Research Article

Prevalence of ESBL-Producing Enterobacter Species Resistant to Carbapenems in Iran: A Systematic Review and Meta-Analysis

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Background. Carbapenems are the last-line therapy for multidrug-resistant (MDR) infections caused by Enterobacteriales, including those caused by Enterobacter species. However, the recent emergence of carbapenem-resistant (CR) and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae pathogens, which are resistant to nearly all antibiotics, has raised concerns among international healthcare organizations. Hence, because there is no comprehensive data in Iran, the current study aimed to evaluate the prevalence of antibiotic resistance among Enterobacter species, especially CR and ESBL-producing strains, in Iran. Methods. The literature search was performed up to June 21, 2021, in national and international databases using MeSH-extracted keywords, i.e., Enterobacter, antibiotic resistance, carbapenem, ESBL, and Iran. Study selection was done based on the predefined inclusion and exclusion criteria, and data analysis was carried out using the Comprehensive Meta-Analysis (CMA) software. Results. The pooled prevalence of Enterobacter species resistant to various antibiotics is as follows: imipenem 16.6%, meropenem 16.2%, aztreonam 40.9%, ciprofloxacin 35.3%, norfloxacin 31%, levofloxacin 48%, gentamicin 42.1%, amikacin 30.3%, tobramycin 37.2%, tetracycline 50.1%, chloramphenicol 25.7%, trimethoprim/sulfamethoxazole 52%, nalidixic acid 49.1%, nitrofurantoin 43%, ceftriaxone 49.3%, cefixime 52.4%, cefotaxime 52.7%, ceftriaxime 47.9%, cefepime 43.6%, and ceftizoxime 45.5%. The prevalence rates of MDR and ESBL-producing Enterobacter species in Iran were 63.1% and 32.8%, respectively. Conclusion. In accordance with the warning of international organizations, our results revealed a high prevalence of ESBL-producing Enterobacter species in Iran, which is probably associated with the high prevalence of Enterobacter species resistant to most of the assessed antibiotics, especially MDR strains. However, the resistance rate to carbapenems was relatively low, and these drugs can still be considered as drugs of choice for the treatment of Enterobacter infections in Iran. Nevertheless, continuous monitoring of drug resistance along with antibiotic therapy based on the local data and evaluation of the therapeutic efficacy of new antibiotics or combination therapeutic strategies, such as ceftazidime/avibactam, meropenem/vaborbactam, plazomicin, and eravacycline, is recommended.

1. Introduction

The genus Enterobacter includes three medically important species, i.e., Enterobacter cloacae complex, Enterobacter aerogenes complex, and Enterobacter sakazakii [1, 2]. These enteric Gram-negative rods belong to the Enterobacteriaceae family and rarely cause infection in immunocompetent patients, but they are commonly associated with nosocomial infections, especially by the Enterobacter cloacae complex, in neonates and immunocompromised patients [1–6]. The most common nosocomial infections associated with these lactose-fermenting Enterobacter species include pneumonia, urinary tract infection, septicemia, and wound infection, as well as device-associated infections [1, 2]. Like many
bacterial infections, in which an increasing trend of antibiotic resistance has led to the emergence of public health problems and imposed economic costs on healthcare, such an increasing trend of antibiotic resistance has also been reported for Enterobacter species [3, 6]. Among different mechanisms of resistance to various antibiotics in these Gram-negative rods, the intrinsic or acquired production of antibiotic-inactivating enzymes such as β-lactamases is very important [1]. Enterobacter species producing AmpC chromosomal cephalosporins are intrinsically resistant to ampicillin as well as first- and second-generation cephalosporins [2]. Plasmid-encoded extended-spectrum β-lactamase (ESBL) genes are involved in Enterobacter species’ resistance to most β-lactam antibiotics, including second- and third-generation cephalosporins and aztreonam [6]. On the other hand, acquired resistance to quinolones, aminoglycosides, and carbapenems has been identified in hospital-acquired strains, which is highly important because these antibiotics are the last line of treatment [2, 4].

Recently, based on the World Health Organization (WHO) report, CR and ESBL-producing Enterobacteriaceae have been identified as one of the greatest threats to human health [5]. Although Escherichia and Klebsiella species are two main threats among CR and ESBL-producing Enterobacteriaceae [3], in the United States, CR Enterobacter species are considered the second most common CR Enterobacteriaceae [6].

However, there is no comprehensive data on antibiotic resistance patterns of Enterobacter species, especially CR strains, and ESBL-mediated resistance mechanisms in Iran. Therefore, the current systematic review and meta-analysis were designed to determine the prevalence of antibiotic resistance patterns of Enterobacter species, especially carbapenem-resistant strains, along with the frequency of ESBL-producing strains in Iran.

2. Methods

2.1. Literature Search and Study Selection. International databases including PubMed, Scopus, and Google Scholar, along with national databases including Scientific Information Database (https://www.sid.ir/) and Magiran (https://www.magiran.com/), were searched independently by two investigators to find studies conducted on the prevalence of antibiotic resistance and ESBL-producing Enterobacter species in Iran. The search was performed from 1996 to June 21, 2021. The most common Medical Subject Headings (MeSH)-extracted keywords used for the literature search were as follows: Enterobacter, antibiotic resistance, carbapenem, ESBL, and Iran. We defined the inclusion and exclusion criteria for the studies retrieved in the search and selected studies that met our criteria after a review of the titles, abstracts, and full text of the articles. The following studies were removed from the meta-analysis: studies reporting antibiotic resistance and ESBL-positive isolates published in languages other than English or Persian, studies conducted in other countries, studies reporting other bacteria in the Enterobacteriaceae family, studies with a small sample size (less than 10 bacterial isolates), studies with insufficient data, and nonoriginal articles, abstracts, and duplicates. Reference lists of the included articles were checked in order to find any possible missed studies. The current systematic review and meta-analysis were designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [7].

2.2. Data Extraction. Two different investigators extracted the data, and a third investigator tabulated the required information in Table 1 after resolving possible disagreements in the results of the search and reaching a consensus. Required data were as follows: first author’s surname, study location, study enrollment date, the number of isolates, antibiotic susceptibility testing methods, the prevalence of Enterobacter species resistance to different drugs, the prevalence of multidrug-resistant (MDR) Enterobacter species, and the frequency of ESBL-positive isolates. It is noteworthy that Enterobacter species have intrinsic resistance to β-lactam antibiotics including ampicillin, amoxicillin-clavulanate, ampicillin-sulbactam, cephalosporins I (cefazolin and cephalexin), cephemycins (cefotaxin and cefotetan), and cephalosporin II (cefoxoxime). According to the Clinical and Laboratory Standards Institute (CLSI) guideline, susceptibility testing is unnecessary for the above-mentioned antibiotics [8]. For this reason, these antibiotics are not included in Table 1.

2.3. Data Analysis. In the current study, Cochrane’s Q test (chi-squared, χ²) and Higgins I² statistics were used to assess heterogeneity across the included studies. For this purpose, if the p value was less than 0.1 for the χ² test and the I² value was higher than 25%, the presence of heterogeneity was considered and a random-effects model was applied for the meta-analysis. Extracted data on the prevalence of Enterobacter species’ antibiotic resistance and ESBL-producing species in Iran were expressed as a percentage and 95% confidence intervals (95% CIs). Additionally, a subgroup analysis was performed based on the location of the study. A funnel plot-based method was used for reporting the presence or absence of publication bias in the meta-analyses, and it was considered a potential sign of publication bias if the graph showed an asymmetric shape. The Comprehensive Meta-Analysis (CMA) software (Biostat, Englewood, NJ) was used for the meta-analysis.

3. Results

Among 19,669 eligible studies published from 1996 until June 21, 2021, 49 articles (20 in Persian and 29 in English) met the inclusion criteria and were included in the meta-analysis (Figure 1). As shown in Table 1, data were obtained from 19 cities (Ahvaz (n = 5), Arak (n = 1), Babol (n = 2), Bojnord (n = 1), Fasa (n = 1), Hamadan (n = 1), Ilam (n = 1), Isfahan (n = 2), Jahrom (n = 1), Kashan (n = 1), Kerman (n = 1), Kermanshah (n = 2), Rasht (n = 2), Sanandaj (n = 4), Semnan (n = 1), Shiraz (n = 4), Tabriz (n = 2), Tehran (n = 13), and Zahedan (n = 1)) in Iran. All studies used the disk diffusion method for antimicrobial susceptibility
Table 1: Required data were extracted from included articles in the meta-analysis.

| Author (Ref)    | City         | Year          | Isolate (n) | AST       | Resistance rate (n) |
|-----------------|--------------|---------------|-------------|-----------|---------------------|
| Amin et al. [9] | Ahvaz        | 2015-2016     | 152         | Disk diffusion | IPM 80 MEM 53 ATM ND CIP ND LVX 63 GEN ND AMK ND TOB ND TET ND CHL ND SXT ND NAL ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Afrugh et al. [10] | Ahvaz    | 2013-2014     | 17          | Disk diffusion | IPM 15 MEM 15 ATM ND CIP ND LVX 14 GEN 16 AMK 17 TOB 17 TET 12 CHL 13 SXT 16 NAL ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Mousavian et al. [11] | Ahvaz | 2012          | 65          | Disk diffusion | IPM 0 MEM ND ATM 6 CIP ND LVX 5 GEN 3 AMK ND TOB ND TET ND CHL ND SXT ND NAL ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR 27 |
| Khosravi et al. [12] | Ahvaz | 2009-2012     | 156         | Disk diffusion | IPM 98 MEM ND ATM 91 CIP ND LVX 102 GEN 60 AMK ND TOB ND TET ND CHL 94 SXT ND NAL ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Khosravi et al. [13] | Ahvaz | 2009-2010     | 209         | Disk diffusion | IPM 124 MEM ND ATM 88 CIP ND LVX 117 GEN 174 AMK ND TOB ND TET ND CHL 124 SXT 146 NAL ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Didgar [14]     | Ahvaz        | 2010-2012     | 47          | Disk diffusion | IPM 6 MEM ND ATM 19 CIP ND LVX 18 GEN 20 AMK ND TOB ND TET ND CHL ND SXT ND NAL ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Ghasemi et al. [15] | Babol   | 2020          | 30          | Disk diffusion | IPM 6 MEM ND ATM ND CIP ND LVX 4 GEN 6 ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Bayani et al. [16] | Babol | 2011-2012     | 30          | Disk diffusion | IPM 2 MEM ND ATM ND CIP ND LVX 2 GEN 2 ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Ghafouri et al. [17] | Bojnurd | 2013         | 12          | Disk diffusion | IPM 3 MEM ND ATM 3 CIP ND LVX 8 GEN 8 ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Peymani et al. [18] | Different cities | 2014 | 49          | Disk diffusion | IPM 2 MEM ND ATM 2 CIP ND LVX 27 GEN 16 ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Peymani et al. [19] | Different cities | 2011-2012 | 137        | Disk diffusion | IPM 2 MEM ND ATM 1 CIP ND LVX 67 GEN 22 ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Poorabbas et al. [20] | Different cities | 2008-2009 | 38         | Disk diffusion | IPM 38 MEM ND ATM ND CIP ND LVX 24 GEN 26 ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Molazade et al. [21] | Fasa    | 2012-2013     | 28          | Disk diffusion | IPM ND MEM ND ATM ND CIP ND LVX 8 GEN 0 ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Esmaeili et al. [22] | Hamadan | 2011         | 15          | Disk diffusion | IPM ND MEM ND ATM ND CIP ND LVX ND GEN ND ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Yasemi et al. [23] | Ilam       | 2007–2009     | 20          | Disk diffusion | IPM ND MEM ND ATM ND CIP ND LVX ND GEN ND ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Fatemi et al. [24] | Isfahan     | 2014–2015     | 135         | Disk diffusion | IPM 13 MEM 16 ATM 93 ND CIP 58 GEN 54 ND NIT 46 ND CRO 96 ND CFM 26 ND CTX 23 ND CAZ 23 ND ZOX 23 ND MDR 89 ND 98 ND |
| Shokri et al. [25] | Isfahan     | 2012–2013     | 35          | Disk diffusion | IPM 3 MEM ND ATM 3 CIP ND LVX 21 GEN 22 ND NIT ND CRO ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Kargar et al. [26] | Jahrom      | 2011–2012     | 25          | Disk diffusion | IPM ND MEM ND ATM ND CIP ND LVX 17 GEN 7 ND NIT 11 ND CRO 24 ND CFM 24 ND CTX 20 ND ZOX 24 ND MDR 10 ND 1 ND |
| Shajari et al. [27] | Keshan      | 2005–2006     | 35          | Disk diffusion | IPM 10 MEM ND ATM ND CIP ND LVX 14 ND NIT 12 ND CRO 28 ND CFM 21 ND ZOX 27 ND MDR 18 ND 22 ND |
| Sepehri et al. [28] | Kerman      | 1996, 2000    | 72          | Disk diffusion | IPM ND MEM ND ATM ND CIP ND LVX 43 GEN 46 ND NIT 12 ND CRO 28 ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Mortazavi et al. [29] | Kermanshah | 2016-2017    | 72          | Disk diffusion | IPM 7 MEM ND ATM ND CIP ND LVX 29 ND NIT 35 ND CRO 30 ND CFM 36 ND ZOX 35 ND MDR 36 ND 54 ND |
| Amini et al. [30] | Kermanshah | 2015          | 18          | Disk diffusion | IPM ND MEM ND ATM ND CIP ND LVX 7 ND NIT 8 ND CRO 9 ND CFM 9 ND ZOX 13 ND MDR 7 ND 6 ND |
| Karambin and Zarkesh [31] | Raht | 2008–2010     | 50          | Disk diffusion | IPM ND MEM ND ATM ND CIP ND LVX 15 ND NIT 41 ND CRO 40 ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Yaghoubi et al. [32] | Raht         | 2013–2015     | 147         | Disk diffusion | IPM 79 MEM ND ATM ND CIP 61 ND NIT 80 ND CRO 80 ND CFM 66 ND ZOX 80 ND MDR 78 ND 80 ND |
| Rouhi et al. [33] | Sanandaj    | 2013–2014     | 10          | Disk diffusion | IPM 2 MEM ND ATM ND CIP ND LVX 5 ND NIT 2 ND CRO 2 ND CFM ND CTX ND CAZ ND ZOX ND MDR ND |
| Author (Ref)          | City            | Year           | Isolate | Resistance rate (n) |
|----------------------|-----------------|----------------|---------|---------------------|
| Nikhoo et al. [34]   | Sanandaj        | 2009-2010      | 11 Disk | AST                  |
| Ramazanzadeh et al. [35] | Sanandaj       | 2007-2008      | 15 Disk | AST                  |
| Sohrabi fard et al. [46] | Tehran         | 2014-2015      | ND      | ND                  |
| Ghanavati et al. [47] | Tehran         | 2013-2014      | 57 Disk | AST                  |
| Salimian rizi et al. [48] | Tehran       | 2012-2013      | ND      | ND                  |
| Mahmoudi et al. [49] | Tehran         | 2011-2012      | 100 Disk| AST                  |
| Afsharpaiman et al. [51] | Tehran        | 2011           | 5 0 Disk | AST                  |
| Rahbar et al. [52]   | Tehran         | 2010-2011      | 83 Disk | AST                  |
| Taheri et al. [54]   | Tehran         | 2004–2012      | ND      | ND                  |
| Haghi et al. [55]    | Tehran         | 2003-2004      | 39 Disk | AST                  |
| Navidinia et al. [56] | Tehran        | NA             | 69 Disk | AST                  |
| Sadeghibojd et al. [57] | Zahedan      | 2013–2015      | 32 Disk | AST                  |
| IPM-imipenem; MEM-meropenem; ATM-amikacin; CIP-ciprofloxacin; NOR-norfloxacin; LVX-levofoxacin; GEN-gentamicin; AMK-amikacin; TOB-tobramycin; TET-tetracycline; CHL-chloramphenicol; SXT-trimethoprim/sulfamethoxazole; NAL-nalidixic acid; NIT-nitrofurantoin; CRO-ceftriaxone; CFM-cefixime; CTX-cefotaxime; CAZ-ceftazidime; CZP-cefepime; ZOX-ceftizoxime; MDR-multidrug-resistant; ESBL-extended-spectrum β-lactamase; AST-antimicrobial susceptibility testing; ND-not determined.
Articles identified after international database searching (n = 19,265) → Articles selected after reviewing the titles and abstracts (n = 586) → Full texts of the articles reviewed for eligibility (n = 137) → Included records in meta-analysis (n = 49)

Articles identified after national database searching (n = 404) → Excluded articles (n = 69) → Full texts of the articles reviewed for eligibility (n = 24) → Excluded articles (n = 64) → Included records in meta-analysis (n = 49)

29 in English → 20 in Persian

Figure 1: A schematic view of the study selection process.

It should be noted that a random-effects model was applied for the meta-analysis due to the existence of high heterogeneity across the included studies in this study.

4. Discussion

The emergence of MDR- and ESBL-producing Enterobacteriaceae, including Enterobacter species, has increased the necessity to deal with these organisms [5, 6]. The Centers for Disease Control and Prevention (CDC) estimated 197,400 cases of ESBL-producing Enterobacteriaceae along with 9,100 deaths among hospitalized patients in the United States in 2017 [58]. The antibiotic of choice to treat infections caused by MDR and ESBL-producing Enterobacteriaceae is carbapenem [3, 58, 59]. However, the widespread use of carbapenem antibiotics has led to the emergence of CR bacteria [3, 59]. According to the CDC report for 2019, increased prevalence of CR Enterobacteriaceae, especially CR Enterobacter cloacae complex, has become a public health issue in the United States [58].

In Iran, the prevalence of MDR (63.1%) and ESBL-producing Enterobacter species (32.8%) was high. This is an alarming rate despite the relatively low frequency of imipenem- and meropenem-resistant Enterobacter species in Iran. The results suggest that carbapenems are still the drugs of choice for the treatment of infections caused by MDR and ESBL-producing Enterobacter species in Iran. The distribution of ESBL-producing Enterobacter species in other countries was as follows: Pakistan 14.9%, Nigeria 37.5%, and Ethiopia 50% [60, 61].

The CDC has reported that CR Enterobacteriaceae-associated infections frequently occur in patients using medical devices, including catheters (intravenous and urinary) and ventilators, and some of these microorganisms are resistant to all available antibiotics, hence their infections are...
### Meta Analysis

| Study name     | Subgroup within study | Statistics for each study | Event rate and 95% CI |
|----------------|-----------------------|---------------------------|-----------------------|
| Amin           | Ahvaz                 | Event rate: 0.526          | Event rate and 95% CI |
| Afrugh         | Ahvaz                 | 0.447                      |                       |
| Mousavian      | Ahvaz                 | 0.604                      |                       |
| Khorasv-i      | Ahvaz                 | 0.649                      |                       |
| Khorasv-2      | Ahvaz                 | 0.649                      |                       |
| Didgar         | Arak                  | 0.008                      |                       |
| Ghasemi        | Babol                 | 0.008                      |                       |
| Bayani         | Babol                 | 0.017                      |                       |
| Ghafari        | Babol                 | 0.037                      |                       |
| Peymani-1      | Different cities      | 0.011                      |                       |
| Peymani-2      | Different cities      | 0.014                      |                       |
| Fateni         | Isfahan               | 0.006                      |                       |
| Shokri         | Isfahan               | 0.028                      |                       |
| Shajari        | Kashan                | 0.016                      |                       |
| Mortazavi      | Kermaneshan           | 0.017                      |                       |
| Taghibi        | Rasht                 | 0.037                      |                       |
| Rouhi          | Sanandaj              | 0.011                      |                       |
| Khosravi-1     | Shahrak               | 0.012                      |                       |
| Khosravi-2     | Shahrak               | 0.012                      |                       |
| Didgar         | Tabriz                | 0.021                      |                       |
| Ghasemi        | Tehran                | 0.016                      |                       |
| Peymani-1      | Tehran                | 0.016                      |                       |
| Fateni         | Tehran                | 0.011                      |                       |
| Shokri         | Tehran                | 0.019                      |                       |
| Shajari        | Tehran                | 0.011                      |                       |
| Mortazavi      | Tehran                | 0.017                      |                       |
| Taghibi        | Tehran                | 0.037                      |                       |
| Rouhi          | Tehran                | 0.011                      |                       |
| Khosravi-1     | Tehran                | 0.016                      |                       |
| Khosravi-2     | Tehran                | 0.016                      |                       |
| Didgar         | Tehran                | 0.018                      |                       |
| Ghasemi        | Tehran                | 0.018                      |                       |
| Peymani-1      | Tehran                | 0.018                      |                       |
| Fateni         | Tehran                | 0.018                      |                       |
| Shokri         | Tehran                | 0.018                      |                       |
| Shajari        | Tehran                | 0.018                      |                       |
| Mortazavi      | Tehran                | 0.018                      |                       |
| Taghibi        | Tehran                | 0.018                      |                       |
| Rouhi          | Tehran                | 0.018                      |                       |
| Khosravi-1     | Tehran                | 0.018                      |                       |
| Khosravi-2     | Tehran                | 0.018                      |                       |

**Figure 2:** Forest plots (a) and funnel plots (b) illustrate the prevalence of imipenem-resistant *Enterobacter* species in Iran.
Table 2: Antibiotic resistance profile of *Enterobacter* isolates from cities in Iran.

| City        | IPM | MEM | ATM | CIP | NOR | LVX | GEN | AMK | TOB | TET | CHL | SXT | NAL | NIT | CRO | CFM | CTX | CAZ | CEP | ZOX |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ahvaz       | 58  | 64.4| NA  | 46.8| 46.1| 41.4| 53.1| 40.9| NA  | 56.7| NA  | 69.6| 61.2| 55.1| 63.6| 70.7| 68.8| 50.9| 82.4| 61.8|
| Arak        | 12.8| NA  | NA  | 40.4| NA  | NA  | 40.4| 38.3| NA  | NA  | NA  | 42.6| NA  | NA  | 61.7| NA  | NA  | 85.1| 53.2| 40.4|
| Babol       | 13.2| NA  | NA  | 13.2| NA  | NA  | 13.2| NA  | NA  | NA  | NA  | NA  | NA  | 30  | NA  | NA  | 33.3| 16.7| 58.8| NA  |
| Bojnurd     | 25  | 41.7| NA  | 66.7| NA  | NA  | 66.7| 16.7| NA  | 25  | 3.8 | 50  | NA  | 8.3 | 50  | 3.8 | 3.8 | 8.3 | NA  | NA  |
| Fasa        | NA  | NA  | NA  | 39.3| NA  | NA  | 28.6| 1.7 | NA  | 39.3| NA  | 50  | NA  | 39.3| 39.3| 39.3| 39.3| 1.7 | NA  | NA  |
| Hamadan     | NA  | NA  | NA  | 86.7| NA  | NA  | 86.7| NA  | NA  | 66.7| 40  | 26.7| 73.3| NA  | NA  | NA  | NA  | NA  | NA  | NA  |
| Ilam        | NA  | NA  | NA  | NA  | NA  | 15  | NA  | NA  | 45  | NA  | NA  | 30  | NA  | NA  | NA  | NA  | NA  | NA  | NA  |
| Isfahan     | 9.4 | 11.3| 68.9| 49.9| NA  | NA  | 50.3| 33  | 39.3| 71.1| 19.3| 17  | NA  | 17.1| NA  | 66.5| 64.1| 51.4| NA  | NA  |
| Jahrom      | NA  | NA  | NA  | NA  | NA  | 68  | 28  | 44  | 96  | NA  | 80  | 96  | NA  | NA  | 40  | NA  | NA  | NA  | NA  |
| Kashan      | 28.6| NA  | NA  | 37.1| NA  | NA  | 40  | 34.3| 31.4| NA  | NA  | 60  | 80  | NA  | 51.4| 62.9| 62.9| NA  | NA  |
| Kerman      | NA  | NA  | NA  | NA  | NA  | 59.7| NA  | NA  | NA  | NA  | 63.9| 16.7| 38.9| NA  | NA  | NA  | NA  | NA  | NA  |
| Kermanshah  | 9.7 | NA  | 40.3| 46.7| 41.7| NA  | 48.9| 48.9| NA  | NA  | NA  | 68.9| 42.2| 23.4| 33.3| 46.8| 51.4| 53.3| NA  | NA  |
| Rasht       | 53.7| 41.5| 11.8| NA  | NA  | 42.8| 65.1| 53.1| 0.3 | NA  | 75  | 71.4| 69.4| 69.4| 81  | 79.4| 62.6| NA  | 54.4|
| Sanandaj    | 20  | NA  | 43.2| 34.2| NA  | 33.5| 40.5| NA  | 51.6| NA  | 45.2| 36.4| 4.5 | 50.7| 45.5| 51.2| 28.6| NA  | 30.7|
| Semnan      | NA  | NA  | 45.5| NA  | NA  | 45.5| NA  | NA  | NA  | NA  | 90.9| 90.9| 90.9| NA  | 72.7| NA  | NA  | NA  | NA  |
| Shiraz      | 15.1| 5.9 | 47.2| 26.9| NA  | 46.8| 34.7| 42.4| 72.7| 31.1| 37.5| 4.9 | 29.9| 51.7| 65.1| 54.8| 66.5| 38.2| NA  |
| Tabriz      | 21.6| NA  | NA  | 9.1 | NA  | 38.3| 7.5 | NA  | NA  | 27.7| 85.3| 98.8| 70.8| 37.4| NA  | 75.9| 19.5| NA  | 19  |
| Tehran      | 6.3 | 6.7 | 22  | 22.9| 3.3 | 25  | 33.1| 18.9| 31.2| 42.8| 26.4| 39.4| 36.3| 63.1| 45.3| 47.6| 58.6| 41.8| 28.8|
| Zahedan     | NA  | NA  | NA  | 9.4 | NA  | NA  | 6.3 | 9.4 | NA  | NA  | NA  | 43.8| 28.1| 6.3 | 18.8| 18.8| 18.8| NA  | NA  |

NA—not available.
difficult to treat [58]. Currently, the available antimicrobial agents for the treatment of CR Enterobacteriaceae are limited [62]. Historically, aminoglycosides, tigecycline, polymyxins, and fosfomycin have been used as therapeutic options for this purpose [62]. However, according to the included articles in this study, there is insufficient data on the prevalence of tigecycline-, polymyxins-, and fosfomycin-resistant Enterobacter species in Iran. Hence, the evaluation of Enterobacter species resistance rates to these antibiotics is recommended. In the present study, the rate of tetracycline-resistant Enterobacter species was high (50.1%).

On the other hand, aminoglycosides, including gentamicin, amikacin, and tobramycin, are also recommended as anti-CR Enterobacteriaceae therapies [62]. However, based on the present study, the prevalence of gentamicin-, amikacin-, and tobramycin-resistant Enterobacter species was high in Iran. It is recommended that older antibiotics such as trimethoprim/sulfamethoxazole and chloramphenicol may be effective for the treatment of infections caused by CR Enterobacteriaceae pathogens [62]. Our results showed that the prevalence of Enterobacter species resistant to chloramphenicol was higher than those resistant to trimethoprim/sulfamethoxazole (25.7% vs. 52%). Other treatment options for infections caused by CR Enterobacteriaceae include combination strategies (high-dose tigecycline, high-dose carbapenem, and double-carbapenem therapy), new antibiotics (ceftazidime/avibactam, meropenem/vaborbactam, plazomicin, and eravacycline), and new antibiotics in development (imipenem/cilastatin, relebactam, and cefiderocol) [62]. However, information on the therapeutic efficacy of these drugs against CR Enterobacter species is not available in Iran (according to the included articles in this study). Based on the current study, the frequency of meropenem and ceftazidime-resistant Enterobacter species was 16.2% and 47.9%, respectively. Enterobacter species’ drug resistance rates to the third-generation cephalosporins and aztreonam were high in Iran. Considering the prevalence of ESBL-producing Enterobacter species in this study (32.8%), it seems that these ESBLs are involved in resistance to third-generation cephalosporins and aztreonam in Iran. The CDC estimated the rate of quinolone-resistant Enterobacter species as 30% [3]; however, the prevalence of Enterobacter species resistant to quinolones was higher in this study.

Such a high antibiotic resistance of Enterobacter species, especially MDR, in this study can be attributed to the indiscriminate use of antibiotics and easy, without a prescription, access to antibiotics and self-medication in Iran [63, 64]. On the other hand, since Enterobacter species are responsible for nosocomial infections, using appropriate infection control programs and practices of hygiene such as hand decontamination, glove use, sterilization, and disinfection practices can play an important role in preventing the spread of resistant strains in healthcare settings.

One of the limitations of the current study was the inability to compare the obtained results with other countries, particularly adjacent countries, which needs to be addressed in future multicenter and international studies.

5. Conclusion

This study is the first systematic review and meta-analysis reporting Enterobacter species antibiotic resistance in Iran. The results of this meta-analysis indicated the high prevalence of Enterobacter species resistant to the majority of assessed antibiotics in the included studies, i.e., quinolones, aminoglycosides, third- and fourth-generation cephalosporins, aztreonam, tigecycline, chloramphenicol, trimethoprim/sulfamethoxazole, and nitrofurantoin. In addition, the prevalence rates of ESBL-producing Enterobacter species (32.8%) and MDR (63.1%) strains were high in Iran. Such an increasing trend of antibiotic resistance in Enterobacter species can impose more economic costs on healthcare systems in Iran due to prolonged periods of hospitalization, increased drug consumption, poor patient outcomes, and higher mortality and morbidity. In total, we suggest the management of antibiotic prescription, launching and developing health education and infection control programs, continuous monitoring of drug resistance, and evaluation of the therapeutic efficacy of new antimicrobial agents (herbal medicine and new antimicrobial peptides) or combination therapeutic strategies are required to control Enterobacter species-associated infections and antibiotic resistance in Iran. Finally, in comparison with the above-mentioned antibiotics, the prevalence of CR Enterobacter species was relatively low in Iran, and it seems that carbapenems can still be considered as drugs of choice for the treatment of MDR and ESBL-producing Enterobacter species.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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