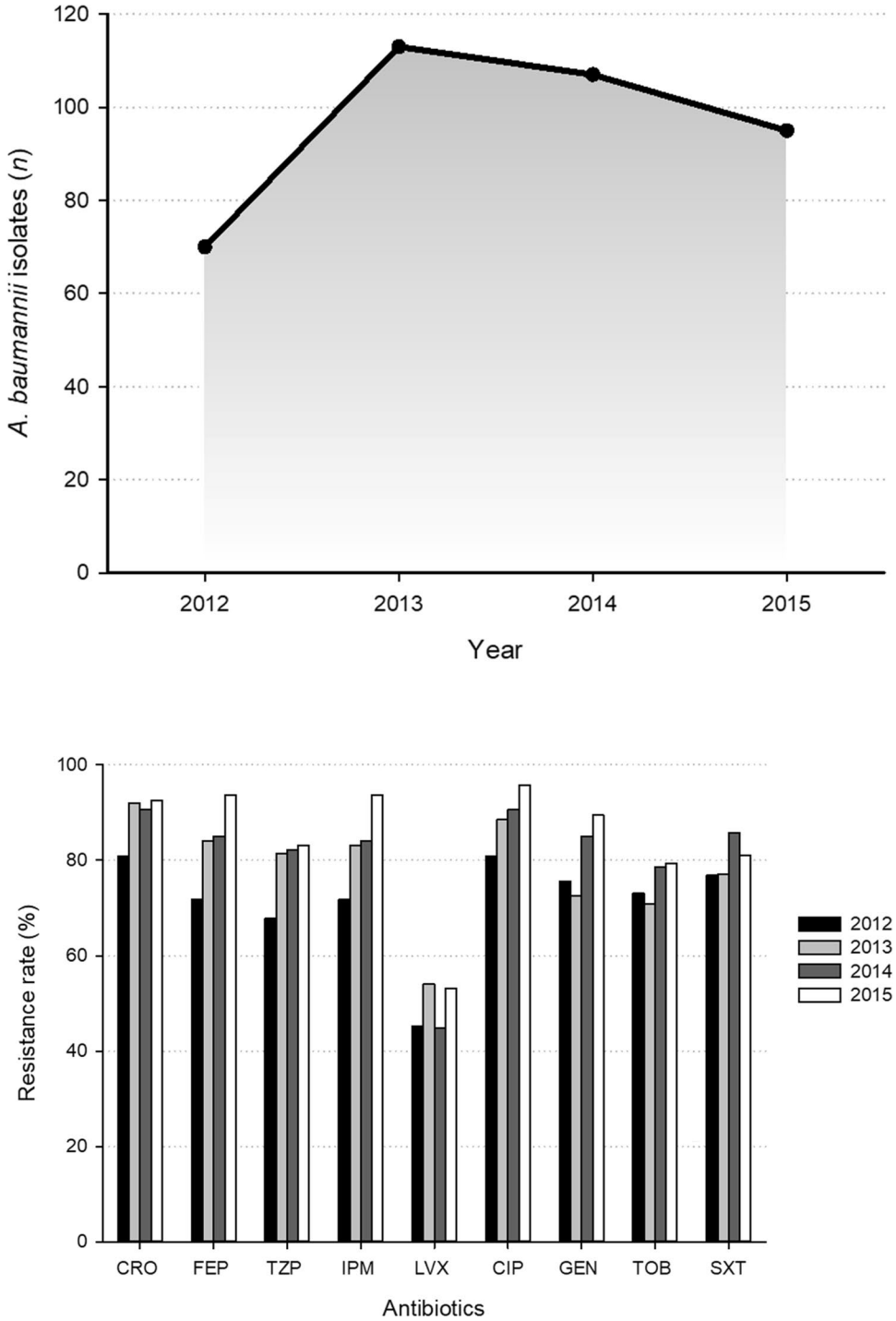

Fig. 1 Distribution of *A. baumannii* isolates recovered at the ICU (*upper panel*) and their resistance rates for individual antibiotics (*lower panel*) over the period of 2012 to 2015

a major epidemic strain spreading at different hospital units in Hunan province of southern China (Chen et al. 2016). In our study, the spread of *A. baumannii* strains in the ICU lasted for a substantial period and their resistance rates to antibiotics were extremely high. We found that among the 9 subtypes of strains within cluster A, the most frequent type of AMR gene combination was bla_{OXA23} -bla_{TEM-1}-*aph (3')-I-armA*. Strains harboring this gene combination could be routinely isolated throughout the study period, suggesting the existence of entrenched extrinsic factors favoring their spread. Cross-transmission and contamination within the ward environment might underpin this process, which calls for greater awareness for monitoring and timely disinfection of the ward environment (Protano et al. 2019).

In our study, we found that multidrug-resistant *Acinetobacter baumannii* (MDRAB) strains simultaneously

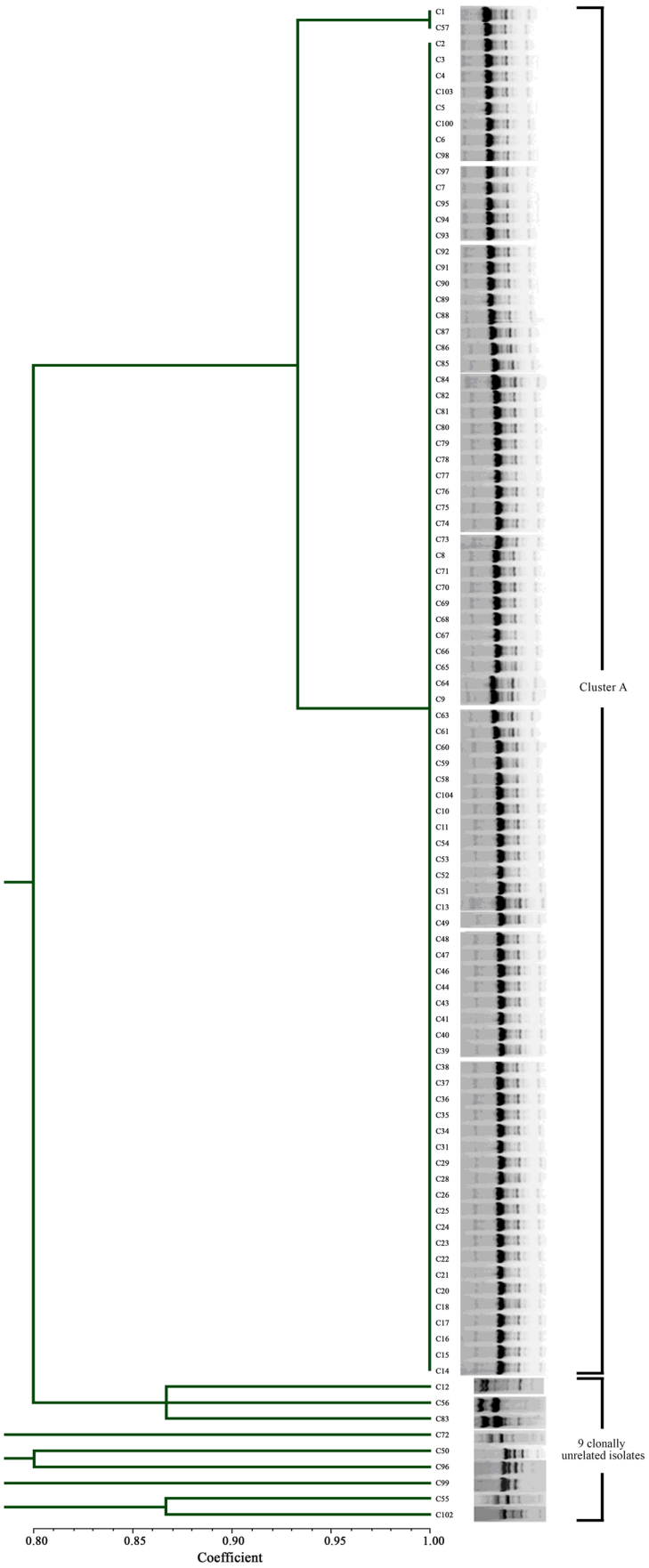

Fig. 2 Dendrogram depicting genetic relationships of *A. baumannii* isolates

Table 3 Classification of MDR *A. baumannii* isolates based upon ERIC-PCR and genotypic profiles

Cluster	*n* (%)	Subtype (*n*)	Resistance genes[a]	Resistance patterns (R + I)[b]
A	86 (90.35)	Ai (55)	bla_{OXA23}, bla_{TEM-1}, *armA*, *aph(3')-I*	FEP, CRO, IPM, GEN, TOB, LVX, CIP, SXT (40)
				FEP, CRO, IPM, GEN, TOB, LVX, CIP, SXT (6)
				FEP, CRO, IPM, GEN, TOB, LVX, CIP (5)
				FEP, CRO, IPM, GEN, TOB, LVX, CIP (4)
				FEP, CRO, IPM, GEN, TOB, CIP (1)
		Aii (22)	bla_{OXA23}, bla_{TEM-1}, *armA*, *aph(3')-I*, *aac(6')-Ib*, *ant(3")-I*	FEP, CRO, IPM, GEN, TOB, LVX, CIP, SXT (20)
				FEP, CRO, IPM, GEN, TOB, LVX, CIP (1)
				FEP, CRO, IPM, GEN, TOB, LVX, CIP (1)
		Aiii (2)	bla_{OXA23}, bla_{TEM-1}, *armA, aac(6')-Ib*, *ant(3")-I*	FEP, CRO, IPM, GEN, TOB, LVX, CIP, SXT
		Aiv (1)	bla_{OXA23}, bla_{TEM-1}, *armA*, *ant(3")-I*	FEP, CRO, IPM, GEN, TOB, LVX, CIP
		Av (1)	bla_{OXA23}, bla_{TEM-1}, *aph(3')-I*, *ant(3")-I*	FEP, CRO, IPM, GEN, LVX, CIP, SXT
		Avi (1)	bla_{OXA23}, bla_{TEM-1}, *armA*, *aac(6')-Ib*, *ant(3")-I*	FEP, CRO, IPM, GEN, TOB, LVX, CIP, SXT
		Avii (2)	bla_{OXA23}, bla_{TEM-1}, *armA*	FEP, CRO, IPM, GEN, TOB, LVX, CIP, SXT
		Aviii (1)	bla_{OXA23}, bla_{TEM-1}, *aph(3')-I*	FEP, CRO, IPM, LVX, CIP, SXT
		Aix (1)	bla_{OXA23}, *ant(3")-I*	FEP, CRO, IPM, LVX, CIP
B	1 (1.05)	–	bla_{OXA23}, *armA*	FEP, CRO, IPM, SXT
C	1 (1.05)	–		CRO
D	1 (1.05)	–	, *aph(3')-I*, *ant(3")-I*	CRO, GEN, LVX, CIP, SXT
E	1 (1.05)	–		CRO, CIP
F	1 (1.05)	–	bla_{TEM-1}	FEP, CRO, IPM, GEN, TOB, LVX, CIP, SXT
G	1 (1.05)	–	bla_{OXA23}, bla_{TEM-1}, *armA*, *aph(3')-I*	FEP, CRO, IPM, GEN, TOB, LVX, CIP
H	1 (1.05)	–	*aph(3')-I*	CRO
I	1 (1.05)	–		CRO
J	1 (1.05)	–		CRO, CIP, SXT

[a] All isolates were tested negative for bla_{SHV}, bla_{VIM-2}, bla_{IMP}, bla_{NDM}, bla_{OXA58}, and bla_{OXA24}

[b] *R* + *I* resistant and intermediate

carrying the bla_{OXA23} gene and multiple aminoglycoside resistance genes are apparently spreading in southern China. The carriage of bla_{OXA23} carbapenemases in *A. baumannii* has been documented worldwide and bla_{OXA23} was one of the most prevalent carbapenemase genes detected in Chinese hospitals (Ruan et al. 2013; Shoja et al. 2017). While the prevalence of *A. baumannii* co-expressing aminoglycoside resistance genes and carbapenemase genes has been reported in eastern China (Wang et al. 2016), to the best of our knowledge, there have been no studies on the epidemicity of *A. baumannii* co-carrying AMR genes against aminoglycosides and carbapenems in southern China. It is noteworthy that the bla_{TEM-1} gene was the most prevalent ESBL gene in the present study, which differs from a previous study, where bla_{CTX-M} was reported to be the predominant ESBL gene (Mahamat et al. 2016).

Aminoglycoside resistance of *A. baumannii* has been reported with increasing frequency in China in recent years (Gao et al. 2017; Jiang et al. 2014; Lin et al. 2015). In a study on *A. baumannii* from Jiangsu province, China, the most prevalent AMEs were identified as *aac(3')-I* and *aac(6')-Ib* (Wen et al. 2014). The resistance rates for GEN and TOB in this study were 89.47% and 86.32%, respectively (Table 2), and the most representative aminoglycoside resistance gene combination in the present study was *armA-aph(3')-I* (58.95%). Interestingly, the isolate exhibited susceptibility to both GEN and TOB with only *armA* gene being detected. The most prevalent of the AMEs was *aph(3')-I* (86.32%), followed by *ant(3")-I* (30.53%), with 84 (88.42%) of the strains carrying *armA*. In addition, high levels of aminoglycoside resistance co-occurring with carbapenem resistance have been reported in epidemic clones of *A. baumannii* from western China (Lin et al. 2015). The imipenem resistance rates of *A. baumannii* were extremely high in China and numerous studies have raised concerns over the emergence and spread of imipenem-resistant *A. baumannii* in hospitals (Neves FC et al. 2016). Resistance rates for imipenem reported in different Chinese ranged from 58 to 100% (Jiang et al. 2016; Zong et al. 2008; Ji et al. 2014; Wu et al. 2015). Our current results suggested that efficacy of carbapenems as treatment for MDR-AB infections seemed to be fast diminishing, especially in ICU contexts. A growing body of literature documents bla_{OXA23} as a predominant carbapenemase genotype among epidemic clones in China (Chen et al. 2017;

Thummeepak et al. 2016) and outbreaks caused by bla_{OXA23} producing *A. baumannii* paralleled those occurring worldwide (Neves et al. 2016; Hammoudi et al. 2015; Novovic et al. 2015; Koh et al. 2007; Martins et al. 2009). In this present study, we found that 88 of the *A. baumannii* strains (92.63%) harbored a bla_{OXA23} gene, suggestive of a level of prevalence seen in other parts of China (Ana Kovacic et al. 2017). Collectively, we proposed that the presence of bla_{OXA23} gene could be a cardinal molecular determinant of carbapenem resistance in our study.

Conclusion

In this study, we described the resistance traits and genetic relatedness of MDR *A. baumannii* strains with high resistance that prevailed at the ICU of a teaching tertiary hospital in the Chaoshan area of Guangdong province, a populous yet epidemiologically overlooked region in southern China. Those strains highly resistant to carbapenem and aminoglycoside including imipenem and gentamycin/tobramycin may be associated with the carriage of bla_{OXA23} and AME genes as determined in PCR assays. A single cluster A of epidemic clones seemed to dominate the spread of MDR *A. baumannii* in the ICU of our hospital. Surveillance work in this study represents a first step towards a better understanding of MDR *A. baumannii* as a causative agent in ICUs, which calls for greater attention to continued monitoring and rational use of antibiotics.

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Author contribution Yuan-Chun Huang designed the experiments, carried out the study, interpreted the data, and reviewed the manuscript. Zhuo-Ran Chen and Hui-Wu Guo designed and performed the experiments and wrote the paper. Jun Liu, Mao-Zhang Fu, Ying-Kun Qiu, and Qing Pan collected and analyzed the data. All the authors read and approved the final manuscript.

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Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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