The threat of carbapenem-resistant gram-negative bacteria in a Middle East region

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Abstract: Data on the status of carbapenem-resistant microorganisms in the Middle East countries are scarce. The aim of this review was to collect available data regarding resistance to carbapenems in a Middle East region. Available data regarding carbapenem-resistant isolates were considered for evaluation in this review. Biomedical electronic databases were systematically searched to find related articles. The key terms used were “carbapenem-resistant, resistant gram-negative bacilli, Enterobacteriaceae, fermenting and non-fermenting gram-negative bacilli, Pseudomonas, Acinetobacter, Klebsiella and Iran”. After primary screening, 275 relevant articles were selected to be assessed thoroughly. Resistance rate to carbapenems was reported between 1% and 86% during years 2006–2018. Most of the carbapenem-resistant microorganisms were isolated from burn patients. Modified Hodge test was a commonly used phenotypic test. Only in few studies, genotypic assays were considered. Pattern of antibiotic use can affect emergence of resistant microorganisms. Rational use of drugs, and specifically, antibiotics is a challenging issue in developing countries. Mean number of drugs per prescription in these countries was higher than the World Health Organization standards. Overuse of antibiotics, especially injectable ones, and easy access to antibiotics without prescription is a warning alarm for future antibiotic resistance in developing countries. Establishing antimicrobial stewardship’s programs is new in the hospitals. Unfortunately, rules and regulatory issues to restrict antibiotic access in community pharmacies and prescription by general physicians are limited.

Keywords: carbapenem, resistant, gram-negative bacteria, antibiotics

Introduction
Carbapenem-resistant gram-negative bacteria are now a global concern around the world. Most of these strains are also resistant to other antimicrobial agents including aminoglycosides and fluoroquinolones. Few therapeutic options without the desired efficacy are available to treat infections caused by carbapenem-resistant microorganisms. This real threat necessitates applying reliable methods to determine prevalence of these isolates.

The methods to detect carbapenemase-producing microorganisms are divided into two classes: phenotypic and genotypic methods. Phenotypic methods are nonmolecular assays that detect structure of the carbapenemase enzyme (mostly active site) through a chemical or microbiological process. The carbapenemases enzymes are structurally classified according to their active sites. Ambler class A (known as Klebsiella-producing carbapenemase [KPC]) has serine amino acid in its active site and can be inhibited by β-lactamase inhibitors. Ambler class B has zinc in its active site and is called metallo-β-lactamase (MBL), so it can react with EDTA and dipicolinic acid (DPA). The last
class, Ambler class D, has serine in its active site, but it may or may not be inhibited by β-lactamase inhibitors. According to these classes, various phenotypic methods are proposed to detect carbapenemase enzyme in gram-negative isolates.

Genotypic methods are targeted to detect resistance genes (mostly bla type genes) and polymerase chain reaction (PCR) is a common method. Other genotypic method is clonal typing. Although detection of resistant-encoding genes is more accurate, however, these methods are usually expensive and not available anywhere. Some other mechanisms of resistance to carbapenems including loss of porins, efflux pump mutation, and target site inactivation have been identified.

Data on the status of carbapenem-resistant microorganisms in the Middle East countries are scarce. The aims of this review were to collect available data regarding methods of detection and prevalence of resistance to carbapenems in a Middle East region.

Methods

Databases

Biomedical electronic databases (Scopus, Medline, Google Scholar, and Science Direct) were systematically searched to find related articles. The key terms used were “carbapenem-resistant, resistant gram-negative bacilli, Enterobacteriaceae, fermenting and non-fermenting gram-negative bacilli, Pseudomonas, Acinetobacter, Klebsiella and Iran”. A total of 586 articles were found. After primary screening, 275 relevant articles were selected to be assessed thoroughly.

Study settings

Of the 275 articles, case reports, systematic reviews, meta-analysis, and articles in Persian language were excluded, and finally 97 English-language articles were included in the present review. These studies were published between 2006 and 2018 and were reported from different regions of Iran. Forty-eight studies were from Tehran and most of them were done at Motahari hospital (Level I Iranian burn hospital). The number of publications from other areas were as follows: ten in Isfahan, eight in northwest of Iran, five in south of Iran, four in Shiraz, three each in Hamadan, Arak and Mazandaran, two each in Shahrekord, Kermanshah, Mashhad, and Zanjan, and one each in Kerman, Khorraramabad, and Qom. All the studies considered the standards and guidelines of the clinical and laboratory standards institute (CLSI) for the preparation and interpretation of the tests. Figure 2 illustrates data processing in this review.

Clinical and microbiological setting

All the studies included inpatients, with eight also considering outpatients. If the source of the samples was specific, they

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**Figure 1** Screening methods for carbapenem-resistant microorganisms.

**Notes:** 1MHT was the most used phenotypic method in Iranian studies. MHT originally detects KPC, but if zinc sulfate is added to MHT culture media, it can detect MBL. It is based on carbapenemase inhibition by betalactamase inhibitors. CDT consists of two disks: a carbapenem and the other combination of a carbapenem and a betalactamase inhibitor. If the disk with inhibitor shows a bigger inhibition zone, the result is considered positive. DDST consists of carbapenem discs at a variable distance to inhibitor discs. The observation of synergy between disks is noted as a positive result. 3These phenotypic methods can detect different Ambler classes. 4CIM is a newer phenotypic method that was introduced in 2015 by van der Zwaluw. A carbapenem disk is inserted in culture media of suspected strain. Then it is transferred to another culture media with an inhibitor. If the disk with inhibitor shows a bigger inhibition zone, the result is considered positive. 5Some other phenotypic methods like spectrometric assays are also used and have higher sensitivity and specificity, but they are costly and time consuming.

**Abbreviations:** CDT, combination disk test; CIM, carbapenem inactivation method; DDST, double disk synergy test; ESBL, extended spectrum β-lactamase; KPC, Klebsiella-producing carbapenemase; MBL, metallo-β-lactamase; MHT, modified Hodge test; MIC, minimum inhibitory concentration; PCR, polymerase chain reaction.
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are mentioned and if they were collected from different sites, they are named as “different sites”.

All studies have been categorized into four distinct groups:

1. Studies that reported carbapenem-resistant microorganisms according to the disk diffusion method
2. Studies that considered phenotypic methods
3. Studies that used genotypic methods
4. Studies that applied both genotypic and phenotypic assays

Results

Studies that reported carbapenem-resistant microorganisms according to the disk diffusion method (early detection of resistance to a carbapenem)

In this category, detection of resistance to a carbapenem was described only by disk diffusion method. However, in some of them, minimum inhibitory concentration (MIC) values were determined. No phenotypic or genotypic assay was considered for carbapenemase detection. A total of 3,396 isolates were reported in this group (Table 1).

Screening of resistance to a carbapenem according to the disk diffusion method was common among the studies. Although this method may be applicable for many antimicrobials, however, for carbapenems more confirmatory tests beyond the disk diffusion assay are needed. In this setting, MIC would help for detection of resistant isolates.

Five studies were multicenter, but the sample sizes for three of them were small. The trend of resistance to a carbapenem did not follow a specific pattern. However, in two studies, 40% of the isolates were resistant to a carbapenem.

Studies that considered phenotypic methods

A total of 4,264 isolates were included in this category and Acinetobacter spp. and K. pneumonia were the common isolates. Modified Hodge test (MHT) was used as a common phenotypic test in most studies. MHT can detect Ambler class A (KPC), although it may be positive with the presence of other carbapenemase enzymes. Other applied tests were combination disk test (CDT) for detection of MBL or extended spectrum β-lactamase and the double disk synergy test for detection of MBL. In the study by Raategar Lari et al, 92% of A. baumannii isolates were resistant to imipenem and only 24% of them were MBL positive in the CDT test, but in the next study, 54% of isolates were resistant to imipenem and all of them were KPC producers according to the phenotypic tests.

The rates of resistance to aminoglycosides and fluoroquinolones were similar to those of carbapenems, although no special trend can be followed through different years. The results are provided in Table 2.

Studies that included genotypic methods

A total of 2,195 strains were included in this group and except for three studies, all assessed Acinetobacter spp. mostly A. baumannii. PCR was performed in order to determine types of bla genes. In some studies, MIC values were correlated with the presence of bla genes. In the study by Taherikalani et al, the MIC values of 256 mcg/mL were detected in strains with more than two blaOXA genes. In the study by Azizi et al, higher MIC value was associated with presence of bla-OXA-24/40 like. Bahador et al detected Isba genes. When these elements were placed upstream of OXA-type genes, they enhanced the expression of OXA-type genes. Presence of
Table 1 Screening of carbapenem-resistant isolates (disk diffusion method)

| Author (year)          | Setting                     | Population          | Samples                | Microorganism (No.) | MIC<sup>a</sup> | Resistance rate to FQ and AG | Results<sup>b</sup>                                                                 | Weak points                          | Strength points |
|------------------------|-----------------------------|---------------------|------------------------|---------------------|-----------------|-----------------------------|--------------------------------------------------------------------------------|-------------------------------------|-----------------|
| Mobaraki et al (2018)<sup>15</sup> | Hospitals in Tabriz         | Inpatients and outpatients | Different sites        | Pseudomonas aeruginosa (200) | –               | TOB 57% GEN 62% CIP 62%     | 46.5% of isolates were resistant to IPM                                           | –                                   | Multicenter study |
| Ghanbari et al (2017)<sup>16</sup> | One hospital in Fuladshahr  | General inpatients   | Urine                  | Different strains (317) | –               | –                           | 9.5% of Escherichia coli, 11% of Klebsiella and 25% of Proteus spp. isolates were resistant to IPM | –                                   | Large sample size |
| Chahoofard et al (2017)<sup>17</sup> | One hospital in Bandar Abbas | General inpatients   | Urine                  | Different strains (296) | –               | –                           | Resistance rate to IPM: Enterobacter spp. 7.1% Citrobacter spp. 0% E. coli 4.9% Klebsiella pneumonia 19.2% P. aeruginosa 21.4% Acinetobacter baumannii 53.2% | –                                   | Adequate sample size, Clinical status of patients including duration of hospital stay and comorbidities were evaluated |
| Ansari et al (2017)<sup>18</sup> | Two hospitals in Shahrekord | General inpatients   | Urine, blood, sputum, wound | A baumannii (30) | –               | NAL 80%, OFX 86% LVX 66%   | About 55% of strains were resistant to IPM and DOR Intermediate resistance rate was 10%–33.3% | Small sample size, AGs were not tested | Multicenter study, Large sample size |
| Douraghi et al (2016)<sup>19</sup> | Four hospitals in Tehran    | General inpatients and outpatients | Different sites        | A baumannii (400) | ✓               | –                           | 97% were resistant to carbapenems MIC values of all resistant isolates were above 32 mcg/mL | –                                   | Multicenter study, Large sample size |
| Ghasemian et al (2016)<sup>20</sup> | Four hospitals in Mazandaran | General ICU patients  | Different sites         | Acinetobacter spp. (50) | ✓               | CIP 96% AMK 100%            | Resistance to IPM and MEM according to E-test was 100%, and according to disk diffusion was 76% and 96%, respectively Most common site for sampling was endotracheal tube | –                                   | Multicenter study |
| Babamahmood et al (2015)<sup>21</sup> | Three hospitals in Mazandaran | ICU patients         | Wound, respiratory secretions, urine, blood | Different strains (114) | –               | –                           | 14% of P. aeruginosa, 60% of Acinetobacter spp., 33% of E. coli, 16% of Enterobacter and none of K. pneumonia isolates were resistant to IMP | –                                   | Multicenter study, Demographic features and risk factors for hospital-acquired infection were described |

(Continued)
### Table 1 (Continued)

| Author (year)       | Setting                              | Population                      | Samples              | Microorganism (No.)                      | MICa                      | Resistance rate to FQ and AG | Resultsb                                                                 | Weak points                                                                 | Strength points |
|---------------------|--------------------------------------|---------------------------------|----------------------|------------------------------------------|--------------------------|----------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------|
| Mohajeri et al (2014)⁴ | Three hospitals in Kermanshah         | General inpatients              | Blood, urine, sputum | Acinetobacter spp. (104)                 | –                        | Not defined                | • 48% of isolates were resistant to carbapenems (imipenem and meropenem). 76% of carbapenem-resistant strains were isolated from sputum samples | • Few antibiotics were tested                                               | • Multicenter study |
| Babakhani et al (2014)⁵ | One hospital in Khorramabad           | General inpatients (mostly ICU) | Different sites      | Klebsiella spp. (80)                     | –                        | GEN 52 % AMK 7.5% CIP 82 % OFX 75% NAL 60% CIP 97%                       | • Resistance rates to MEM and IPM were 100% and 62% (27.5% intermediate resistant to IPM) | –                                                                            |
| Kamalbeik et al (2013)⁶ | One Poisoning center in Tehran        | ICU patients                    | Different sites      | Acinetobacter spp. (40)                  | –                        | CIP 60% GEN 60% AMK 26%                                               | • Resistance rates to IPM were 32% in inpatients and 4% in outpatients. Resistance rates to IPM in inpatients: *Enterobacter* 56%, *Serratia* 54%, *Klebsiella* 35%, *E. coli* 32%, and *Proteus* 11% | –                                                                            | • Small sample size |
| Hashemi et al (2013)⁷  | Two hospitals in Hamadan              | General inpatients and outpatients | Different sites     | Enterobacteriaceae spp. (574)            | –                        | –                          | • 73% of isolates were resistant to IPM                                | • Very small sample size                                                   | –                                                                            |
| Shakibaie et al (2012)⁸ | One hospital in Kashan                | ICU patients                    | Different sites      | Acinetobacter spp. (15)                  | ✓                        | CIP 60% GEN 60% AMK 26%                                               | • MIC range for resistant strains was 128–240 and MIC of IPM for seven isolates was 240 mcg/mL | –                                                                            | • Demographic and medical data of patients were provided                  |
| Rahbar et al (2010)⁹  | One hospital in Tehran                | General inpatients              | Different sites      | P. aeruginosa (109) Acinetobacter spp. (88) Stenotrophomonas maltophilia (48) Burkholderia cepacia (12) | –                        | –                          | • 1%, 16%, and 98% of *A. baumannii*, *P. aeruginosa*, and *S. maltophilia* isolates were resistant to IPM, respectively | –                                                                            | –                                                                            |

(Continued)
Table 1 (Continued)

| Author (year) | Setting | Population | Samples | Microorganism (No.) | MIC<sup>+</sup> | Resistance rate to FQ and AG | Results<sup>+</sup> | Weak points | Strength points |
|---------------|---------|------------|---------|--------------------|-----------------|-----------------------------|------------------|-------------|----------------|
| Soroush et al (2010)<sup>2</sup> | One pediatric hospital in Tehran | General pediatric patients | Different sites | Acinetobacter spp. (145) | | | In 2007: CIP 79% AMK 58% KAN 71% GEN 65% TOB 61% | • Resistance rate to IPM and MEM was analyzed in years 2006 and 2007 that was about 50% | • Carbapenem resistance was evaluated only in the last 2 years (2006–2007) | • Evaluated carbapenem resistance status in pediatrics |
| Yousefi et al (2010)<sup>1</sup> | One hospital in Orumie | General inpatients and outpatients | Different sites | P. aeruginosa (160) | ✓ | | | • Approximately 40% of isolates were resistant to IPM, which means MIC for them was 31 mcg/mL | • Just IPM was tested | |
| Rahbar et al (2008)<sup>3</sup> | One hospital in Tehran | General inpatients and ICU patients | Not defined | Different strains (202) | ✓ | c | | • 40% and 7% of P. aeruginosa and 38% and 27% of A. baumannii isolates were resistant to MEM and IMP, respectively | | |

Notes: MIC values of carbapenems (and not other antimicrobial agents) were determined. Resistance rates were reported according to the disk diffusion test. The unit for all reported MIC values is mcg/mL. For complete information about the resistance to AG and FQ, refer to the original reference.

Abbreviations: AG, aminoglycoside; AMK, amikacin; CDT, combination disk test; CIP, ciprofloxacin; DD, disk diffusion; DDST, double disk synergy test; DOR, doripenem; ERT, ertapenem; ESBL, extended spectrum β-lactamase; FQ, fluoroquinolones; GEN, gentamicin; ICU, intensive care unit; IPM, imipenem; KAN, kanamycin; LVX, levofloxacin; MBL, metallo-β-lactamase; MEM, meropenem; MHT, modified Hodge test; MIC, minimum inhibitory concentration; NAL, nalidixic acid; NOR, norfloxacin; OFX, ofloxacin; TOB, tobramycin.
### Table 2: Studies that considered phenotypic methods for detecting carbapenemase enzymes

| Author (year)               | Setting                          | Population          | Samples          | Microorganism (no.)                  | MIC<sup>a</sup> | Method of carbapenemase detection | Resistance to FQ and AG | Results<sup>+</sup>                                                                                     | Weak points                                           | Strength points |
|-----------------------------|----------------------------------|---------------------|------------------|-------------------------------------|----------------|-----------------------------------|------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|-----------------|
| Ghotaslou et al (2018)<sup>26</sup> | Five hospitals in East and West Azerbaijan | General inpatients | Different sites | Enterobacteriaceae (307)            | –             | DD, BA and DPA for MBL detection  | –                      | Resistance rate to carbapenem was observed only in K. pneumonia (57 isolates; 25%–45%)<br>Of these 57 isolates, phenotypic methods revealed that 15%, 7%, and 3% isolates of Klebsiella had MBL, KPC, and OXA-48 genes, respectively<br>Most of the carbapenemase strains were isolated from urine and blood<br>Resistance rate to IPM was 45%<br>6 (7.4% of all) isolates were positive for MHT test<br>Resistance rates to IPM, MEM, and ERT were 95%, 96%, and 53%, respectively<br>53% of all strains were MHT positive | Small sample size for each species | –                |
| Saadatian Farivar et al (2018)<sup>27</sup> | Three hospitals in Tehran | Inpatients and outpatients | Different sites | Klebsiella pneumonia (81)           | –             | DD, MHT for MBL detection        | –                      | –                                                                                                                   | –                                                      | –                |
| Moosavian et al (2014)<sup>28</sup> | Two hospitals in Ahvaz | General inpatients | Different sites | Acinetobacter spp. (100)            | –             | DD, MHT                          | –                      | –                                                                                                                   | –                                                      | –                |

<sup>a</sup> Method of carbapenemase detection: DD = Disappearance of diffusion, BA = Bacterial aggregation, DPA = Diffusion pattern analysis, MHT = Modified Hodge test, OFX = Ormeroxime, CIP = Ciprofloxacin, NOR = Norfloxacin, AMK = Amikacin, KAN = Kanamycin, GeN = Gentamicin, IPM = Imipenem, MeM = Meropenem, eRT = Ertapenem, TOB = Tobramycin, KAN = Kanamycin.
Table 2 (Continued)

| Author (year)                     | Setting                  | Population     | Samples       | Microorganism (no.) | MIC $^a$ Method of carbapenemase detection | Resistance to FQ and AG | Results $^a$ | Weak points                                                                 | Strength points   |
|----------------------------------|--------------------------|----------------|---------------|---------------------|------------------------------------------|-------------------------|--------------|------------------------------------------------------------------------------|------------------|
| Jonaidi Jafari et al (2014)$^{19}$ | One hospital in Tehran   | General inpatients | Different sites | Different strains (350) | ✓                                        |                         |              | • MIC was determined by E-test                                                |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • 95 strains were ESBLs                                                       |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • Resistance rates to IPM and MEM according to MIC, respectively, were:       |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • Acinetobacter baumannii 42%, 37%                                            |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • Pseudomonas aeruginosa 42%, 60%                                             |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • K. pneumonia 15%, 0%                                                         |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • 95 strains were ESBLs                                                       |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • Resistance rates to IPM and MEM according to MIC, respectively, were:       |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • Acinetobacter baumannii 42%, 37%                                            |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • Pseudomonas aeruginosa 42%, 60%                                             |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • K. pneumonia 15%, 0%                                                         |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • 5 isolates were ESBL positive                                               |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • 67 isolates were ESBL producers and resistance to carbapenem in this group was about 10% |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • 21 isolates were MBL producers and resistance to carbapenem among them was almost 100% |                  |
|                                  |                          |                |               |                     |                                          |                         |              | • 5 isolates were both MBL and ESBL positive                                   |                  |
| Ghadiri et al (2014)$^{20}$       | Three laboratories in Tehran | General outpatients | Urine          | Escherichia coli (300) | • DD                                    |                         |              | • Small sample size for each microorganism                                      |                  |
|                                  |                          |                |               |                     | • CDT for ESBL detection                  |                         |              | • Large sample size                                                           |                  |
|                                  |                          |                |               |                     | • DDST for MBL detection                  |                         |              |                                                                              |                  |

(Continued)
| Author (year)               | Setting                      | Population                     | Samples            | Microorganism (no.) | MIC<sup>a</sup> | Method of carbapenemase detection | Resistance to FQ and AG | Results<sup>b</sup>                                                                 | Weak points                                                                                      | Strength points |
|---------------------------|------------------------------|--------------------------------|--------------------|---------------------|-----------------|-----------------------------------|-----------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------|
| Fazeli et al (2014)<sup>31</sup> | Teaching hospitals in Isfahan | General inpatients and ICU patients | Different sites   | *K. pneumonia* (142) | –               | • DD                              | Resistance rate to GEN and AMK and CIP: 70%–80% LVX: 50%–60%                  | • Resistance rates to IPM, MEM, and ERT among all strains were 57%, 52%, and 47%, respectively | • It is not clear that the study was multicenter or not |
| Mirsalehi et al (2014)<sup>32</sup> | Motahari hospital            | Burn patients                  | Probably burn wounds | *P. aeruginosa* (100) | ✓               | • DD                              | • AmpC disk test and CDT were positive for 54 and 17 isolates, respectively showing a probable activation of one of the efflux pump and impermeability systems, or both | • All IPM-resistant *Pseudomonas* were chosen and mean MIC for IPM was 64 mcg/mL | –                 |

<sup>a</sup> Method of carbapenemase detection

<sup>b</sup> Results of susceptibility testing

(Continued)
Table 2 (Continued)

| Author (year) | Setting | Population | Samples | Microorganism (no.) | MIC * | Method of carbapenemase detection | Resistance to FQ and AG | Results * | Weak points | Strength points |
|---------------|---------|------------|---------|---------------------|-------|----------------------------------|-----------------------|-----------|-------------|-----------------|
| Moayednia et al (2014) | One hospital in Isfahan | General inpatients and outpatients | Urine | K. pneumonia (484) and E. coli (1,080) | DD | Double Disk for ESBL | Just reported for ESBL producer | • Resistance rate to carbapenem for E. coli was 1%–2% and for Klebsiella spp., it was 41%–46% | • MIC was done by E-test, but cutoffs were not reported | • Large sample size |
| Erfani et al (2013) | Three hospitals in Tehran | General inpatients | Different sites | Acinetobacter sp. (107) | DD | CDT for MBL detection | CIP 95% LVX 93% GEN 51% TOB 64% | • Resistance rate to IPM and MEM was about 95% and 92% of these resistant isolates were MBL positive | • Mortality rate was reported | • Detection of Integron genes |
| Lari et al (2013) | One hospital in Tehran (Motahhari) | Burn patients | Mostly burn wound | Acinetobacter spp. (69) | SDDT for ESBL detection | GEN 64.7% AMK 95.7% KAN 97.1% TOB 2.9% CIP 97.1% | • Resistance rate to IPM was 92% | • ESBL was positive in 10% of isolates | • 24% of all baumannii isolates were MBL positive | • The mortality rate in this study was 20% |

(Continued)
### Table 2 (Continued)

| Author                  | Setting                                  | Population     | Samples       | Microorganism (no.) | MIC<sup>a</sup> Method of carbapenemase detection | Resistance to FQ and AG | Results<sup>b</sup> | Weak points                                                                 | Strength points                  |
|-------------------------|------------------------------------------|----------------|---------------|---------------------|-------------------------------------------------|------------------------|-------------------|-----------------------------------------------------------------------------|----------------------------------|
| Rastegar Lari et al (2013)<sup>15</sup> | One hospital in Tehran (Motahari)         | Burn patients  | Burn wounds   | Klebsiella spp. (35) | –                                               | AMK 71% GEN 72% TOB 86% | • Resistance rate to IPM was 54% and all were KPC producers<br>• 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes<br>• Rate of mortality in patients infected with resistant strain was 33% | • FQ and colistin were not tested<br>• MIC values were not reported<br>• Small sample size | • Mortality rate was reported |
| Safari et al (2013)<sup>15</sup> | Three educational hospitals in Hamadan   | ICU patients   | Trachea, blood, urine, sputum, wounds | A. baumannii (100) | ✓                                               | Resistant: CIP 97% LVX 91% AMK 84% GEN 88% | • Resistance rate to carbapenem was 85%–94% but according to MIC, it was 87%–99%<br>• 99% of all isolates were MBL producers<br>• The result of disk diffusion for carbapenem was not reported<br>• 126 isolates (30% of all) were MBL positive<br>• Risk factors like immunosuppression and use of antibiotics during the past 2 weeks were correlated with infection by MBL producers | • Multicenter study<br>• MIC was reported |                                               |
| Masaeli et al (2012)<sup>16</sup> | Two hospitals in Sanandaj                | General inpatients | Different sites | Different strains (423) | –                                               | GEN 70% AMK 80% CIP 37% NOR 42% | • The resistance pattern of each group of microorganisms was not fully defined |                                               | • Correlation between being MBL and different clinical risk factors was assessed |

<sup>a</sup> Method of carbapenemase detection
- DD
- MHT for KPC production
- e-test for MBL detection

<sup>b</sup> Results
- AMK 71%
- GEN 72%
- TOB 86%
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>c</sup> Multicenter study

<sup>15</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>16</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>17</sup> Multicenter study

<sup>18</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>19</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>20</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>21</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>22</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>23</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>24</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>25</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>26</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>27</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>28</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported

<sup>29</sup> Resistance to FQ and AG
- Resistance rate to IPM was 54%
- 7 out of 28 patients had two Klebsiella isolates with two different antibiotypes
- Rate of mortality in patients infected with resistant strain was 33%
- FQ and colistin were not tested
- MIC values were not reported
- Small sample size
- Mortality rate was reported
### Table 2 (Continued)

| Author (year)                          | Setting                       | Population                          | Samples                  | Microorganism (no.)       | MIC<sup>a</sup> | Method of carbapenemase detection | Resistance to FQ and AG | Results<sup>b</sup>                                                                 | Weak points                                                                                           | Strength points                                      |
|----------------------------------------|-------------------------------|-------------------------------------|--------------------------|---------------------------|-----------------|-----------------------------------|-------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------------------------|
| Japoni-Nejad et al (2013)<sup>27</sup> | One hospital in Arak           | General inpatients and environmental isolates | Different strains       | A. baumannii (63)           | ✓               | MHT for KPC detection             |                         | Amikacin 80% Netilmicin 54%                                                   | 84% were resistant to carbapenem                                                                  | Isolates from environment of hospital were also included                                 |
|                                        |                               |                                     |                          |                           |                 | E-test                             |                         | 84% were resistant to carbapenem                                                  | 60 strains had MIC more than 256                                                               | Small sample size                                                    |
|                                        |                               |                                     |                          |                           |                 |                                    |                         | 47 isolates were MBL producers according to E-test and three of them were MHT positive | From all, 30 and 36 isolates were KPC producers according to MHT and CHROMagar, respectively. The infection of burn wounds at the highest percentage: 27 cases (75%) | Multicenter study                                                |
| Haji Hashemi et al (2012)<sup>28</sup> | Different hospitals in Tehran and Isfahan | General inpatients and outpatients | Different sites           | Klebsiella pneumoniae (244) | –               | DD and MHT for KPC detection      |                         | MHT and CHROMagar were compared                                                   | Mic was not reported                                                                                        | Mic was not reported                                                                   |
|                                        |                               |                                     |                          |                           |                 |                                    |                         | From all, 30 and 36 isolates were KPC producers according to MHT and CHROMagar, respectively. The infection of burn wounds at the highest percentage: 27 cases (75%) | Multicenter study                                                | Multicenter study                                                |
| Author (year) | Setting | Population | Samples | Microorganism (no.) | MIC<sup>a</sup> Method of carbapenemase detection | Resistance to FQ and AG | Results<sup>b</sup> | Weak points | Strength points |
|--------------|---------|------------|---------|--------------------|-------------------------------------------------|------------------------|----------------|-------------|----------------|
| Azimi et al (2012)<sup>c</sup> | Two burn hospitals in Tehran | Infant and pediatric patients | Not defined (probably burn wounds) | Klebsiella, Acinetobacter, and Pseudomonas (64 strains from 20 patients) | – | DD, MHT for KPC production, CDT for ESBL detection | Not defined | 36 isolates were resistant to all tested antibiotic (not mentioned which antibiotics) except Colistin | Types of samples were not defined, The sample size is very small (7 A. baumannii, 16 Enterobacteriaceae, 12 Pseudomonas) |
| Japoni et al (2006)<sup>c</sup> | One hospital in Shiraz | General inpatients | Different sites (mostly wound) | P. aeruginosa (70) | ✓ | DD, DDST for ESBL, MHT for MBL detection | CIP 73% AMK 93% TOB 97% | Resistance rate to carbapenems was 33% | Small sample size |

Notes: <sup>a</sup>MIC values for carbapenems (but not other antimicrobial agents) were determined. <sup>b</sup>Resistance rates were according to the result of disk diffusion test. <sup>c</sup>For complete information about the resistance to AG and FQ, please refer to the original reference.

Abbreviations: AG, aminoglycoside; AMK, amikacin; BA, boronic acid; CDT, combination disk test; CIP, ciprofloxacin; DD, disk diffusion; DDST, double disk synergy test; DOR, doripenem; DPA, dipicolinic acid; ERT, ertapenem; ESBL, extended spectrum β-lactamase; FQ, fluoroquinolones; GEN, gentamicin; ICU, intensive care unit; IPM, imipenem; KAN, kanamycin; KPC, Klebsiella-producing carbapenemase; LVX, levofloxacin; MBL, metallo-β-lactamase; MEM, meropenem; MHT, modified Hodge test; MIC, minimum inhibitory concentration; NAL, nalidixic acid; NOR, norfloxacin; OFX, ofloxacin; TOB, tobramycin.
these elements in genetic contents of gram-negative isolates would lead to higher rate of resistance to carbapenems. Table 3 describes the details of each study in this category.42,45–61

Studies that considered both phenotypic and genotypic methods
A total of 6,759 isolates were identified in this category. In most studies more than one phenotypic method was applied. In the study by Hosseinirad et al, 29 strains were carbapenem resistant, in which 27 and 23 of them were MHT positive and carried blaNDM-1 gene, respectively.62 However, in another study by Bina et al, although MHT tests were positive, no resistance gene was found.63

The detection of resistance genes was much lower for strains other than A. baumannii. In the study by Lari et al in 2015, only 9 strains of P. aeruginosa (out of 255) contained resistance genes,64 but in the study by Bagheri Josheghani et al, at the same time, more than 90 strains (out of 124) of A. baumannii harbored resistance genes.65 Data are summarized in Table 4.66–105

Discussion
Increase in the rate of resistance to carbapenem antibiotics among gram-negative isolates is a worldwide concern, especially in developing countries. The results of this review also showed this threat in the recent decade in a country of Middle East area, Iran. Although the prevalence of carbapenem-resistant gram-negative rods was reported according to the disk diffusion method in most studies, phenotypic and genotypic assays confirmed this pattern in some available surveys.

Resistance to carbapenem antibiotics in the same years in a country of neighborhood, Saudi Arabia, shows lower resistance rate in comparison with Iran.106 In 2010, resistance to carbapenems was reported in 10%–66% of gram-negative isolates in Saudi Arabia, which was lower than that in Iran (86%).11 The results were different in Europe. In the year 2006–2007, 4% and 85% of gram-negative isolates were carbapenem resistant in North and South of Europe, respectively. Although data were limited to year 2006, Iran had a better condition compared with the South of Europe, but worse than North of Europe.107 The results of another study in year 2012 also confirmed this pattern in North and South of Europe.108 In case of P. aeruginosa, MIC values that were reported for carbapenem-resistant strains were dramatically different from European countries. In year 2011, Castanheira et al detected a mean MIC value >2 mcg/mL for carbapenem-resistant P. aeruginosa in 14 European countries.109 Yousefi et al in Iran reported an MIC >32 mcg/mL for most of carbapenem-resistant P. aeruginosa isolates. At these times, the CLSI and European Committee on Antimicrobial Susceptibility Testing cutoff values for carbapenem resistance were 2 and 8 mcg/mL, respectively.11

Incremental trend of resistance to carbapenem antibiotics was evident through 2006–2018. The least resistance rate was reported by Rahbar et al in year 2010 at Milad Hospital. In this year, 1.1% of A. baumannii isolates were resistant to imipenem.22 This conclusion may be misleading, because 2 years earlier (in 2008), in this hospital, 27% and 40% of the same isolates were resistant to imipenem and meropenem, respectively.12 Tarashi et al assessed the trend of antibiotic resistance in A. baumannii through years 2012–2015.71 The results showed that resistance in P. aeruginosa increased from 83% in year 2012 to 96% in year 2015. Also 100% of A. baumannii were resistant to carbapenem among these years.

The resistance patterns for other microorganisms did not follow specific trends. For example, 60% of P. aeruginosa isolates were imipenem resistant in the year 2010,101 but this rate was 25% in another hospital in the year 2016.59 Outpatients-isolated P. aeruginosa strains showed less resistance rates (13% in Ahangarzadeh Rezaee et al10 and 4.4% in Hashemi et al21). However, carbapenem-resistant rates were dramatically high in studies that included ICU samples.9,20 In an earlier study,9 100% and 62% of P. aeruginosa isolates were resistant to imipenem and meropenem, respectively, and in a latter study,20 about 100% of them were resistant to both carbapenems.

Most of the carbapenem-resistant microorganisms were isolated from burned patients, and many studies placed in this group were from Motahari Hospital. Motahari is a referral teaching burn hospital in center of Iran and most complicated burned patients are referred from all areas of the country. Increasing resistance rates can be observed through different years in burn patients; 50%–60% in year 2008 to 90% in year 2017.42,46 Also, the presence of blaOXA type genes has increased from half of the resistant strains to almost 80% of them. This can be a warning alarm regarding administration of antibiotics in burned patients.

Disk diffusion is the initial method for detection of resistant strains; however, it does not have enough accuracy for antimicrobial agents like carbapenem. Most evaluated studies considered disk diffusion method. Beside disk diffusion, MIC breakpoints can be used to confirm the results of disk diffusion (Figure 3).

Although MHT has been widely used as the preferred phenotypic method for detection of MBL, it is not recommended in latest version of CLSI, due to its low sensitiv-
| Author (year)     | Setting                  | Population                        | Samples                      | Microorganism (no.)          | MIC            | Method of carbapenemase detection | Resistance to FQ and AG | Results | Weak points | Strength points | Found carbapenemase genes* |
|------------------|--------------------------|-----------------------------------|------------------------------|-------------------------------|----------------|----------------------------------|-------------------------|---------|-------------|----------------------|---------------------------|
| Sharikhani et al (2017) | Four hospitals in Qom       | General inpatients (mostly ICU)   | Different sites              | Acinetobacter baumannii (108) | –              | DD, PCR                           | CIP and AMK 93% GEN 81% LVX 91% TOB 47% | –       | –           | –                     | bla<sub>OXA-23</sub>, bla<sub>OXA-58</sub>, bla<sub>OXA-40</sub>, bla<sub>OXA-143</sub> |
| Mohammadi et al (2017)   | Two hospitals in Tehran    | General inpatients                | Burn wound and trachea       | A. baumannii (103)            | –              | DD, PCR                           | About 90% of isolates were resistant to carbapenem, bla<sub>OXA-23</sub>, bla<sub>OXA-58</sub>, bla<sub>TeM</sub>, and bla<sub>PER</sub> genes were detected in 90%, 38%, 1%, 60%, and 18.5% of all isolates, respectively | –       | –           | –                     | bla<sub>OXA-23</sub>, bla<sub>OXA-58</sub>, bla<sub>TeM</sub>, bla<sub>PER</sub> |

(Continued)
Table 3 (Continued)

| Author (year) | Setting | Population | Samples | Microorganism (no.) | MIC Method of carbapenemase detection | Resistance to FQ and AG | Results | Weak points | Strength points | Founded carbapenemase genes |
|---------------|---------|------------|---------|---------------------|--------------------------------------|------------------------|---------|-------------|------------------|-----------------------------|
| Bahador et al (2015)¹⁴ | One hospital in Tehran | Burn patients | Not defined (probably burn wounds) | A. baumanii (62) | ✓ | DD | Not reported specifically | • According to MIC values, 61% were resistant to IPM | • Resistance to each antibiotic was not reported specifically | • MIC values of IPM, tigecycline, and colistin were reported | bla<sub>oxa-51</sub>, bla<sub>oxa-23</sub>, bla<sub>oxa-47</sub>, bla<sub>oxa-143</sub> |
| Kooti et al (2015)¹⁷ | Four hospitals in Shiraz | General inpatients | Different sites | A. baumanii (200) | – | DD, PCR | GEN 84.5%, AMK 86.5%, CIP and LVX 99.5% | • About 99% of isolates were resistant to IPM and MEM | – | Multicenter study | bla<sub>oxa-23</sub>, bla<sub>oxa-24</sub>, bla<sub>oxa-58</sub> |
| Author (year)          | Setting                  | Population          | Samples                  | Microorganism (no.)                          | MIC Method of carbapenemase detection | Resistance to FQ and AG | Results§                  | Weak points                                                                 | Strength points | Founded carbapenemase genes§ |
|-----------------------|--------------------------|---------------------|--------------------------|---------------------------------------------|---------------------------------------|----------------------------|----------------------------|--------------------------------------------------------------------------------|----------------|-----------------------------|
| Azizi et al (2015)²³  | Two hospitals in Kerman  | ICU patients        | Different sites          | A. baumannii (65 MDR strains from 266)     | ✓ DD, PCR                              | CIP 100% AMK 78.5% TOB 93% | • MIC values for IPM and MEM for 76% of strains were >256 mcg/mL<br>• ble oxa-23 was found in all isolates including sensitive and resistant isolates<br>• Presence of ble OXA-24/40 (29 strains) associated with higher MIC<br>• 81% of strains were resistant to carbapenem<br>• All resistant isolates had at least one ble OXA-23 and/or ble OXA-24 and about half of them had both genes | --                                                            | --                        | ble oxa-23, ble oxa-24 |
| Mahdian et al (2015)²⁰ | One hospital in Tehran (Motahari) | Burn patients | Burn wounds, blood, urine | A. baumannii (37)                          | -- DD, PCR, Clonal typing            | CIP 100% GEN 94.6%            | • Small sample size<br>• Few antibiotics were tested<br>• MIC values for colistin and polymyxin B were reported<br>• ISAba genes were assessed | --                                                            | --                        | ble oxa-23, ble oxa-24 |

(Continued)
| Author (year) | Setting | Population | Samples | Microorganism (no.) | MIC | Method of carbapenemase detection | Resistance to FQ and AG | Results | Weak points | Strength points | Founded carbapenemase genes |
|--------------|---------|------------|---------|---------------------|-----|-------------------------------|------------------------|---------|-------------|-----------------|-------------------|
| Farsiani et al (2015) | One hospital in Mashhad | General inpatients and ICU patients | Different sites | A. baumannii (36) | ✓ | DD, PCR, Clonal typing | CIP 97% | - | - | - | bla<sub>OXA-51</sub> and bla<sub>OXA-23</sub> detected in all isolates. From all isolates, bla<sub>OXA-24</sub>, bla<sub>TeM</sub>, bla<sub>ADC</sub>, and bla<sub>vIM</sub> genes were found in 23, 34, 22, and 23 strains, respectively. ISAba1 was detected in 97% of isolates of A. baumannii. |
| Nasrolaei et al (2014) | Two hospitals in Tehran and Sari | ICU and burn patients | Trachea and burn wounds | A. baumannii (100) | - | DD, PCR | STP 90% GEN 83% TOB 83% KAN 80% | - | - | - | bla<sub>OXA-23</sub> |
| Safari et al (2014) | Three hospitals in Hamadan | ICU patients | Different sites | Pseudomonas aeruginosa (100) | ✓ | DD, PCR | AMK 19% GEN 28% TOB 27% LVX 28% CIP 38% | - | - | - | bla<sub>ADC</sub> and bla<sub>IMP</sub> |

(Continued)
Table 3 (Continued)

| Author (year) | Setting | Population | Samples | Microorganism (no.) | MIC | Method of carbapenemase detection | Resistance to FQ and AG | Results | Weak points | Strength points | Founded carbapenemase genes* |
|---------------|---------|------------|---------|---------------------|-----|---------------------------------|-----------------------|---------|-------------|--------------------------|-------------------------------|
| Bahador et al (2014) | Two hospitals in Tehran | ICU patients | Different sites | A. baumannii (100) | ✓ | DD, Clonal typing | | | | | |
| Karmostaji et al (2013) | Two hospitals in Tehran | General inpatients (mostly ICU) | Different sites | Acinetobacter spp. (131) | | DD, PCR | CIP 95%, GEN 77%, AMK 54% | | | | |

- Resistance rates were compared among years 2006 and 2011, according to MIC cutoffs.
- In year 2006, resistance rate to IPM was 30% with MIC ≤4–64 mcg/mL. In year 2011 it was 48% and MIC values were ≤4 to ≥256 mcg/mL.
- Genotypes I and F were the most frequent genotypes in years 2006 and 2011, respectively.
- Resistance rate to IPM and MEM were 67% and 84%, respectively.
- 107, 17, and 1 of the resistant isolates carried \( \text{bla}_{OXA-23} \), \( \text{bla}_{OXA-24} \), and \( \text{bla}_{OXA-58} \), respectively. From these strains, seven strains had both \( \text{bla}_{OXA-23} \) and \( \text{bla}_{OXA-24} \).
| Author (year)          | Setting                        | Population   | Samples      | Microorganism (no.) | MIC Method of carbapenemase detection | Resistance to FQ and AG | Results | Weak points | Strength points | Founded carbapenemase genes |
|-----------------------|--------------------------------|--------------|--------------|---------------------|----------------------------------------|-------------------------|---------|-------------|--------------------------|----------------------------|
| Shoja et al (2013)     | Two hospitals in Ahvaz         | ICU patients | Trachea      | A. baumannii (206)  | --                                    | --                      | --      | --          | --                       | blaOXA-23, blaOXA-24        |
| Sohrabi et al (2012)   | One hospital in Tabriz         | General inpatients | Different sites | A. baumanii (100)  | DD, PCR                                | CIP and GEN 86%, LVX 84%, AMK 81% | --      | --          | --                       | blaOXA-23, blaOXA-58, blaOXA-40 |
| Sepehriseresht et al (2012) | One hospital in Tehran (Motahari) | Burn patients | Burn wounds | P. aeruginosa (483) | DD, PCR                                | --                      | --      | --          | --                       | blaIMP, blaVIM             |

(Continued)
| Author (year) | Setting | Population | Samples | Microorganism (no.) | MIC | Method of carbapenemase detection | Resistance to FQ and AG | Results | Weak points | Strength points | Founded carbapenemase genes |
|---------------|---------|------------|---------|---------------------|-----|----------------------------------|------------------------|---------|-------------|-------------------------|----------------------------|
| Forozesh Fard et al (2012) | One hospital in Isfahan | CF patients | Sputum | P. aeruginosa (11) | – | • DD  
• PCR | CIP 0%  
TOB 45.4% | None of the isolates was resistant to IPM. None was positive for bla<sub>44</sub> gene  
All IPM-resistant isolates were chosen for study  
44% of isolates were from tracheal samples  
All were positive for bla<sub>OXA-23</sub>, and IS<sub>Aba1</sub> was present upstream of all bla<sub>OXA-23</sub> genes  
Resistance rate to IPM was 48%  
Range of MIC values for IPM was 0.004–32 mcg/mL  
From all strains, bla<sub>TEM</sub> and bla<sub>TEM</sub> genes were present in 52% and 43% of isolates, respectively, 21% and 17% of isolates had bla<sub>OXA-23</sub> and bla<sub>OXA-24</sub> genes, respectively | Very small sample size  
Few antibiotics were tested | – | – | bla<sub>44</sub> |
| Peymani et al (2012) | One hospital in Tabriz | General inpatients | Different sites | A. baumannii (68) | – | • PCR  
• Clonal typing | – | – | – | – |
| Asadollahi et al (2012) | One teaching hospital in Tehran | ICU burn patients | Burn wounds | A. baumannii (23) | ✓ | • DD  
• PCR | CIP 100%  
GEN 30%  
AMK 47% | Small sample size | MIC values were reported for each antibiotic  
CarO and tet genes were assessed | bla<sub>TEM</sub>  
bla<sub>SHV</sub>  
bla<sub>44</sub>  
bla<sub>OXA-23</sub>  
bla<sub>OXA-24</sub> |

(Continued)
Table 3 (Continued)

| Author et al (year) | Setting | Population | Samples | Microorganism (no.) | MIC Method of carbapenem detection | Resistance to FQ and AG | Results | Weak points | Strength points | Founded carbapenemase genes |
|---------------------|---------|------------|---------|----------------------|-----------------------------------|--------------------------|---------|-------------|------------------|----------------------------|
| Taherikalani et al (2009) | Six hospitals in Tehran | General inpatients | Different sites | A. baumannii (80) | ✓ | DD, PCR, Clonal typing | – | 52% of isolates were carbapenem resistant | Number of tested antibiotics were few | – |
| Feizabadi et al (2008) | One hospital in Tehran | General inpatients | Different sites | Acinetobacter spp. (A. baumannii =108 and other Acinetobacter =20, total =128) | ✓ | DD, PCR | CIP 81% LVX 74% AMK 61% NTL 86% TOB 79% GEN 81% | About 50% of strains were resistant to carbapenems | Multicenter study |

### Notes
- FQ: Fluoroquinolones
- AG: Aminoglycosides
- DD: Disk diffusion
- PCR: Polymerase chain reaction
- MIC: Minimum inhibitory concentration
- CIP: Ciprofloxacin
- LVX: Levofloxacin
- AMK: Amikacin
- NTL: Tobramycin
- TOB: Tobramycin
- GEN: Gentamicin
- Various carbapenemase genes detected.

(Continued)
Carbapenem-resistant bacteria in Middle East

Table 3 (Continued)

| Author (year) | Setting | Population | Samples | Microorganism (no.) | MIC | Results a | Method of carbapenemase detection | Resistance to FQ and AG | Resistance to carbapenem | Resistance rates (%), according to the results of disk diffusion test. |
|---------------|---------|------------|---------|---------------------|-----|-----------|---------------------------------|----------------------|------------------------|---------------------------------------------------------------|
| Taherikalani et al (2008) | Two hospitals in Tehran | Burn patients | Burn wounds | A. baumannii (38) | 1 | • PCR | • DD | Resistance rate to carba - penem was about 60% | Resistance rate to carba - penem was about 60% | Resistance rates were according to the results of disk diffusion test. |
|               |         |            |         |                     |     |           |                                 |                      |                        | • Half of the carba - penem-resistant strains had at least two blaOXA genes. |

Notes: Results about blaOXA-51 were not provided because this gene has no correlation with occurrence of resistance, unless it has ISAba genes in its upstream. "Resistance rates were according to the results of disk diffusion test."

Abbreviations: AG, aminoglycoside; AMK, amikacin; CIP, ciprofloxacin; DD, disk diffusion; FQ, fluoroquinolones; GEN, gentamicin; ICU, intensive care unit; IPM, imipenem; KAN, kanamycin; LEV, levofloxacin; MEM, meropenem; MIC, minimum inhibitory concentration; NAL, nalidixic acid; PCR, polymerase chain reaction; STP, streptomycin; TOB, tobramycin; NTL, netilmicin.

Emergence of some genes including blaNDM-1 is a serious global warning. This gene is highly transmissible and was first discovered in a Swedish patient who had traveled to Pakistan. Although almost all identified cases were originally from Pakistan and India, the first case of blaNDM-1 that was reported in Iran in the year 2012, did not have a history of traveling to these countries. In two studies from Shiraz and Isfahan, 27 and 6 strains of K. pneumonia harbored blaNDM in years 2015 and 2017, respectively. Genotypic methods to identify other mechanisms of resistance to carbapenems have recently been considered by researchers. OmpK and carO genes that regulate expression of mutated efflux pump were detected in Hashemi et al and Pajand et al studies, respectively. In another study, efflux pump’s activity and mutations in porins were investigated. These results can expand the view about true mechanisms of resistance to carbapenems in developing countries.
Table 4 Details of studies that used both phenotypic and genotypic methods for detection of carbapenemase-producing strains

| Author (year)          | Setting                                      | Population (no.) | Samples        | Microorganism               | MIC- | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome                                                                 | Weak points                                                                 | Strength points                                                                 |
|------------------------|----------------------------------------------|-------------------|----------------|-----------------------------|------|-----------------------------------------|-------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Solgi et al (2017)     | Two hospitals (city was not defined)         | General inpatients (mostly ICU) | Rectal swab    | Enterobacteriaceae spp. (95) | ✓    | MHT for MBL detection                  | AMK 24% GEN 35% CIP 74% | • 36 resistant strains were detected according to the phenotypic methods that among them carbapenem-resistance rates were between 88% and 100% | • MIC values were determined, but not analyzed                              | • Risk factors for infection with resistant strains were investigated    |
| Khorvash et al (2017)  | One hospital in Isfahan                      | ICU patients      | Different sites | Pseudomonas aeruginosa (48) |      | MHT                                      | AMK 79% CIP 85%         | • 7 isolates carried bla_imp were detected in 15 and 7 isolates (all were MHT positive) | • Ratio of MDR pathogens for each sample was defined                         | • bla_imp, bla_imp           |

(Continued)
| Author (year)         | Setting             | Population (no.) | Samples | Microorganism | MIC<sup>a</sup> | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome                                                                 | Weak points                                                                                   | Strength points                                                                 |
|----------------------|---------------------|------------------|---------|---------------|-----------------|------------------------------------------|------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Hosseinzadeh et al (2017)<sup>2</sup> | Two hospitals in Shiraz | General inpatients and ICU patients | Different sites | Klebsiella pneumonia (211) | ✓ | • MHT for MBL detection  
• DDST for MBL detection  
• PCR | AMK 78%  
CIP 85%  
GEN 89% | • 13% of isolates (29 ones) were resistant to IPM and MEM and had an MIC value of 1.5–32 mcg/mL  
(25 isolates had MIC ≥4 mcg/mL)  
• Among carbapenem-resistant isolates, DDST and MHT were positive for 27 strains  
• 2 and 27 isolates had <i>bla</i><sub>OXA-48</sub> and <i>bla</i><sub>NDM</sub>, respectively  
• 13% of isolates (29 ones) were resistant to IPM and MEM and had an MIC value of 1.5–32 mcg/mL  
(25 isolates had MIC ≥4 mcg/mL)  
• Among carbapenem-resistant isolates, DDST and MHT were positive for 27 strains  
• 2 and 27 isolates had <i>bla</i><sub>OXA-48</sub> and <i>bla</i><sub>NDM</sub>, respectively | Large sample size                                                                 | <i>bla</i><sub>OXA-48</sub>, <i>bla</i><sub>NDM</sub> |
| Akhi et al (2017)<sup>3a</sup> | Seven hospitals in Tabriz and Orumie | General inpatients | Different sites | P. aeruginosa (245) | – | • DD  
• MHT  
• MCNP test  
• CIM  
• PCR | CIP 66%  
LVX 66%  
AMK 25% | • 49% (121) of isolates were carbapenem resistant  
• From 121 resistant strains, <i>bla</i><sub>IMP</sub> and <i>bla</i><sub>vIM</sub> genes were positive in 29 and 6 strains, respectively, and 40, 39, and 35 isolates showed positive results for MHT, MCNP, and CIM tests, respectively | Large sample size  
Sensitivity and specificity of three phenotypic methods were estimated according to PCR  
Multicenter study | <i>bla</i><sub>vIM</sub>, <i>bla</i><sub>IMP</sub> |
| Author (year) | Setting | Population (no.) | Samples | Microorganism | MIC $^a$ | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome | Weak points | Strength points | bla-type genesc |
|--------------|---------|------------------|---------|---------------|---------|----------------------------------------|-------------------------|---------|--------------|-----------------|----------------|
| Falahat et al (2016)$^{29}$ | Three hospitals in Arak | General inpatients | Different sites | *P. aeruginosa* (108) | – | MHT and CDT for KPC detection • PCR | CIP 20% AMK 21% GEN 23% | • Resistance rate to carbapenem was about 25% • 38 and 26 of all isolates were MHT and CDT positive respectively • 13 isolates had *bla*$_{KPC}$ gene • 7% of isolates were IPM resistant • 35, 24, and 3 isolates were *Acinetobacter* spp., *Pseudomonas* spp., and *Enterobacteriaceae*, respectively • Carbapenem resistance was confirmed phenotypically (17% and 9%) and genotypically (15% and 9%) among *Acinetobacter* and *Pseudomonas*, respectively | – | • Multicenter study | *bla*$_{KPC}$ |
| Mohammadzadeh et al (2016)$^{30}$ | Two hospitals in Tehran | General inpatients | Not defined (probably different sites) | Different strains (864) | – | CDT, MHT, and DDST for MBL detection • PCR | Not defined | – | • Large sample size | *bla*$_{IMP}$ *bla*$_{VIM}$ |

(Continued)
| Author (year)            | Setting                          | Population (no.) | Samples         | Microorganism                                           | MIC- | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome                                                                 | Weak points                                                                 | Strength points                                                                 |
|-------------------------|----------------------------------|------------------|-----------------|---------------------------------------------------------|------|------------------------------------------|------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Tarashi et al (2016)    | One hospital in Tehran           | Burn patients    | Burn wounds     | Acinetobacter baumannii (189) P. aeruginosa (309)       | –    | –                                        | –                      | –                                                                        | –                                                                              | –                                                                                 |
|                         |                                  |                  |                 |                                                         |      | CDT for MBL                              |                        | –                                                                        | –                                                                              | –                                                                                 |
|                         |                                  |                  |                 |                                                         |      | PCR                                      |                        | –                                                                        | –                                                                              | –                                                                                 |
|                         |                                  |                  |                 |                                                         |      |                                          |                        | –                                                                        | –                                                                              | –                                                                                 |
|                         |                                  |                  |                 |                                                         |      |                                          |                        | –                                                                        | –                                                                              | –                                                                                 |
|                         |                                  |                  |                 |                                                         |      |                                          |                        | –                                                                        | –                                                                              | –                                                                                 |
|                         |                                  |                  |                 |                                                         |      |                                          |                        | –                                                                        | –                                                                              | –                                                                                 |
|                         |                                  |                  |                 |                                                         |      |                                          |                        | –                                                                        | –                                                                              | –                                                                                 |

**Outcome**
- Carbapenem resistance rate of *P. aeruginosa* was 83% in 2012 and 96% in 2015
- Carbapenem resistance rate of *A. baumannii* in all years was 100%
- Among 278 resistant *P. aeruginosa* isolates, 178 strains were MBL producers
- Of the 187 resistant *A. baumannii*, 85 isolates were MBL producers
- *bla*<sub>IMP</sub>-1 and *bla*<sub>vIM</sub>-1 genes were isolated in 30 and 52 of resistant strains of *P. aeruginosa*, respectively
- *bla*<sub>IMP</sub>-1 and *bla*<sub>vIM</sub>-1 genes were detected in 10 and 34 of resistant *A. baumannii*, respectively

**Weak points**
- Large sample size
- Providing trend of resistance through different years

**Strength points**
- *bla*<sub>Gly-351</sub>, *bla*<sub>IMP</sub>, *bla*<sub>vIM</sub>
| Author (year)         | Setting                          | Population (no.) | Samples                              | Microorganism | MIC<sup>a</sup> | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome                                                                 | Weak points                                      | Strength points                                      | bla-type genes |
|-----------------------|----------------------------------|------------------|--------------------------------------|---------------|----------------|------------------------------------------|-------------------------|------------------------------------------------------------------------|--------------------------------------------------|------------------------------------------------------|---------------|
| Maspi et al (2016)<sup>22</sup> | One hospital in Tehran           | General inpatients and ICU patients | Different sites (mostly BAL and wounds) | A. baumannii (86) | -             | CDT for MBL detection, PCR                | TOB 75%                  | Resistance rates to MEM and IMP were 90% and 73%, respectively         | MIC was not reported                               | First report of bla<sub>vIM</sub>, bla<sub>IMP</sub>, bla<sub>SPM</sub>, bla<sub>GIM</sub>, and bla<sub>SIM</sub> genes |<br>bla<sub>vIM</sub>, bla<sub>IMP</sub>, bla<sub>SPM</sub>, bla<sub>GIM</sub>, and bla<sub>SIM</sub> genes |
| Moghadam et al (2016)<sup>23</sup> | Two hospitals in Shiraz          | General inpatients and ICU patients | Different sites                      | A. baumannii (98) | ✓             | E-test for MBL detection, PCR              | AMK 69%, GEN 75%, CIP and LVX 100% | Resistance to carbapenem was about 95% and according to MIC, it was 98% | -                                                              | Results of general and ICU patients were discussed separately |<br>bla<sub>qep</sub>, bla<sub>qep</sub> |
Table 4 (Continued)

| Author (year)                     | Setting                  | Population (no.) | Samples | Microorganism | MIC\* | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome | Weak points                                                                 | Strength points | blo-type genes |
|-----------------------------------|--------------------------|-------------------|---------|---------------|-------|------------------------------------------|-------------------------|---------|-----------------------------------------------------------------------------|----------------|----------------|
| Pakbaten Toupkanlou et al (2015)  | One hospital in Tehran   | Burn patients     | Not defined | *P. aeruginosa* (50) |       | CDT for ESBL detection, PCR             | CIP 98%, AMK, GEN, and TOB 96% |         | All resistant strains to IPM were chosen for study                        |                |                |
|                                   |                          |                   |          |               |       |                                          |                         |         | 23 and 17 strains were positive in two different phenotypic methods for ESBL detection |                |                |
|                                   |                          |                   |          |               |       |                                          |                         |         | 7, 18, 18, and 18 strains had *bla*<sub>PER</sub>, *bla*<sub>OX-A-10</sub>, *bla*<sub>IPM</sub>, and *bla*<sub>SHV</sub> genes, respectively |                |                |
|                                   |                          |                   |          |               |       |                                          |                         |         | 10 (20%) isolates carried *bla*<sub>-TEM</sub>, *bla*<sub>OX-A-10</sub>, and *bla*<sub>SHV</sub> genes, simultaneously |                |                |
|                                   |                          |                   |          |               |       |                                          |                         |         | Resistance rate to carbapenem was 14% (41 strains)                       |                |                |
|                                   |                          |                   |          |               |       |                                          |                         |         | –14.5% (33 out of 41) strains were MHT positive and all 41 strains did not carry *bla*<sub>-KPC</sub> gene |                |                |
|                                   |                          |                   |          |               |       |                                          |                         |         | Few antibiotics were tested                                               |                |                |
| Bina et al (2015)                 | Three hospitals in Tehran | General inpatients | Different sites | *K. pneumonia* (270) |       | MHT test for KPC detection, PCR          | GEN 41.3%               |         | Small sample size                                                          |                |                |
|                                   |                          |                   |          |               |       |                                          |                         |         | Origins of samples were not defined                                       |                |                |
|                                   |                          |                   |          |               |       |                                          |                         |         | –                                                                           |                |                |

(Continued)
| Author (year)                        | Setting                          | Population (no.) | Samples      | Microorganism | MICa | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome                                                                 | Weak points             | Strength points | bla-type genes |
|------------------------------------|----------------------------------|-------------------|--------------|---------------|------|----------------------------------------|-------------------------|--------------------------------------------------------------------------|-------------------------|----------------|----------------|
| Eftekhar and Naseh (2015)          | Two hospitals in Tehran          | Thirty nonburn and 25 burn patients | Different sites | K. pneumonia (30 nonburn and 25 burn, total 55) | 1860 | -                                      | Burn and nonburn patients respectively: CIP 84%, AMK 52%, GEN 84%,     | Resistance rates to carbapenem were 20% in burn and 0% in nonburn patients | Small sample size | Comparison of resistance pattern in burn and nonburn patients |
|                                   |                                  |                   |              |               |      | -                                      |                          | -                                                                        |                         |                |                |
| Lari et al (2015)                  | One hospital in Tehran           | Burn patients     | Burn wounds  | P. aeruginosa (255) | 1860 | -                                      | Were tested but not reported specifically | -                                                                        |                         |                |                |
|                                   |                                  |                   |              |               |      | -                                      |                          | -                                                                        |                         |                |                |

(Continued)
### Table 4 (Continued)

| Author (year)       | Setting                        | Population (no.) | Samples             | Microorganism | MIC<sup>*</sup> | Method of carbapenemase enzyme detection                                                                 | Resistance to FQ and AG | Outcome                                                                 | Weak points                                                                 | Strength points                                                                 |
|---------------------|--------------------------------|------------------|---------------------|---------------|----------------|-----------------------------------------------------------------------------------------------|------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Bagheri Josheghani et al (2015)<sup>6</sup> | One hospital in Kashan         | General inpatients | Different sites     | A. baumannii (124) | –             | • CDT for ESBL detection  
  • DDST for MBL detection  
  • PCR                                                                 | AMK 78%  
  GEN 83%  
  LVX and CIP 99% | Resistance rates to carbapenems was about 90%  
  • 5% were ESBL positive and 54% isolates were MBL  
  • 79%, 25%, and 3% carried bla<sub>OXA-23</sub>, bla<sub>OXA-24</sub>, and bla<sub>OXA-58</sub> genes, respectively | –                                      | –                                      |
| Azimi et al (2016)<sup>76</sup>  | One hospital in Tehran         | Burn patients     | Burn wounds         | Different strains (161) | –             | • MHT and DDST for MBL detection  
  • CDT for KPC detection  
  • PCR                                                                 | –                                    | All IPM-resistant strains were included  
  • 85, 51, and 112 of them were MHT, boronic acid, and dipicolinic acid positive, respectively | –                                      | –                                      |
| Azimi et al (2015)<sup>77</sup>  | One hospital in Tehran         | Burn patients     | Burn wounds         | A. baumannii (65) | –             | • CDT for ESBL detection  
  • PCR                                                                 | 80% of strains were resistant to all AG | Exact number of resistance genes was not reported | –                                      | –                                      |

<sup>Continued</sup>
| Author (year)          | Setting                          | Population (no.) | Samples | Microorganism | MICa | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome                                                                 | Weak points                      | Strength points                                                                 | bla-type genes |
|-----------------------|----------------------------------|-------------------|---------|---------------|------|-------------------------------------------|--------------------------|----------------------------------------------------------------------|----------------------------------|--------------------------------------------------------------------------------|-----------------|
| Fazeli et al (2015)   | One hospital in Isfahan           | General inpatients | Different sites | K. pneumonia (112) | ✓    | MHT and E-test for MBL detection         | CIP 63.4% AMK 51% GEN 64% | 42% of strains (49 isolates) were resistant to IPM and MEM            | • 32 out of 49 resistant isolates were positive for MHT | • 5 isolates were positive in E-test and 6 strains harbored NDM-1       |                |
|                       |                                  |                   |         |               |      | • PCR                                      |                          | • Out of the 36 Enteraggregative E. coli isolates, 19 (52%) were ESBL positive and none were MBL positive | • MIC was not tested          | • Large sample size                                                            |                |
| Khoshvaght et al (2014)| Four hospitals in Zanjan          | General pediatrics | Stool   | Escherichia coli (230) | –    | DDST for ESBL and MBL detection          | CIP 37% AMK 21% GEN 29% | IPM resistance rate was 2.1%                                         | • Comparing data of healthy children with those with diarrhea           | • No comparison between healthy and sick children                         |                |
| Author (year)       | Setting                        | Population (no.) | Samples | Microorganism       | MIC type | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome | Weak points | Strength points | bla-type genes |
|---------------------|-------------------------------|------------------|---------|---------------------|----------|------------------------------------------|------------------------|---------|-------------|----------------|----------------|
| Noori et al (2014)  | Two hospitals in Tehran       | General inpatients | Different sites | Acinetobacter spp. (108) | ✓        | DD                                       | CIP 92% AMK 80% GEN 40% | 91% (99 isolates) were resistant to IPM and MEM | –         | –           | birp            |
|                     |                               |                  |         |                     |          | CDT for MBL                              |                        | 86 isolates were MBL producers |          |             |                |
|                     |                               |                  |         |                     |          | Out of these 86 MBL producers, three isolates harbored birp |                      | Out of these 86 MBL producers, three isolates harbored birp |         |             |                |
|                     |                               |                  |         |                     |          | MIC50 values for MeM and IPM were 32 and 128 mcg/mL, respectively |                      | MIC50 values for MeM and IPM were 32 and 128 mcg/mL, respectively |         |             |                |
|                     |                               |                  |         |                     |          | Resistance rate to MEM was 14% (eight strains) that MHT was positive in three of them |                      | Resistance rate to MEM was 14% (eight strains) that MHT was positive in three of them |         |             |                |
|                     |                               |                  |         |                     |          | The EDTA disk synergy was also positive in four isolates |                      | The EDTA disk synergy was also positive in four isolates |         |             |                |
|                     |                               |                  |         |                     |          | birp and blad were detected in five and two strains of Acinetobacter xylosoxidans |                      | birp and blad were detected in five and two strains of Acinetobacter xylosoxidans |         |             |                |
| Vali et al (2014)   | Two pediatric hospitals in Tehran | Cystic fibrosis inpatients | Sputum | Different gram negative (52) | ✓        | CDT for ESBL detection DDST for MBL detection PCR | GEN 24.5% CIP 18% | –         | –           | Data provided from cystic fibrosis patients | blacXM, blarp, blarm |

(Continued)
### Table 4 (Continued)

| Author (year) | Setting | Population (no.) | Samples | Microorganism | MIC<sup>a</sup> | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome | Weak points | Strength points | bla-type genes<sup>c</sup> |
|---------------|---------|-------------------|---------|---------------|----------------|-----------------------------------------|------------------------|---------|-------------|-----------------|--------------------------|
| Azimi et al (2014)<sup>10</sup> | One hospital in Tehran | Burn patients | Burn wounds | K. pneumonia (28) | ✓ | MHT, CarbaNP test, BA, PCR | GEN 90% AMK 79% | All isolates were resistant to IPM and MEM | • Small sample size | • CarbaNP test was done | bla<sub>OXA-48</sub>, bla<sub>vIM-4</sub> |
| Hashemi et al (2014)<sup>10</sup> | Two hospitals in Tehran | General inpatients and infants | Different sites | K. pneumonia (83) | ✓ | CDT, AmpC screening, MHT, PCR | Resistance and intermediate: CIP 39.7%, 4.8% GEN 61.5%, 3.6% AMK 80.7%, 4.8% | Resistance rates to IPM, MEM, and DOR were between 68% and 74% | • Detection of porin-related genes | bla<sub>OXA-48</sub>, bla<sub>CTX-M-15</sub> |

<sup>a</sup> MIC: Minimum Inhibitory Concentration.

(Continued)
| Author (year) | Setting | Population (no.) | Samples | Microorganism | MIC<sup>a</sup> | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome | Weak points | Strength points | bla-type genes<sup>c</sup> |
|--------------|---------|------------------|---------|---------------|----------------|----------------------------------------|------------------------|---------|-------------|----------------|---------------------|
| Japoni-Nejad et al (2014)<sup>34</sup> | One hospital in Arak | ICU patients | Surgical wounds, urine, blood, respiratory secretions | *K. pneumonia* (100) | – | • MHT  
• E-test for MBL detection  
• DDST  
• CDT for KPC detection  
• PCR | –  
• Resistance rate to carbapenems in Amp C producers and carbapenemase producers was 5% and 66%, respectively  
• *bla<sub>vIM</sub>* and *bla<sub>GES</sub>* were detected in ten and two isolates  
• One isolate (1%) contained both *bla<sub>vIM</sub>* and *bla<sub>AmpC</sub>* genes | –  
| Farajzadeh Sheikh et al (2014)<sup>35</sup> | Hospitals in Ahvaz | General inpatients | Different sites | *P. aeruginosa* (223) | ✓ | • CDT and E-test for MBL detection  
• PCR | GEN 66% AMK 55% TOB 67% CIP 66%  
58%, 31%, 13%, and 74% of isolates were resistant to IMP, MEM, DOR and ERT, respectively. Thirty isolates were resistant to all carbapenems  
All imipenem-resistant isolates were MBL producers, except one  
*bla<sub>IMP</sub>* and *bla<sub>VIM</sub>* genes were detected in 26 and 1 of the all strains, respectively  
13%–74% of resistant isolates had an MIC >16 mcg/mL for different carbapenems | –  
• Large sample size  
• *bla<sub>IMP</sub>*
Table 4 (Continued)

| Author (year)       | Setting                        | Population (no.) | Samples       | Microorganism | MIC<sup>a</sup> | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome | Weak points | Strength points | bla-type genes<sup>c</sup> |
|---------------------|--------------------------------|------------------|---------------|---------------|-----------------|------------------------------------------|-------------------------|---------|-------------|----------------------|-----------------------------|
| Aghamiri et al (2014)<sup>b</sup> | Several hospitals in Tehran    | General inpatients | Different sites | *P. aeruginosa* (212) | ✓               | • DD                                     | 47% of isolates were resistant to IPM and all had an MIC >16 mcg/mL | - 70 isolates were MBL positive  
- 20 and 70 strains had bla<sub>IMP</sub> and bla<sub>vIM</sub> genes, respectively | | | | bla<sub>IMP</sub>bla<sub>vIM</sub> |
| Nobari et al (2014)<sup>i</sup> | Eight hospitals in Tehran      | General inpatients | Different sites | *K. pneumonia* (180) | • DD                          | 7% to 23% (66% of urine isolates were resistant to carbapenems) | Resistance rate to carbapenem was between 7% and 23% (66% of urine isolates were resistant to carbapenems) | - 25 isolates were MHT positive  
- bla<sub>CTX-M</sub>, bla<sub>SHv</sub>, bla<sub>TeM</sub>, and bla<sub>PeR</sub> genes were detected in 69%, 59.5%, 35.7%, and 16.6% of carbapenem-resistant isolates respectively  
- bla<sub>NDM-1</sub>, bla<sub>vIM-1</sub>, and bla<sub>KPC</sub> were detected in 3, 5, and 1 isolates | | | | bla<sub>CTX-M</sub>bla<sub>SHv</sub>bla<sub>TeM</sub>bla<sub>PeR</sub>bla<sub>NDM-1</sub>bla<sub>vIM-1</sub>bla<sub>KPC</sub> |
| Author (year)                  | Setting                          | Population (no.) | Samples                  | Microorganism | MIC<sup>*</sup> | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome | Weak points | Strength points | bla-type genes|
|-------------------------------|----------------------------------|------------------|--------------------------|---------------|---------------|-----------------------------------------|------------------------|---------|-------------|----------------|---------------|
| Hakemi Vala et al (2014)      | One hospital in Tehran           | 88               | Burn patients            | P. aeruginosa (47) and Acinetobacter spp. (28) | ✓             | CDT for MBL and ESBL detection          | P. aeruginosa GEN 72% CIP 69% A. baumannii GEN 96% CIP 100% | • 100% of A. baumannii and about 75% of P. aeruginosa isolates were resistant to carbapenems • MIC range of IPM for P. aeruginosa was 2–128 and for A. baumannii was 4–128 mcg/mL • 17% of the P. aeruginosa isolates and 16% of the A. baumannii isolates were MBL producers • Mortality rate of MBL producer was 20% • 8% of isolates were ESBL producers that bla<sub>TEM</sub> was detected in all ESBL producers and 50% (4 isolates) of them were resistance to IPM | – | • Mortality rate was reported |
| Tavajohi et al (2013)         | One hospital in Kashan           | 89               | General inpatients and environmental isolates | P. aeruginosa (100) | –             | DDST for ESBL detection                  | GEN 50% CIP 12%         | –       | –           | • Small sample size (only eight strains were evaluated for carbapenem resistance and genes) | bla<sub>GES</sub> |
| Author (year) | Setting | Population (no.) | Samples | Microorganism | MIC | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome | Weak points | Strength points | bla-type genes |
|--------------|---------|------------------|---------|---------------|-----|----------------------------------------|-----------------------|---------|-------------|----------------|---------------|
| Azimi et al (2013) | One hospital in Tehran (Motahari) | Burn patients | Burn wounds | K. pneumonia (44) | | DD | MHT for KPC detection | 64% of isolates were resistant to carbapenem | | | | |
| Noori et al (2013) | Two hospitals in Mashhad | General inpatients | Wounds and respiratory secretions | Acinetobacter spp. (70) | | DDST for MBL production | CIP 100% GEN 88% | | | | |
| Azimi et al (2013) | One hospital in Tehran | Burn patients | Not defined (probably burn wounds) | A. baumannii (93) and Acinetobacter lwoffii (1) | | CDT for MBL detection | No MBL producers | 85% of isolates were resistant to IPM that MIC range for them was 16–128 mcg/mL | | | |

(Continued)
Table 4 (Continued)

| Author (year)          | Setting                  | Population (no.) | Samples                      | Microorganism                | MICa | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome                                                                 | Weak points | Strength points | bla-type genes  |
|------------------------|--------------------------|-------------------|------------------------------|------------------------------|------|---------------------------------------|------------------------|-------------------------------------------------|-------------|----------------|-----------------|
| Pajand et al (2013)    | Two hospitals in Tehran  | Inpatients and burn patients | Burn wounds and other sites | A. baumannii (43 burn and 32 nonburn patients, total 75) | ✔    | DDST for MBL detection                | Nonburn and burn patients: CIP 87%, 97% AMK 56%, 95% TOB 47%, 84% | Resistance rate to carbapenem in burn and nonburn patients was 98% and 68%, respectively | • 66% of nonburn and 70% of burn isolates had blaOXA-23 | • blaOXA-40-like gene was detected in 12% and 74% of nonburn and burn isolates, respectively | • MIC values for all carbapenems were reported | • All isolates were positive for AmpC and ISAba genes and 71 of them were positive for carO gene | • Detection of OMP gene (carO) for evaluation of carbapenem resistance | |
| Azami et al (2013)     | Three hospitals in Tehran | General inpatients | Not defined                  | P. aeruginosa (130)          | ✔    | CDT for MBL detection                 | GEN 63% CIP 59%        | • According to MIC, 53% of isolates were resistant to IPM and MIC values were ≥16 mcg/mL for IPM | • 56% had class I integrons | • blaOXA-23 was found in 10 strains | • Few antibiotics were tested | • Assessment of integrin genes (genes for mobility of beta-lactamase) | • Multicenter study | |
| Author (year) | Setting | Population (no.) | Samples | Microorganism | MIC<sup>a</sup> | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome | Weak points | Strength points | bl<sup>a</sup>-type genes<sup>c</sup> |
|--------------|---------|------------------|---------|--------------|-------------|---------------------------------|--------------------------|---------|-------------|--------------------------|-------------------|
| Mohajeri et al (2013)<sup>65</sup> | Three hospitals in Kermanshah | General inpatients | Sputum, blood, urine | Acinetobacter spp. (104) | – | E-test for MBL detection • DDST • PCR | CIP 69%, GAT 43% LVS 62% TOB 39% GEN 68% AMK 53% | Resistance rate to carbapenems was 75%–80% • 84 of isolates were MBL producers • The bl<sub>a</sub><sub>OXA-23</sub> and bl<sub>a</sub><sub>OXA-24</sub> were found among 77% and 19% of the isolates, respectively • Correlation between rate of resistance to carbapenem and presence of bl<sub>a</sub><sub>OXA-23</sub>-like gene was statistically significant 63% of isolates were resistant to IPM that 41 of them had an MIC >4 mcg/mL • DDST was positive for all of them • 36 isolates were MBL producers • From 41 of isolates with high MIC breakpoints, 10 isolates had bl<sub>a</sub><sub>APR</sub> and 23 had bl<sub>a</sub><sub>MIR</sub> | • MIC was not reported | • Multicenter study | bl<sub>a</sub><sub>OXA-23</sub> bl<sub>a</sub><sub>OXA-24</sub> |
| Doosti et al (2013)<sup>66</sup> | One hospital in Zanjan | General inpatients | Different sites | P. aeruginosa (70) | ✓ | DD • DDST for MBL detection • PCR | CIP 40% GEN 55% | – | – | – | – |
| Author (year) | Setting | Population (no.) | Samples | Microorganism | MIC<sup>a</sup> | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome | Weak points | Strength points | bla-type genes<sup>c</sup> |
|--------------|---------|------------------|---------|---------------|----------------|-----------------------------|-----------------------|---------|-------------|------------------|---------------------|
| Shahcheraghi et al (2013)<sup>97</sup> | Five hospitals in Tehran | General inpatients | Mostly urine and feces | Different strains (360) | – | • MHT  
• MBL E-test  
• PCR | CIP 61.3%  
AMK 14.4%  
KAN 38.6% | • 6%, 3%, and 1% were resistant to MEM, ER, and IPM, respectively  
• MHT was positive in 11 resistant isolates | • MIC was not reported | • Multicenter study  
• Large sample size  
• Recognition of new K. pneumonia containing bla NDM | bla<sub>NDM</sub>  
bla<sub>SHV</sub>  
bla<sub>TEM</sub>  
bla<sub>SHV</sub>  
bla<sub>CTX-M</sub>  
bla<sub>NDM</sub>  
bla<sub>PER</sub> |
| Kalantar et al (2012)<sup>96</sup> | One hospital in Sanandaj | General inpatients | Different sites | P. aeruginosa (100) | ✓ | • DD  
• DDST for MBL detection  
• PCR | • 22 isolates were MBL positive and among them 8 isolates were resistant to IPM  
• 8 isolates had bla<sub>VIM</sub>  
• All isolates had an MIC ≥8% and 47% had an MIC =64 mcg/mL  
• From IPM-resistant isolates, 9% were MBL producers  
• The bla<sub>SPM</sub>, bla<sub>GES</sub>, bla<sub>OXA-23</sub>, and bla<sub>OXA-51</sub> genes were detected by PCR among 6, 2, 94, and 84 isolates of A. baumannii, respectively | | | bla<sub>TEM</sub>  
bla<sub>SHV</sub>  
bla<sub>OXA-23</sub>  
bla<sub>GES</sub> |
| Shahcheraghi et al (2011)<sup>99</sup> | Seven hospitals in Tehran | General inpatients | Different sites | Acinetobacter spp. (203) | ✓ | • DD  
• CDT for MBL detection  
• PCR | Of the 100 strains that were IPM resistant: CIP 84%  
AMK 84% | • All isolates had an MIC ≥8% and 47% had an MIC =64 mcg/mL  
• From IPM-resistant isolates, 9% were MBL producers  
• The bla<sub>SPM</sub>, bla<sub>GES</sub>, bla<sub>OXA-23</sub>, and bla<sub>OXA-51</sub> genes were detected by PCR among 6, 2, 94, and 84 isolates of A. baumannii, respectively | | | bla<sub>SHV</sub>  
bla<sub>GES</sub> |
### Table 4 (Continued)

| Author (year) | Setting | Population (no.) | Samples | Microorganism | MIC<sup>a</sup> | Method of carbenemase enzyme detection | Resistance to FQ and AG | Outcome | Weak points | Strength points | bla-type genes<sup>c</sup> |
|---------------|---------|------------------|---------|---------------|---------------|---------------------------------------|------------------------|---------|-------------|----------------|--------------------------|
| Peymani et al (2011)<sup>100</sup> | One hospital in Tabriz | General inpatients | Different sites | *A. baumannii* (100) | – | E-test for MBL detection, PCR | AMK 83% GEN 91% CIP 90% LVX 86% | About 55% of isolates were resistant to carbapenem | • 31 of carbapenem-resistant isolates were MBL producers and 28 of them were positive for bla genes | – | bla<sub>IMP</sub> |
| Saderi et al (2010)<sup>101</sup> | One hospital in Tehran | General inpatients | Burn wounds | *P. aeruginosa* (100) | – | CDT for MBL detection, PCR for MBL genes | GEN 86% AMK 73% CIP 55% | • 69% of isolates were resistant to IPM | • MIC was not determined | – | bla<sub>IMP</sub> |
| Yousefi et al (2010)<sup>102</sup> | Two hospitals in Orumieh and Tabriz | General inpatients | Different sites | *P. aeruginosa* (324) | ✓ | DDST for detection of MBL, PCR | CIP 83% GEN 86% AMK 85% | • Resistance rate to MEM was 86% | • Large sample size | bla<sub>IMP</sub> |

(Continued)
| Author (year) | Setting | Population (no.) | Samples | Microorganism | MIC<sup>a</sup> | Method of carbapenemase enzyme detection | Resistance to FQ and AG | Outcome | Weak points | Strength points | bla-type genes |
|--------------|---------|------------------|---------|---------------|---------------|----------------------------------------|------------------------|---------|-------------|----------------|----------------|
| Bahar et al (2010)<sup>103</sup> | One hospital in Tehran (Motahari) | Burn patients | Burn wounds | P. aeruginosa (186) | – | • Disk inhibitor synergy test  
• PCR | It was not reported for all isolates (only reported in MBL producers) | • EDTA disk showed that 23 strains produced MBL and all had bla<sub>vIM</sub> gene  
• Mortality of MBL producer strains was 82% and non-MBL producer was 22%  
• Large sample size  
• Mortality rates of MBL and non-MBL producers were reported | • FQ and AG were not tested | bla<sub>vIM</sub> |
| Khosravi et al (2008)<sup>104</sup> | One hospital in Ahvaz | General inpatients | Different sites | P. aeruginosa (100) | – | • E-test for MBL detection  
• PCR | – | • Resistance rate to carbapenems was 41%  
• Of the resistant isolates, eight isolates were MBL producers and all contained bla<sub>vIM</sub>  
• Few antibiotics were tested | – | bla<sub>vIM</sub> |
| Yazdi et al (2007)<sup>105</sup> | Two hospitals in Tehran | Not defined | Not defined | P. aeruginosa (126) | ✓ | • DD  
• E-test for MBL detection  
• PCR | According to MIC, resistance to IPM was 29%  
• 70 isolates were MBL producers  
• 8 isolates had bla<sub>vIM</sub>  
• MIC of these eight strains was 32–64 mcg/mL for IPM | • PCR, combination disk test (CM), carbapenem inactivation method (CIM), ciprofloxacin (CIP), doripenem (DOR), ertapenem (ERT), extended spectrum β-lactamase (ESBL), fluoroquinolones (FQ), gentamicin (GEN), imipenem (IPM), meropenem (MEM), modified Hodge test (MHT), nalidixic acid (NAL), norfloxacin (NOR), ofloxacin (OFX), polymeric chain reaction (PCR), tobramycin (TOB), tranexamic acid (TXA), vancomycin (VAN)  
Abbreviations: AG, aminoglycoside; AMK, amikacin; BA, boronic acid; CDT, combination disk test; CIM, carbapenem inactivation method; CIP, ciprofloxacin; DD, disk diffusion; DDT, double disk synergy test; DOR, doripenem; ERT, ertapenem; ESBL, extended spectrum β-lactamase; FQ, fluoroquinolones; GAT, gatifloxacin; GEN, gentamicin; ICU, intensive care unit; IPM, imipenem; KAN, kanamycin; KPC, Klebsiella-producing carbapenemase; LVX, levofloxacin; MBL, metallo-β-lactamase; MCNP, modified CarbaNP; MEM, meropenem; MHT, modified Hodge test; MIC, minimum inhibitory concentration; NAL, nalidixic acid; NOR, norfloxacin; OFX, ofloxacin; PCR, polymerase chain reaction; TOB, tobramycin; BAL, Broncho Alveolar Lavage. |
Most studies included biological samples from different sites like urine, trachea, and wounds. However, sites with highest or lowest resistant rates were not defined, except in a few studies. In the study by Nobari et al, urine was the source with more resistant strains. In the study by Khorvash et al, one *P. aeruginosa* strain that was isolated from urine samples harbored both *bla*<sub>IMP</sub> and *bla*<sub>VIM</sub> genes.

Lack of clinical insight was the main limitation of almost all studies. Only in three studies, mortality rates in patients infected with resistant strains were addressed. Mortality rate of patients infected with carbapenem-resistant *K. pneumonia* isolates was 33% in 2013 (Rastegar Lari et al study). In the same year, infections with carbapenem-resistant *A. baumannii* strains caused 20% mortality. In the study by Bahar et al, the mortality rate of MBL-producer *P. aeruginosa* isolates vs non-MBL producers was 82% vs 22%. In some studies, patients’ conditions including requiring mechanical ventilation and days of hospital stay were considered, but no correlation between these data and acquiring carbapenem-resistant strains was found. Also in most studies, difference between infection and colonization was not clear.

Restrictions in technical facilities and standard laboratories in small cities are important issues. Access to a standard microbiological laboratory is not feasible in most regions. Disk diffusion was the main method for detecting carbapenem resistance until recently. Also, MIC breakpoints were adapted from CLSI and national data regarding these cutoffs are lacking. National antimicrobial resistance surveillance studies have not been well organized. Interpreting data from different regions of a country, considering the local standards, is essential.
Pattern of antibiotic use can affect emergence of resistant microorganisms. Rational use of drugs, and specifically antibiotics, is a challenging issue in developing countries. Mean number of drugs per prescription in Iran was higher than the World Health Organization standards.\textsuperscript{113,114} Approximately, 50% of inpatients, prescriptions contained at least one antibiotic, and this percentage was even higher in outpatient settings.\textsuperscript{115} Overuse of antibiotics, especially injectable ones, and easy access to antibiotics without prescription is a warning alarm for future antibiotic resistance in developing countries.

Establishing antimicrobial stewardship’s programs is new in our hospitals. Unfortunately, governmental rules and supports to restrict antibiotic access in community pharmacies and prescription by general physicians are limited.

Following issues may be considered in future studies. Considering combination of antimicrobials for assessing the resistance is an important finding. Evaluating effects of combination disks (ie, a carbapenem with an aminoglycoside or a fluoroquinolone) on resistant gram-negative bacilli may be helpful.\textsuperscript{116} Although combination therapy may increase the

**Figure 4** Carbapenem-resistant rates in different areas of Iran (according to the phenotypic and genotypic methods).

**Notes:** The data were extracted from the latest available studies. Multicenter studies from different cities were not considered for mapping due to pooled data. The studies in the special populations (ie, pediatrics or cystic fibrosis) and outpatients were excluded. Some genes like blaSPM and blaSHv are mostly known as genes that encode ESBL enzymes, but they were included in this map, because these genes were assessed along with carbapenemase genes, and also overexpression of these genes concomitant with harboring efflux pump may be responsible for resistance to carbapenems.\textsuperscript{*} Data for these five provinces were extracted from 2011 to 2014 articles, so new data are needed.

\begin{itemize}
  \item Data were extracted from a 2015 study with 36 samples; another study in 2013 confirmed the presence of the genes of resistance in 4% of strains.\textsuperscript{116} Data from Tehran province were conflicting; genes encoding resistance were detected in 15%-50% of isolates through 2015–2016.\textsuperscript{116} Data from Kahan (a city in Isfahan province) showed presence of resistance genes in 80% of isolates in 2015.
  \item Data were extracted from a 2015 study with 36 samples; another study in 2013 confirmed the presence of the genes of resistance in 4% of strains.\textsuperscript{116} Data from Tehran province were conflicting; genes encoding resistance were detected in 15%-50% of isolates through 2015–2016.\textsuperscript{116} Data from Kahan (a city in Isfahan province) showed presence of resistance genes in 80% of isolates in 2015.
  \item In Mazandaran and West Azerbaijan, these genes were reported, but rates of resistance were not included because the studies included different cities from different provinces.\textsuperscript{116} blaOXA-23, blaOXA-24, blaOXA-40, blaOXA-48, blaOXA-10, blaIMP, blaVIM, blaSPM, blaGES, blaPER, blaNDM, blaKPC, blaTEM, blaSHV, blaADC, blaSIM, or blaGIM.
\end{itemize}

**Abbreviations:** ESBL, extended spectrum \( \beta \)-lactamase; KPC, Klebsiella-producing carbapenemase; MBL, metallo-\( \beta \)-lactamase.
risk of side effects, it remains an initial therapeutic option for MDR isolates. Another issue is studying of antibiotics’ resistance pattern in health-care facilities. Remarkable increase in resistance rates among isolates from health-care facilities were reported. These strains may act as KPC-producing reservoirs. A higher resistance rate in long-term care facilities in comparison with intensive care units has been identified. Although some studies in Iran have included outpatients to evaluate carbapenem resistance, patients in long-term health-care facilities have not been included.

Authors’ contributions
All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

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Table 5 Types of bla genes, first location of isolation, and the relevant microorganisms in Iran

| Ambler classes | Types of pf bla genes | First location of isolation | Yeara | Total genesb | Microorganismc |
|---------------|-----------------------|-----------------------------|-------|--------------|---------------|
| A             | GES                   | Tehran, by Shahecheraghi F. | 2011  | 12           | Mostly P. aeruginosa |
|               | KPC                   | Tehran, by Nobari S.        | 2014  | 61           | Mostly K. pneumonia |
| B             | NDM                   | Tehran, by Shahecheraghi F. | 2012  | 44           | Mostly K. pneumonia |
|               | VIM                   | Tehran, by Rezaei Yazdi H.  | 2007  | 437          | Mostly P. aeruginosa |
|               | IMP                   | Tabriz and Orumieh, by Yousefi S. | 2010  | 271          | Mostly P. aeruginosa |
|               | SIM                   | Tehran, By Maspi H.         | 2016  | 2            | Only in A. baumannii |
|               | GIM                   | Tehran, By Maspi H.         | 2016  | 4            | Only in A. baumannii |
| D             | OXA-23                | Tehran, by Taherikalani M.  | 2008  | 1,287        | Only in A. baumannii |
|               | OXA-24                | Tehran, by Taherikalani M.  | 2008  | 213          | Only in A. baumannii |
|               | OXA-58                | Tehran, by Taherikalani M.  | 2008  | 96           | Only in A. baumannii |
|               | OXA-40                | Tabriz, by Sohrabi N.       | 2012  | 59           | Only in A. baumannii |
|               | OXA-48                | Tehran, by Azimi L.         | 2014  | 52           | In K. pneumonia and others |
|               | OXA-10                | Tehran, by Pakbaten S.      | 2015  | 12           | Only in P. aeruginosa |
|               | OXA-143               | Qom, by Sharikhani Z.       | 2017  | 14           | Only in A. baumannii |

Notes: aYear that the genes were isolated for the first time. bTotal number of genes that were reported in Iranian studies. cThe microorganisms in which the genes were isolated.
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