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Six-Year Epidemiologic Analysis of Antibiotic Resistance Patterns of *Klebsiella pneumoniae* Infections in a Tertiary Healthcare Center in Western Romania

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Abstract: Background and Objectives: *Klebsiella pneumoniae* is a major nosocomial pathogen with a remarkable ability to develop resistance to multiple antibiotics, posing significant treatment challenges. This study aims to evaluate the antimicrobial resistance patterns among multidrug-resistant (MDR) and non-MDR strains of *K. pneumoniae* isolated over a six-year period (2018–2023) at the Clinical Hospital of Infectious Diseases and Pulmonology "Dr. Victor Babes" in Timisoara, Romania. The objectives include categorizing isolates based on their antibiotic resistance profiles and identifying trends in resistance to key antibiotics to optimize treatment strategies and enhance infection control measures. Materials and Methods: A cross-sectional analysis was conducted on *K. pneumoniae* isolates obtained from various clinical samples between January 2018 and December 2023. Identification was performed using standard bacteriological procedures, and antimicrobial susceptibility testing was conducted using the Kirby–Bauer disk diffusion method in accordance with EUCAST guidelines. Isolates were classified as susceptible, resistant, MDR, extensively drug-resistant (XDR), or pandrug-resistant (PDR) based on ECDC definitions. Data were analyzed using GraphPad Prism 6, with chi-square tests and Cochran–Armitage trend tests applied where appropriate. Statistical significance was set at $p < 0.05$. Results: A total of 1,081 *K. pneumoniae* isolates were identified over the six-year period, increasing from 118 isolates in 2018 to 319 in 2023. The proportion of XDR and PDR strains showed a significant upward trend from 30.5% in 2018 to 57.4% in 2023 ($p < 0.001$). Specifically, XDR strains increased from 22.9% in 2018 to 39.8% in 2023, while PDR strains rose from 7.6% to 17.6%. Among monomicrobial infections in 2023, XDR and PDR strains accounted for 42.4% and 16.5%, respectively. Resistance to carbapenems also showed a significant increase; for instance, resistance to ertapenem rose from 35.6% in 2018 to 54.2% in 2023 ($p < 0.001$). Subgroup analysis revealed that isolates from bronchial aspirates had the highest rates of XDR and PDR strains in 2023, at 38.0% and 17.2%, respectively. Additionally, polymicrobial infections where both *K. pneumoniae* and co-infecting pathogens were XDR/PDR increased from 24.2% in 2018 to 46.6% in 2023 ($p < 0.001$).

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Conclusions: The study demonstrates a significant escalation in antimicrobial resistance among *K. pneumoniae* isolates over the six-year period, particularly in XDR and PDR strains. The rising trend of resistance to critical antibiotics like carbapenems underscores the urgent need for enhanced antimicrobial stewardship and infection control measures. Targeted interventions are essential to curb the spread of these resistant strains and to optimize therapeutic strategies.

Keywords: *Klebsiella pneumoniae*; antibiotic resistance; carbapenemase; drug resistance; ESBL

1. Introduction

Carl Friedlander first discovered *K. pneumoniae* in 1882 as a Gram-negative, non-motile, encapsulated bacterium found in the environment [1]. The bacterium, originally known as Friedlander's bacillus, underwent a name change in 1886 and was subsequently referred to as *Klebsiella* [2]. It frequently establishes itself in the gastrointestinal tract and oropharynx of humans [3]. *K. pneumoniae* is associated with severe healthcare-related infections, including pneumonia, urinary tract infections, bloodstream infections, wound or surgical site infections, and meningitis [4,5]. *K pneumoniae* is a highly common bacterium responsible for nosocomial infections, especially in critically ill patients in the intensive care unit (ICU) [6].

According to the literature, *K. pneumoniae* strains are the primary source of multidrug-resistant Gram-negative bacterial infections [7,8]. The pathogenicity of the organism is attributed to the presence of the lipopolysaccharide (LPS) layer in its cell envelope and the cell wall protein receptors [9]. The frequency of multidrug-resistant *K. pneumoniae* (MDRKP) has significantly increased worldwide in recent decades, posing a pressing risk to public health [10–13].

The term "superbug" has long been used to refer to bacterial strains, particularly those that are resistant to the majority of existing antibiotics [14]. *K. pneumoniae*, a superbug that has gained significant recognition in the past two decades, has developed MDR strains, including extended-spectrum β-lactamases (ESBLs), various carbapenemases, and the colistin resistance gene mcr-1 [14].

K. pneumoniae exhibits antibiotic resistance primarily through five mechanisms: enzymatic antibiotic inactivation and modification, alteration of antibiotic targets, loss and mutation of porins, increased production of efflux pumps for antibiotics, and biofilm formation [15–19].

Microorganisms exploit several antibiotic-inactivating strategies, although enzyme synthesis is the most prevalent [20]. The enzymes that break down β-lactams are known as β-lactamases, which include carbapenemases (CPNs), ESBLs, and Ambler class C cephalosporinases (AmpCs) [21,22].

Carbapenem resistance is a major threat to public health, as these antibiotics effectively combat severe bacterial infections due to their ability to resist nearly all β-lactams [23]. Traditional β-lactamase inhibitors are generally ineffective against carbapenemases, except for metallo-β-lactamases (MBLs). *K. pneumoniae* is the most prevalent producer of carbapenemase, with KPC-type carbapenemase, classified under Ambler class A β-lactamases, being the most common [24,25]. Other notable carbapenemases include Ambler class B MBLs, such as IMP and VIM types, as well as New Delhi metallo-β-lactamase type 1 (NDM-1) and OXA-type β-lactamases of class D [26]. ESBLs, categorized as Ambler class A β-lactamases, are plasmid-mediated enzymes that hydrolyze most penicillins, monobactams, and cephalosporins, including third- and fourth-generation cephalosporins. While ESBLs do not hydrolyze cephamycins or carbapenems, their activity is inhibited by β-lactamase inhibitors such as clavulanate, sulbactam, tazobactam, and diazabicyclooctanones like avibactam [27,28]. Clinically significant ESBL families include CTX-M-like, TEM-like, and SHV-like enzymes [29]. *K. pneumoniae* strains producing ESBL are globally prevalent, with some regions exhibiting endemic rates as

high as 50% [30]. Carbapenems have traditionally been the treatment of choice for infections caused by ESBL-producing bacteria.

Therefore, the primary aim of this study is to evaluate the antimicrobial resistance patterns among MDR and non-MDR strains of *K. pneumoniae* isolated from various samples over a six-year period at the Clinical Hospital of Infectious Diseases and Pulmonology "Dr. Victor Babes" Timisoara. Specifically, the study seeks to categorize the isolates based on their antibiotic resistance profiles in the western region of Romania. Additional objectives are to describe and analyze susceptibility, extensively drug-resistant (XDR), and pandrug-resistant (PDR) statuses as proposed by the European Centre for Disease Prevention and Control (ECDC). The objective is to identify trends in resistance to key antibiotics, thereby facilitating the optimization of treatment strategies and enhancing infection control measures.

2. Materials and Methods

2.1. Study Design

The current retrospective study was conducted at the Clinical Hospital of Infectious Diseases and Pneumology "Dr. Victor Babes", a tertiary-care hospital in Timisoara, Romania. This analysis collected data from January 2018 to December 2023. The research comprised *K. pnuemoniae* isolates from different clinical samples of patients admitted in our hospital.

The PICO statement of the current study was considered as follows: the population consists of *K. pneumoniae* isolates obtained from various clinical samples at the Clinical Hospital of Infectious Diseases and Pulmonology "Dr. Victor Babes" in Timisoara, Romania. The intervention is the annual collection and categorization of these isolates based on their antimicrobial resistance profiles, using criteria for susceptibility, resistance to one or two antimicrobial categories, and classifications such as MDR, XDR, and PDR as defined by the ECDC. The comparison aims to identify trends and changes in resistance patterns over time. The outcome of interest is the determination of specific resistance patterns to key antibiotics over these years, which will inform about the effectiveness of existing antibiotic strategies and contribute to the development of targeted treatment protocols for managing infections caused by *K. pneumonia*.

2.2. Identification of K. pneumoniae Strains

K. pneumoniae was isolated from the following sources: bronchial aspirates, urocultures, blood cultures, wound secretions, bronchial catheters, bronchoalveolar lavages, venous and arterial catheters, cerebrospinal fluids, pleural fluids, and other puncture fluids.

The isolates were identified as *K. pneumoniae* using standard bacteriological procedures. *K. pneumoniae* was identified through the examination of their colony morphology on MacConkey agar, their Gram-staining pattern, and various biochemical tests including catalase, oxidase, urease, indole test, gas generation, motility, citrate utilization test, and lactose fermentation. The ATCC strain of *K. pneumoniae* 700603 was utilized in culture, biochemical assays, and other phenotypic tests to validate the identity of the test isolates. In addition, the samples that tested positive were analyzed using the Vitek 2 Compact automated system to determine their identification and/or evaluate their susceptibility to antibiotics.

2.3. Antimicrobial Susceptibility Testing

The antimicrobial susceptibility of the isolated organism was tested using the disk diffusion method, specifically the "Kirby–Bauer method". Mueller–Hinton agar and commercially available antibiotic disks were employed for this purpose [23]. The following antibiotics were used for sensitivity testing: amoxicillin/clavulanic acid (20/10 μg), ceftriaxone (30 μg), ceftazidime (10 μg), ciprofloxacin (5 μg), levofloxacin (5 μg), gentamicin (10 μg), amikacin (30 μg), tobramycin (10 μg), meropenem (10 μg), ertapenem (10 μg), imipenem (10 μg), piperacillin–tazobactam (30/6 μg), trimethoprim/sulfamethoxazole (1.25/23.75 μg), ceftazidime–avibactam (10/4 μg), and colistin (microdilution method). Furthermore, the disk contents and the zone of inhibition were employed in accordance

with the guidelines set out by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [31].

The strains were classed based on their antimicrobial resistance profile, which included susceptibility, resistance to one or two antimicrobial categories, multidrug resistance (MDR), extensive drug resistance (XDR), or pandrug resistance (PDR). The European Centre for Disease Prevention and Control (ECDC) proposed the criteria for multidrug resistance (MDR), extensive drug resistance (XDR), and pandrug resistance (PDR).

An isolate is categorized as PDR if it is resistant to all specified antimicrobial agents, XDR if it is resistant to at least one agent in all but two or fewer antimicrobial categories, and MDR if it is resistant to at least one agent in at least three antimicrobial categories [32].

2.4. ESBL and Carbapenemase Identification

Extended-spectrum β-lactamase production was evaluated by the ESBL test and carbapenemase production was analyzed according to the methods proposed by EUCAST guidelines. The most frequent carbapenemases identified were OXA-48 and NDM, found in XDR and PDR strains. The interpretation of phenotypic tests is shown in Table 1 [33].

Table 1. Interpretation of phenotypic tests.

	Synergy Observed as Increase in Zone Diameter (mm) with 10 µg Meropenem Disk/Tablet				**Temocillin MIC > 32 mg/L or Zone Diameter < 11 MBL mm**
	DPA/EDTA	**APBA/PBA**	**DPA+APBA**	**CLX**	
MBL	+	-	-	-	Variable
KPC	-	+	-	-	Variable
MBL+KPC	Variable	Variable	+	-	Variable
OXA-48-like	-	-	-	-	Yes

MBL—Metallo-β-lactamase; KPC—*Klebsiella pneumoniae* carbapenemase; DPA—Dipicolinic Acid; EDTA—Ethylenediaminetetraacetic Acid; APBA—p-Aminophenylboronic Acid; PBA—Phenylboronic Acid; CLX—Cefalexin.

The RESIST-5 O.K.N.V.I. assay, developed by CORIS BioConcept in Gembloux, Belgium, is a novel immunochromatography test. The test was used in certain *K. pneumoniae* strains for rapid detection of carbapenemases. It consists of two lateral-flow cassettes, with one cassette designed to detect VIM and IMP carbapenemases and the other cassette designed to detect OXA-48-like, KPC, and NDM carbapenemases. This assay allows for the detection of five specific carbapenemases. These tests utilize a membrane technology that incorporates several colloidal gold nanoparticles. A nitrocellulose membrane is coated with individual monoclonal antibodies that target OXA-48-like, KPC, NDM, VIM, and IMP carbapenemases, as well as their different forms [34].

The interpretation of the sensitivity testing is that absence of any line other than a reddish-purple line at the control line (C) position indicates negative test findings. Positive test results are identified by the presence of a noticeable reddish-purple line at OXA-48-like ("O" line), KPC ("K" line), NDM ("N" line), VIM ("V" line), and/or IMP ("I" line), as well as a line at the "C" line. A weak line should be considered a positive result.

2.5. Data Input and Analysis

The data input and analysis were performed using GraphPad Prism 6, version 6.01. For categorical variables, percentages were calculated. The groups were compared using the chi-square test. Statistical significance was determined for all p-values below 0.05.

3. Results

Table 2 presents the distribution of antibiotic resistance patterns among *K. pneumoniae* isolates categorized by infection type (monomicrobial and polymicrobial) from 2018 to 2023. Over the six-year period, the proportion of susceptible isolates significantly decreased from 30.51% in 2018 to 13.79% in 2023 ($p < 0.05$), indicating a declining trend in antibiotic

susceptibility. Conversely, the prevalence of XDR and PDR strains markedly increased from 22.88% and 7.63% in 2018 to 39.81% and 17.55% in 2023, respectively (both $p < 0.001$). These trends were observed in both monomicrobial and polymicrobial infections, underscoring a growing challenge in managing *K. pneumoniae* infections. The statistically significant increase in XDR and PDR categories highlights the escalating resistance and the diminishing effectiveness of standard antimicrobial therapies over the study period.

Table 2. Association between antibiotic resistance pattern and complexity of *K. pneumoniae* infection (2018–2023).

Year	Infection Type	Number of *K. pneumoniae* Isolates	Susceptible	Resistant	MDR	XDR	PDR
2018	Monomicrobial (n = 83)	83	28 (33.73%)	19 (22.89%)	13 (15.66%)	17 (20.48%)	6 (7.23%)
	Polymicrobial (n = 35)	35	8 (22.86%)	9 (25.71%)	5 (14.29%)	10 (28.57%)	3 (8.57%)
	Total (n = 118)	118	36 (30.51%)	28 (23.73%)	18 (15.25%)	27 (22.88%)	9 (7.63%)
2019	Monomicrobial (n = 94)	94	29 (30.85%)	22 (23.40%)	14 (14.89%)	21 (22.34%)	8 (8.51%)
	Polymicrobial (n = 35)	35	8 (22.86%)	9 (25.71%)	6 (17.14%)	9 (25.71%)	3 (8.57%)
	Total (n = 129)	129	37 (28.68%)	31 (24.03%)	20 (15.50%)	30 (23.26%)	11 (8.53%)
2020	Monomicrobial (n = 111)	111	28 (25.23%)	27 (24.32%)	16 (14.41%)	31 (27.93%)	9 (8.11%)
	Polymicrobial (n = 40)	40	10 (25.00%)	11 (27.50%)	6 (15.00%)	10 (25.00%)	3 (7.50%)
	Total (n = 151)	151	38 (25.17%)	38 (25.17%)	22 (14.57%)	41 (27.15%)	12 (7.95%)
2021	Monomicrobial (n = 131)	131	26 (19.85%)	29 (22.14%)	20 (15.27%)	44 (33.59%)	12 (9.16%)
	Polymicrobial (n = 42)	42	8 (19.05%)	10 (23.81%)	9 (21.43%)	11 (26.19%)	4 (9.52%)
	Total (n = 173)	173	34 (19.65%)	39 (22.54%)	29 (16.76%)	55 (31.79%)	16 (9.25%)
2022	Monomicrobial (n = 146)	146	22 (15.07%)	30 (20.55%)	9 (6.16%)	76 (52.05%)	9 (6.16%)
	Polymicrobial (n = 45)	45	5 (11.11%)	8 (17.78%)	4 (8.89%)	22 (48.89%)	6 (13.33%)
	Total (n = 191)	191	27 (14.14%)	38 (19.90%)	13 (6.81%)	98 (51.31%)	15 (7.85%)
2023	Monomicrobial (n = 231)	231	31 (13.42%)	36 (15.58%)	28 (12.12%)	98 (42.42%)	38 (16.45%)
	Polymicrobial (n = 88)	88	13 (14.77%)	14 (15.91%)	14 (15.91%)	29 (32.95%)	18 (20.45%)
	Total (n = 319)	319	44 (13.79%)	50 (15.67%)	42 (13.17%)	127 (39.81%)	56 (17.55%)
p-value			<0.05	0.08	0.12	<0.001	<0.001

XDR—Extensive Drug Resistance; PDR—Pandrug Resistance; MDR—Multidrug Resistance; P-values calculated using the Cochran–Armitage trend test.

Table 3 illustrates the resistance patterns of *K. pneumoniae* and co-infecting pathogens within polymicrobial infections from 2018 to 2023. There was a significant upward trend in the proportion of XDR/PDR *K. pneumoniae* isolates, increasing from 37.1% in 2018 to 53.4% in 2023 ($p < 0.001$). Similarly, the co-infecting pathogens exhibited an increase in XDR/PDR rates from 31.4% to 54.5% over the same period ($p < 0.001$). Additionally, the occurrence of both K. pneumoniae and the co-infecting pathogen being XDR/PDR rose from 22.9% in 2018 to 46.6% in 2023 ($p < 0.001$). These findings indicate a significant escalation in multidrug resistance within polymicrobial infections, complicating treatment regimens and increasing the risk of adverse patient outcomes.

Table 4 details the antibiotic resistance patterns of *K. pneumoniae* isolates based on their source from 2018 and 2023. In 2023, isolates from bronchial aspirates exhibited a substantial increase in XDR and PDR strains, rising to 38.14% and 15.46%, respectively, compared to 16.13% and 3.23% in 2018. Similarly, urocultures showed elevated resistance, with XDR strains increasing to 39.74% and PDR strains to 15.38% in 2023 from 12.50% and 4.17% in 2018. Blood cultures and wound secretions also demonstrated significant rises in XDR and PDR categories. Notably, isolates from other sources saw a dramatic increase in PDR strains from 10.00% in 2018 to 32.08% in 2023. These changes reflect a worsening resistance landscape across various infection sites, emphasizing the need for targeted antimicrobial strategies and enhanced infection control measures.

Table 3. Resistance patterns in *K. pneumoniae* and co-infecting pathogens in polymicrobial infections.

Year	Total Polymicrobial Infections with *K. pneumoniae*	*K. pneumoniae* XDR/PDR	Co-Infecting Pathogen XDR/PDR	Both XDR/PDR	Most Frequent Co-Infecting Pathogens
2018	35	13 (37.1%)	11 (31.4%)	8 (22.9%)	*Enterococcus* spp. (7), *Escherichia coli* (6), *Pseudomonas aeruginosa* (4)
2019	35	15 (42.9%)	13 (37.1%)	9 (25.7%)	*Escherichia coli* (8), *Acinetobacter baumannii* (7), *Staphylococcus aureus* (3)
2020	40	19 (47.5%)	17 (42.5%)	12 (30.0%)	*Pseudomonas aeruginosa* (9), *Staphylococcus aureus* (6), *Enterobacter* spp. (5)
2021	42	23 (54.8%)	21 (50.0%)	15 (35.7%)	*Acinetobacter baumannii* (10), *Staphylococcus aureus* (8), *Escherichia coli* (7)
2022	45	28 (62.2%)	23 (51.1%)	19 (42.2%)	*Enterococcus* spp. (11), *Enterobacter* spp. (6), *Pseudomonas aeruginosa* (6)
2023	88	47 (53.4%)	48 (54.5%)	41 (46.6%)	*Pseudomonas aeruginosa* (13), *Enterococcus* spp. (12), *Escherichia coli* (10)
p-value		<0.001	<0.001	<0.001	

XDR—Extensive Drug Resistance; PDR—Pandrug Resistance; P-values calculated using the Cochran–Armitage trend test.

Table 4. Antibiotic resistance patterns of *K. pneumoniae* by source of isolate (2018–2023).

Year	Source of Isolate	Number of Isolates	Susceptible	Resistant	MDR	XDR	PDR
2018	Bronchial Aspirates	31	12 (38.71%)	8 (25.81%)	5 (16.13%)	5 (16.13%)	1 (3.23%)
	Urocultures	24	9 (37.50%)	7 (29.17%)	4 (16.67%)	3 (12.50%)	1 (4.17%)
	Blood Cultures	23	7 (30.43%)	6 (26.09%)	5 (21.74%)	4 (17.39%)	1 (4.35%)
	Wound Secretions	20	5 (25.00%)	5 (25.00%)	4 (20.00%)	4 (20.00%)	2 (10.00%)
	Other Sources	20	3 (15.00%)	5 (25.00%)	5 (25.00%)	5 (25.00%)	2 (10.00%)
2023	Bronchial Aspirates	97	15 (15.46%)	18 (18.56%)	12 (12.37%)	37 (38.14%)	15 (15.46%)
	Urocultures	78	12 (15.38%)	13 (16.67%)	10 (12.82%)	31 (39.74%)	12 (15.38%)
	Blood Cultures	49	6 (12.24%)	8 (16.33%)	8 (16.33%)	21 (42.86%)	6 (12.24%)
	Wound Secretions	42	5 (11.90%)	6 (14.29%)	7 (16.67%)	18 (42.86%)	6 (14.29%)
	Other Sources	53	6 (11.32%)	5 (9.43%)	5 (9.43%)	20 (37.74%)	17 (32.08%)

Table 5 highlights the significant increases in resistance rates of *K. pneumoniae* to multiple antibiotics from 2018 to 2023. Resistance to amoxicillin/clavulanic acid surged from 41.5% to 73.0% ($p < 0.001$), while resistance to ceftazidime and ceftriaxone rose from 34.7% to 65.5% ($p < 0.001$) and 36.4% to 65.2% ($p < 0.001$), respectively. Carbapenem resistance showed alarming growth, with imipenem and meropenem resistance rates increasing from 25.4% to 54.5% ($p < 0.001$) and 25.4% to 54.5% ($p < 0.001$). Ertapenem and piperacillin–tazobactam resistance also significantly escalated (both $p < 0.001$). Aminoglycoside resistance to amikacin and gentamicin increased from 20.3% to 50.2% ($p < 0.001$) and 22.0% to 58.4% ($p < 0.001$), respectively. Additionally, resistance to colistin rose dramatically from 10.2% to 58.4% ($p < 0.001$).

Table 6 examines the trends in carbapenemase production among *K. pneumoniae* isolates from 2018 to 2023. While the proportion of ESBL-positive isolates remained relatively stable (p = 0.45), there was a significant increase in carbapenemase-positive isolates from 15.3% in 2018 to 51.7% in 2023 ($p < 0.001$). Specifically, OXA-48-like carbapenemases increased from 7.6% to 31.3% ($p < 0.001$), and NDM carbapenemases rose from 5.1% to 16.9% ($p < 0.001$). KPC carbapenemases showed a slight but significant increase from 2.5% to 3.4% ($p = 0.02$). These findings reveal a marked rise in carbapenemase-mediated resistance, particularly OXA-48-like enzymes, which are pivotal in conferring high-level resistance to carbapenems.

Table 5. Changes in Resistance Rates of *K. pneumoniae* to Antibiotics from 2018 to 2023.

Antibiotic	2018 Resistance	2023 Resistance	*p*
Amoxicillin/Clavulanic Acid (AMC)	41.5%	73.0%	<0.001
Ceftazidime (CAZ)	34.7%	65.5%	<0.001
Ceftriaxone (CRO)	36.4%	65.2%	<0.001
Imipenem (IPM)	25.4%	54.5%	<0.001
Meropenem (MEM)	25.4%	54.5%	<0.001
Ertapenem (ETP)	35.6%	54.2%	<0.001
Piperacillin–Tazobactam (TZP)	42.4%	64.6%	<0.001
Trimethoprim/Sulfamethoxazole (SXT)	38.1%	62.4%	<0.001
Amikacin (AK)	20.3%	50.2%	<0.001
Gentamicin (GE)	22.0%	58.4%	<0.001
Tobramycin (TOB)	29.7%	66.5%	<0.001
Ciprofloxacin (CIP)	34.7%	64.9%	<0.001
Levofloxacin (LEV)	34.7%	64.6%	<0.001
Ceftazidime–Avibactam (CZA)	15.3%	26.4%	0.005
Colistin (CO)	10.2%	58.4%	<0.001

Table 6. Trends in carbapenemase-producing *K. pneumoniae* isolates over six years.

Year	Total Isolates	ESBL-Positive	Carbapenemase-Positive	OXA-48-like	NDM	KPC
2018	118	6 (5.1%)	18 (15.3%)	9 (7.6%)	6 (5.1%)	3 (2.5%)
2019	129	7 (5.4%)	22 (17.1%)	12 (9.3%)	7 (5.4%)	3 (2.3%)
2020	151	9 (6.0%)	30 (19.9%)	17 (11.3%)	9 (6.0%)	4 (2.6%)
2021	173	10 (5.8%)	46 (26.6%)	25 (14.5%)	16 (9.2%)	5 (2.9%)
2022	191	11 (5.8%)	103 (53.9%)	60 (31.4%)	35 (18.3%)	8 (4.2%)
2023	319	22 (6.9%)	165 (51.7%)	100 (31.3%)	54 (16.9%)	11 (3.4%)
p-value		0.45	<0.001	<0.001	<0.001	0.02

Table 7 explores the association between patient age groups and the presence of XDR/PDR K. pneumoniae from 2018 to 2023. In 2018, the prevalence of XDR/PDR strains was 22.9% in patients under 50, 27.3% in those aged 50–70, and 46.4% in patients over 70. By 2023, these percentages had escalated to 41.2%, 50.0%, and 86.9%, respectively. The chi-square test revealed a highly significant association between age groups and the presence of XDR/PDR strains ($p < 0.001$).

Table 7. Association between patient age groups and presence of XDR/PDR K. pneumoniae (2018–2023).

Year	Age Group	Total Patients	XDR/PDR Cases	%
2018	<50	35	8	22.9%
	50–70	55	15	27.3%
	>70	28	13	46.4%
2023	<50	85	35	41.2%
	50–70	150	75	50.0%
	>70	84	73	86.9%
p-value				<0.001

4. Discussion

4.1. Literature Findings

K. pneumoniae has gained notoriety as a "superbug" due to its ability to develop resistance to cephalosporins, carbapenems, and colistin. Its compatibility with a variety of AMR plasmids contributes to its rapid acquisition of drug resistance. The global emergence and spread of antibiotic resistance genes, including ESBL and carbapenemase genes, in *K. pneumoniae* isolates have significant negative implications for public health [35]. Moreover, there is a marked rise in carbapenemase-mediated resistance, particularly OXA-48-like enzymes,

which are pivotal in conferring high-level resistance to carbapenems. This trend underscores the critical need for enhanced molecular surveillance and the implementation of stringent infection control practices to mitigate the spread of these highly resistant strains.

The widespread perception of carbapenems as the last-resort treatment for infections caused by multidrug-resistant Gram-negative bacteria has led to their overuse and inappropriate use. This has accelerated the evolution of *K. pneumoniae* strains resistant to virtually all β-lactam antibiotics, including carbapenems, highlighting the organism's remarkable adaptability to environmental pressures. Resistance mechanisms in *K. pneumoniae* often involve genes encoding plasmid-mediated carbapenemases or enzymes that degrade all β-lactams [35].

In our analysis, *K. pneumoniae* showed noteworthy antibiotic resistance, as observed in the work conducted by Wang et al. [36]. Carbapenems are commonly employed as the initial treatment for infections caused by both Gram-positive and Gram-negative bacteria due to their long-standing reputation as very efficient antibiotics [37]. Nevertheless, our analysis revealed a substantial and progressive rise in medication resistance.

Historically, aminoglycosides have exhibited notable efficacy against clinically relevant Gram-negative bacteria [38]. Unlike previous studies, our examination found that *K. pneumoniae* isolates had a high resistance rate for both medicines [39]. In this study, most *K. pneumoniae* isolates showed resistance towards gentamicin (44.27% vs. 58.38%), amikacin (37.5% vs. 50.31%), and meropenem (65.62% vs. 54.34%). The results of this study align with other literature [40–43], which also showed a comparable level of resistance for gentamicin, amikacin, and meropenem.

The isolates were subjected to a double-disk synergy test (DDST) to phenotypically detect ESBL in *K. pneumoniae*. A total of 233 *K. pneumoniae* isolates were identified as makers of extended-spectrum β-lactamases (ESBLs). The current investigation found a decreased prevalence of ESBL compared to the study conducted by Chakraborty et al. in Bangladesh, where the proportion of ESBL-producing *K. pneumoniae* was greater [44]. According to Nicolas et al., the ESBL reduces phenotypically and is substituted by the presence of metallo-β-lactamase (MBL) or *K. pneumoniae* carbapenemase (KPC) producers among isolates of *K. pneumoniae* [45]. Riaz et al. observed a comparable frequency of ESBL expression in Pakistan [46].

Researchers have utilized many technologies to tackle the significant problem of antimicrobial medication resistance when it comes to treating *K. pneumoniae* infections. The novel tactics encompass host-directed treatment, virulence factor inhibitors, quorum sensing inhibitors, and nanoenzymes [47]. Host-directed treatment, a potentially effective substitute for antibiotics, has the capability to eliminate harmful bacteria by focusing on host elements and eradicating the internal reproduction of pathogenic bacteria, while also enhancing the host's immunological response to the pathogen.

Virulence factors of *K. pneumoniae* confer the ability of biofilm formation, with important significance in orthopedics and in the presence of foreign material implants [48,49]. Therefore, inhibitors were designed specific compounds that target pathogen virulence factors, are anticipated to neutralize bacteria, impede the emergence of resistance, and diminish the pathogenicity of the strain. Conversely, quorum sensing inhibitors provide antimicrobial effects by impeding the transmission of signaling molecules between bacteria and facilitating the control of physiological processes, such as bacterial metabolism, pathogenicity, and biofilm formation [50].

Furthermore, there exist intervention options for the management of *K. pneumoniae* infections that specifically aim at targeting virulence factors, such as determinants associated with the attachment to host cells, modulation of the host immune response, and regulation of biofilm formation [51–53]. The research and development of these tactics are anticipated to yield more efficient methods for treating drug-resistant *K. pneumoniae* infections [54].

Nevertheless, in recent years, due to the global increasing trend of MDR germs [55], the hospital where the resistance patterns were analyzed in this study has implemented strict contact precautions, requiring healthcare workers to don gloves and gowns when

entering rooms of patients with known or suspected infections. Patient rooms are subject to rigorous disinfection protocols with hospital-grade disinfectants, focusing particularly on high-touch surfaces to reduce environmental contamination. The hospital also enforces patient cohorting, where those infected or colonized with resistant strains are isolated in dedicated wards or rooms to prevent cross-transmission, especially in high-risk patients that are immunocompromised, receiving chemotherapy, or the elderly [56,57]. Additionally, visitor restrictions are in place to limit external sources of infection, and staff are regularly trained on the latest guidelines for infection prevention, emphasizing the importance of hand hygiene and the correct use of personal protective equipment.

In addressing the challenge of antibiotic resistance, recent studies have proposed innovative approaches focusing on unique bacterial mechanisms [58–60]. Ezzeddine et al. discussed the potential of targeting bacterial metallophores, which are vital for bacterial growth and virulence due to their role in metal ion assimilation. This approach involves exploiting metallophores' ability to chelate and transport metal ions, suggesting a novel antimicrobial strategy that could impede bacterial pathogenicity by disrupting essential metal ion uptake. Similarly, Tillotson highlights the "Trojan horse" strategy, which leverages siderophores—natural iron-chelating compounds produced by bacteria [60]. By attaching antibiotics to siderophores, medications could stealthily enter bacteria, overcoming some traditional resistance mechanisms found in Gram-negative bacteria. These strategies represent promising directions in the development of new antimicrobial therapies, focusing on undermining bacterial survival mechanisms rather than merely inhibiting growth, which may offer a pathway to more effective treatments against resistant bacterial strains.

In a similar manner, the COVID-19 pandemic has inadvertently contributed to the escalation of antimicrobial resistance, particularly in pathogens like *K. pneumoniae*, which is already a significant concern due to its high resistance rates. A study conducted by Chaaban et al. highlighted a surge in antibiotic misuse during the pandemic, with a substantial portion of the population taking antibiotics without proper medical oversight [61]. This misuse stems from the widespread, unregulated access to antibiotics and a lack of adherence to prescribed treatment regimens, where many individuals ceased taking antibiotics as soon as they felt better, rather than completing the prescribed course. Such practices can lead to incomplete eradication of infections, allowing bacteria to survive and adapt, thereby accelerating the development of resistance. This scenario underscores the critical need for stringent antibiotic stewardship and public health campaigns to educate on proper antibiotic use, which is essential to mitigate the development of resistance in pathogens like *K. pneumoniae* during and beyond pandemic conditions.

4.2. Limitations

This study has several limitations that should be considered. It was conducted at a single hospital, which may limit the generalizability of the findings and the ability to observe long-term trends in antimicrobial resistance. Additionally, the lack of data on antibiotic usage patterns and the absence of molecular analysis of the bacterial strains limit our understanding of the factors driving the observed resistance patterns. Potential confounding factors such as patient demographics, underlying health conditions, and infection control practices were not accounted for, which could influence the results.

5. Conclusions

The escalating trend of antimicrobial resistance in *K. pneumoniae* isolates over the past six years is alarming. The significant increase in XDR and PDR strains, particularly the heightened resistance to carbapenems, poses a substantial challenge to clinical management and public health. Our findings highlight the necessity for stringent infection control policies, regular surveillance of resistance patterns, and the judicious use of antibiotics. Implementing targeted treatment protocols and reinforcing antimicrobial stewardship programs are crucial steps toward mitigating the spread of these resistant strains and improving patient outcomes.

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