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Clonal spread of carbapenem-resistant OXA-72-positive *Acinetobacter baumannii* in a Croatian university hospital☆

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SUMMARY

Background: From July to October 2008, 34 *Acinetobacter baumannii* isolates were involved in an outbreak at the Clinical Hospital Center, Zagreb. The aim of this study was to characterize the mechanisms of carbapenem resistance in our *A. baumannii* isolates and determine their epidemiology.
Methods: Antibiotic susceptibilities were determined by broth microdilution. PCR was used to detect the presence of carbapenemases. Genotyping of the isolates was performed by random amplification of polymorphic DNA (RAPD), pulsed-field gel electrophoresis (PFGE), and repetitive sequence-based PCR (rep-PCR).
Results: Thirty-three carbapenem-resistant isolates were positive for the acquired bla_{OXA-72} and one unrelated isolate was positive for bla_{OXA-58}. The bla_{OXA-72}-positive isolates were shown to be clonally related by RAPD, rep-PCR, and PFGE.
Conclusions: On the basis of susceptibility testing, β-lactamase characterization, and genotyping of the isolates we can conclude that clonal spread of endemic isolates was responsible for the high frequency of OXA-72-positive multidrug-resistant *A. baumannii* in this setting. Most of the isolates originated from the intensive care unit indicating local dissemination within the hospital and pointing to the potential source of isolates.

1. Introduction

Carbapenems have a potent activity against Acinetobacter and are often used as a last resort for the treatment of infections due to multi-resistant *Acinetobacter baumannii* isolates.[1] However, *A. baumannii* may develop resistance to carbapenems through various combined mechanisms, including decreased permeability, altered penicillin binding proteins (PBPs) and, rarely, efflux pump overexpression.[2] The most frequent mechanism of resistance is through the production of class D oxacillinases (OXA). The intrinsic $bla_{OXA-51-like}$ and the acquired bla_{OXA} genes (23-like, 40-like, 58-like, and 143) are often associated with insertion elements that are thought to upregulate expression.[3] Less common are class B IMP- and VIM-type metallo-β-lactamases (MBLs).[4] Recently an increase in the prevalence of carbapenem-resistant *A. baumannii* isolates has been observed at the Clinical Hospital Center Zagreb. The aim of this study was to characterize the mechanisms of carbapenem resistance in our *A. baumannii* isolates and their molecular epidemiology.

2. Materials and methods

2.1. Bacterial isolates

Thirty-four non-duplicate *A. baumannii* isolates (one isolate per patient) with reduced susceptibility to imipenem and meropenem by disk diffusion (zone diameter ≤16 mm) were collected between July and October 2008 from various clinical specimens and hospital units (Table 1).

2.2. Susceptibility testing

The antimicrobial susceptibility to a wide range of antibiotics was determined by broth microdilution in accordance with the

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Table 1
Minimum inhibitory concentrations (μg/ml) of various antibiotics and genotyping of oxacillinase-producing *Acinetobacter baumannii* strains

Strain	Specimen	Hospital ward	Date of isolation[a]	OXA-51-like	Acquired oxacillinase	FEP	TZP	SAM	IPM	MEM	GEN	AMK	CIP	COL
1[b]	Gastric fluid	ICU	11/08/08	OXA-68	OXA-58	16	256	64	16	16	32	8	32	2
2	Urine	ICU	10/07/08	OXA-66/76	OXA-72	16	256	64	64	64	32	32	8	2
3	Gastric fluid	ICU	10/07/08	OXA-66/76	OXA-72	16	256	64	64	256	128	8	2	2
4	Urine	Ophthalmology	14/07/08	OXA-66/76	OXA-72	16	>256	128	256	>256	32	8	4	2
5	Tr. aspirate	ICU	16/07/08	OXA-66/76	OXA-72	16	256	16	128	128	64	8	8	2
6	Tr. aspirate	ICU	16/07/08	OXA-66/76	OXA-72	16	>256	>128	256	>256	512	8	8	2
7	CSF	ICU	17/07/08	OXA-66/76	OXA-72	32	>256	128	256	>256	256	8	8	2
8	Tr. aspirate	ICU	21/07/08	OXA-66/76	OXA-72	16	256	128	128	>256	256	8	8	2
9	Tr. aspirate	ICU	21/07/08	OXA-66/76	OXA-72	32	>256	64	256	>256	64	16	8	2
10	Drain	Surgery	27/07/08	OXA-66/76	OXA-72	16	>256	64	128	>256	64	8	8	2
11[b]	Tr. aspirate	ICU	28/07/08	OXA-66/76	OXA-72	16	>256	128	256	>256	32	8	8	2
12	Tr. aspirate	ICU	31/07/08	OXA-66/76	OXA-72	32	>256	>128	256	>256	64	16	8	2
13[b]	Canulla swab	Ped ICU	01/08/08	OXA-66/76	OXA-72	16	>256	>128	128	>256	64	16	8	2
14	Tr. aspirate	Ped ICU	01/08/08	OXA-66/76	OXA-72	16	>256	128	128	>256	64	16	8	2
15	Tr. aspirate	Ped ICU	14/08/08	OXA-66/76	OXA-72	16	>256	128	128	>256	64	32	32	2
16[b]	Tr. aspirate	Ped surgery	14/08/08	OXA-66/76	OXA-72	32	>256	64	128	>256	64	8	64	2
17	Tr. aspirate	ICU	21/08/08	OXA-66/76	OXA-72	16	>256	128	128	>256	64	4	8	2
18	Wound swab	Hematology	21/08/08	OXA-66/76	OXA-72	16	256	128	128	256	64	8	8	2
19	Tr. aspirate	ICU	28/08/08	OXA-66/76	OXA-72	16	>256	>128	128	>256	64	8	8	2
20	Gastric fluid	ICU	22/09/08	OXA-66/76	OXA-72	32	>256	128	128	32	64	32	16	1
21	Drain tip	ICU	23/09/08	OXA-66/76	OXA-72	16	>256	64	128	>128	32	16	4	1
22	Tr. aspirate	ICU	29/09/08	OXA-66/76	OXA-72	32	>256	128	256	>256	128	32	8	2
23	Tr. aspirate	ICU	29/09/08	OXA-66/76	OXA-72	32	>256	128	256	>256	32	16	8	1
24	Tr. aspirate	ICU	02/10/08	OXA-66/76	OXA-72	32	>256	128	>256	>256	32	16	8	1
25[b]	Tr. aspirate	ICU	02/10/08	OXA-66/76	OXA-72	16	>256	64	256	>256	64	8	8	2
26[b]	Blood culture	ICU	03/10/08	OXA-66/76	OXA-72	32	>256	128	256	>256	64	8	8	2
27	Gastric fluid	ICU	06/10/08	OXA-66/76	OXA-72	32	>256	64	128	32	32	64	8	2
28	Tr. aspirate	ICU	06/10/08	OXA-66/76	OXA-72	64	>256	>128	256	>256	64	16	4	1
29	Tr. aspirate	ICU	09/10/08	OXA-66/76	OXA-72	32	>256	128	256	>256	32	16	4	2
30[b]	Gastric fluid	ICU	13/10/08	OXA-66/76	OXA-72	64	>256	128	>256	>256	64	16	8	2
31	Tr. aspirate	ICU	15/10/08	OXA-66/76	OXA-72	64	>256	128	>256	>256	64	16	8	1
32	Abdominal swab	ICU	20/10/08	OXA-66/76	OXA-72	16	256	16	64	256	256	8	8	2
33	Tr. aspirate	ICU	22/09/08	OXA-66/76	OXA-72	64	>256	64	>256	>256	32	8	4	2
34[b]	Tr. aspirate	ICU	27/10/08	OXA-66/76	OXA-72	32	>256		256	>256	32	16	8	1

FEP, cefepime; TZP, piperacillin/tazobactam; SAM, sulbactam/ampicillin; IPM, imipenem; MEM, meropenem; GEN, gentamicin; AMK, amikacin; CIP, ciprofloxacin; COL, colistin; ICU, neurosurgical intensive care unit; Ped ICU, pediatric intensive care unit; Tr. aspirate, tracheal aspirate; CSF, cerebrospinal fluid.
[a] Day/month/year.
[b] Isolates on which rep-PCR was performed.

Clinical and Laboratory Standards Institute (CLSI) guidelines.[5] Minimum inhibitory concentrations (MICs) of imipenem and meropenem were also determined in the presence of sodium chloride (200 mM) to inhibit OXA-58 β-lactamase and cloxacillin (200 mg/l) to inhibit chromosomal AmpC β-lactamase.[6] *Pseudomonas aeruginosa* ATCC 27853 was used as the quality control strain.

2.3. Detection of metallo-β-lactamases

Etest MBL strips were used for the detection of metallo-carbapenemases following the manufacturer's instructions (AB Biodisk, Solna, Sweden). Furthermore, the isolates were tested by synergy test using imipenem and ethylenediaminetetraacetic acid (EDTA)-containing disks to screen for metallo-β-lactamase production.[7]

2.4. Characterization of β-lactamases

PCR was used to detect the presence of the genes encoding metallo-β-lactamases, OXA-encoding genes, and bla_{TEM} genes as previously described.[8–10] The genetic context of $bla_{OXA-40-like}$ and $bla_{OXA-58-like}$ genes was determined by PCR mapping using IS*AbaI* and IS*AbaIII* primers.[11,12] Partial sequences of selected $bla_{OXA-51-like}$, $bla_{OXA-40-like}$, and $bla_{OXA-58-like}$ genes were determined.

To determine if acquired oxacillinase genes were plasmid-encoded, plasmid DNA was extracted using the QIAprep Spin Miniprep Kit (Qiagen, Hilden, Germany) and transferred to *A. baumannii* ATCC 19606 recipient isolate by electroporation. Transformants were selected on 100 μg/ml ticarcillin. In addition, plasmid DNA was used as template for PCR for the detection of bla_{OXA-40} and bla_{OXA-58} genes.

2.5. Genotyping of the isolates

All *A. baumannii* isolates were initially genotyped by random amplification of polymorphic DNA (RAPD) using M13 primer.[13] Sequence groups (1–3) corresponding to EU clones I–III were determined by multiplex PCR as described previously.[14] Representative isolates were further investigated by repetitive sequence-based PCR (rep-PCR) (DiversiLab System; bioMérieux, Nurtingen, Germany) following the manufacturer's instructions. Isolates that clustered above 95% were considered related.[15] Pulsed-field gel electrophoresis (PFGE) genotyping of *Xba*I-digested genomic DNA was performed with a CHEF-DRIII system (Bio-Rad, Zagreb, Croatia),[16] the images were processed using Gel-Compar software, and a dendrogram was computed after band intensity correlation using global alignment with 1.5% optimization and UPGMA (unweighted pair group method with arithmetic mean) clustering.[17,18]

3. Results

3.1. Antimicrobial susceptibility

MIC data are summarized in Table 1. All isolates were uniformly resistant to ceftazidime, cefotaxime, ceftriaxone, piperacillin/

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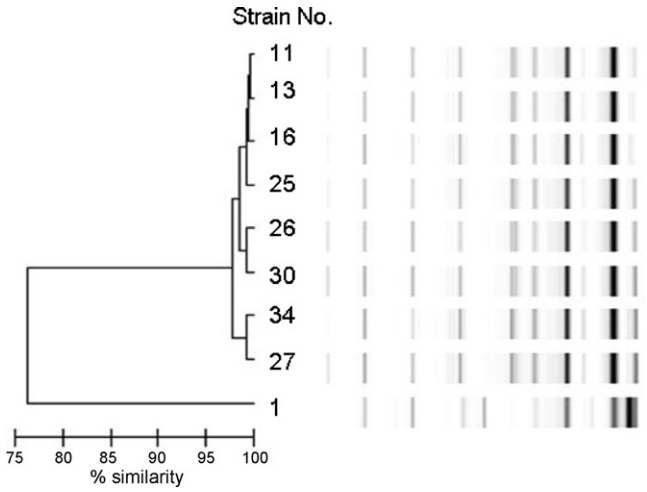

Figure 1. rep-PCR analysis: dendrogram and computer-generated image of rep-PCR banding patterns showing representatives of the OXA-72 isolates and the OXA-58 isolate.

tazobactam, gentamicin, and ciprofloxacin, and to meropenem and imipenem. All isolates remained susceptible to colistin. Addition of sodium chloride lowered the carbapenem MICs of the OXA-58 β-lactamase-producing strain by two dilutions. Addition of cloxacillin did not have any effect on MICs of imipenem or meropenem.

3.2. Characterization of β-lactamases

Thirty-three isolates were positive for the gene encoding OXA-40-like β-lactamase and one OXA-58-like. IS*AbaIII* was found upstream of the $bla_{\text{OXA-58-like}}$ gene and IS*AbaI* was associated with the $bla_{\text{OXA-40-like}}$ genes. IS*AbaI* was not associated with $bla_{\text{OXA-51-like}}$. Only OXA-58-like β-lactamase was inhibited by sodium chloride, lowering the imipenem MIC from 16 mg/l to 4 mg/l. No MBLs were found. All isolates were positive for bla_{TEM}. Sequencing of the acquired OXA genes revealed $bla_{\text{OXA-72}}$ and $bla_{\text{OXA-58}}$ (Table 1). Electroporation experiments using plasmid extracts from $bla_{\text{OXA-72}}$- and $bla_{\text{OXA-58}}$-positive isolates were unsuccessful in transferring carbapenem resistance to electrocompetent *A. baumannii* ATCC 19606. Plasmid bands were not visible after electrophoresis of plasmid DNA and these plasmid preparations were negative for $bla_{\text{OXA-72}}$. Partial sequencing of the $bla_{\text{OXA-51-like}}$ genes revealed that the $bla_{\text{OXA-72}}$ isolates possessed $bla_{\text{OXA-66/76}}$. These genes differ at nucleotide 808, which was not covered by the sequencing reaction. The $bla_{\text{OXA-58}}$ isolate possessed $bla_{\text{OXA-68}}$ (Table 1).

3.3. Genotyping of the isolates

The OXA-72 producers belonged to EU clone 2, which is in agreement with possession of $bla_{\text{OXA-66/76}}$ (sequence group I). The OXA-58 strain did not cluster with any of the European clones. RAPD analysis grouped the OXA-72 isolates together, and these isolates showed identical banding patterns in rep-PCR (Figure 1). The OXA-58 isolate was distinct. PFGE confirmed the clonality of the predominant *A. baumannii* $bla_{\text{OXA-72}}$-positive isolates.

4. Discussion

Previously in Croatia, carbapenem resistance was associated with upregulation of the $bla_{\text{OXA-51}}$ gene by IS*AbaI*.[19] This study found OXA-72, a member of the OXA-40 subclass, to be the most prevalent carbapenem resistance determinant among our *A. baumannii* isolates, and this represents the first report of OXA-72 in Croatia. Outbreaks of OXA-40-like are generally rare except in Spain,[20] as they are the least prevalent of OXAs and when tested have been found more often in EU complex II.[21–23] Our isolates emerged in the summer of 2008. In January 2009, OXA-72-producing *A. baumannii* isolates were reported from University Hospital Split in Croatia. In contrast to our isolates, these isolates were shown to possess integron-associated metallo-β-lactamase in addition to OXA-72.

Clustering of *A. baumannii* isolates suggests either patient-to-patient transmission or a common source of acquisition (e.g., contaminated equipment for mechanical ventilation). The wide dissemination of EU clone II OXA-72 isolates has probably resulted from its selective advantage in the antibiotic-rich hospital environment and could further be facilitated by the lack of effective measures to prevent hospital transmission. Other European studies have already demonstrated the spread of EU clone II isolates and the association of carbapenem resistance with these isolates.[21–23] OXA-72 β-lactamase with similar properties has previously been reported in France,[24] South Korea,[25] Taiwan,[26] China,[27] and Brazil.[28] In contrast to our results, they proved the plasmid location of $bla_{\text{OXA-72}}$ gene.

The isolates displayed high MICs for carbapenems, which could also be attributed to other resistance mechanisms, such as porin loss or upregulated efflux pumps,[2,3] but clarification of these additional resistance mechanisms was beyond the scope of this study. Resistance to ampicillin/sulbactam is worrying and was most likely due to the production of TEM β-lactamases.[22] Colistin became the antibiotic of choice for the treatment of infections caused by our *A. baumannii* isolates, as this was the only antimicrobial to have activity. However, the risk of nephrotoxicity is of clinical concern. Tigecycline has been shown to be effective in vitro and in vivo against multidrug-resistant *A. baumannii*,[29] but is not yet licensed in Croatia. The combination of tigecycline, colistin, and meropenem has been shown to yield a favorable clinical outcome against multi-resistant *A. baumannii*.[30]

In conclusion, this study highlights the propensity of clonal spread of multidrug-resistant *A. baumannii*, in particular carbapenem-resistant isolates. Furthermore, the factors responsible for dissemination of such isolates need to be identified, controlled, and prevented to avoid major outbreaks.

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