Review Article

Genotypic Patterns of Multidrug-Resistant *Acinetobacter baumannii*: A Systematic Review

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Abstract

Acinetobacter baumannii (A. baumannii) is one of the most common bacteria in nosocomial infections. Inappropriate usage of antibiotics has led to expanding emergence resistance to *A. baumannii* as a multidrug-resistant (MDR) strain. Empirical antibiotic therapy is necessary to evaluate the resistant gene pattern of MDR *A. baumannii*. For this purpose, the present study evaluated the resistance genes pattern of MDR *A. baumannii* collected from hospitalized patients using a genotypic diagnostic technique. To find evidence related to the study objectives, databases were searched such as Google Scholar, Web of Science, Science Direct, PubMed, and Scopus from 2000 to 2022, with specified keywords in the title and text of the articles. Articles were included based on inclusion and exclusion criteria. The mentioned database displayed 284 articles. After screening, 65 eligible articles were included. The results showed that various b-lactamases genes, aminoglycoside-modifying enzymes (AMEs) genes, and pump-expressing genes are resistance gene patterns in MDR *A. baumannii* isolates. MDR *A. baumannii* has significantly become resistant to b-lactams, carbapenems, and aminoglycosides.

Keywords: *Acinetobacter baumannii*, molecular diagnostic, multidrug-resistant, systematic review

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Introduction

Acinetobacter baumannii (A. baumannii) is one of the most common bacteria in nosocomial infections, which causes many infections including skin and soft tissues, wound infections, bacteremia, endocarditis, urinary tract infections (UTIs), meningitis, and pneumonia. The mortality rate of ventilator-associated pneumonia (VAP) and infected blood caused by *A. baumannii* are reported from 40% to 70% and 28% to 43%, respectively.[1,2]

Currently, *A. baumannii* has been recognized as a multidrug-resistant (MDR) strain. According to the guidelines, MDR strains are known to be resistant to more than two different antibiotic classes containing carbapenems, aminoglycosides, ampicillin–sulbactam, cephalosporins, and fluoroquinolones. The principal mechanisms of resistance are membrane alterations, overexpression of efflux pumps, over expression of antibiotic-modifying enzymes, and modifications of target sites for antimicrobial agents.[3]

B-lactamases have made *A. baumannii* resistant to b-lactam antibiotics.[3] Carbapenems were recommended as the most effective drug for the treatment of *A. baumannii* infections.[3,4] However, this strain acquired metallo-beta-lactamases (MBLs), and oxacilinases, and has limited the effectiveness of this drug.[5] Furthermore, the emergence of colistin-resistant *A. baumannii* (Col-R-Ab) strain is reported. This resistance occurs due to changes in the structure of the lipopolysaccharide (LPS) and the presence of plasmid-carrying genes (*mcr-1*, *mcr-2*, *mcr-3*, and *mcr-4.3*).[3]

The prevalence of antibiotic resistance and experimental prescription of antibiotics has increased without knowing

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the antibiotic resistance genes pattern in various countries.[6] To detect the antibiotic resistance gene patterns in various countries and choose the correct antibiotics, screening the antibiotic resistance genes pattern of MDR *A. baumannii* over time may provide valuable data.

During the past two decades, molecular approaches have been introduced as a valuable technique to detect antibiotic resistance gene patterns in MDR *A. baumannii* isolates.[7-14] For this purpose, this study is to evaluate the antibiotic resistance gene patterns of MDR *A. baumannii* isolates using a genotypic diagnostic technique.

Materials and Methods

To find evidence related to the study purpose objectives, databases such as Google Scholar, Web of Science, Science Direct, PubMed, and Scopus were searched from 2000 to 2022, with keywords specified in the title and text of the articles. The specified keywords for searching English language databases included "MDR *A. baumannii,*" "PCR," "RT PCR," "multiplex PCR," "b-lactamases," "efflux pumps," and "aminoglycoside-modifying enzymes," which were used by the MeSH strategy.

The inclusion criteria included studies published in English, genotypic diagnostic techniques, and MDR *A. baumannii* isolates. The exclusion criteria included studies published in Persian, articles that were presented at national and international congresses, letters to editors, review articles, and phenotypic diagnostic techniques.

Finally, studies were identified and reviewed after excluding duplicates during primary screening. In the secondary screening, the full text of the articles was evaluated [Figure 1]. Data were extracted and recorded, including first author, duration isolation of MDR *A. baumannii*, country, number of samples, resistant gene patterns, and genotypic diagnostic technique, resistance to antibiotics [Table 1].

Results

The mentioned databases displayed 284 articles. After the exclusion of duplicate articles, 268 articles were reviewed. Finally, 65 articles were selected based on the exclusion and inclusion criteria [Figure 1]. The results showed different classes or subclasses of b-lactamases, AMEs, and efflux pumps genes were isolated from MDR *A. baumannii* isolates from the wound, blood, urine, catheter tips, soft tissue, bronchial aspirates, sputum, vascular catheter, stool, and cerebrospinal fluid (CSF).

Discussion

This study systematically reviewed 65 published English studies in various countries from 2000 to 2022 and evaluated the antibiotic resistance gene pattern of MDR *A. baumannii,* which were isolated from the wound, blood, urine, catheter tips, soft tissue, bronchial aspirates, sputum, vascular catheter, stool, and CSF. Out of 65 studies, 55 studies showed resistance to b-lactams, aminoglycosides, and fluoroquinolones.

Resistance to b-lactams can due to the expression of oxacillinases, MBLs, b-lactamases genes. Higgins *et al*.,[20,21] and other studies detected oxacillinases and MBLs such as *blaOXA-23*, *blaOXA-24*, *blaOXA-51*, *blaOXA-58*, *blaOXA-143*, *bla IMP*, *blaVIM*, *bla GIM*, *bla SMP*, and *bla NDM* in MDR *A. baumannii*.[15-49,51-55,68-77,79]

Oxacillinases significantly hydrolyze some antibiotics belonging to cephalosporins such as methicillin and amoxicillin. They are part of the epidemiological problem of the resistant *A. baumannii* strains. Its expression considerably increases the resistance to carbapenems and cephalosporins.[9,10] *blaOXA-58* confers the antibiotics resistance mechanism to penicillin, imipenem, and oxacillin, whereas it cannot hydrolysis expanded-spectrum cephalosporins[11] *blaOXA-23*-like hydrolyze ticarcillin, meropenem, amoxicillin, and imipenem.[12] In the study by Higgins and other studies, the *blaOXA-23* gene was detected in MDR *A. baumannii*.[20-24,27,34,35,37,38,40,43,45,49,52,54,68,69,73,76,79]

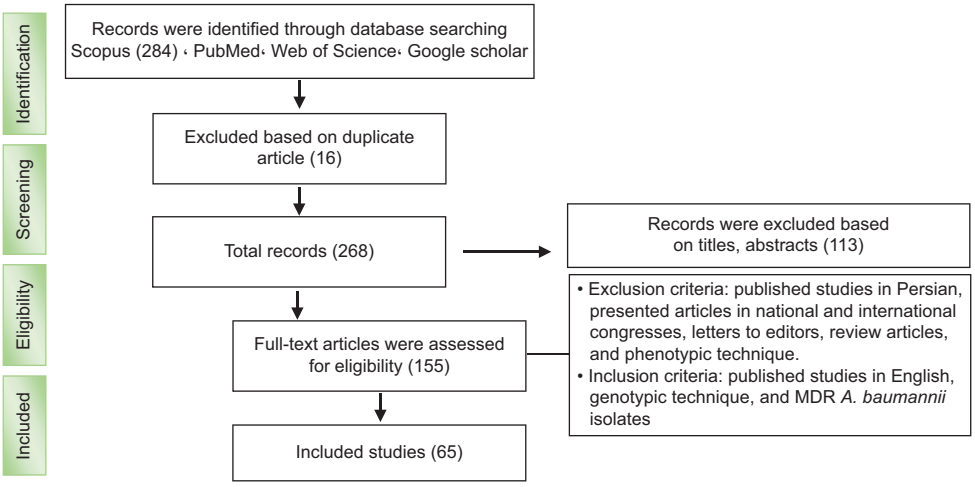

Figure 1: Flowchart of study selection

Table 1: Information of studies selection

References	No	First author	Duration of isolation	Country	No. Sa	Samples	Resistant genes pattern	PCR	Multiplex PCR	RT. PCR	Resistance to antibiotics
[15]	1	Jeong *et al.*	2005	Korea	10	respiratory secretions	PER-1, PER-2	■			carbapenems, b-lactams, aminoglycosides
[16]	2	Lee *et al.*	2003-2004	Korea	1234	sputum, urine	blaIMP-1, blaVIM-2	■			carbapenems, b-lactams, aminoglycosides
[17]	3	Hujer *et al.*	2005	Atlanta	800		AmpC b-lactamases, blaADC-7	■			ampicillin, piperacillin, cephalothin,Ceftazidime, cefepime, cefoxitin, cefotaxime,
[18]	4	Jeon *et al.*	2002-2006	Korea	48	blood	blaADC-68	■			carbapenems, b-lactams, aminoglycosides
[19]	5	Bou *et al.*	2000	Spain	23	bronchial aspirate	bla OXA-24				carbapenems, b-lactams, aminoglycosides
[20]	6	Higgins *et al.*	2004	Brazil	3	blood	blaOXA-23, blaOXA-40, blaOXA58, bla IMP, VPM, GIM, SPM, SIM	■			carbapenems, b-lactams, aminoglycosides
[21]	7	Higgins *et al.*	2013	USA, Mexico	10	wound, blood, sputum, tracheal secretion	blaOXA-23, blaOXA-24, blaOXA-51, blaOXA-58, blaOXA-143, bla IMP, blaVIM, blaGIM, blaSPM, blaSIM, blaNDM, blaOXA235, blaOXA236, blaOXA237	■	■		carbapenems, b-lactams, aminoglycosides
[22]	8	Huang *et al.*	2012	Iraq	57	wound	blaOXA-23, blaOXA-24/40, blaOXA-51, blaOXA-58		■	■	carbapenems, b-lactams, aminoglycosides
[23]	9	Poirel *et al.*	2003	France	13	skin burn infection	blaOXA-58	■			penicillin, Oxacillin, Imipenem, aminoglycosides
[24]	10	Adams *et al.*	2008	New York	6	blood	blaTEM-1, blaVEB-1, AmpC, blaOXA- 69, blaOXA-23, blaOXA-10, blaOXA-51, blaOXA-66, blaOXA-20, blaOXA-75, blaOXA-58, tetA, cat, cmlA; sulI, dhfrX	■			ampicillin, ampicillin-sulbactam, cefazolin, Imipenem, cefepime, meropenem, azteronam, gentamicin, amikacin, tigecyclin, ciprofloxacin, Ttrimethoprim-sulfamethoxazole
[25]	11	Bogaerts *et al.*	2008-2009	Belgium	125	wounds, abscesses, endotracheal aspirates, pleural fluid, blood	GES-11, GES-1, GES-14	■	■		ampicillin, ampicillin-sulbactam, cefazolin, Imipenem, cefepime, meropenem, azteronam, gentamicin, amikacin, tigecyclin, ciprofloxacin, Ttrimethoprim-sulfamethoxazole
[26]	12	Bonnin *et al.*	2010	France	1	bronchial lavage	bla PER-1, bla PER-7, OXA-23, laTEM, blaSHV, blaPER-1, blaVEB-1, blaGES-1, and blaCTX-M, blaampC, blaIMP, blaVIM, blaSIM, blaNDM	■			ampicillin, ampicillin-sulbactam, cefazolin, Imipenem, cefepime, meropenem, azteronam, gentamicin, amikacin, tigecyclin, ciprofloxacin, Ttrimethoprim-sulfamethoxazole
[27]	13	Brown *et al.*	1993-1994	Argentina	6	BAL, bronchial alveolar lavage	blaOXA-51, blaOXA-23, blaOXA-24	■			amoxicillin, co-amoxiclav, cephaloridine, cefotaxim, Imipenem, gentamicin, meropenem, sulbactam

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References	No	First author	Duration of isolation	Country	No. Sa	Samples	Resistant genes pattern	PCR	Multiplex PCR	RT. PCR	Resistance to antibiotics
[28]	14	Chu *et al.*	1994-1998	Hong Kong	97	wound, blood	blaIMP11, blaIMP 12, blaIMP 4	■			aztreonam, piperacillin, piperacillin-tazobactam, cefotaxim, Imipenem, gentamicin, meropenem, sulbactam
[29]	15	Dhabaan *et al.*	2015	Malaysia	1	blood	pilN, pilV, pilT, pilQ, pilM, pilW, pilP, pilJ, pilO, pliL, pilY			■	Carbapenems, aminoglycosides
[30]	16	Endimiani *et al.*	1999-2005	Italy	470	wound, blood, urine, Soft tissue, Vascular catheter, sputum	TEM, SHV, PER, VEB, CTX-M	■			Tobramycin, Ciprofloxacin, piperacillin, Levofloxacin, Cefepime, Ceftriaxone, gentamicin, Ceftazidime, Cefotaxime, Aztreonam
[31]	17	Gales *et al.*	2002	Brazil	1	tracheal secretion	TEM-4, SHV-1, SHV-3, SHV-4, SHV-5	■			Carbapenems, aminoglycosides
[32]	18	Hamidian *et al.*	2015	Sydne	1	wound	blaPER, aadB, aadA13/2, aadA2, strAB, sul1	■			neomycin, nalidixic acid, streptomycin, sulfamethoxazole, spectinomycin, trimethoprim
[33]	19	Sohrabi *et al.*	2008-2009	Iran	100	Sputum, E-tube, wound, urine, blood, catheter, bronchial washing, csf, absecces	blaOXA-51, bla, OXA-23, blaOXA-40, bla OXA-58	■			ampicillin, ampicillin-sulbactam, piperacillin, piperacillin-tazobactam, cepha-lothin, cefoxitin, cefoperazone, Ceftazidime, cefotaxime, cefepime and aztreonam
[34]	20	Koh *et al.*	1996-2001	Singapore	114	various clinical sources	blaIMP-4, blaOXA-23	■			carbapenems, b-lactams, aminoglycosides
[35]	21	Sun *et al.*	2019	China	87	various clinical sources	blaoxa-23, Ade-B, int-1, ISCR-1		■		carbapenems, b-lactams, aminoglycosides
[36]	22	AlAmri *et al.*	2017-2018	Saudi Arabia	103	wound, blood, urine, catheter tips, soft tissue, bronchial aspirates sputum	OXA-51, OXA-23, NDM, VIM, KPC				Ceftazidime, piperacillin/ tazobactam, cefepime, ciprofloxacin. Carbapenem, meropenem, levofloxacin, trimethoprim
[37]	23	Genteluci *et al.*	2010-2011	Brazil	92	urine, blood, catheter, tracheal secretion, wound, broncho alveolar lavage	blaOXA-23, blaOXA-24, blaOXA-51, blaOXA-58, blaOXA-143	■			piperacillin/tazobactam, cefepime, ciprofloxacin, carbapenems, ceftazidime, amikacin ampicillin/ sulbactam, gentamicin
[38]	24	Raro *et al.*	2010	Brazil	858	gloves healthcare workers, hospital rooms, bronchial lavage, skin biopsy, sputum, urine	blaOXA-51, blaOXA-23	■			Ceftazidime, piperacillin/ tazobactam, cefepime, ciprofloxacin. Carbapenem, meropenem, levofloxacin, trimethoprim
[39]	25	Reem *et al.*	2018-2019	Egypt	206	various clinical sources	blaOXA-51-like, OXA-23, blaNDM-1, blaSPM, blaVIM, blaSIM-1, bla KPC		■		Ceftazidime, piperacillin/ tazobactam, cefepime, ciprofloxacin. Carbapenem, meropenem, levofloxacin, trimethoprim

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References	No	First author	Duration of isolation	Country	No. Sa	Samples	Resistant genes pattern	PCR	Multiplex PCR	RT. PCR	Resistance to antibiotics
[40]	26	Qureshi *et al.*	2007-2014	Pennsylvania	38	various clinical sources	blaOXA-51-like, blaOXA-23, blaOXA-40, blaOXA-58	■	■		colistin, piperacillin-tazobactam, gentamicin, Imipenem, meropenem, doripenem, ciprofloxacin, trimethoprim-sulfamethoxazole, tobramycin, amikacin, ampicillin-sulbactam
[41]	27	Goudarzi *et al.*	2018	Iran	128	various clinical sources	blaIMP, blaVIM, blaNDM		■	■	cefixime, piperacillin-tazobactam, gentamicin, Imipenem, doripenem, ertapenem, cefotaxime, ciprofloxacin, trimethoprim-sulfamethoxazole, tobramycin, amikacin, ampicillin-sulbactam, cefteriazon
[42]	28	Yang *et al.*	2010-2014	China	400	stool, Sputum	blaNDM, blaOXA-23-like, blaOXA-40-like, blaOXA-51-like, blaOXA-58-like		■	■	carbapenems, b-lactams, aminoglycosides
[43]	29	Yamamoto *et al.*	2004-2010	Japan	490	blood, urine, wound, sputum, nasal swab, bile juice, drainage tube	blaIMP, blaVIM, blaSIM, blaNDM-1, blaOXA-23-like, blaOXA-24-like, blaOXA-51-like, blaOXA-58-like, aacA4, aacC1, aacC2, aadB, aadA1, aphA1, aphA6	■			colistin, piperacillin-tazobactam, gentamicin, Imipenem, meropenem, gentamicin, doripenem, ciprofloxacin, trimethoprim-sulfamethoxazole, tobramycin, amikacin, ampicillin-sulbactam, tobramycin;
[44]	30	Vala *et al.*	2012	Iran	75	wound samples	IMP, VIM, SPM, GIM, OXA-48, BIC, NDM, DIM, KPC	■			gentamicin, Imipenem, meropenem, gentamicin, ciprofloxacin, amikacin, aztreonam, Cefepime, Ceftazidime, Ceftriaxone
[45]	31	Tsakris *et al.*	2004-2005	Greece	5	blood, urine, CSF, bronchial fluid	blaIMP, blaVIM, blaSPM, blaOXA-23-like, blaOXA-24-like, blaOXA-58-like, blaOXA-51-like	■			cefixime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin
[46]	32	Brown *et al.*	1996-2000	Argentina, South Africa, Hong Kong, Spain, Singapore, Turkey	226	faecal samples	OXA-51	■			Carbapenems, b-lactams, aminoglycosides

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References	No	First author	Duration of isolation	Country	No. Sa	Samples	Resistant genes pattern	PCR	Multiplex PCR	RT. PCR	Resistance to antibiotics
[47]	33	Peymani *et al.*	2008-2009	Iran	100	rachea, urine, sputum, blood, catheter, bronchial washings, wound, ascite fuid, abscess drainage, cerebrospinal fluid	Int1, Int2	■			cefipime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid
[48]	34	Nemec, *et al.*	1991-2001	Belgium, Bulgaria, Denmark, Spain, France, Greece, Italy, Netherlands, Poland, Portugal	106	various clinical sources	aacC1, aphA1, aphA6, aadB, aacA4	■			cefipime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, azteronam
[49]	35	Peymani, *et al.*	2008-2009	Iran	100	Sputum, E-tube, wound, urine, blood, catheter, bronchial washing, csf, absecces	BlaIMP, blaVIM	■			amikacin, gentamicin, tetracycline, tobramycin, ampicillin, piperacillin, piperacillin-tazobactam, cephalothin, cefoxitin, cefoperazone, Ceftazidime, cefotaxime, cefepime, aztreonam, Imipenem
[50]	36	Yoon, *et al.*	2011	France	14	various clinical sources	AdeABC, AdeFGH, AdeIJK	■		■	cefipime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline
[51]	37	Khaledi, *et al.*	2011-2012		100	various clinical sources	abaye1582001, abaye002647, abaye 2281468		■	■	cefipime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline

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References	No	First author	Duration of isolation	Country	No. Sa	Samples	Resistant genes pattern	PCR	Multiplex PCR	RT. PCR	Resistance to antibiotics
[52]	38	Merkier, *et al.*	1982-2005	Buenos Aires	200	various clinical sources	blaOXA-24,25,26,40, blaIMP-1,4,5,6,7,9,10,16,18,21, blaVIM-1,2,3,4,5,11,8, blaOXA-23,27,49, 58	■			Carbapenems, aminoglycosides
[53]	39	Naas, *et al.*	2003	France	290	Blood, catheters, urine, respiratory tract, skin, wounds	blaVEB-1	■			cefipime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline
[54]	40	Shahcheraghi, *et al.*	2009-2010	Iran	2300	blood, wound, urine, sputum, respiratory tract	blaVIM-2, blaSPM-1, blaIMP-2, blaGES-1, blaOXA-51, blaOXA-23	■			cefipime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline
[55]	41	Yum, *et al.*	1998-1999	Korea	28	various clinical sources	blaVIM-2, blaIMP-1	■			carbapenems, b-lactams, aminoglycosides
[56]	42	Beheshti, *et al.*	2010-2011	Iran	98	wound	adeSR, adeB 1	■			aminoglycosides, fluoroquinolones, β-lactams, chloramphenicol, trimethoprim, erythromycin and tetracycline
[57]	43	Ranjbar, *et al.*	2016	Iran	79	ulcer, urine, blood, sputum	adeA, adeB, adeC	■			aminoglycosides, fluoroquinolones, β-lactams, chloramphenicol, trimethoprim, erythromycin and tetracycline
[58]	44	Nogbou, *et al.*	2018-2020	Africa	103	various clinical sources	adeR, adeS, adeB			■	aminoglycosides, fluoroquinolones, β-lactams, chloramphenicol, trimethoprim, erythromycin and tetracycline
[59]	45	Mobasseri, *et al.*	2016-2017	Iran	51	various clinical sources	adeJ, abeM			■	cefipime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline

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References	No	First author	Duration of isolation	Country	No. Sa	Samples	Resistant genes pattern	PCR	Multiplex PCR	RT. PCR	Resistance to antibiotics
[60]	46	Angoti, *et al.*	2013-2014	Iran	26	blood, wound, abscesses, urine, sputum, respiratory tract, fluid bodies	adeA, adeB, adeC, abeM	■		■	cefipime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline
[61]	47	AlQumaizi, *et al.*	2021	India	30	blood, sterile body fluids (BF), cerebrospinal fluids	CarO porin, AdeB, AdeG, AdeJ, AdeY, AbeM, oprD, carO	■		■	Tigecycline, cefipime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline
[62]	48	Rafei, *et al.*	2019	Iran	70	pulmonary secretions	adeB, adeG, adeJ, abeM	■		■	β-lactams, tetracycline, fluoroquinolones, chloramphenicol, trimethoprim, rifampin, fusidic acid, erythromycin, lincosamides, novobiocin, acridine, pyronine, safranin
[63]	49	Rajamohan, *et al.*	2005-2007	USA	86	various clinical sources	adeB, adeJ, qacE				β-lactams, tetracycline, fluoroquinolones, chloramphenicol, trimethoprim, rifampin, fusidic acid, erythromycin, lincosamides, novobiocin, acridine, pyronine, safranine
[64]	50	Tahbaz, *et al.*	2018	Iran	47	burn sample	ACC (6'), aph (3')-Via, aph (3')-IIb, aadA1, aphA1, aph 6			■	cefipime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline, Amikacin, Gentamicin, Tobramycin

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Table 1: Contd...

References	No	First author	Duration of isolation	Country	No. Sa	Samples	Resistant genes pattern	PCR	Multiplex PCR	RT. PCR	Resistance to antibiotics
[65]	51	Asadollahi, *et al.*	2010	Iran	100	various clinical sources	aphA6, aacC1, aacC2, aacA4, aadB, aadA1,	■			amikacin, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline, Amikacin, Gentamicin, Tobramycin
[66]	52	Kishk, *et al.*	2019	Egypt	52	urine, sputum, blood, wound	aphA6, addA1, aacC1, aphA6	■			amikacin, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline, Amikacin, Gentamicin, Tobramycin
[67]	53	Rashvand, *et al.*	2016-2018	Iran	192	sputum, trachea, Broncho alveolar lavage, urine, blood, wounds	aph (30)-VI, aac (60)-Ib, aac (3)-II, aph (30)-Ia, armA	■			cefipime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, gentamicin, tobramycin, Levofloxacin
[68]	54	Hammoudi, *et al.*	2012	Egypt, Turkey, Spain, Italy	*n*	various clinical sources	blaoxa-23, blaoxa-24, blaoxa-40, blaoxa-58, blaKPC, blaGES, blaIMP-1, blaIMP-2, blaNDM, blaVIM	■			β-lactams, tetracycline, fluoroquinolones, chloramphenicol, trimethoprim, rifampin, fusidic acid, erythromycin, lincosamides, novobiocin, acridine, pryonine, tazobactam
[69]	55	Ghaith, *et al.*	2015	Egypt	50	Blood, urine	blaOXA-23-like, blaOXA-24-like, blaOXA-51-like, blaOXA-58-like		■		β-lactams, tetracyclines, cefepime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin

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References	No	First author	Duration of isolation	Country	No. Sa	Samples	Resistant genes pattern	PCR	Multiplex PCR	RT. PCR	Resistance to antibiotics
[70]	56	Khalilzadegan, *et al.*	2013	Iran	588	surface of ICUs	blaCTX, blaTEM		■		Imipenem, meropenem, ceftizoxime, oxacillin, ceftazidime, meropenem, gentamicin, lincomycin, ciprofloxacin, Ceftazidime, cefotaxime, ampicillin, tetracycline, cefixime, colistin
[71]	57	lowe, *et al.*	2017	South Africa	150	various clinical sources	csuA, csuD				Imipenem, meropenem, ceftizoxime, oxacillin, ceftazidime, meropenem, gentamicin, trimethoprim/sulfamethoxazole
[72]	58	Mak, *et al.*	2006-2007	Australia	32	wound, catheter, blood, urine, bed railings, air-conditioning vents	SAbaI, ISAbaI, OXA-23-like, OXA-51-like, OXA-58-like, aacC1, orfX, orfX', aadA1		■		Cefepime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline
[73]	59	Nojookambari, *et al.*	2019-2020	Iran	60	CSF, blood, urine, tracheal tube, central venous line, dialysis fluid, respiratory secretions	blaOXA-51-like, blaOXA-23-like, blaTEM, blaOXA-24-like, blaPER, blaSHV, blaCTX-M, blaOXA-58-like, blaIMP, ISAba1, ISAba1	■			Cefepime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline
[74]	60	Rynga, *et al.*	2014	Delhi	100	Blood, Urine	IM, VIM, SIM, IMP	■			Cefepime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline
[75]	61	Soltani, *et al.*	2015-2016	Iran	92	eye, blood, urine, blood, urine, respiratory, skin, soft tissue	bla, VIM, blaIMP, blaSPM, sul1, sul2	■			polymyxin B, cefipime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline

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Table 1: Contd...

References	No	First author	Duration of isolation	Country	No. Sa	Samples	Resistant genes pattern	PCR	Multiplex PCR	RT. PCR	Resistance to antibiotics
[76]	62	Uddin, *et al.*	2014-2015	Pakistan	7	tracheal aspirates, urine, blood, pus, stool	blaOXA-23, CTX-M, AmpCs	■			Cefepime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline
[77]	63	asaad, *et al.*	2018-2019	Egypt	94	blood, sputum	bap, ompA, blaPER-1	■			Cefepime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam, Levofoxacin, Ticarcillin-clavulanic acid, tetracycline
[78]	64	Behdad, *et al.*	2019	Iran	100	blood, sputum, trachea, wound	AdeIJK, AdeAC, AdeRS, AdeFH, AdeA, AdeC, AdeF, AdeH, AdeS, AdeR, AdeR, AdeI, AdeJ, AdeK			■	Cefepime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam
[79]	65	Ben, *et al.*	2013	Taiwan	213	blood, sputum, urine, pleural fluid, ascitic fluid, wounds	blaOXA-23, blaTEM-1, blaOXA-51,		■		Cefepime, aztreonam, gentamicin, Imipenem, Ceftazidime, meropenem, cefotaxime, ciprofloxacin, piperacillin, ampicillin/sulbactam, piperacillin/ tazobactam, ofloxacin, ciprofloxacin, amikacin, gentamicin, aztreonam

The *blaOXA-40*-like weakly hydrolyzes cephalosporins and carbapenems such as imipenem and ceftazidime. This enzyme is resistant to tazobactam and sulbactam clavulanic acid.[13-14] Qureshi[40]and Hammoudi[68] reported *A. baumannii* isolates were resistant to b-lactams and tazobactam by detection of *blaOXA-40*-like.

In previous reports, the incidence rate of MDR *A. baumannii* was reported to be 74%.[80] The prevalence of MDR *A. baumannii* has increased from 50% in 2001–2007 to 74% in 2010–2015 in Iran. Reasons for such an increase are uncontrolled and overuse of antimicrobial agents, trade among nations, lack of surveillance of MDR strains, lack of use of sensitive techniques for MDR detection in clinical labs, and a rising number of patients with prolonged hospitalization.[81,82]

The antibiotic choice for treating MDR *A. baumannii* infections is restricted, and lipopeptides can be an alternative treatment option. Polymyxin B and colistin can be effective in the treatment of urinary tract infections, infected wounds, and blood infections. However, nephrotoxicity is a detriment to their utilization.[83,84] Previous studies showed a combination of imipenem with aminoglycosides, glycylcyclines, ampicillin, rifampicin, aztreonam, sulbactam, and lipopeptides can produce a synergistic effect against MDR *A. baumannii*.[85] Combination therapies can significantly enhance bactericidal activity from 8.4–26.4 to 60.3–86.7%. A previous meta-analysis reported combinations of colistin–glycopeptide and polymyxin–carbapenem to have synergistic effect for 70% of isolates with relatively low toxicity.[85]

Other mechanisms of enzymatic resistance include AME expression. Mak *et al*.[72] and other studies detected *aacC1*, *orfX*, *orfX'*, and *aadA1* genes in MDR *A. baumannii* isolates.[64-67]

In the present study, 10 studies showed that overexpression of an efflux system can be an efficient mechanism for drug resistance in *A. baumannii* isolates[50,56-63,78] The corresponding structural efflux pump genes are part of plasmids, transposons, or resistance islands,[86] which MDR *A. baumannii* acquires in hospital units such as intensive care units (ICU) and burns units or from the environment. Efflux pumps with other antibiotic resistance mechanisms allow bacteria to reach high-level resistance; moreover, they weakly increase the MICs.[87] Five superfamilies of efflux systems are associated with drug resistance: ATP-binding cassette (ABC) transporters, small multidrug resistance (SMR), and multidrug and toxic compound extrusion (MATE) families, major facilitator superfamily (MFS), and the resistance-nodulation-cell division (RND) family, which are the most clinically relevant.[88]

Efflux pumps confer multidrug resistance to gram-negative bacteria. AdeABC is the first characterized RND system in *A. baumannii*. AdeABC extrudes aminoglycosides, b-lactams, fluoroquinolones, tetracycline, tigecycline, macrolides, chloramphenicol, and trimethoprim. Overexpression of AdeABC significantly causes higher-level carbapenem resistance.[89] Beheshti *et al*., and other studies reported resistance to the mentioned antibiotics and detected *adeA*, *adeB*, *adeC*, *adeJ*, and *abeM* genes.[56-60,62,78] AdeIJK is the second RND efflux system, which contributes to intrinsic resistance to b-lactams.[63]

According to data in Table 1, antibiotic resistance gene pattern in MDR isolates is different in various countries even in different hospitals in the same country. Antibiotic resistance gene pattern, through rapid genotypic diagnostics technique (PCR, RT.PCR), can avoid or reduce the risk of clinical response failure, guide antibiotic prescribing for MDR isolates, and reduce the socioeconomic burden associated with antibiotic-resistant infections in the community. Detection of antibiotic resistance gene patterns in various regions causes the development of a better understanding of the relationship between antibiotic prescribing levels and significant non-development of antibiotic resistance in the community. Although matrix-assisted laser desorption ionization-time of flight (MALDI-TOF), next-generation sequencing (NGS), and whole-genome sequencing (WGS) are rapid and new genotypic diagnostic techniques to detect MDR isolates, in the present study, we did not investigate these methods to detect antibiotic resistance genes pattern in MDR isolates.

Conclusion

MDR *A. baumannii* isolates are about many times more likely to resist than other bacteria related to hospital infections. MDR *A. baumannii* has widely become resistant to b-lactam antibiotics. Significant resistance to oxacillins has become part of the epidemiological problem of MDR *A. baumannii* isolates.

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Conflicts of interest

There are no conflicts of interest.

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