Incidence of Dominant Metallo-β-Lactamase Resistance Genes Produced in Pseudomonas aeruginosa Burn Infections in Iran: A Systemic Review and Meta-Analysis

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ABSTRACT

Backgrounds: Metallo-β-Lactamase (MBL) enzymes-producing *Pseudomonas aeruginosa* strains are one of the most important causes of nosocomial infections and are very difficult to treat, leading to high mortality rate. Therefore, control of these cases is very important, especially in burns. This study aimed to systematically review published data on MBL genes prevalence among *P. aeruginosa* strains isolated from burn patients.

Materials & Methods: ISI Web of Science, Scopus, PubMed, and Google Scholar were searched using appropriate key terms as follows: *P. aeruginosa*, metallo-β-lactamase, burn patients, imipenem resistant, and Iran. Antibiotic susceptibility tests were conducted by Kirby-Bauer disc diffusion and broth microdilution methods according to the CLSI guidelines. The MBL producers was evaluated by the combination disk diffusion test (CDDT), and detection of genes such as bla_{IMP}, bla_{VIM}, bla_{SPM} and bla_{NDM} was performed with polymerase chain reaction (PCR). In this review statistical analyses were performed using STATA statistical software Ver.13.

Results: Out of 410 retrieved articles, 18 articles were eligible to be included in this systematic review and meta-analysis. These studies were carried out in Tehran, Shiraz, Yazd, Zahedan, and other locations. Pooled estimation of all *P. aeruginosa* strains included in 18 studies showed that the prevalence of MBL-producing *P. aeruginosa* strains in Iranian population was about 49% (95% CI: 33-65). The present study findings also revealed that in Iranian population, the most prevalent MBL genes were bla_{IMP} with 17% (95% CI) and bla_{VIM} with 13% (95% CI), respectively.

Conclusion: Detection of these bacterial resistance genes should be performed nationally, and strict control measures should be put on the agenda to reduce the incidence of these cases.

Keywords: *Pseudomonas aeruginosa,* Imipenem resistant, Metallo-β-lactamase, Burn patients, Iran

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Introduction

A major leading cause of life-threatening infections is *Pseudomonas aeruginosa* in burn patients worldwide [1]. *P. aeruginosa* is one of most important causes of hospital-acquired infections [2]. It is an opportunistic microorganism involved in many infections, such as urinary tract infections, respiratory infections, bacteremia, and wound and soft tissue infections, especially in immunocompromised patients and in patients with dermal injuries [3-4].

Notwithstanding advances in medicine, *P. aeruginosa* is considered a significant infectious threat to patients with burn injuries. *P. aeruginosa* shows a primary resistance to many antimicrobial agents through the outer membrane barriers, multidrug efflux pumps, and endogenous antimicrobial inactivation. Selection of an appropriate antibiotic is predicated based on the capability of *P. aeruginosa* to develop resistance to multiple categories of antibacterial agents, and the selection of a suitable antibiotic to begin treatment is a necessity optimizing the clinical outcome [4]. This pathogen has a considerable capacity to develop resistance to multiple categories of antimicrobial agents and as a result, it is considered as a multidrug resistant pathogen [5].

Today, carbapenem-resistant *P. aeruginosa* has increased significantly, causing high mortality rate among patients with nosocomial infections. One of the most important mechanisms of resistance in this pathogen is the ability to produce metallo-β-lactamase (MBL) enzymes [6-8]. These enzymes could hydrolyze antibiotics, such as penicillins and cephalosporins [9], and have different types, including São Paulo metalo-β-lactamase (SPM), Germany imipenemase (GIM), Verona integron-encoded metallo-β-lactamase (VIM), Seoul imipenemase (SIM), New Delhi metallo-β-lactamase, and imipenemase (IMP). VIM and IMP are the most common types of acquired MBLs [10-11]. VIM type was first reported in Italy, whereas in early 1991, the IMP-type enzymes initially emerged in Japan. However, both types have been increasingly reported in other parts of the world [12]. These genes are encoded by mobile genetic elements (integrons, plasmids, transposons) and transmitted among Gram-negative bacteria [13].

For this reason, they are found in all parts of the world. In Iran, the first case of *P. aeruginosa* metallo-β-lactamase resistance in burn centers was reported in 2008. After that, from 2008 to 2016, its rate in burn centers increased from 41 to 57% and caused serious concerns [6-7].

Despite advances in antimicrobial therapies, bacterial infections are one of the major problems among burn patients. About 75% of deaths in this group of patients is due to refractory infections [13]. Recently, *P. aeruginosa* has been identified as one of the main causes of various nosocomial infections, especially in burn units. The spread of drug resistance is very fast, which in turn could cause many problems in the treatment process [14].

With all these interpretations, there is no standard phenotypic corroborant test for the detection of MBLs among *P. aeruginosa* isolates [15]. Molecular procedures are essential to verify the presentment of MBL genes in clinical isolates and are also considered as suitable instruments for detection and screening. PCR (Polymerase chain reaction) test has high sensitivity and reliability for the detection of MBL genes between MBL-producing *P. aeruginosa* isolates [16].

One of the reasons for high resistance of *P. aeruginosa* to antimicrobials is the ability to form strong biofilms because the bacteria in the biofilm are resistant not only to the host immune system but also to antibiotics. For

this reason, effective treatment strategies should be used to deal with such cases [17].

In recent years, the role of probiotics in controlling *P. aeruginosa* infections in burn patients has been investigated and introduced as one of the therapeutic options. For this reason, many studies have examined the role of antibacterial probiotics in inhibiting the growth of resistant pathogens [18].

Objectives: This meta-analysis study aimed to systematically review published data on MBL genes prevalence among *P. aeruginosa* strains isolated from burn patients in different locations of Iran during 2011-2020, with the aim of emphasizing the importance of this issue and providing useful suggestions to solve these problems.

Materials and Methods

Search strategies: In this study, international databases (ISI Web of Science, Scopus, PubMed, and Google Scholar) as well as two national scientific search engines including Magiran (www.magiran.com) and Iranian Scientific Information database (www.sid.ir) were searched for articles published from 2011 to 2020 without limitation using the following terms: *Pseudomonas aeruginosa* or *P. aeruginosa,* metallo-β-lactamases or MBLs, and burn patients in combination with Iran and "multidrug-resistant P. *aeruginosa*". Those articles reporting the prevalence of MBLs in burn patients were considered. Cross-sectional or cohort studies reporting the prevalence of MBLs in burn patients were considered. Review studies revealing the prevalence or incidence of MBLs genes in burn patients were restricted to studies published in English and Persian languages. Studies with the following characteristics were included: studies conducted only on burn patients and reporting the frequency of carbapenem resistance and MBLs genes. Studies that had one or more of the following characteristics were excluded:

studies using phenotypic methods, duplicate and overlapping studies, studies published in languages other than English or Persian, studies performed on patients other than burn patients, studies that did not report CRPA and MBLs prevalence, nonhuman studies, review articles, congress abstracts, meta-analyses, systematic reviews, as well as articles available only in abstract form. References list of all studies was also reviewed for any other related publication. Some references were also entered manually.

Inclusion criteria: Inclusion criteria used in the present study were as follows:

• *P. aeruginosa* isolates collected from patients referring to Iranian hospitals.

• *P. aeruginosa* strains collected from clinical samples.

• *P. aeruginosa* strains collected from burn patients.

Phenotypic methods (imipenem/meropene) alone and in combination with EDTA were used according to CLSI guidelines to detect the prevalence of MBL producing isolates of *P. aeruginosa* because these are approved methods that are widely available.

Exclusion criteria: Studies with unclear materials, methods, and the origin of samples were excluded.

Statistical analysis: Statistical analyses were performed using STATA statistical software Ver.13 (Stata Corp. 2013. Stata Statistical Software: Release 13. College Station, TX: Stata Corp LP). Heterogeneity assessment between studies was performed using the I^2 statistic (the I^2 values of 25, 50, and 75% indicated low, moderate, and high heterogeneities, respectively) which represents the percentage of total variation that is true between-studies heterogeneity. A random-effects model was used if heterogeneity was high ($I^2 > 50\%$); otherwise, a fixed effects model was applied. Double arcsine transformations were applied to stabilize the variance in the meta-analyses, Significance level was set at $p < .05$. Then the

Table 1) Prevalence of MBL genes based on different locations.

|	First Author	Location (Ref.)	Time of Study	Total Samples	MBL Proportion (%)	MBL-Genes (Proportion %)	
						VIM	IMP
1	Hakemi Vala	Tehran(36)	2013-2014	47	17.8	0.1	2.1
2	Sadredinamin	Tehran(37)	2014-2015	100	81	0	16
3	Hashemi.	Tehran(38)	2012	100	62.33	0	7.7
4	Radan	Esfahan(39)	2013-2014	150	96	NA	74.3
5	Saffari	Esfahan(40)	2014-2015	150	96	23.5	NA
6	Tarashi	Tehran(41)	2012-2015	309	64.02	29.2	16.8
7	Rostami.	Ahvaz(4)blaVIM, blaSPM and blaNDM	2011-2012	107	14.9	1.2	17.9
8	Azimi	Tehran(42)	2015-2016	160	43.7	17.5	15.6
9	Emami	Shiraz(43)	2017-2018	48	33.33	61.6	0
10	Farajzadeh Sheikh	Iran(44)	2013-2016	369	31.43	28.8	21.6
11	Kalantar	Kurdistan(14)	2011-2012	145	22	NA	NA
12	Asadpour	Northen iran(45)	2018	90	35.6	NA	NA
13	Salimi	Tehran(46)	2014	32	100	46.8	56.2
14	Ghamgosha	Zahedan(47)	2012-013	191	4.7	3.7	0.3
15	Hemati	Zanjan(48)	2012-2013	120	29.2	NA	23.3
16	Nakhaei	Mashhad(49)	2014	70	35.7	11.4	NA
17	Rostamour	Shiraz(50)	2012-2013	42	61.9	NA	11.9
18	Akhavan	Yazd(28)	2011-212	54	29.5	NA	NA

data weighted by the inverse variance of the individual studies were pooled to derive an overall proportion and the associated 95% CI. **Data extraction and definitions:** The following data were extracted from each study: name of first author, location of study, time of study, total number of samples, and reported MBL resistance genes prevalence (Table 1). Furthermore, to minimize the potential bias caused by an inadequate sample size, articles with less than 40 subjects and antibiotic resistant table

were omitted. Inconsistency between the reviewers was resolved through discussion.

Findings
In this study, a total of 410 articles were found through databases search, of which overall participants of 18 (abstract with full-text articles) eligible studies were included in this meta-analysis to determine the prevalence of MBL producing *P. aeruginosa* strains (Figure1).
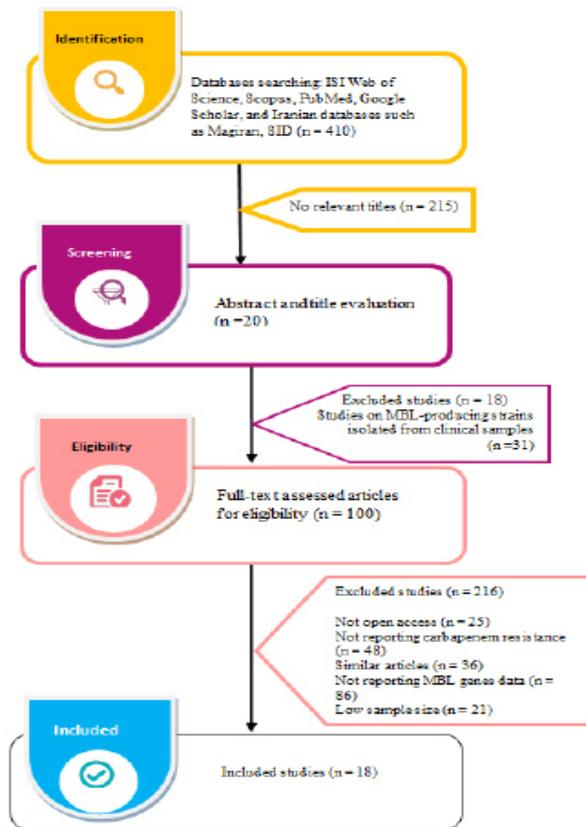
Figure 1) Schematic diagram of the literature search and study selection.

In the present study, the results of some MBL genes (SPM, NDM) were not reported for some reasons, including: negative results and not being included in the reviewed studies. Also, the results of antibiotic resistance were not mentioned in some articles due to lack of reporting. Considering the location of the studies, most of the studies were conducted in Tehran (n = 6), Esfahan (n=2), and Shiraz (n=2) compared to studies conducted in

other locations (n = 8).

Based on the present study findings, the prevalence of MBL-producing *P. aeruginosa* strains in Iranian population was about 49% (95% CI: 33-65). However, publication bias was not significant. In addition, in Iranian population, the most prevalent MBL genes were bla_{IMP} with 17% (95% CI) and bla_{VIM} with 13% (95% CI), respectively (Figure 2, 3).

Discussion
Today, pathogens such as *P. aeruginosa* strains are considered as the leading cause of nosocomial infections due to the formation of very strong biofilms and the development of various antibiotic resistances in many areas, including Iran [17,19]. For this reason, this study was conducted to investigate the prevalence of such resistance mechanisms, including the presence of metallo-β–lactamase (MBL) resistance genes in this microorganism, in order to point out the importance of this issue and to make constructive suggestions to deal with such cases in not so far future. Thus, the present analysis revealed that the prevalence of MBL-producing *P. aeruginosa* strains in Iranian hospitals in burn units is alarmingly high, with an overall estimated prevalence rate of about 49% (95% CI: 33-65). According to the analysis, it seems that the prevalence of MBLs genes in Iranian burn infections is very significant.

In various studies, the prevalence of such resistance genes has been further investigated. For example, a study by Lautenbach et al. (2010) revealed a high degree of carbapenem resistance in *P. aeruginosa* strains, and its relationship with mortality was discussed [20]. Another study conducted in three German hospitals also noted the importance of such resistance, while the other study by Erlandsson et al. (2008) in Swedish ICUs expressed that the prevalence of MBL production by this microorganism (*P. aeruginosa)* was about
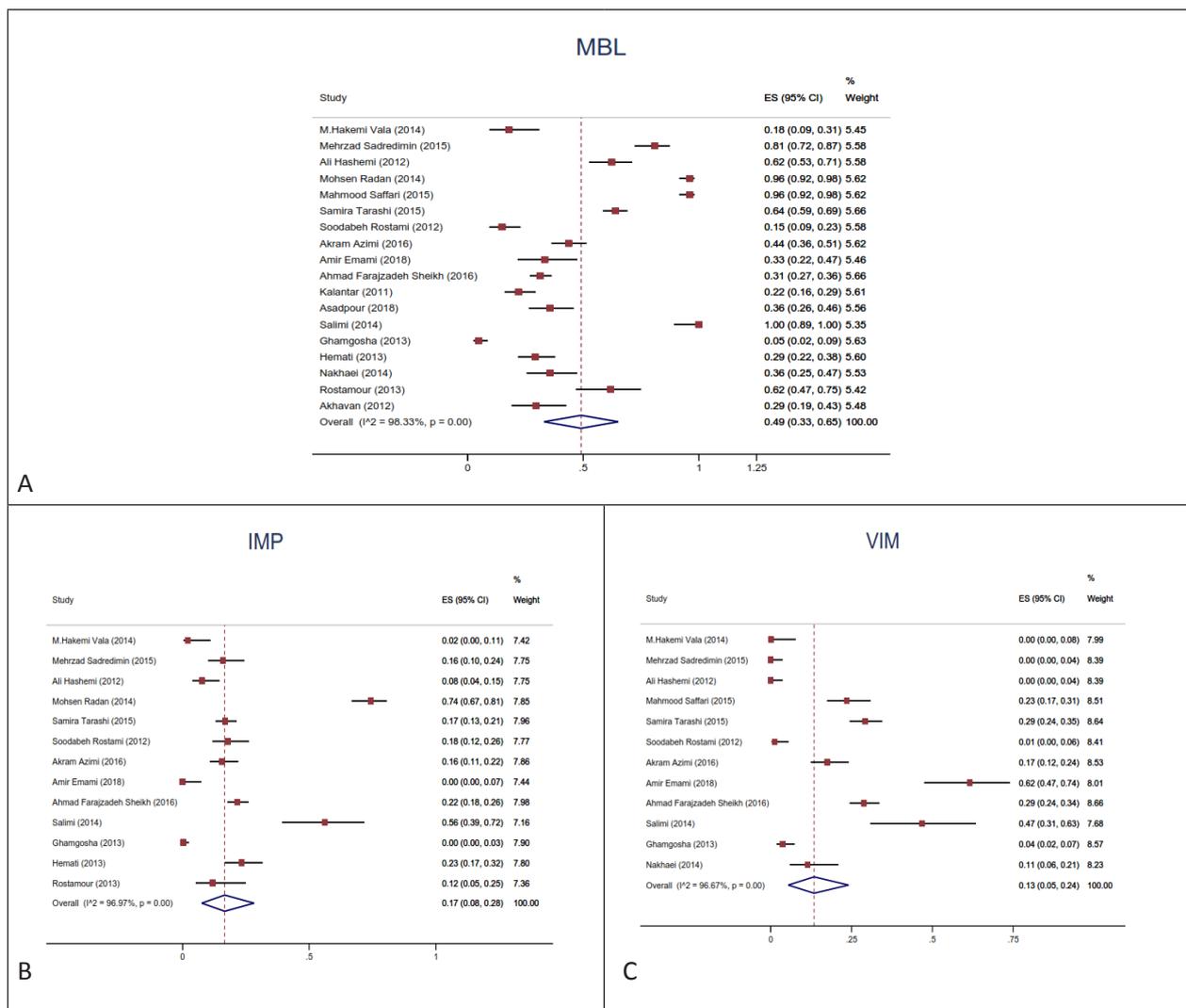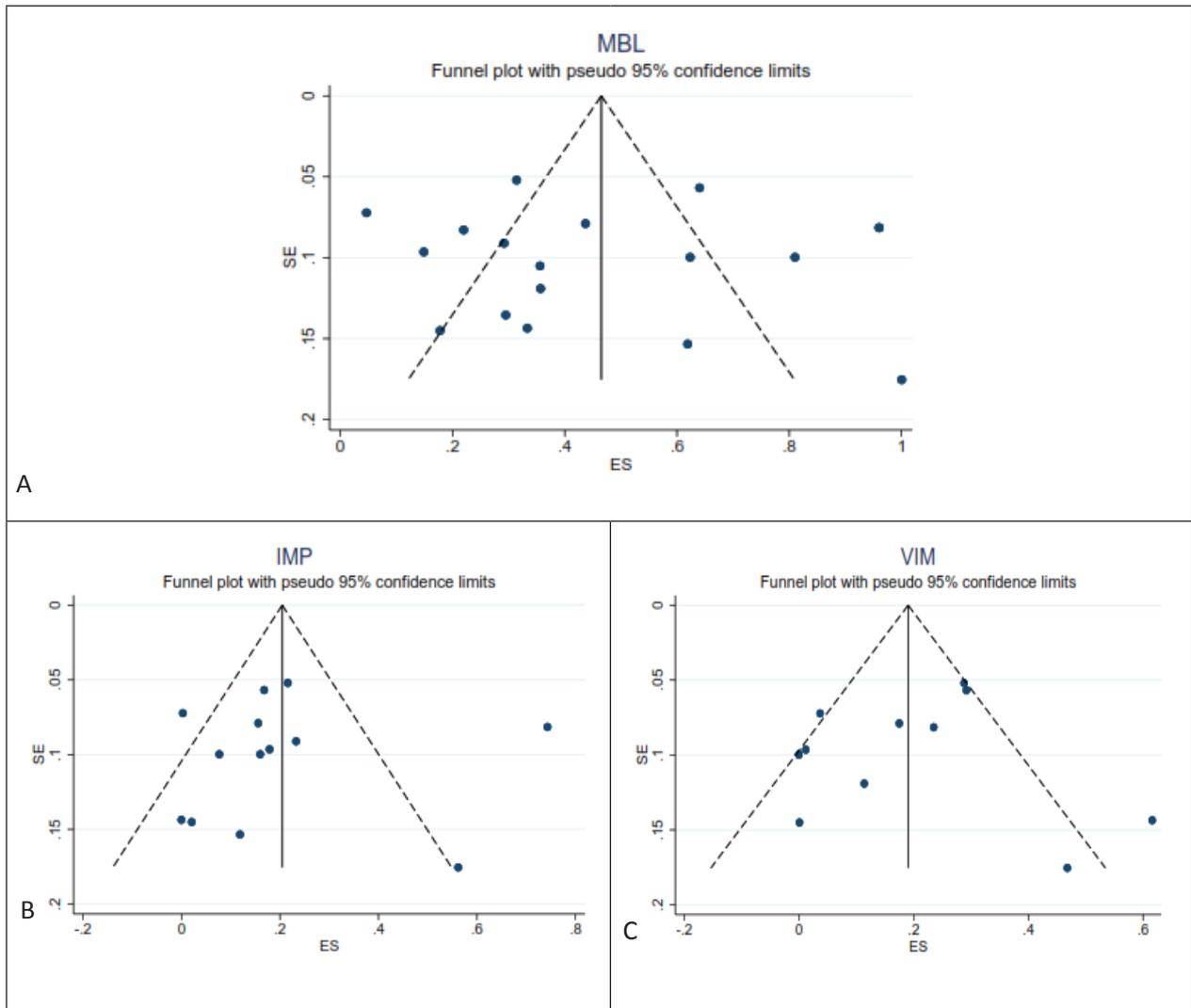
Figure 2) Forest plot of the studies on burn patients (meta-analysis). (A), (B), and(C) represent the prevalence of MBL, IMP, and VIM genes.

less than 1% [21]. Liakopoulos et al. (2013) in Greece revealed that 28% of investigated isolates were MBL-producer [22]. Also, another study conducted in 23 Korean hospitals during 2005 demonstrated that 10.8% of *P. aeruginosa* isolates could produce MBL [23]. Kaleem et al. (2010) in Pakistan revealed that the prevalence of MBL-producing *P. aeruginosa* isolates was about 78% [24]. Also, Hashem et al. (2017) showed that the prevalence of MBL-producing *P. aeruginosa* was 64% in Egypt [25]. In another study by Ghasemian et al. (2018), some important results were found from different parts of Iran. They reported that 55% of *P. aeruginosa* isolates were resistant to imipenem and

meropenem, among which 37.72% were MBL producers, and the prevalence rates of bla_{VIM} and bla_{IMP} in burn isolates were 11.50%±3.5% and 24.65%±23, respectively [26].

In comparison with all the above mentioned results, in the present study, the highest prevalence rate was reported for bla_{IMP} (17%) (95% CI) and bla_{VIM} (13%) (95% CI), respectively.

Therefore, the analysis in this study shows that genes bla_{IMP} and bla_{VIM} are prevalent among burn patients in Iran. This study results are similar to previous studies results reported by other authors, but in this study we tried to both point out the importance

Figure 3) (A) Funnel plot of the studies on burn patients (meta-analysis). (A), (B), and(C) represent the prevalence of MBL, IMP, and VIM genes.

of this issue and suggest a useful and constructive solution to deal with this issue. According to the results of this study, the prevalence of MBL resistance among burn centers in Iran is relatively high compared to industrialized countries such as Sweden and Norway [27]. One of the reasons for this difference is the existence of effective programs in infection control systems to combat various types of nosocomial infections and their more attention to this issue. But in a developing country like Iran, these cases are poorly controlled due to the lack of a coherent and effective program to deal with these cases, and this causes a lot of problems in the treatment of various drug-

resistant nosocomial infections [1].

Along with other problems caused by *Pseudomonas*, we could mention the ability of this bacterium to grow well in the humid hospital environments. Low sensitivity to antibiotics is a prominent feature of this bacterium, which makes treatment difficult. This bacterium is resistant to various antibiotics by different mechanisms. Class B beta-lactamases are metallo-β-lactamases that require the presence of one or two ions (Zn) in their active site. Metallo-β-lactamases have the ability to inactivate all beta-lactam antibiotics except monobactam. Multidrug-resistant strains are on the rise today due to the overuse of antibiotics [28].
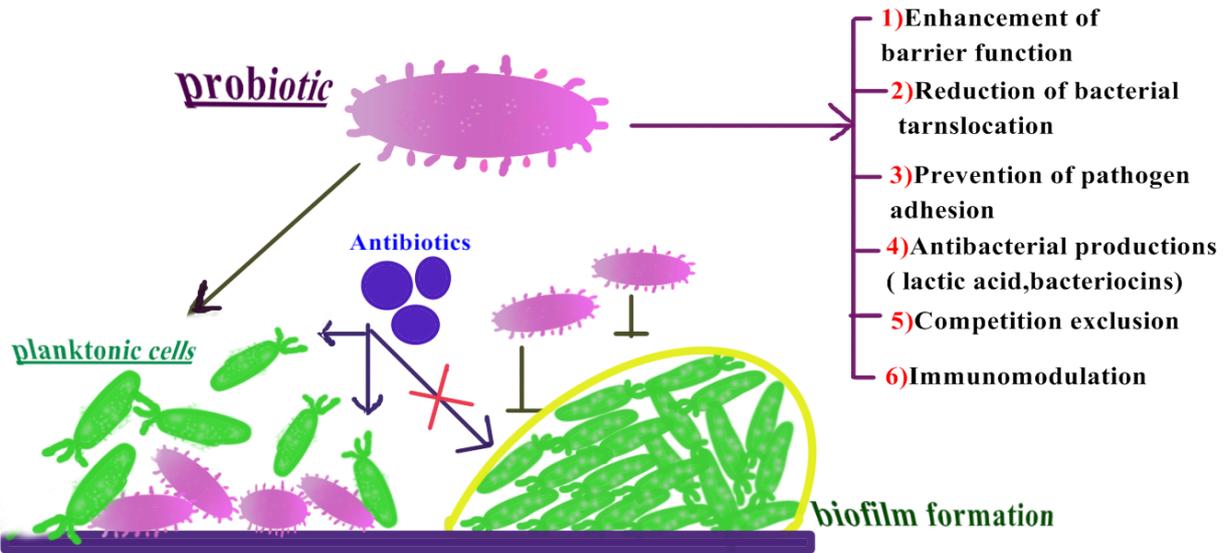
Figure 4) Probiotic activities against pathogens.

Since imipenem is prescribed as a preventative treatment in the burn injury wards to prevent burn wound infection, increased resistance is inevitable, and the common use of carbapenems to prevent *Pseudomonas* infection in burn units could be effective in preventing its spreading. In burn units, antibiotic susceptibility testing and MBL-producing *P. aeruginosa* strains should be considered prior to drug administration. Due to the fact that MBL enzymes are of different classes with various prevalence rates in different regions; thus, it is necessary to perform molecular studies in this field [28]. As mentioned earlier, one of the most important virulence factors of pathogens such as *P. aeruginosa* is the ability to form biofilms on different biotic and abiotic surfaces. Microorganisms within the biofilms are not only resistant to the host immune system but also to a wide range of antibiotics due to their impenetrable biofilm structure, including extracellular matrix polymer [29-30]. Therefore, in order to deal with resistant strains, special therapeutic strategies are needed. Accordingly, it is suggested to use probiotics as antibacterial and anti-biofilm agents producing appropriate products with antagonistic effects against many pathogens, including *P. aeruginosa*, *Klebsiella pneumoniae*, *Salmonella*, and other microorganisms [17].

Among the important probiotics used to prevent and eradicate bacterial infections such as resistant *P. aeruginosa* are lactobacilli, the use of cell free supernatant (CFS) containing antibacterial products has recently been considered by many researchers as a new treatment strategy for controlling and preventing the colonization of pathogens, it shows us a clear vision of the future. Lactobacilli could exhibit antibacterial activity through a variety of mechanisms, including: production of inhibitory compounds (such as bacteriocins, biosurfactants, and organic acids), modulation of the host immune system, competition with pathogens for binding to cellular receptors, and nutrient uptake. As a result, they show antagonistic activities against pathogens [17](Figure 4).

All of these factors indicate how potent this pathogen is in causing infection, and it is a global concern. Therefore, serious solutions must be sought to deal with this important pathogen.

Due to the local conditions, in order to be more effective, it is better to

carry out infection control schedule recommended by WHO (the World Health Organization). Accordingly, countries with low and medium revenues (such as Iran) could not handle infection control schedules as developed countries in terms of cost and cultural requirements [31-32] In other words, close cooperation of microbiology laboratory with clinicians, quick reporting, the use of some effective treatment strategies, and the use of combination regimens are essential to decrease the spread of antibiotic-resistant *P. aeruginosa* strains in burn infections [30, 33-34]. Nevertheless, combination regimens should be used very carefully only in patient who has symptom; otherwise, they may cause new resistances [35].

The restrictions of this study should be discussed as follows: (1) the potential influence of sex and age could not be analyzed because the role of age and gender was not studied in most articles. (2) Some articles had to be paid for. (3) Only published articles were considered in the present meta-analysis. Then by comparing the results of this study and several other studies in Iran, attempts were made to provide constructive suggestions to prevent these infections. (4) This study could not entirely indicate the prevalence of MBL-producing *P. aeruginosa* infections in Iran owing to the fact that imipenem resistance has not yet been investigated in some locations of Iran and also because of the inability to detect such resistances.

Finally, in most burn hospitals in Iran, routine diagnosis of MBL production by *P. aeruginosa* isolates is not performed. Hence, the diagnosis of carbapenem resistance genes is suggested to be included in the agenda of various laboratories in order to properly prescribe appropriate therapeutic antibiotics to combat various nosocomial infections.

Conclusion

According to the results of this study, the high prevalence of MBL-producing *P. aeruginosa* strains due to lack of timely diagnosis is one of the most important problems in Iranian hospitals. Prevention strategies are needed to reduce the prevalence rate of MBL positive strains in Iran. Basically, standard guidelines are needed to prevent the spread of these strains in hospitals, which are resistant to antibiotics administrated by doctors and healthcare staff. Because prevention is always better than cure. Indiscriminate use of antibiotics, high biofilm formation, and lack of timely diagnosis have resulted in the development of multidrugresistant *P. aeruginosa* infections, which is a serious threat to patients' health. To prevent and eradicate these infections, it is suggested to use probiotics (as beneficial microorganisms by producing various antibacterial products) along with antibiotics in order to speed up the healing process.

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