METALLO-BETA-LACTAMASES PRODUCING ACINETOBACTER BAUMANNII: A MAJOR THREAT TO PATIENTS HEALTH

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ABSTRACT:
Acinetobacter baumannii is common gram-negative non-fermenter opportunistic bacteria associated with nosocomial infections, especially among hospitalized patients. In this study, PubMed, Scopus and Google Scholar were searched using the following keywords: “Acinetobacter baumannii,” “metallo-β-lactamases,” “Iran”. Of Ninety-eight articles, twenty-eight were eligible to be included in our systematic review. These studies were carried out in Tehran, Tabriz, Arak, Hamadan and Mashhad city in Iran. SPM-producing A. baumannii reported of Tehran, IMP-producing A. baumannii reported of Tehran, Tabriz and Arak and VIM-producing A. baumannii reported of Tehran, Tabriz, Hamadan and Mashhad in Iran. Among MBL genes, blavim is more than other genes in Iran. The prevalence of β-lactamase-producing isolates, and their isolation from life-threatening infections, is increasing worldwide at an alarming rate.

Keywords: Acinetobacter baumannii; metallo-β-lactamases; Iran; Antibiotic resistance.

INTRODUCTION
Acinetobacter baumannii is an opportunist Gram-negative pathogen associated with nosocomial infections around the world(1). In addition to causing broad range of infections(e.g. pneumonia, urinary tract, bloodstream and skin infections), this organism is responsible for 10% of all nosocomial infections (2). Since 1970s, the expansion of multidrug-resistant (MDR) Acinetobacter strains become a great challenge among hospitalized patients (3). A. baumannii is developing into multidrug resistant (MDR), extensively drug resistant (XDR), and pandrug resistant (PDR) bacteria, and its adaptation to the environment with drug resistance has previously been reported(1). Antimicrobial resistance among Acinetobacter species is problematic especially in the past decade (4). The emergence and spread of carbapenem-resistant A.baumannii limits therapeutic options and the control of its outbreak (5). Antibiotic resistance mechanisms generally classified into 3 categories: (1) enzyme production, (2) reduced penetration of the antibiotics to the target sites, or (3) target mutations (4). The most common
mechanism of resistance is the production of beta-lactamases, including enzymes of Ambler classes A, D, and B, with their genes being often associated with mobile genetic elements such as plasmids (6, 7). Some Acinetobacter strains express class B metallo-beta-lactamases (MBLs) including IMP (imipenemase), German imipenemase (GIM), Japan, Kyorin University Hospital imipenemase (KHM), Verona integron-encoded metallo-beta-lactamases (VIM), Sao Paolo metallo (SPM), Seoul imipenemase (SIM), New-Delhi metallo-beta-lactamase (NDM-1) and Australian imipenemase (AIM) (8). MBLs have threatened hospital infection control because they are often located on mobile genetic elements and horizontally transferred among bacteria (4). In the present study, we aimed to systematically review the published data about the prevalence rate of MBL genes in Iran.

MATERIALS AND METHODS:
The PubMed, Scopus and Google Scholar database were searched for studies published from January 2008 to June 2015 with the following keywords: “Acinetobacter baumannii,” “metallo-beta-lactamases,” “Iran”. To identify resistance genes, eight of the studies were selected (by polymerase chain reaction and sequencing methods). Of art Ninty-eight articles, twenty-eight were eligible to be included in our systematic review. In this article A. baumannii samples was collected from patients in Iranian hospitals.

RESULTS
Twenty-eight articles were eligible to be included in our systematic review. These studies were carried out in Tehran, Tabriz, Arak, Hamadan and Mashhad. SPM-producing A. baumannii reported of Tehran, IMP-producing A. baumannii reported of Tehran, Tabriz and Arak and VIM-producing A. baumannii reported of Tehran, Tabriz, Hamadan and Mashhad in Iran. Among MBL genes, blavIM is more than other genes in Iran. All MBL genes producing isolates were resistant to imipenem and susceptible to Colistin.
DISCUSSION

*A. baumannii* has been cause of severe infections in hospitalized patients(17). Although, some of these bacteria can cause a serious disease, there are two possible reasons which the superbug status of the *A. baumannii* is depends on that, including pathogenicity or virulence and resistance to multiple antimicrobial agent(18). The recent report from the United Kingdom indicates the human costs of the antibiotic resistance are increasing and this amount will be reached to the 300 million progressive premature deaths by 2050 with the decrease of $100 trillion. Infectious Diseases Society of America has been underlined this serious situation and now it becomes as one of the priority of the U.S government(19). Until recently, carbapenems, such as imipenem, were most effective antibiotic against resistant gram-negative organisms, but some strains have now applied effective mechanisms to become resistance to carbapenems. Moreover, the common presence of these β-lactamase genes of gram-negative bacteria in transferable mobile elements means that these genes could horizontally transfer between gram-negative bacterium and become a significant threat in the future. Recognition carbapenemas producer strains in a gram-negative organism is of paramount importance, since strict infection-control measures are required to avert hospital epidemics and the dissemination of these genes to other gram-negative species(20).

Among MBL genes, *bla*<sub>VIM</sub> is more than other genes in Iran. During the recent years, assays for identification of MBL genes in *A. baumannii* and *P. aeruginosa* became popular among Iranian researchers. Based on these studies, we reported the prevalence of MBL genes reported of patients in Iran. The IMP-type enzymes, which were described first in Japan in the late 1980s, have been detected in Enterobacteriaceae, *A. baumannii* and *P. aeruginosa* strains(8). More than 53 different IMP allotypes have been described (http://www.lahey.org/Studies/other.asp). The VIM-type β-lactamase was first described in a MDR *P. aeruginosa* strain in Italy during 1990s and it has been reported around the world scince then (16). More than 46 different VIM allotypes are described (http://www.lahey.org/Studies/other.asp). Emergence of NDM-1 has been considered as a global hazard because bacteria which have this MBLs are resistant to almost all β-lactam antibiotics, fluoroquinolones , aminoglycosides, and other classes of antimicrobial agents. The rapid emergence of NDM-1 has been related to transmissible plasmids which can transfer horizontally among different isolates and spread around the world(16). MBLs are resistant to all antibiotics expect colistin. In Iran, the best coverage against the study isolates was obtained with colistin. Mortality in severe infections with metallo-β-lactamase-producing *P. aeruginosa* ranged from 70% to 95%: metallo-β-lactamase-producing Enterobacteriaceae range from 19% to 67% and mortality in bloodstream infections that are caused by VIM-1-producing *K. pneumoniae* range from 13% to 54%(21, 22). Carbapenems have been considered as the good therapeutic option but carbapenem resisatnace have appeared significantly in some areas. Sulbactam has been applied for treatment of serious *A. baumannii* infections; however, the activity of this agent against carbapenem-resistant isolates is decreasing. Polymyxins show reliable antimicrobial activity against *A. baumannii* isolates. Although the effectiveness of the Polymixins against *A. baumannii* has been supported by a small number of the clinical reports, the previous concern about toxicity is decreased. High antimicrobial activity against *A. baumannii* is related to the Minocycline and its specific derivative, tigecyclen; however, the number of documents is rare. Future research is needed to be
clarified the possible issues which are related to the ideal therapeutic choice for multi-drug resistant infection of the A baumannii(23). The rate of resistance to the most of antibiotics is increasing and this includes several pathogenic bacteria such as A baumannii and Pseudomonas aeruginosa (24). While it seems difficult to control the problem of antibiotic resistance, the new approaches for the main concept of resistance, diseases and prevention are required (25).

CONCLUSIONS
The prevalence of metallo-ß-lactamase-producing isolates, and their isolation from life-threatening infections, is increasing worldwide at an alarming rate. The spread of metallo-ß-lactamase presents a major challenge both for treatment of individual patients.

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REFERENCES


