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Prevalence of *Acinetobacter baumannii* in Iran: Systematic Literature Review

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Abstract: Acinetobacter species, especially *Acinetobacter baumannii* (*A. baumannii*) that show resistance to a wide range of antibiotics is thought to be the most important cause of nosocomial infections among patients hospitalized in different wards. In this study, we aimed to systematically review the literatures and study the frequency and resistance of *A. baumannii* in Iran. A systematic literature search was performed in the PubMed, Scopus and Google scholar using the following key terms "*Acinetobacter baumannii*", "frequency" and "Iran" in the title, abstract and keywords of articles to study the dissemination, resistance and susceptibility of *A. baumannii* to some conventional antibiotics in Iran. After collecting the relevant articles, the data of desired were extracted and analyzed based on the purpose of this study. Of total 384 articles found, 364 were excluded in several steps of article selection and only 20 relevant documents with 1911 studied patients were included. The results of this study showed that prevalence of multidrug resistance *A. baumannii* is very high in Iran. Moreover, it was shown that polymyxin B, colistin, tigecylcin and minocycline were most effective antibiotics against *A. baumannii* infections. Respiratory tract and burn samples were the most common place for isolation of bacterial strains. The results of this review showed that *A. baumannii* is widely disseminated in Iran and it shows high resistance to most antibiotics. In addition, *A. baumannii* is responsible for nosocomial infection in patients, especially those who are hospitalized at ICU and burn unit.

INTRODUCTION

Acinetobacter species are of gram-negative bacteria that are found in bacillus or coccobacillus forms. They are important soil bacteria and are opportunistic pathogen of Neisseriaceae family. Acinetobacter is thought to be the main pathogen in traumatic wounds as well as the source of traumatic infections during the wars[1, 2]. Acinetobacter

species are oxidase negative and immovable and do not ferment glucose[3]. These bacteria are resistant to most antibiotics like penicillin but often sensitive to quinolones. Acinetobacter is commonly found in domesticated and non-domesticated animals as well as soil and water samples[4]. Acinetobacter which is an important cause of nosocomial infections is also found in many sources such as milk, frozen foods, hospital environment, angiographic catheters, ventilators, laryngoscope, hospital pillows and soaps. Alcohol consumption, smoking, chronic lung disease and diabetes can be considered as a risk factor for infection with Acinetobacter[5]. Risk factors for nosocomial infection include long hospital stay, surgical wounds, previous infection, treatment with antibiotics, central venous catheters or urinary catheters, admission to the burn unit or Intensive Care Unit (ICU), parenteral nutrition, mechanical ventilation and failure at controlling infection protocols[6, 7].

Acinetobacter species, particularly *Acinetobacter baumannii* (*A. baumannii*) is one of the causal factors responsible for nosocomial infections, particularly in the ICU that show resistance to a wide range of antibiotics[4, 8, 9]. Hospital infections are the most common causes of mortality, morbidity and increased length of hospital stay that impose heavy financial burden on society an health care system[10]. Although, efforts to control hospital infections were successful but frequent medical interventions and extensive drugs use that suppress the immune system as well as extensive use of antibiotics have resulted in the increase of vulnerable people to infections and these factors would lead to the creation of transferable resistance pathogens to antibiotics[11]. These infections are difficult to treat and sometimes are fatal. Also, they are a growing threat risk and almost all patients admitted to hospitals are at risk of developing these infections[12]. Due to the transient colonization of the pharynx in healthy individuals as well as high rates of colonization in people who have a tracheostomy, the respiratory system is the most common place for *A. baumanniii* nfection[13, 14]. The results show that *A. baumannii* can cause bronchiolitis and tracheal bronchiolitis in healthy children as well as in adults[15].

In some countries, the rate of nosocomial infections due to lack of management, lack of infection prevention, improper use of antibiotics and overcrowding of hospitals is very high[16]. *A. baumannii* is distributed all over the world. Several studies have reported the frequency and resistance pattern of *A. baumannii* in Iran. In this survey, we aim to systematically review the literatures in which the distribution, resistance pattern and susceptibility of *A. baumannii* to antibiotics had been investigated in Iran.

MATERIALS AND METHODS

Search methods: A systematic literature search was conducted in the PubMed, Scopus and Google scholar using the following key terms "*Acinetobacter baumannii*"", "frequency" and "Iran" in the title, abstract and keywords of documents to study the frequency, resistance and susceptibility of *A. baumannii* to some conventional antibiotics in Iran. For this purpose, following search strategy (*Acinetobacter baumannii* OR *A. baumannii*) AND (prevalence OR distribution OR frequency OR incidence) AND (resistance OR resistance rate OR resistance pattern OR susceptibility OR vulnerability OR sensitivity) AND Iran was used to find relevant literatures in PubMed with customized search wherein the results were limited to articles that were published with English language. Google scholar was also searched using following search method (*Acinetobacter baumannii*) AND (frequency) AND Iran. As well, to find relevant documents in the Scopus, a similar search method was used where customized search of (TITLE-ABS-KEY (*Acinetobacter baumannii*) AND (Iran) AND (LIMIT-TO (AFFILCOUNTRY, "Iran") AND (LIMIT-TO (DOCTYPE, "ar") AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (SRCTYPE, "j") was performed. For this purpose, "*Acinetobacter baumannii*" was searched in Scopus and subsequently "Iran" was searched within the results. Afterwards, the records were limited to articles published in English language. Finally, the records were further limited in Country/Territory to Iran. In addition, to include other potentially eligible articles as well as to minimize the possibility of data loss, a manual search of the reference lists was conducted.

Study selection and inclusion/exclusion criteria: No time limitation was defined during literature search for the collection of relevant articles. Therefore, all documents relevant to the purpose of this review in which the distribution of *A. baumannii* had been studied in Iran were selected and used for additional data analysis. In order to collect all available data on the desired issue, almost all articles with various types of study design including clinical trial, observational, comparative, prospective, multicenter, cross-sectionals and evaluation studies were included in this study. However, conference abstracts and presentations, book chapters, editorials, letters, review articles and meta-analysis were excluded from further evaluation. As well, to avoid any false impression during data analysis, the records were limited to those articles only published in English language. We excluded articles with subject and language irrelevancy in the first step of article selection. Similarly, duplicated documents or articles reporting the same study populations as well as articles with full text unavailability were excluded from

further evaluation. But in necessary cases, inaccessible articles were obtained by contacting to the corresponding authors. Hence, inclusion criteria in this literature review included all documents in which the distribution of *A. baumannii* as a main cause of nosocomial infection had been studied in Iran.

Data extraction: All necessary information including author's name, publication date, territory of study and total studied samples in each study were extracted. Based on the main purpose of this literature review, other necessary information including target population, age and sex ratio of studied population (if available), methods of assessment, type of study design and the place or wards wherein the samples had been collected as well as the key findings of each study were extracted and used for additional data processing. According to the defined inclusion/exclusion criteria, qualified publications among the collected articles were identified and data were extracted by two independent reviewers. To avoid any probable errors or miscalculation dealing with data processing, any potential disagreements between the reviewers were resolved in each step of article selection and data processing prior to additional data analysis. All procedures including literature search strategy and selection of eligible articles as well as data processing were performed according to the protocol recommended in PRISMA checklist 2009[17].

Measured variables: Various methods including standard microbiological tests, biochemical reactions, Polymerase Chain Reaction (PCR), Metallo-beta-lactamase production, antimicrobial susceptibility tests, colonial morphology and colony culture in various media such as blood agar plates, chocolate agar and nutrient agar had been used for identification and clinical evaluation of bacterial colonies in the selected literatures. The variables of interest that were extracted and used for analysis included location of sampling and underlying conditions or diseased that had led to the infection with *A. baumannii*. Other variables that were extracted and evaluated were bacterial susceptibility and colony resistance to some conventional antibiotics.

RESULTS AND DISCUSSION

Literature search results: Almost 369 articles were collected through search in the PubMed, Scopus and Google scholar. Of these documents, 56 potentially relevant articles were in PubMed, 285 were in Scopus and 33 other were in Google scholar. Ten other potentially eligible articles were also found through manual reference list screening of collected documents at final assessment of included literatures. Of all collected literatures, 198 articles were excluded in the first step after reviewing the title and abstract due to subject irrelevancy. By limiting the records to studies conducted in specific territory (Iran), 25 additional documents were also omitted from collected document pool. In addition, 39 articles were disqualified due to language irrelevancy. Likewise, 65 documents including 12 review articles and 53 articles with inadequate data were excluded from additional assessment. Finally, full text of 57 articles were collected and used for additional data analysis. After reviewing the full text of eligible documents, only 20 relevant articles that fully met the inclusion/exclusion criteria and contained all necessary information wherein the prevalence, resistance pattern and susceptibility of *A. baumannii* to antibiotics had been investigated in Iran, were included and used for data processing. The step by step process of literature search and selection is illustrated in Fig. 1.

General characteristics of the included articles: The total number of patients studied for the frequency of *A. baumannii* in Iran was 1911. The number of studied population for *A. baumannii* species varied from 10 in a study with unknown study design to 200 in a retrospective study among the included literatures. Almost all patients had various kinds of underlying disease such as burning, diabetes mellitus or underlying causes such as surgical procedures and previous took of antibiotic. The studied populations included both male and female and of these patients, 691 were male and 401 were female. But, the sex

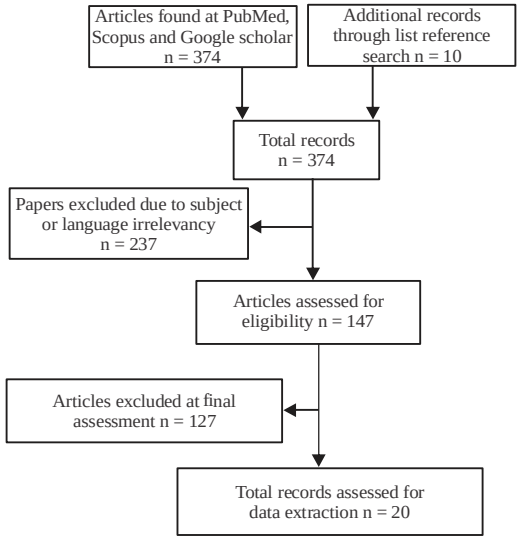

Fig. 1: Flowchart of the literature search and strategy for the selection of relevant document

Table 1: General information of the included literatures

First author	Years	Province	Study design®	Mean age*	Sex (M/F)	Patients number
Gholami M	2015	Tehran	RS	7-65 years	45/15	60
Azimi L	2015	Tehran	CSS	9 months to 72 years	50/15	65
Kooti S	2015	Shiraz	RS	-	109/91	200
Salimizand H	2015	Mashhad	CSS	1-83 years	-	30
Yadegarynia D	2015	Tehran	CrSS	1-87 years	-	100
Farshadzadeh Z	2015	Tehran	-	-	-	92
Shaykh Baygloo N	2015	Isfahan	-	2-47 years	8/2	10
Fazeli H	2014	Isfahan	-	-	68/53	121
Vakili B	2014	Isfahan	CSS	43.1	34/26	60
Peerayeh SN	2014	Tehran, Bandar-Abbas	RS	-	-	157
Yadegarynia D	2014	Tehran	DS	32.4	31/24	55
Bahador A	2014	Tehran	-	-	-	100
Farahani R	2013	Kashan	DS	39.3	35/25	60
Bahador A	2013	Shiraz, Gonbad, Tehran	RS	-	-	91
Mohajeri P	2013	Kermanshah	RS	-	-	104
Yadegarynia D	2013	Tehran	RS	43.87	63/32	95
Vahdani P	2011	Tehran	RS	42	80/34	114
Azimi L	2011	Tehran	DS	33.73	111/53	164
Rahbar M	2010	Tehran	RS	60	57/31	88
Soroush S	2010	Tehran	PS	-	-	145

® RS = Retrospective study; PS = Prospective study; DS = Descriptive study; CSS = Cross-Sectional Study; CrSS = Cross Series Survey; *Age rage is mentioned for studies wherein the mean age is not reported

of 819 patients had not been reported in some articles. The age of participated patients also varied from 9 months to 88 years among the included literatures. The most old and recent publication that were included and used for data extraction had been published in 2010 and 2015, respectively. Included literatures that were used for data extraction and further assessment included 1 prospective, 8 retrospective, 3 cross-sectional, 3 descriptive study, 1 cross series survey and 4 studies with unknown study design. The general information of articles included in this review is demonstrated in Table 1 in chronological order of their publication date.

Study findings: In this literature review, *A. baumannii* had been identified from different geographical locations of the country, indicating that this opportunistic pathogen is widely distributed in Iran. The results also showed that patients hospitalized at ICU and burn units are at higher risk of developing nosocomial infections with *A. baumannii*. Moreover, it was demonstrated that respiratory tract and wound samples are the most common place for isolation of *A. baumannii*. In almost all studies included in this survey, it was reported that *A. baumannii* is completely or relatively resistant to the most conventional antibiotics including cotrimoxazole, chloramphenicole, ciprofloxacin, imipenem, meropenem, ceftazidime, cefotaxime, tigecycline, aztreonam, piperacillin/tazobactam and ampicillin/sulbactam. However, the results of included articles indicated that Polymyxin B and colistin are the most effective antibiotics against *A. baumannii*. The methods of assessment, location and sources of sampling as well as main findings of literatures included in this survey are demonstrated in Table 2.

Due to the antibiotic resistance, microorganisms causing nosocomial infections can result in great difficulties for patients and health system. Acinetobacter species, especially *A. baumannii* are opportunistic pathogens and are considered as important cause of nosocomial infections. Due to high rate of resistance to most of the antimicrobial agents, *A. baumannii* is thought to be responsible for outbreaks of infection as well as the incidence of health care-associated infections such as urinary tract infection, meningitis, pneumonia and wound infection[18, 19]. Isolation of *A. baumannii* from different parts of the hospital particular ICUs represents that patients in almost all wards of the hospital are at risk of secondary infection with this opportunistic pathogen. Reports show that *A. baumannii* has developed as a challenging infectious pathogen that can cause several secondary infections such as meningitis, especially in neurosurgical patients. Also, it was shown that *A. baumannii* can change to a completely resistant strain during therapy. Findings strongly suggest that genetic modifications are responsible for resistance against metallo-beta-lactams[20]. Hence, diagnosis and treatment of *A. baumannii* induced infections seems very essential[21].

Increasing the prevalence of multidrug-resistant bacteria, particularly *A. baumannii* is a global challenge of the recent years[4, 22, 23]. Studies show that the prevalence of drug resistance among Acinetobacter species, particularly *A. baumannii* against most of the conventional antibiotics is increased in recent years[24]. In consistent with the previously described study, findings of the present review showed that most isolates of *A. baumannii* are resistant to the most of widely used antibiotics including chloramphenicole, ciprofloxacin,

Table 2: Methods of assessment, sources of sampling and main findings of included literatures

First author	Methods*	Source of sampling ¥	Sampling ward ®	Effective antibiotics	Main findings
Gholami M	PCR, AST	WS	BU	Colistin	The ability of *A. baumannii* to acquire drug resistance is mainly through the efflux pump mechanism
Azimi L	PCR, Multiplex PCR, AST	WS	BU	Colistin and tetracycline	Klebsiella Pneumoniae Carbapenemase (KPC) can be developed in burned patients as a result of nosocomial infections caused by *A. baumannii*
Kooti S	Multiplex PCR, AST	Urine, WS, blood, sputum, ETT, body fluid, nose, throat, eye	ICU, SW, Neu, PW, IU, OTW	Colistin, polymyxin B	*A. baumannii* is an important cause of infection in hospitalized patients in ICU. *A. baumannii* is an important cause of infection in hospitalized patients in ICU
Salimizand H	REP-PCR, AST	WS, body fluids ETT	BU	Colistin	Carbapenem resistant *A. baumannii* (CRAB) is widely distributed in Burn wards
Yadegarynia D	PCR, AST	RTS, WS, urine, CSF	ICU, SW, Neu, PW, IU, BU	Colistin	Multidrug-resistant Acinetobacter is an important problem in the world
Farshadzadeh Z	MLVA, MLST, multiplex PCR, AST	Burn wounds	BU	Colistin, tigecycline	There is rapid increase in the carbapenem resistance rate of *A. baumannii* in burned patients
Shaykh Baygloo N	PCR, AST	Burn wounds	ICU	Amikacin and piperacillin	*A. baumannii* species were identified among almost all the isolates obtained from patients with infected burns
Fazeli H	PCR, AST	RTS, urine, blood, wound, CSF	ICU, PW, SW	Ampicillin-sulbactam	Resistant strains of *A. baumannii* increasingly cause public health problems
Vakili B	AST	RTS, urine, blood, ETT, CSF	ICU	Colistin	The use of colistin is recommended for treatment of MDR *A. baumannii* strains
Peerayeh SN	PCR, AST	Sputum, pus, urine, CSF, ascites, ears, catheters, burn wounds, pleural effusion	ICU, IU, SW, Neu, PW, EU, CCU, ENT	Colistin, Polymyxin-B	Tigecycline is effective against *A. baumannii* isolates
Yadegarynia D	AST	CSF	ICU, EU, Neu	Colistin	The rate of postneurosurgical meningitis due to carbapenem-resistant *A. baumannii* has been increased
Bahador A	PCR, AST	Wound, RTS, urine, blood and CSF	ICU	Colistin, tigecycline	The *A. baumannii* strains are rapidly changing toward growing resistance to various antimicrobials including colistin and tigecycline
Farahani R	PCR, AST	Blood, CSF, urine, Pleural fluid, sputum	EU, IU, ICU, PW	Imipenem, ampicillin/ sulbactam, gentamicin	*A. baumannii* isolates were resistant to most clinically antibiotic classes
Bahador A	Multiplex PCR, molecular typing	RTS, wound, urine, blood, CSF	ICU	Ampicillin-sulbactam	Ampicillin-sulbactam alone or plus tobramycin exhibited a potent activity against Colistin, Rifampicin and Tigecycline (CRT) resistance *A. baumannii* isolates
Mohajeri P	PCR, AST	Sputum, blood, urine	EU, ICU, PW, IW	Polymyxin B, colistin, tigecylcin, minocycline	*A. baumannii* was responsible for the outbreak in the hospitals
Yadegarynia D	AST	Blood, urine	HE, OTW, ICU, GR, Onc	-	*A. baumannii* was responsible for 10.5% of infections in patients with nosocomial
Vahdani P	LT, CM	RTS, tracheal secretion, secretion, lavage, sputum	ICU	Imipenem	*A. baumannii* is the most frequent cause of respiratory tract infections fever and neutropenia
Azimi L	BT, LT	Blood, burn swab	ICU, BU	-	New antibiotics can be useful for treatment
Rahbar M	BT, CM	RTS	ICU	Imipenem	Previous antibiotics use, long duration of ICU stay and mechanical ventilation were the major risk factors for resistance in *A. baumannii*

Table 2: Continue

First author	Methods*	Source of sampling ¥	Sampling ward ®	Effective antibiotics	Main findings
Soroush S	AST, BT	RTS, sterile fluids and catheter tube, CSF, blood, wound	IW, SW, PW, Neu, GR, HE, ICU	-	Carbapenem resistance is becoming more common in Iran

*AST = Antibiotic Susceptibility Tests; PCR = Polymerase Chain Reaction; BT = Biochemical Tests; REP-PCR = Repetitive Extragenic Palindromic elements-PCR; CM = Colonial Morphology; LT = Laboratory Tests; MLVA = Multiple Locus Variable number tandem repeat Analysis; MLST = Multilocus Sequence Typing; ¥ WS = Wound Samples; ETT = Endotracheal Tube; RTS = Respiratory Tract Specimens; CSF = Cerebrospinal Fluid; ®ICU: Intensive Care Unit; BU = Burn Unit; PW = Pediatric Ward; IW = Infectious Ward; SW = Surgeries Ward; IU = Internal Unit; EU = Emergency Unit; OTW = Organ Transplantation Ward; HE = Hematology and Endocrinology; GR = Gastrointestinal and Roumatology; Onc = Oncology; Neu = Neurology ward; ENT = Ear, Nose, Throat; CCU = Coronary Care Unit

cefotaxime, tigecycline and aztreonam but these multidrug resistant bacteria are almost susceptible to polymyxin B and colistin[25]. Hence, the findings of this study necessitated the proper use of antibiotics to prevent the occurrence and progression of *A. baumannii* induced infections and consequently the incidence of nosocomial infections. The results showed that mechanical ventilation, previous use of antibiotic and surgical procedures as well as disease such as diabetes mellitus, chronic obstructive pulmonary disease and neurosurgical meningitis are the major risk factors for the incidence or recurrence of *A. baumannii* induced infections[21, 26]. Based on our previous results, increased resistance to antibiotics may be partly due to unlimited application of these antibiotics in treatments procedures[27]. Although, the results showed that respiratory tract was the most common place for the isolation of *A. baumannii* but the bacteria had also been isolated from urine, wound, blood, sputum, nose, throat and eye[28,29]. As the results showed, the burn patients may be very sensitive to infections due to loss of skin which is the primary defense system to prevent the penetration of microorganisms. In addition, findings show that *A. baumannii* isolates are not only collected from burn and ICU wards but also are found in orthopaedic ward[30]. The samples had been collected from different parts of the hospitals including ICU, surgeries ward, neurosurgical ICU, neonates, male and female internal wards and organ transplantation ward. Findings suggest that bacterial resistance to antibiotics is going to be a challenging issue[31]. Therefore, there is an urgent need to apply some practical approaches and health policies in order to control further spread of resistant bacterial species[32, 33]. Henceforth, it is necessary to further study in the field of drug discovery and finding new antibacterial agents such as antimicrobial peptides or other agents with bactericidal potency from natural sources, especially medicinal plants[31, 34, 35]. It is also recommended to use medical devices with potential antibacterial properties, especially in ICU wards[36].

Insufficient documents reporting the frequency of *A. baumannii* infection from different areas of the country, small sample size and inaccessible demographic data in some articles were the most important limitations of this study. Therefore, several multicenter studies with large sample size wherein the samples are collected from different populations in different parts of the country are required to be conducted to obtain more reliable data. However, as suggested by many investigators[37], the results of documents included in this literature review showed that *A. baumannii* infection is one of the major concerns of recent years in Iran and further attempts in the field of drug discovery are needed to combat these pathogenic bacteria.

CONCLUSION

The results of this study showed that *A. baumannii* strains are widely disseminated in Iran and it is often considered as an important cause of infection in patients hospitalized at almost all wards of hospitals, especially ICU and burn unit. In addition, it was shown that *A. baumannii* is resistant to most of the conventional antibiotics.

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