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Comparison of Antibiotic Susceptibility of *Klebsiella* Species Causing Urinary Tract Infection in Iran and Other Countries around Asia

Moein Hamidi Hesari[1,4], Taban Hashemi[1], Jafar Hemmat[2]*, Noorkhoda Sadeghifard[3]

[1] *Islamic Azad University of Nishapur, Department of Biology, Nishapur, Iran*
[2]*Biotechnology Department, Iranian Research Organization for Science and Technology,IROST , Tehran, Iran*
[3]*Medical University of Ilam, Clinical Microbiology Research Center, Ilam, Iran*
[4]*Imam Khomeini Hospital, Shirvan, North Khorasan University of Medical Sciences, Bojnurd, Iran*

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Abstract

This study aimed to evaluate the antibiotic-susceptibility pattern of Klebsiella pneumoniae causing urinary tract infection (UTI) in two geographical regions of Iran and then compare it to the rest of Iran and other countries. Over a year, from winter 2014 to winter 2015, 80 cases of Klebsiella were isolated from 2584 urine samples and identified using biochemical and microbiological tests. The disk diffusion method was used to determine antibiotic susceptibility based on the standard protocols provided by the CLSIs. The results of this study were compared with several reports from Iran and other countries, before the COVID-19 pandemic from 2007 to 2018. Based on the results of the antibiotic susceptibility of 80 isolated K. pneumoniae, amikacin (AN), Meropenem (MEN), gentamicin (GM), and ciprofloxacin (CP) were identified as the most sensitive antibiotics with 77.5%, 77%, 75%, and 58.75% sensitivity, respectively. A comparison of 17 report results showed imipenem (IPM) is the most sensitive antibiotic against the K. pneumoniae isolates, with a sensitivity range of 85% -100%. Followed by amikacin (AN), which was reported as the first or second antibiotic or third or fourth antibiotic in less than 30% of the cases. CP was reported as a second or third option in 22% of the cases. This study evaluated the sensitivity pattern of K. pneumoniae to antibiotics, and the results show that it has the potential to be applied to further studies and related programs, including periodic screening, regional screening, and revision in therapeutic approaches.

1. Introduction

Urinary tract infections (UTIs) are one of the most common human infections, second only to respiratory tract infections with 150 million UTIs, include uncomplicated and complicated urethritis, cystitis, and pyelonephritis, occurring worldwide each year (Clegg *et al*., 2016; Coskun *et al*., 2011; Mirzarazi *el al*., 2013). Although most UTIs are not life-threatening and do not generally cause irreversible damage; when the kidneys get involved, bacteremia increases, and there is a risk of irreversible damage to them. Half of the female population suffers from this infection at

*Corresponding author. Jafar Hemmat, *Biotechnology Department, Iranian Research Organization for Science and Technology, IROST , Tehran, Iran*
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least once in their lives (Hamidi *et al*., 2022). *Escherichia coli* and *Klebsiella pneumoniae* are considered two of the most important and common causes of UTI etiological factors. Moreover, the antibiotic resistance of *Klebsiella* is a virulent bacterial factor (Maleki *et al*., 2018). Physicians may have to treat many infectious diseases, including acute UTIs before a definitive diagnosis of an infectious agent and its antibiotic susceptibility are determined. In this case, they should have sufficient information about the potential cause of the infection and the antibiotic susceptibility of the agents to recommend an appropriate antibiotic (Rath *et al*., 2014; Senbayrak *et al*., 2017). Several national and international surveillance programs have been run to monitor susceptibilities of clinically important pathogens in UTIs (Yilmiz *et al*., 2016; Yang *et al*., 2017; Arato *et al*., 2021).

The frequency of UTIs caused by *K. pneumoniae* varies from person to person: 4% in ICU-acquired UTIs, 10% in Nosocomial catheter-associated UTIs, and 16% in Community-acquired UTIs (Clegg *et al.*, 2016). Pneumonia, UTIs, and bloodstream infections (BSIs), caused by highly drug-resistant (XDR) *K. pneumoniae*, have been closely related to increased hospital stay duration, morbidity, mortality, and, consequently, increased healthcare costs. This opportunistic pathogen is now considered one of the major pathogenic bacteria of septicemia, accounting for 11.3% of this condition in China between 2011 and 2012 (Bi *et al*., 2017). Today, *K. pneumoniae* is considered an "Emerging Anti-Microbial Resistant Global Threat", especially in low- and middle-income countries already influenced by antibiotic resistance genes, and consequently, considered to be at higher risk of further morbidity and mortality (Arato *et al*., 2021). High multi-drug resistance and extended-spectrum beta-lactamase (ESBL) producing *Klebsiella* species have been detected in UTIs (Ameshe *et al*., 2022). Achieving a precise understanding of the management and control process of this serious public health threat requires accurate information on its past and present antibiotic sensitivity. Therefore, this study aimed to determine the antibiotic susceptibility pattern of *Klebsiella* isolates from UTI in two different border regions in Iran. In addition, the susceptibility pattern of this bacterium was compared in the various regions of Iran and Asia before the COVID-19 pandemic from 2007-2018.

2. Materials and methods

2-1. Data Collection

In 2014-2015, a total of 2,584 urinary cultures were conducted in two Iranian border regions, one in the northeast (Shirvan, located in Bojnurd with a Kurdish population near Turkmenistan) and another in the southwest part of Iran (Ilam province, all Kurds near Iraq). Informed patient consent was waived because this study is partly retrospective, including retrospective observation, does not interfere with patients, and focuses mainly on the isolates. Additionally, the results of 17 previous reports from Iran and other Asian countries were used as a retrospective cross-sectional analysis. Moreover, corresponding reports from South American countries during the mentioned period were also considered as out-group data. Accordingly, no personal data of the patients were used or processed; this paper is a retrospective analysis of patients' medical records.

2-2. Isolation and identification of bacteria

The bacteria were isolated in differential culture media of Enterobacteriaceae, such as MacConkey agar, Eosin-methylene blue agar (EMB), Bromo-thymol blue agar (BTB), and selection culture media. The cases counting over > 10^5 CFU/ml were considered positive for infection. The bacterial identification was conducted using conventional methods. The identified *Klebsiella* species were stored in a Tryptic Soy Broth (TSB) medium containing 30% glycerol at -80 °C.

2-3. Determination of Antibiotic Susceptibility

The antibiotic susceptibility assay was performed using the Kirby-Bauer disk-diffusion method (Padtan Teb Co.) according to the Clinical and Laboratory Standards Institute

(CLSI) standards. *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603 were used as negative and positive control strains, respectively (Maleki *et al.,* 2015). The Chi-square test statistical analysis was performed using Minitab software, version 19.0, and P-values less than 0.05 were considered statistically significant.

3. Results and Discussion

3.1. The frequency of pathogenic Klebsiella species

Among 2584 urinary cultures, 255 (9.86%) were positive. In total, 80 *Klebsiella* species were isolated from two geographical regions of Iran. After the identified tests, 47 isolates (58%) of *K. pneumoniae*, 13 isolates (16.25%) of *Klebsiella oxytoca*, 8 isolates (10%) of *Klebsiella mobilis*, 6 isolates (7.5%) of *Klebsiella ozone*, and 6 isolates (7.5%) of *Rhinoscleromatis* were obtained. Interestingly, the species (except for *K.mobilis*) had roughly the same prevalence in the two geographical regions. The results showed that the most isolated specimens were *K. pneumoniae* and then *K. Oxytoca* (Table 1).

Table 1: The Frequency of Pathogenic *Klebsiella* Isolates from Urinary Tract Infection in the Bojnurd-Shirvan and Ilam Areas, Iran

The isolates	Number/percentage in the regions or Total		
	Bojnoord - Shirvan	Elam	Total
K. pneumonia	27(58.70%)	20(58.83%)	47(58.75%)
K. oxytoca	7(15.21%)	6(17.65%)	13(16.25%)
K. mobilis	6(13.05%)	2(5.88%)	8(10%)
K.ozaenae	3(6.52%)	3(8.82%)	6(7.5%)
K. rhinoscleromatis	3(8.82%)	3(8.82%)	6(7.5%)
Total	46 (100%)	34(100%)	80(100%)

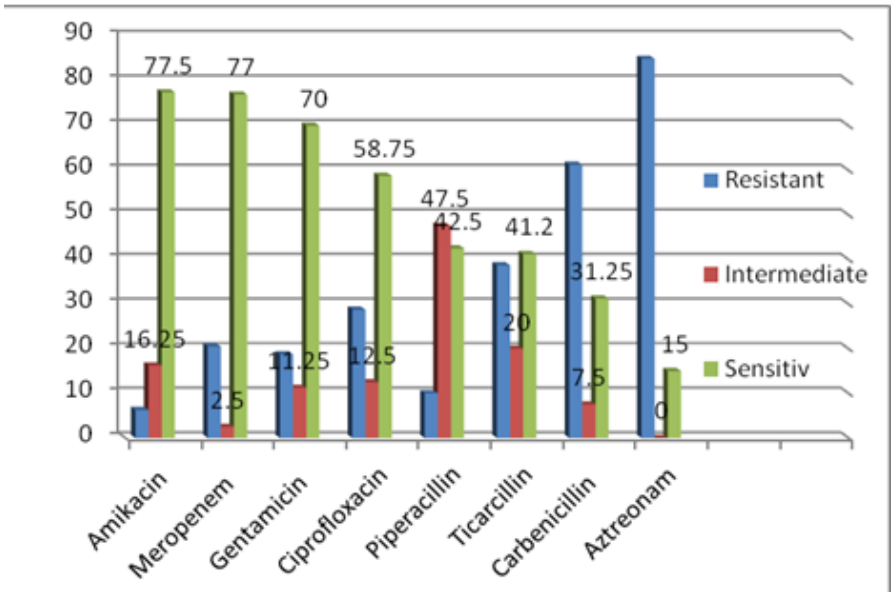
Among 80 isolates, 46 isolated *Klebsiella* were related to the Bojnurd-Shirvan area and the other 34 *Klebsiella* isolates were to Ilam. According to the results in both regions, K. *pneumoniae* showed the highest prevalence (58%) with a similar percentage in both regions, with *K. oxytoca* (15-17%) the next highest prevalence, highlighting the importance of this isolate. While the prevalence of *K. ozone* and *K. rhinoscleromatis* were similar (6.5-8.8%) in the two regions, *K.mobilis* showed a higher prevalence (13.05%) in Bojnurd than Ilam (5.88%). Although the 80 isolates were spread through five different species (Table 1), there are several surveys in which the isolated *Klebsiella* species were restricted to *K. pneumoniae* and another *Klebsiella* species. According to a study in Tehran (the capital of Iran), *K. pneumoniae* and *K. oxytoca,* with 94% and 4% prevalence, were two *Klebsiella* species of UTI (Sultandalal *et al*., 2012).

3.2. Antibiotic susceptibility of Klebsiella sp. isolates

The antibiotic susceptibility of the isolated *Klebsiella* sp. revealed amikacin (AN), meropenem (MEN), gentamicin (GM), and ciprofloxacin (CP) as the most sensitive antibiotics (MSenABs) on the pathogen *Klebsiella* isolates with 77.5%, 77%, 70%, and 58.75% sensitivity, respectively (Fig 2). Similarly, in a study conducted in Shahrekord, Iran (near Esfahan), the isolates showed 89.3% sensitivity to IPM (Latifpour *et al*. 2016). Moreover, the isolated UTIs in Kashan, Iran (the region near Esfahan) showed 100% sensitivity to IPM as the most effective antibiotic, while CP had 53.7% sensitivity (Moini *et al.,* 2015). In another study in Tehran, the antimicrobial susceptibly pattern of 247 *K. pneumonia*e isolated from patients with UTI showed 85.8%, 62.8%, and 60.7% susceptibility to tigecycline, amikacin, and imipenem, respectively (Goudarzi *et al.*, 2015) (Fig 3-7). However, two different studies on UTI caused by *K. pneumonia* in Iran showed different results.

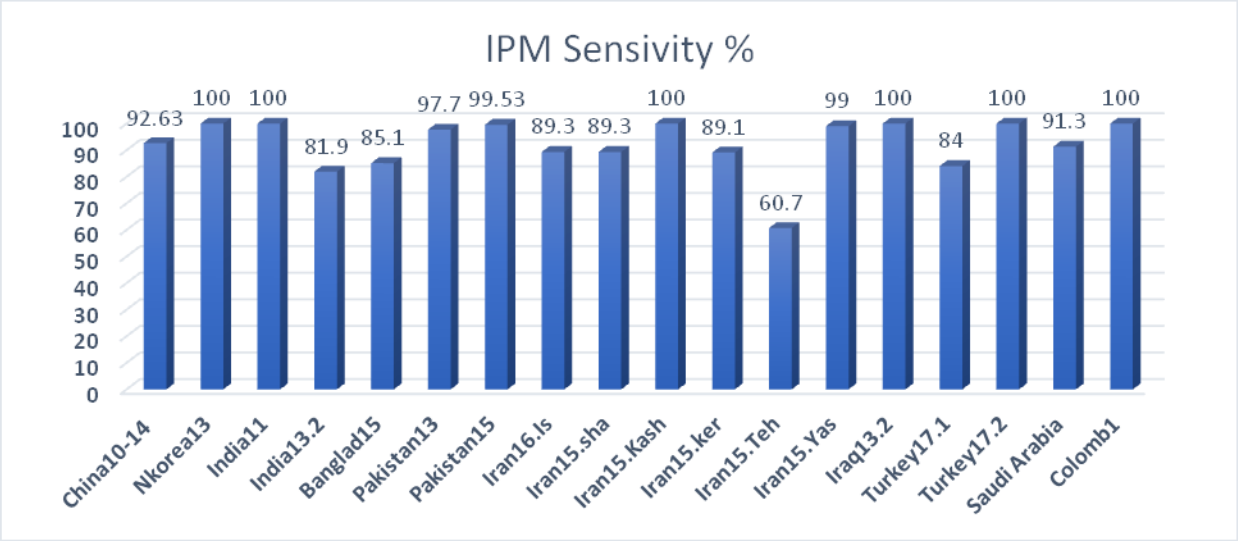
Exploring the beta-lactamase gens of isolated *K. pneumoniae* in Yasuj, Iran, showed antibacterial susceptibility of MEN (100%), IPM (99%),

Figure 2: *Antibiotic Susceptibility of Klebsiella sp. Isolates*



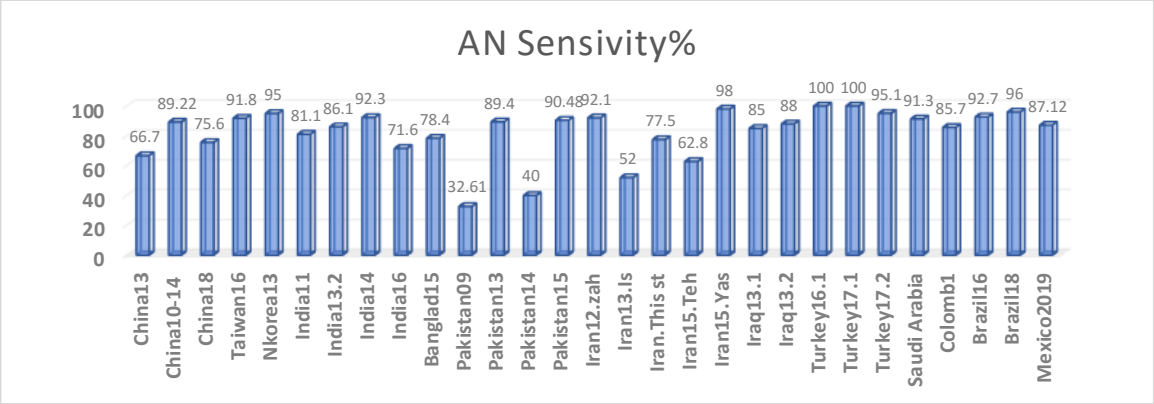
and AN (98%) (Dehshiri *et al*.2018). During another retrospective cross-sectional study in Isfahan, Iran, in 2018, the isolated *k. pneumonia* showed antimicrobial susceptibility to colistin (98%), tigecycline (94.9%), gentamicin (79.6%), CP (76.5%), and piperacillin/tazobactam (73.5%), which was significantly different from the above study (Maleki *et al*., 2018). Overall, all studies in Iran revealed the IPM and AN as the first and second options for the treatment of UTIs caused by *K. pneumonia*, with the isolates showing 89-100% and 62.8-98.99% sensitivity to IPM and AN, respectively (Fig 3-7).

Figure 3: *Comparative Antimicrobial Susceptibilities of IPM Antibiotic against the K. Pneumonia-Causing UTI in Different Countries*



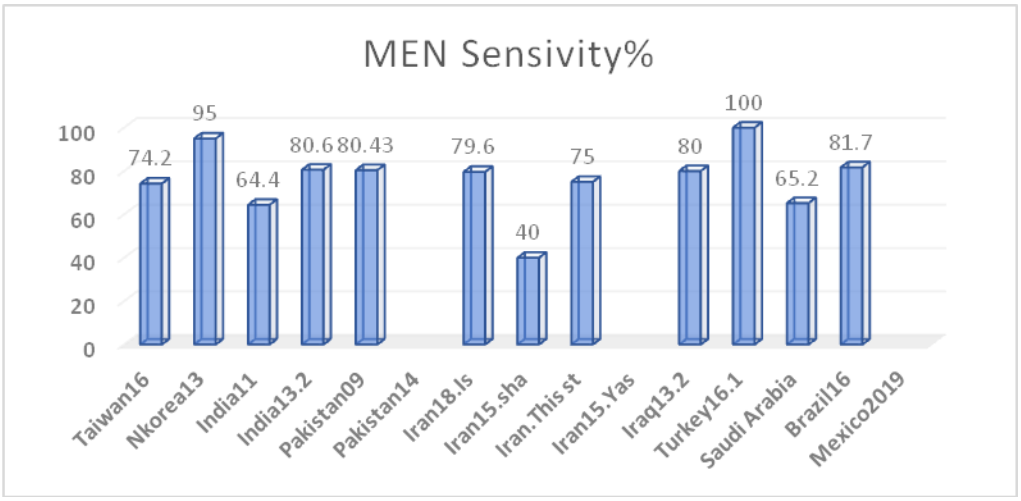
Note: The number at the end of any legend name stands for the times of the study (Iran15.Is: Iran 2015 at Isfahan). The details are presented in Table sup in the supplementary file.

Figure 4: *Comparative Antimicrobial Susceptibilities on AN Antibiotic against the K. Pneumonia-Causing UTI in Different Countries*



Note: The number at the end of any legend name stands for the times of the study (Iran15.Is: Iran 2015 at Isfahan). The details are presented in Table sup in the supplementary file.

Figure 5: *Comparative Antimicrobial Susceptibilities of MEN Antibiotic against the K. pneumonia-causing UTI in Different Countries*



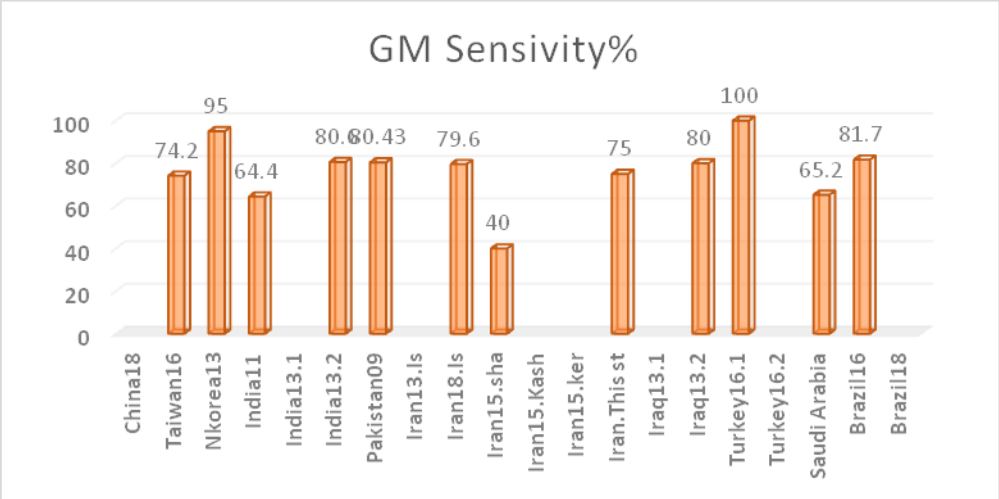
Note: The number at the end of any legend name stands for the times of the study (Iran15.Is: Iran 2015 at Isfahan). The details are presented in Table sup in the supplementary file.

In the eastern neighboring country of Pakistan, two studies showed 97.7% and 99.53% susceptibility of isolated *K. pneumonia* from UTIs to imipenem, although two other surveys evaluated other antibiotics, with *K. pneumonia* showing just 81% sensitivity to meropenem. Moreover, Pakistan's AN showed less susceptibility than Iran, at 32.-90.4% against (62.8-98.99%), (Fig 3-7) (Ullah *et al*., 2009; Abdullah *et al*., 2013; Jamil *et al*., 2014). Three studies in Pakistan presented AN as the MSenAB1 with 71.6-92.3% susceptibility, while IMP was reported as MSenAB1 with a 100% sensitivity and AM with 92.9% sensitivity in two other studies. Moreover, IMP was the MSenAB2 with 81.9% susceptibility in one of five studies (Fig 3-7) (Rizvi *et al*., 2011; Dash *et al.*, 2013; Amsath *et al*. 2013; Varghese *et al.*, 2016).

In the western neighboring country of Iraq, one study showed a 100% susceptibility of isolated *K. pneumonia* from UTIs to imipenem, while another study showed 88% susceptibility to nitrofurantoin (FM) and 85% and 88% to AN and CP, respectively (Iran: 62.8-98.99%) (Fig 3-7)

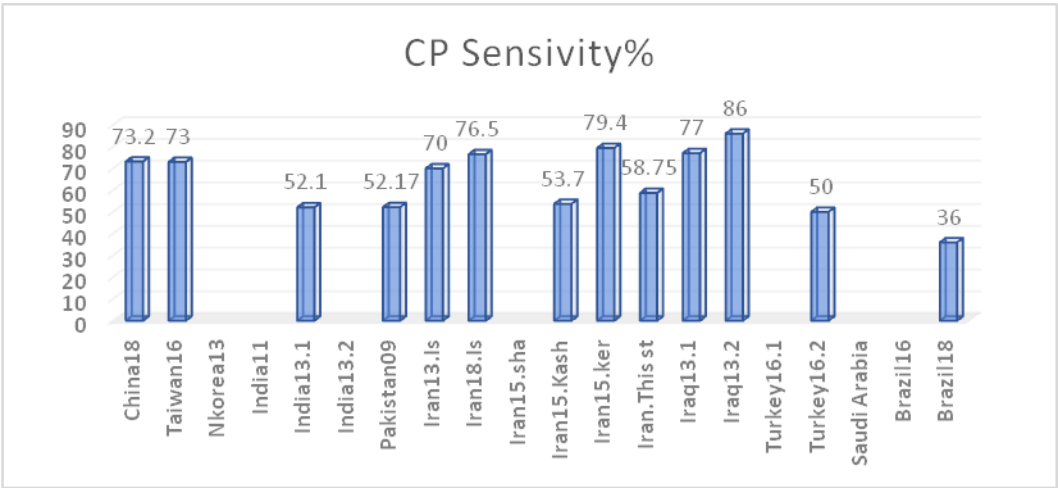
(Al-Jebouri *et al.*, 2013; Jebur *et al*., 2013). There are several different reports in Turkey, another western neighboring country of Iran. In two studies reported in 2016, *K. pneumonia* revealed 100% susceptibility to AN and GM (Fig 4-5) (Koçak *et al*., 2016; Guneysel *et al.*, 2016). However, as a part of the SMART study, Gram-negative pathogens were collected from UTIs, non-ICU, and associated intra-abdominal infections (IAIs) to describe the epidemiology and susceptibility of pathogens (including ESBL producers) from hospital-acquired (HA) versus community-acquired (CA) urinary tract infections (UTIs) and ICU- versus non-ICU associated intra-abdominal infections (IAIs) at six hospitals in Turkey from 2011to 2012. They showed that *E. coli* and *K. pneumoniae* are the principal pathogens of community-acquired (CA) and hospital-acquired (HA) UTIs, and the carbapenems and amikacin maintain a high level of efficiency against a wide range of Enterobacteriaceae; however, it revealed a minus susceptibility in rates in HA UTIs caused by *K. pneumonia*. IAIs, IPM, AN, and ertapenem inhibited 90% of *E. coli*, and IPM, AN, and cefoxitin inhibited 90% of *K. pneumoniae* responsible for IAIs indicating a low susceptibility (Yilmaz *et al.*, 2017).

Figure 6: *Comparative Antimicrobial Susceptibilities of GM Antibiotic against the K. pneumonia-causing UTI in Different Countries*



Note: The number at the end of any legend name stands for the times of the study (Iran15.Is: Iran 2015 at Isfahan). (Note: The not-defined cases have been left empty). The details are presented in Table sup in the supplementary file.

Figure 7: *Comparative Antimicrobial Susceptibilities of CP Antibiotic Against the K. pneumonia-causing UTI in Different Countries*



Note: The number at the end of any legend name stands for the times of the study (Iran15.Is: Iran 2015 at Isfahan). (Note: The not-defined cases have been left empty). The details are presented in Table sup in the supplementary file.

Reviewing data from East Asian countries, a study reported 100%, 95%, and 95% susceptibility of UTI *K. pneumoniae* in South Korea to IMP, AN, and GM, respectively (Lee, 2013). However, *K. pneumoniae* causing UTI in Taiwan revealed 91.8%, 74.2%, 74.2%, and 73% susceptibility to AN, MEN, GM, and CP, respectively (Wu *et al.*, 2015). A four-year retrospective study from 2010 to 2014 in China regarding antimicrobial susceptibilities of aerobic and facultative gram-negative bacilli causing UTIs showed that *K. pneumonia* has the most susceptibility to imipenem (92.6%), amikacin (89.2%) and ertapenem (87.9%) (Yang *et al.*, 2017). The susceptibility pattern of South-Ameriacan countries, as the out-group of the study, showed a similar pattern to that of the Asia countries (Fig 3-7). These retrospective and comparative studies can help us achieve the Klebsiella sp susceptibility patterns in Asia, which may have had some implications during the COVID-19 pandemic.

4. Conclusion

This study summarized and compared results on the sensitivity pattern of *K. pneumoniae* with 17 published reports, reporting IPM with a sensitivity range of 85-100% as the most sensitive antibiotic against the *K. pneumoniae* isolates from UTIs. However, the susceptibility patterns of the isolates have remarkable similarities and relative differences. For example, in some reports, AN was the first or second most effective antibiotic; in others, it was the third or fourth option, with a sensitivity range of 32-100%. Although MEN, GM, and CP were reported as the second or third option in five reports, they lost complete antibiotic activity in some reports. Accordingly, the regional and global antibiotic resistance pattern of the *K. pneumoniae* species showed similarities and differences in studies and related programs from 2007-2018. However, due to the difference in antibiotic susceptibility of bacterial pathogens in different geographical regions and the change in rate sensitivity and resistance over time, the study should be conducted periodically in each region to provide an accurate pattern for physician guidance in UTI treatment. Overall, periodic and regional screening in each region of each country and revision in therapeutic approaches are emphasized both now and in the future. The presented data may provide new subjects and data for future studies.

Author contribution:

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Moein Hamidi Hesari and Taban Hashemi. The first draft of the manuscript was written by Moein Hamidi Hesari, and Jafar Hemmat commented on and edited the subsequent versions. All authors read and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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Not Applicable.

Appendix:

A supplementary file presents the results of the reports regarding the antibiotic resistance of *K. pneumoniae* in UTIs.

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