Iraqi JMS

Published by Al-Nahrain College of Medicine
P-ISSN 1681-6579
E-ISSN 2224-4719
Email: iraqijms@colmed.nahrainuniv.edu.iq
http://www.colmed-alnahrain.edu.iq
http://www.iraqijms.net
Iraqi JMS 2024; Vol. 22(2)

Antibiotic Resistance in *Klebsiella Pneumoniae* and Its Impact in Mixed Type Isolates

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Abstract

Background The *Klebsiella pneumoniae (K. pneumoniae)* is part of the healthy human microbiome, providing a potential reservoir for infection. It is most prevalent in healthcare settings and it is a significant nosocomial pathogen, leading to infections among hospitalized patients.

Objective To investigate the prevalence of multidrug resistance (MDR), extensively drug resistance (XDR) and pan-drug resistance (PDR) patterns among *K. pneumoniae* with their importance in mixed type isolates.

Methods This study is a cross-sectional investigation that included a total of 132 *K. pneumoniae* isolates, isolated from different infections collected from bacteriology laboratories located in six government hospitals in Baghdad. The Vitek2 system confirmed the bacterial and antibiotic susceptibilities.

Results The results showed that 106/132 (80.3%) of the isolates were pure *K. pneumoniae*, and 26/132 (19.7%) were mixed type isolates (*K. pneumoniae* plus other bacteria). It was found that the isolates were most resistant to beta-lactamase drugs and sulfonamide, such as Ticarcillin (97%), Piperacillin (92%), Ceftazidime (90%), Ticarcillin/Clavulanic acid (83%), Azatreonem (86%), and Trimethoprim/Sulfamethoxazole (86%). The antibiotic susceptibility patterns showed that 40/132 (30.3%) had possible XDR, 30/132 (22.7%) had MDR, and 16/132 (12.1%) had possible PDR. In the present study, burn infections followed by respiratory secretions revealed isolates with higher antibiotic resistance.

Conclusion The study revealed that high incidence of XDR and MDR patterns compared to previous studies conducted in Iraq in recent years. The co-existence of two or more bacterial species may lead to syntrophic interactions. The emergence of antibiotic-resistant strains among mixed strains has increased the severity of polymicrobial infection.

Keywords *Klebsiella pneumoniae,* antibiotics susceptibility patterns, poly-microbial infections.

Citation Fouad NA, Totl KJ. Antibiotic resistance in *Klebsiella Pneumoniae* and its impact in mixed type isolates. Iraqi JMS. 2024; 22(2): 369-376. doi: 10.22578/IJMS.22.2.22

List of abbreviations: AST = Antibiotic susceptibility test, H.A. = Hospital acquired, H.V.S = High vaginal swab, ICU = Intensive care unit, *K. pneumoniae* = *Klebsiella pneumoniae*, MDR = Multidrug resistance, NMDR = Non-multidrug resistant, PDR = Pan-drug resistance, RCU = Respiratory care unit, XDR = Extensively drug resistance

Introduction

Klebsiella pneumoniae (*K. pneumoniae*) is the causative agent of various human diseases, such as respiratory, urinary, and blood infections. K. pneumoniae is related to both acquired and community health infections [1]. Many bacterial factors, including virulence

and antibiotic resistance, play an important role in pathogenicity. Additionally, various host intrinsic factors like genetics, age, and immunological condition, as well as extrinsic factors like antibiotic usage, environmental exposure, and alcoholism, influence the susceptibility to K. pneumoniae infection [2]. *K. pneumoniae*, which tops *Enterobacteriaceae* in drug resistance, is known for its quinolone resistance. Many studies indicate Penicillin and Cephalosporin resistance is growing. The uncontrolled use of these antibiotics is to blame. Chromosome-encoded β-lactamases may cause intrinsic resistance. Multidrug-resistant (MDR) opportunistic bacteria provide a major issue for infectious disease clinicians worldwide [3]. Moreover, *K. pneumoniae* is identified with other bacteria in biofilm-mediated chronic wound infections [4]. *K. pneumoniae* is often co-isolated from polymicrobial infections [5]. Polymicrobial infections, caused by many pathogens, are common. Many clinical diagnoses of bacterial infections focus on dominant bacteria and neglect pathogens in smaller numbers. A pure culture laboratory on pathogens has explained single-species infections but not co-infection dynamics. It is important to understand how co-infecting pathogens interact and their impacts, as minority groups of bacteria might impact dominant members' physiology and behavior and impact polymicrobial virulence and antibiotic resistance [5,6].

The present study aims to detect the antibiotic patterns of *K. pneumoniae* and their impact on mixed-type isolates infections.

Methods

Study population and design

This cross-sectional study that was conducted during the period from August 2022 to September 2023 and included a total of 132 *K. pneumoniae* isolates. The isolates were collected from bacteriology laboratories in six government hospitals in Baghdad: Ibn al-Balady Hospital, Medical City Hospitals (Specialized Surgical Hospital, Baghdad Teaching Hospital, Educational Laboratories, Burns Specialist Hospital), and Central Teaching Hospital of Pediatrics. The isolates collected from different specimen sources included urine, respiratory secretions (sputum, endotracheal tube (ETT) swabs, aspiration, bronchial wash), blood, wound and burn infection, stool, and others. The bacteria were isolated on MacConkey agar plates and HiCrome TM UTI agar and incubated them at 37°C for 24 hr to see the differences in how they fermented, their shapes, and their colors. When the colony morphology was presented with lactose fermentation on MacConkey agar, it appeared as a pink color and mucoid. However, when sub-cultured was on HiCrome TM UTI agar, the colonies displayed a bluish-green or turquoise color and mucoid, indicating primarily *Klebsiella spp.*, while *Escherichia coli (E. coli)* appeared as a purple color. The identification of the isolate through morphological characteristics and biochemical tests was guided according to Grimont et al. [7] and Forbes et al. [8]. Vitek2 system was used the for identification and antibiotic susceptibility tests, and on October 14, 2022, the Institutional Review Board of College of Medicine, Al-Nahrain University granted approval for this study (I.R.B/192).

Results

Among the 132 *K. pneumoniae* collected, that identified using the Vitek system, 106/132 (80.3%) were pure *K. pneumoniae* isolates, and some K. pneumoniae isolates were associated with other bacterial isolates. 26/132 (19.7%) appear as mixed types of isolates, including *K. pneumoniae* plus other different bacterial isolates, as shown in table (1). According to hospital records, the isolates that were considered hospital acquired (H.A.) were 75/132 (56.8%) as isolated, 59/106 (55.7%) as pure isolates, and 16/26 (61.5%) as mixed isolates. Community-acquired (C.A.) isolates accounted for 57/132 (43.2%), with 47/106 (44.3%) being pure isolates and 10/26 (38.5%) being mixed isolates. Among all collected isolates, H.A. isolates had the highest percentage. the 75 H.A. isolates, 22/75 (29.3%)

K. pneumoniae isolates were collected from both intensive care unit (ICU) 17 and respiratory care unit (RCU) 5. Among 59/106 H.A. pure *K. pneumoniae* isolates, there were 14/59 (23.7%) isolates collected from the ICU and 5/59 (8.5%) isolates collected from the RCU. Among 16/26 H.A., mixed-type isolates were collected, and 3/16 (18.8%) of the isolates came from the ICU. The neonatal care unit had 14/75 H.A. isolates of *K. pneumoniae* (18.7%). H.A. isolates of *K. pneumoniae* from patients with cancer were 8/75 (10.7%), and isolates in the kidney dialysis unit were 4/75 (5.3%). From 59/132 H.A. isolates of pure *K. pneumoniae* isolates, there were 8/59 (13.6%) diagnosed with sepsis; of them, 6/8 (75.0%) had sepsis included in the age group (<1 year), and most of them were from males (5/6; 83.3%).

Table 1. Distribution of *K. pneumoniae* according to type of isolates and clinical specimens

Type of isolates	No. of isolates	Sex distribution	No. of Community Acquired C.A.	No. of Hospital Acquired H.A.	Clinical specimen
(pure) *K. pneumoniae*	106	Female 53 Male 53	47	59	Urine (56) Respiratory secretions (20) Blood (19) Wound swab (6) Umbilical (1) Lavage (1) Tissue biopsy (1) Foly tip swab (1) H.V.S (1)
K. pneumoiae + E. coli	6	Female 5 Male 1	2	4	Urine (2) Wound swab (1) Burn swabs (3)
K.pneumoniae + P. aeruginosa	8	Female 7 Male 1	3	5	Urine (2) Respiratory secretions (4) Burn swabs (1) Abscess (1)
K.pneumoniae + E. faecium	1	Male 1	0	1	Respiratory secretions (1)
K. pneumoniae + E. cloacae complex	1	Male 1	1	0	Respiratory secretions (1)
K.pneumoniae + B. cepacia	2	Female 1 Male 1	0	2	Respiratory secretions (1) Wound swab (1)
K. pneumoniae + A. baumannii	2	Female 2	0	2	Respiratory secretions (1) Wound swab (1)
K. pneumoniae + E. coli + P. aeruginosa	2	Female 1 Male 1	1	1	Urine (1) Wound swab (1)
K. pneumoniae + E. coli + E. aerogenes	4	Female 2 Male 2	3	1	Stool (3) Wound swab (1)
Total	132	132	57	75	132

K. pneumoniae **isolates and Antibiotics resistance profile**

The antibiotic susceptibility of 132 clinical *K. pneumoniae* isolates were examined to various antibiotics, including Ticarcillin, Ticarcillin/clavulanic acid, Piperacillin/Tazobactam, Ceftazidime, Cefepime, Aztreonam, Imipenem, Meropenem, Amikacin, Gentamycin, Tobramycin, Minocycline, Ciprofloxacin, and Trimethoprim/Sulfamethoxazole. Antimicrobial susceptibility testing was conducted using the automated VITEK-2 compact system and the antibiotic susceptibility test (AST) A222 cards. The Clinical and Laboratory Standards Institute (CLSI, 2022) established guidelines and breakpoints for the interpretation of antibiotic susceptibility testing findings [(9)]. The European Centre for Disease Control (ECDC) and the Centre for Disease Control and Prevention (CDC) in Atlanta have developed globally recognized terminology to characterize MDR, extensively drug-resistant (XDR), and pan-drug resistant PDR [(10)]. The isolates were stratified into various susceptibility patterns of MDR. MDR is defined as non-susceptibility to at least one agent in three or more antimicrobial categories. The term XDR refers to non-susceptibility in all but two or fewer antimicrobial categories. PDR resistance bacterium was insensitive to all antimicrobial classes. Non-susceptible isolates are resistant or not totally susceptible to one or more antibiotics in a specific category.

The AST/VItek2 compact microbiological labs use at least 15 antibiotics across four categories. Therefore, it is likely that "possible XDR" (P-XDR) was used. Bacteria isolates were termed as "P-XDR" if they exhibited resistance to most antimicrobial classes and susceptibility to one or two drugs in one or both categories. P-XDR shows strong resistance. Bacterial isolates resistant to most of the normally tested classes (four or all available and tested categories) were referred to as "possible pan drug resistance" (P-PDR) because most AST/vitek2 had limited categories.

All isolates which were not satisfying the criteria for MDR and XDR were classified as non-multidrug-resistant (NMDR) isolates, which resist to at least on drug in two categories.

In the current study, *K. pneumoniae* isolates show resistance to most types of antibiotics. They exhibited lower resistance to the aminoglycosides compared to the β-lactam antibiotics.

When it came to Ticarcillin (97%), Piperacillin (92%), Ceftazidime (90%), Ticarcillin/Clavulanic Acid (83%), Aztreonem (86%), and Trimethoprim/Sulfamethoxazole (86%), the isolates had the highest resistance rates. The results in table (2) show that 77.3% of the isolates were significantly resistant to antimicrobials. Of these, 16.1% (12.1%) were NMDR, 22.7% (30.1%) were MDR, 30.3% (30.3%) were P-XDR, and 12.1% (16.1%) were P-PDR. Thirty out of 132 (22.7%) were classified as K. pneumoniae isolates under the non-susceptible isolate terminology.

The results showed that the P-XDR pattern had the highest percentage among other antimicrobial susceptibility patterns. The antimicrobial susceptibility patterns among 43 patients <1 year of age were: 11/43 (25.6%) non-susceptible isolates, NMDR 11/43 (25.6%), MDR 14/43 (32.5%), and P-XDR 7/43 (16.3%). The neonate care unit isolated 14/43 K. pneumoniae, of which 10/14 (71.4%) exhibited high resistance among neonates with antimicrobial resistance (NMDR 2, MDR 3, P-XDR 5).

The antibiotic susceptibility patterns of 22 K. pneumoniae clinical isolates collected from the ICU and RCU were 13/22 (59.1%) isolates with P-XDR, 7/22 (31.8%) isolates with P-PDR, 1/22 (4.5%) isolates with MDR, and 1/22 (4.5%) isolates with NMDR. The percentage of P-XDR, MDR, and P-PDR for 26 K. pneumoniae among groups (mixed types) was 11/26 (42.3%), 7/26 (26.9%), and 2/26 (7.7%). Respectively.

A look at table (3) shows that the isolates from burns (100%), respiratory secretions (85.7%), wounds (81.8%), and blood (63.2%) were the ones that were most resistant to antibiotics (MDR, P-XDR, and P-PDR).

Table 2. Distribution of *K. pneumoniae* isolates according to antibiotics susceptibility patterns

Type of isolates	No. of isolates	Antibiotic susceptible patterns of *K. pneumoniae*				
		Non-susceptible isolate	NMDR	MDR	XDR	PDR
(pure) *K. pneumoniae*	106	24 (18.2)	14 (10.6)	25 (18.9)	29 (22)	14 (10.6)
K. pneumoiae + E. coli	6	0 (0)	1 (0.8)	1 (0.8)	3 (2.3)	1 (0.8)
K.pneumoniae + P. aeruginosa	8	2 (1.5)	0 (0)	3 (2.3)	2 (1.5)	1 (0.8)
K.pneumoniae + E. faecium	1	0 (0)	0 (0)	0 (0)	1 (0.8)	0 (0)
K. pneumoniae + E. cloacae complex	1	0 (0)	0 (0)	1 (0.8)	0 (0)	0 (0)
K.pneumoniae + B. cepacia	2	1 (0.8)	0 (0)	0 (0)	1 (0.8)	0 (0)
K. pneumoniae + A. baumannii	2	0 (0)	0 (0)	0 (0)	2 (1.5)	0 (0)
K. pneumoniae + E. coli + P. aeruginosa	2	0 (0)	1 (0.8)	0 (0)	1 (0.8)	0 (0)
K. pneumoniae + E. coli + E. aerogenes	4	3 (2.3)	0 (0)	0 (0)	1 (0.8)	0 (0)
Total	132	30 (22.7)	16 (11.4)	30 (22.7)	40 (30.3)	16 (12.1)

Table 3. Association between antibiotic susceptibility patterns of *K. pneumoniae* isolates and clinical specimens

Resistance patterns	Urine N = 61	Respiratory Secretion N = 28	Blood N = 19	Wound swab N =11	Burn infection swab N= 4	Stool N =3	Other sources N = 6
Non-susceptible isolate	17 (28%)	3 (10.7%)	4 (21%)	0 (0.0%)	0 (0.0%)	3 (100%)	3 (50%)
NMDR	10 (16.4%)	1 (3.6%)	3 (15.8%)	2 (18%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
MDR	19 (31%)	6 (21.4%)	3 (15.8%)	0 (0.0%)	1 (25%)	0 (0.0%)	1 (16.7%)
P-XDR	13 (21%)	10 (35.7%)	6 (31.6%)	8 (72.7%)	2 (50%)	0 (0.0%)	2 (33.3%)
P-PDR	2 (3%)	8 (28.6%)	3 (15.8%)	1 (9%)	1 (25%)	0 (0.0%)	0 (0.0%)

Discussion

The present study faced challenges in obtaining bacterial isolates and patient's data. It was observed a concerning prevalence of XDR *K. pneumoniae* strains.

Beta-lactam/cell wall synthesis inhibitors and folic acid synthesis inhibitors demonstrated the highest rates of antimicrobial resistance among the tested antibiotics. Current findings revealed diverse antimicrobial susceptibility patterns among the 132 *K. pneumoniae* isolates. Notably, P-XDR strains were most prevalent, followed by MDR and P-PDR strains. Isolates from burn infections and respiratory secretions exhibited the highest levels of antibiotic resistance.

Within one category, the *K. pneumoniae* isolates that were considered non-susceptible isolates showed antimicrobial resistance or intermediate resistance to one or more antibiotics. Traditional therapies can still easily cure this.

Multiple investigation confirmed and contradicted current findings. Many factors may explain the differences in the present study, such as antibiotic policy, indiscriminate antimicrobial administration, patient immunology, infection control, or frequent hospitalization.

Studies that support the current study include an Iraqi study from 2023, which found that Ceftazidime and Amoxicillin-Clavulanate exhibit higher levels of antibiotic resistance than carbapenems do [11]. Moreover, Egyptian and Indian studies done in 2022 and 2023, respectively, agree that the XDR pattern represents the highest percentage among other patterns [12,13]. Studies conducted, such as two Iranian studies in 2021 and 2023, respectively, [14,15] and an Iraqi study in 2023 [16] showed a higher incidence of MDR *K. pneumonia*, which contradicts the results of the current study.

The current study found a lot of P-PDR 7/16 and P-XDR 13/40 in 22 isolates from the ICU and RCU. This could be because most patients who are on mechanical ventilation support bacteria that are resistant to it. ICUs are drug-resistant factories. ICUs have high antibiotic resistance rates due to numerous infections, antimicrobial use, and invasive procedures [17].

Uncontrolled antibiotic use causes MDR and XDR because it forces microorganisms to evolve resistance. Indeed, hospitals and healthcare centers transmit antibiotic-resistant bacteria through many routes, promoting community resistance [16]. A Lebanon study in 2021 found the largest amount of AMR genes (47 genes) in a *K. pneumoniae* isolate, which makes it resistant to all widely used antimicrobials, causing a major health issue [18].

Importance of mixed type isolates

In the current study, the majority of clinical isolates were pure *K. pneumoniae*, 106/132 (80.3%). On the culture plate, 26/132 (19.7%) of *K. pneumoniae* isolates mixed with different Gram-negative bacteria, originating from various clinical sources such as patients admitted to the ICU, post-operation wounds, and cancer cases. Mixed types of bacteria in a sample or culture medium may indicate co-infection by two or more pathogens.

The current study included 6 isolates of *K. pneumoniae* plus *E. coli* and 8 isolates of *K. pneumoniae* plus *P. aeruginosa*. Patients with serious infections exhibited patterns of MDR, XDR, and PDR in these isolates.

Two factors that significantly influence the outcome of bacterial infections are the strain's virulence and its resistance to antimicrobial agents [19]. As a result, we must perform AST on both mixed-type isolates.

The study identified two cases of mixed infections involving *Escherichia coli* (*E. coli*) and *K. pneumoniae* in urine samples from female outpatients. While the hospital laboratory focused on *E. coli* as the primary pathogen, our analysis revealed a significant presence of *K. pneumoniae* in both cases. In one case, *E. coli* was non-drug resistant (NDR), whereas *K. pneumoniae* exhibited NMDR. In the other case, *K. pneumoniae* displayed a P-XDR pattern. Additionally, two cases of mixed infections were identified involving *K. pneumoniae* and *A. baumannii* complex isolates from female patients in the ICU. Both cases exhibited a P-XDR pattern on AST. The first case involved a female with a brain tumor and type 2 diabetes mellitus (T2DM), with wound swabs yielding the mixed isolates. The second case involved an unconscious Guillain-Barré patient, with the isolates recovered from ETT swab. In this case, *K. pneumoniae* was susceptible only to Tigecycline, while A. baumannii was susceptible only to trimethoprim-sulfamethoxazole. It is crucial to consider both isolates as mixed infections when interpreting these findings.

Polymicrobial infections commonly isolate opportunistic bacteria, such as *A. baumannii* and *K. pneumoniae* [6]. Infections from both species can be more severe and resistant to treatment than those produced by either species alone [5]. Many studies have shown that polymicrobial infections can result in enhanced virulence and resistance to antimicrobial agents. For instance, studies have observed a

higher death rate in critically ill individuals co-infected with *K. pneumoniae*, *P. aeruginosa*, and/or *A. baumannii* [6,20]. These infections kill millions of people annually [20].

In conclusion, the current study examined 132 clinical isolates of *K. pneumoniae*, identifying 40 (30.3%) as XDR. The majority of these XDR isolates were hospital-acquired, indicating a concerning increase in antibiotic resistance within Iraqi healthcare facilities. The emergence of numerous antibiotic-resistant strains in mixed infections has exacerbated the severity of polymicrobial infections. The coexistence of multiple bacterial species can lead to unique synergistic interactions, potentially impacting health and disease outcomes.

Acknowledgement

The authors express their gratitude to the participant for their generous contribution to this study.

Author contribution

Fouad: Conducted the lab tests of the research and preparation the initial version of this manuscript. Totly: helped with the collection and diagnosis of the bacterial isolates.

Conflict of interest

There are no conflicts of interest.

Funding

Self-funded.

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Received Jan. 21st 2024
Accepted Mar. 17th 2024