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Gram-Negative Challenges: Assessing the Decline in Carbapenem Sensitivity Among Klebsiella Pneumoniae Isolates

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Abstract

General Background: Antimicrobial resistance represents a critical global health challenge, particularly among Gram-negative pathogens such as *Klebsiella pneumoniae*. **Specific Background:** Carbapenems have served as last-resort therapies for multidrug-resistant infections; however, increasing resistance among *K. pneumoniae* threatens their clinical utility. **Knowledge Gap:** Longitudinal epidemiological evidence describing temporal susceptibility trends and associated clinical factors remains underexplored. **Aims:** This study evaluates temporal changes in carbapenem susceptibility among *K. pneumoniae* clinical isolates using cumulative antibiogram surveillance. **Results:** A retrospective analysis of 512 isolates (July 2024–September 2025) demonstrated a marked decline in susceptibility to imipenem (92% to 78%) and meropenem (93% to 82%), with significant reductions between early and late periods ($p < 0.05$; $p < 0.01$). Resistance rates increased alongside higher prevalence of carbapenemase-producing strains and MDR/XDR phenotypes. Epidemiological patterns shifted from mixed community–hospital distribution to predominantly nosocomial transmission, particularly in intensive care units, with associations to mechanical ventilation, prolonged hospitalization, invasive devices, and prior broad-spectrum antibiotic exposure. Temporal clustering indicated outbreak-like dynamics in critical care settings. **Novelty:** This study provides longitudinal antibiogram-based evidence linking declining carbapenem susceptibility with ICU-centered transmission and resistance clustering. **Implications:** Findings underscore the need for strengthened antimicrobial stewardship, continuous surveillance, and targeted infection control strategies to mitigate hospital-driven dissemination of resistant *K. pneumoniae*.

Highlights:
- Progressive reduction in carbapenem sensitivity observed over 15 months
- Resistance patterns concentrated within critical care environments
- Transmission dynamics shifted toward hospital-dominated infection sources

Keywords: Klebsiella Pneumoniae, Antimicrobial Resistance, Carbapenem Resistance, Nosocomial Transmission, Antibiogram Surveillance

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Introduction

The rapidly growing population of antibiotic-resistant bacteria represents a major threat for human health [1]. This case underscores the necessity of a combined, multi-pronged approach to deal with resistance dissemination. The emergence of resistance to antibiotic therapy represents one of the most urgent and expanding challenges in health care, greatly restricting therapeutic options. This challenge is compounded further by the decreasing number of new antibiotics in the discovery pipeline [2]. In 2019, the World Health Organization (WHO) listed Antimicrobial Resistance (AMR), which also includes antimicrobial resistance to antibiotics, among the top ten of global public health threats. This identification called for an immediately international common action plan to fight the serious health and economic repercussions in terms of individual and population health[3]. Antibiotic resistance can be the cause of treatment failure and is not only associated with higher healthcare costs, but also longer duration in hospital stay with rising trends in mortality rates [4] . Drug-resistant infections kill about 5 million people per year. Unless we act promptly and adequately in the fight against AMR spread, especially in low- and middle-income countries, this frightening number is set to rise up to 10 million deaths yearly by 2050 [5].

Bacterial pathogens that are resistant to multiple antibiotic classes have emerged and spread quickly, including bacteria for which the few remaining treatment options are regarded as last-resort drugs. Of these, resistance in Gram-negative pathogens is a serious threat due to their intricate composition of cell wall, native resistance mechanisms as well as incredible ability to obtain and spread resistivity genes through horizontal gene transfer (HGT) [6].

Klebsiella pneumoniae was also identified as a critical pathogen worldwide due to its growing association with severe health care-associated and community acquired infections [7] . It is a major cause of pneumonia, blood stream infections (sepsis), urinary tract infection, wound infection especially in hospitalized patients, the immuno-compromised patient and those on intensive care unit [8] . It has quickly become a leading cause of nosocomial outbreaks worldwide due to its capacity for fast adaptation and propagation among microbiomas/hospital settings[9].

Carbapenems (impipenem, meropenem, ertapenem and doripenem) are the backbone for treating severe infection due to extended-spectrum β-lactamase (ESBL)-producing Enterobacterales in the past [10]. These agents have been the established treatments of choice for multidrug-resistant Gram-negative infections. Nevertheless, the advent and spread of carbapenem-resistant Klebsiella pneumoniae (CRKP) has substantially changed the practice scenario [11] . Carbapenem resistance is becoming more common and poses a risk to the utility of the last-resort antibiotic, leading to an increase in the number of infections with few or no effective treatment options.

The factors responsible for carbapenem resistance in K. pneumoniae are numerous and complicated. These mechanisms are based on the production of carbapenemase enzymes, including KPC (Klebsiella pneumoniae carbapenemase) [12] , NDM (New Delhi metallo-β-lactamase), OXA-48-like enzymes and VIM/IMP metallo-β-lactamases, as well as non-enzymatic mechanisms such as porin loss, efflux pump overexpression and changes in penicillin binding proteins [13] . The combination of different resistance mechanisms in a single strain often yields MDR, XDR and PDR phenotypes involving cross-resistance to multiple antibiotics[14].

The clinical significance of infections with carbapenem resisting K. pneumoniae is enormous. They are related to long hospitalization periods and increased cost, higher rate of failure of treatment, few therapeutic choices and mortality [15] . The spread of carbapenem resisting K. pneumoniae in many healthcare settings has resulted to a resurgence on the use of older and more toxic antibiotics, including colistin, as well as new molecules not available or costly particularly in resource-poor low- and middle-income countries [16] . This landscape places significant strain on healthcare infrastructure and underscores the need for effective surveillance, stewardship, and infection control interventions.

Monitoring systems are pivotal to the perception of the epidemiology and trends of antimicrobial resistance. Of these, antibiogram-guided surveillance is a pragmatic, inexpensive and globally applicable method for tracking resistance profiles and directing empirical treatment [17] . Cumulative antibiograms offer useful trend analysis information that enables healthcare facilities to monitor resistance trends, implement antimicrobial stewardship strategies and justify treatment guidelines geared towards their local environment [18] . Despite their extensive use within the clinic, antibiogram data at large are highly underexploited as regards structured, epidemiologic research -in particular in longitudinal studies of resistance dynamics.

This is very much pertinent in the era of rising global burden of CR and K. pneumoniae being a cornerstone pathogenic sentinel, monitoring of trends in CP susceptibility becomes obligatory [19] . Knowledge of local and regional resistance patterns is important in the introduction of optimal empiric therapy, antibiotic stewardship programs, formulation of infection control measures, and public health decisions.

Thus, the objective of this paper is to evaluate changes over time in carbapenem susceptibility patterns for K. pneumoniae clinical isolates based on cumulative antibiogram data. The longitudinal changes to susceptibility patterns that occur over time to carbapenems will be investigated in this study, both to describe the scale of and dynamics behind resistance to carbapenems, as well as adding scientific depth to an emerging literature characterising the broader evolution of resistance in Gram-negative organisms. The results of this study should help clinicians to more rationally apply antimicrobial agents; further, the study may also support efforts in antimicrobial stewardship and resistance surveillance in both individual institutions and ‘regional systems’.

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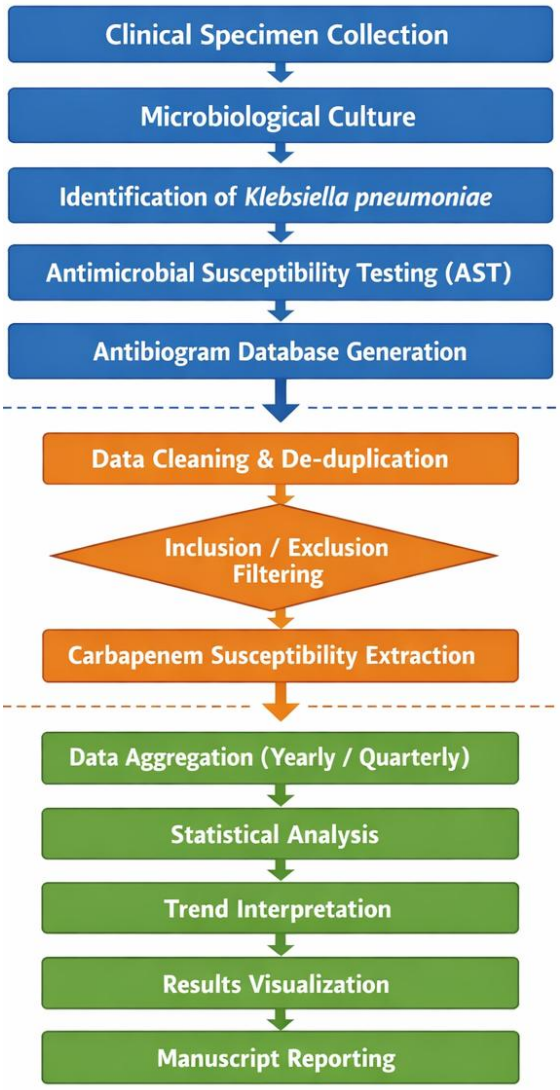
Materials and Methods

Study design and setting

The study was designed as a retrospective observational laboratory-based surveillance study based on pooled antibiogram data. basrah health directorate microbiology lab from July/2024 through September 2025 period was a site of study. The aim of this study was to evaluate the changes over time of susceptibility of Klebsiella pneumoniae clinical isolates to carbapenems. The workflow is mentioned in figure 1.

Figure 1: Workflow diagram.



Data source and collection

Antimicrobial susceptibilities were obtained from the institution-specific antibiogram file generated for clinical microbiology (routine diagnostics). Information on bacteria species identification, clinical sample source, date of isolation and antibiograms profiles was retrieved from the laboratory information system. Only those unique isolates, i.e., patient's first isolate during single episode of infection were considered, in order to comply with CLSI/WHO antibiogram standard operating protocols and to avoid double reporting and sampling bias. Cultures were of diverse origins, such as blood, urine, sputum, wound swabs, endotracheal aspirates and body fluids. A total of five hundred and twelve sample was taken to conduct comparative study.

Antimicrobial susceptibility testing (AST)

as indicated in the laboratory data, antimicrobiological susceptibility tests were performed by standardized methods [disk-diffusion / automated-system / broth-microdilution] on Mueller Hinton agar. Interpretation of susceptibility results was performed according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. Imipenem and meropenem were the carbapenems included in these studies. Interpretations of susceptibility were designated within cut-off points specific to guidelines as S (sensitive), I (intermediate) or R (resistant).

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Data processing and analysis

Antibiogram data were aggregated monthly to generate cumulative susceptibility profiles. The percentage susceptibility for each carbapenem was calculated using the formula:

Susceptibility (%) = Number of sensitive isolates / Total number of isolates tested × 100

Descriptive statistics (frequencies and percentages trend analysis over the study Month) were applied to assess temporal trends in carbapenem susceptibility. Comparative analysis was conducted between early and late periods of the study. Graphs were constructed in the form of line charts and bar graphs (GraphPad Prism 10).

Distribution of the resistant and sensitive isolates between early vs. late periods were compared using Chi-Square test. Two time periods of the examination were taken into account: during study and at end of study. Comparisons between resistant and susceptible isolates of the two periods to Imipenem, Meropenem were made by Chi-Square test. P-values less than 0.05 were considered as statistically significant. The rate of decline in susceptibility was calculated by linear regression analysis. The outcome variable of the regression model was MDR susceptibility for Imipenem and Meropenem, while the predictor was time (months). Through the regression model, an attempt was made to determine if a statistical trend in susceptibility occurred over time within this study. Statistical significance was defined as $p < 0.05$ were applicable unless specified otherwise.

Inclusion and exclusion criteria

The inclusion criteria were positive K. pneumoniae; available carbapenem susceptibility data (non-susceptible or intermediate, resistant) of at least one carbapenem tested, unique isolates and specimens for clinical purposes only. Exclusion criteria were environmental non-duplicates from the same patient and Isolates where AST was not completed.

Ethical considerations

The study employs retrospective anonymized laboratory data without patient identifiers. The study was approved by an ethical board of University of basrah /College of Pharmacy , and no consent form was needed because the study involved retrospective analysis of already collected data.

Results

Subgroup distributions of clinical isolates followed the epidemiology of K. pneumoniae infections in our study population. Respiratory (sputum) comprised the majority (32%) of the isolates, reflecting a high hospital-acquired and ventilator-associated pneumonias prevalence rate. The percentage of isolates from urine was 22.1%, in parallel with the considerable number of urinary tract infections present in community and hospital environments. Isolates originating from blood stream (19.1%) were also captured, inclusive of that due to sepsis and septicemia in neonates, indicative increasing load of invasive infection. Wounds (10.9% of isolates) were overwhelmingly from surgical site infections, whereas those that under other types or sources of (15.8%). Overall, the distribution of specimens reflects the observed epidemiological trend focusing on hospital-acquired infections and severe invasive disease as well as further underscoring that nosocomial transmission dynamics may have been associated with the evolution of carbapenem-resistant Klebsiella pneumoniae.

Table 1: Distribution of clinical specimen types across which Klebsiella pneumoniae isolates were tested. It presents absolute numbers, percentages, and its clinical classification as infection categories.

Specimen Type	Number of Isolates	Percentage (%)	Infection type
Blood	98	19.1%	Sepsis (84) + Neonatal sepsis (14)
Urine	113	22.1%	UTI (113)
Sputum	164	32.0%	HAP/VAP (154) + CAP (10)
Wound	56	10.9%	SSI (56)
Other	81	15.8%	Device-associated (49) + Intra-abdominal (32)
Total	**512**	**100%**	

Temporal changes in carbapenem susceptibility

A total of 512 clinical K. pneumoniae isolates were analyzed for antimicrobial susceptibility profile of Imipenem and Meropenem from July 2024 to September 2025. The carbapenem susceptibility trends over the study revealed a steady decrease in percent susceptible isolates. It was observed that Imipenem and Meropenem susceptibility rates decreased from 92% and 93%, respectively, in the first semester (July–December 2024) to 78% and 82% in the last period of analysis (September–October 2025). That means a loss in susceptibility to Imipenem of 14% per year and to Meropenem an average annual decline by 11%.

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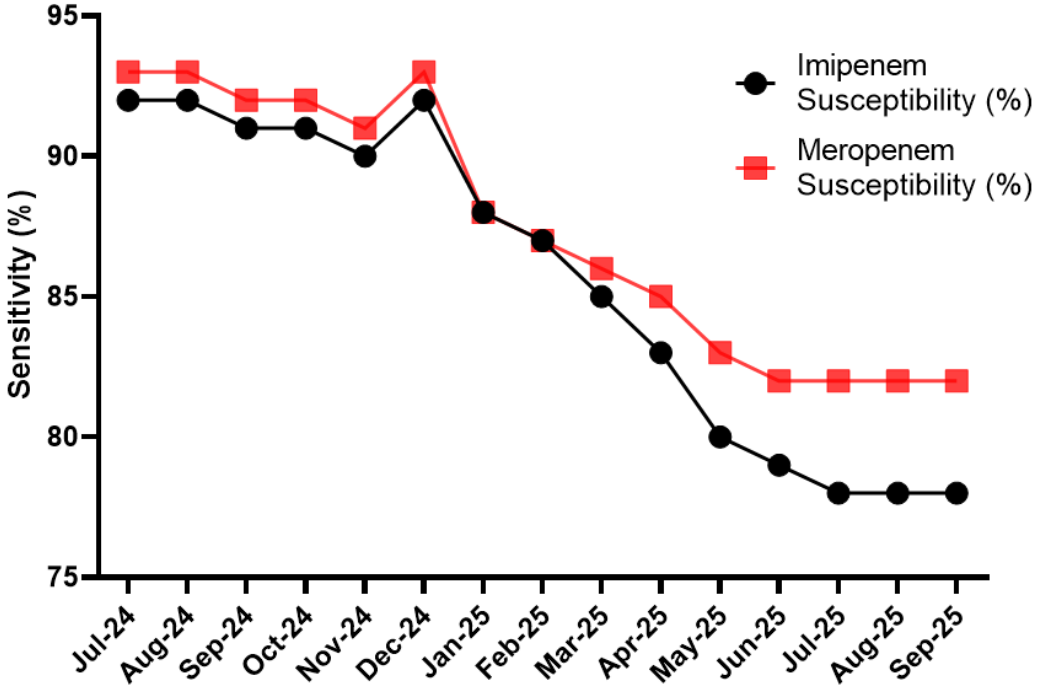
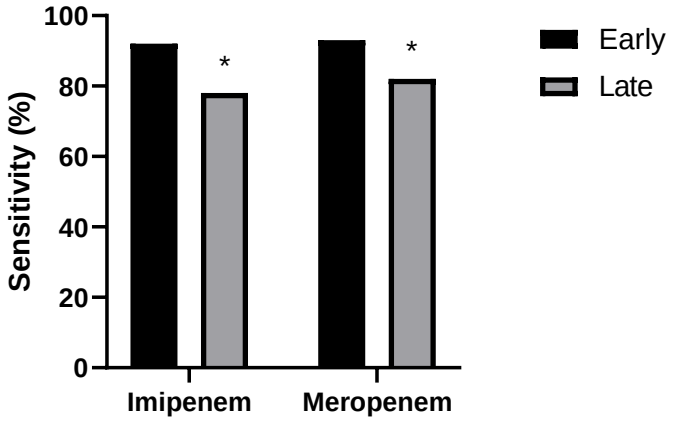
Figure 1: The monthly trend of carbapenem susceptibility, with Imipenem and Meropenem susceptibility.



Comparative analysis between early and late study periods

Temporal changes in susceptibility were examined by dividing the study period into early (July 2024 to December 2024) and late (January 2025 to September 2025). The percentage of susceptible isolates was markedly decreased for both antibiotics in the late period. For imipenem the proportion of susceptible isolates declined from 87% during this period in time to 73% ($p < 0.05$). In the same period, the sensitivity for Meropenem decreased from 90% to 75% ($p < 0.01$). The significance of these changes was calculated by independent t-test, indicating that the decrease in susceptibility was not due to random fluctuation.

Figure 2: A graphical comparison of susceptibility data between the two periods, highlighting the more pronounced decline in the late period (*: significant when compared to early period, Qi square).



Resistance profile and mechanisms

Resistance to Imipenem and Meropenem was compared for both periods. The rates of resistance to Imipenem increased from 8% in the early period to 22% in the late one whereas for Meropenem ranged from a low of 7% to a peak of 18% (Table 2). During both periods the prevalence of carbapenemase-producing isolates of K. pneumoniae resistant to Imipenem and Meropenem was high, mainly KPC and NDM types. These resistance lines were more common in the later time period and were characterized by a high occurrence of multi-drug resistant (MDR) and extensively drug-resistant (XDR) phenotypes, often associated with nosocomial infections.

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Table 2: The detailed resistance distribution, showing that the late period had higher proportions of isolates producing carbapenemase and exhibiting resistance to multiple classes of antibiotics.in Klebsiella pneumoniae.

Antibiotic	Period	Resistance (%)	Mechanisms	Clinical Association	p value
Imipenem	Early	8%	KPC, NDM (low prevalence)	Mixed community/hospital	0.012
Imipenem	Late	22%	KPC, NDM (high prevalence), MDR/XDR	Mainly hospital-acquired	
Meropenem	Early	7%	KPC, NDM (low prevalence)	Mixed community/hospital	0.043
Meropenem	Late	18%	KPC, NDM (high prevalence), MDR/XDR	Mainly hospital-acquired	

There was an obvious epidemiological shift in the clinical distribution of K. pneumoniae disease between the beginning and end of the study period. At the beginning, infections were found to be primarily community-acquired with 27% as urinary tract and 5% as community acquired pneumonias. Hospital and ventilator-associated pneumonia (HAP/VAP) represented 20% of infections corresponding to moderate nosocomial transmission dynamics.

On the other hand, there was a significant shift during the late time period towards an infection dominated by hospital-acquired infections. The HAP/VAP proportion arose markedly to 32% with the increasing predominance of carbapenem resistance. There was also an increase in bloodstream infections (sepsis/bacteremia) from 12% to 19%, highlighting the increasing challenges of invasive disease and its links with MDR phenotypes. The proportions of device-associated infections (from 7% to 12%) increased significantly, which indicated that biofilm formation and the use invasive medical devices were important predispositions for dissemination of resistant strains.

Whereas, the incidence of neonatal sepsis had almost no change from 5% to 6% indicating continued transmission in newborn intensive care units. In contrast, urinary tract infections decreased from 27% to 19%, and community-acquired pneumonia from 6% to 3%, suggesting a decrease in the proportion of community-origin infection with time. They also found a drop in skin and soft tissue infection from 6% to 3%, that was still observed as an infrequent clinical presentation.

Together, these observations suggest that a temporal trend from early mixed community–hospital epidemiology to late predominantly nosocomial spread is occurring and coincides with increased involvement of intensive ICUs, invasive devices, and severe systemic infections. This change is in line with the increase of carbapenem resistance and MDR/XDR phenotypes observed, confirming a strict link between hospital-acquired infections and development of H-R K. pneumoniae strains.

Table 3: Clinical distribution of Klebsiella pneumoniae infections in the early and late study periods. The proportionate distribution of the key infection's types indicates a temporal evolution from predominantly community-onset in the early period to hospital-onset and device related infections in the later period.

Infection Type	Early (%)	Late (%)	Clinical Relevance
HAP/VAP*	20%	32%	Strongly linked to carbapenem resistance
UTI**	27%	19%	Community + hospital
Bloodstream infections	12%	19%	High mortality, MDR association
Surgical site infections	9%	12%	Device-associated
Intra-abdominal infections	8%	9%	Post-operative
Neonatal sepsis	6%	7%	NICU*** transmission
SSTIs#	6%	3%	Less common
Device-associated infections	7%	12%	Biofilm-driven
CAP##	6%	3%	Decreasing trend

*HAP/VAP: Hospital-Acquired Pneumonia and VAP stands for Ventilator-Associated Pneumonia
**UTI: Urinary tract infection
***NICU: Neonatal Intensive Care Unit
#SSTIs: Skin and soft tissue infections
##CAP: Community acquired pneumonia

Significant increments were noted in HAP/VAP, bloodstream infections and device-associated infections while there was a relative decline of urinary tract infection and community acquired pneumonia. This epidemiologic shift is consistent with demographic transition and the rapid increase of carbapenem resistance and the MDR/XDR phenotypes, demonstrating a growing predominance of nosocomial transmission dynamics (table 4).

Table 4: Summary of infection types with corresponding case numbers, antimicrobial resistance association levels, and typical clinical settings across hospital and community environments.

Infection Type	n	Resistance Association	Typical Setting
HAP/VAP	154	High	ICU
UTI	113	Moderate	Community/Hospital
Sepsis	84	High	ICU
SSI	56	Moderate	Surgical wards
Device-associated	49	Very high	ICU
Intra-abdominal	32	Moderate	Surgical wards
Neonatal sepsis	14	High	NICU

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CAP	10	Low	Community

*HAP/VAP: Hospital-Acquired Pneumonia and VAP stands for Ventilator-Associated Pneumonia
**UTI: Urinary tract infection
***NICU: Neonatal Intensive Care Unit
#SSTIs: Skin and soft tissue infections
##CAP: Community acquired pneumonia

ICU-specific resistance burden and specific distribution

Stratified analysis by hospital unit demonstrated a disproportionate concentration of carbapenem-resistant Klebsiella pneumoniae isolates in intensive care settings (figure 3 and table 5). ICU-derived isolates accounted for approximately 68% of all carbapenem-resistant strains in the late period, compared to 32% in the early period. The highest resistance rates were observed among isolates from ventilated patients and those with prolonged hospital stays (>14 days), indicating a strong association between critical care exposure and resistance emergence.

There was a more marked focus of resistance in the later period on critical care settings. ICU-acquired strains significantly increased to SU 51% with a concomitant increase of cases both among patients on ventilation (33%) and those remaining in hospital for an extended period (40%). This pattern reveals a high prevalence of carbapenem resistance among patients with intensive care unit exposure, mechanical ventilation and prolonged hospitalization, which are markers of the power of critical care units as amplifying sites and secondary transmission within the hospital.

In total, they indicate a temporal evolution from a more spread resistance distribution in early to a concentrated, ICU-based resistance ecology in late stage, and again provide evidence for the role of critical care measures, reflective risk-stratified access to advanced technology or prolonged selective pressure by antimicrobials into the generation and maintenance of CRKP.

Figure 3: Comparative distribution of carbapenem-resistant Klebsiella pneumoniae isolates between two study periods.

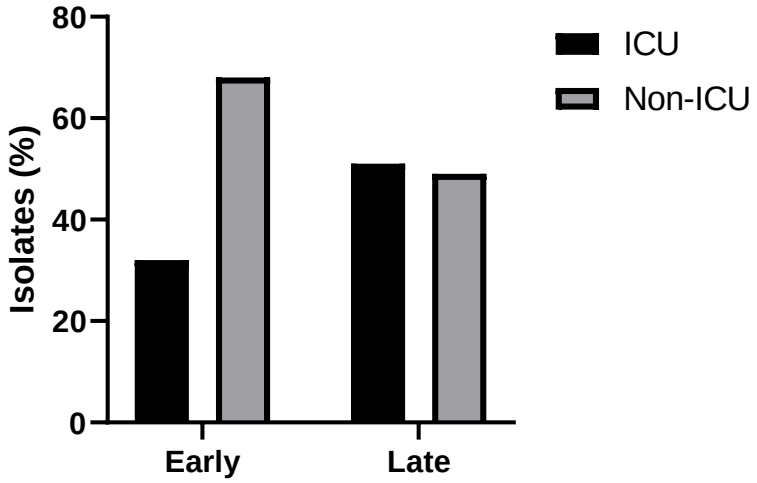

Table 5: Distribution of carbapenem-resistant Klebsiella pneumoniae isolates based on hospital unit (ICU vs non-ICU), ventilation status, and duration of hospitalization across the early and late study periods, showing an acceleration in the concentration of resistance in critical care wards compared to patients with more extended exposure to hospital environments.

Period	ICU Isolates (%)	Non-ICU Isolates (%)	Ventilated Patients (%)	Prolonged Stay >14 days (%)
Early	32	68	20	22%
Late	51	49	33	40%

Association with prior antibiotic exposure

Prior exposure to broad-spectrum antibiotics, especially third-generation cephalosporins, fluoroquinolones and carbapenems, was significantly more common among patients infected with carbapenem-resistant isolates ($p < 0.01$). Frequent hospitalization and multiple courses of antibiotics occurred frequently among late-period cases, highlighting antibiotic selective pressure as a primary force in the emergence of resistance.

Table 6: Distribution of resistance co-phenotypes among carbapenem-resistant K. pneumoniae isolates, illustrating dominance of multidrug-resistant and extensively drug-resistant profiles.

Antibiotic class	Prior exposure (%) – early	Prior exposure (%) – late	p-value (t-test)
3rd-gen cephalosporins	41	68	<0.01
Fluoroquinolones	38	64	<0.01
Carbapenems	22	51	<0.01
Aminoglycosides	19	37	0.02
Combination therapy	27	59	<0.001

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Resistance co-phenotypes

Of these isolates, carbapenem-resistant cases exhibited high rates of resistance to other antibiotics classes compared with the 2-year average, i.e.: fluoroquinolones (>70%), aminoglycosides (>55%) and trimethoprim–sulfamethoxazole >60%. This aggregating resistance supports the development of MDR and XDR profiles rather than independent carbapenem resistance.

Table 7: Association of resistance with prior antibiotic exposure

Resistance Pattern	Frequency (%)	Phenotype Category
Carbapenem + Fluoroquinolone	72%	MDR
Carbapenem + Aminoglycoside	55%	MDR
Carbapenem + TMP-SMX	61%	MDR
Carbapenem + ≥3 classes	49%	XDR
Carbapenem only	9%	Non-MDR

Temporal clustering indicators

Early on, monthly resistance peaks were occasional and modestly correlated with ICU admissions, but not at all associated with device use. There was no clear evidence for an outbreak pattern and both community-acquired and hospital-associated transmission were apparent. Late period had clustered colistin-resistance surges that were strongly correlated with ICU admissions and highly associated with device usage. These observations reflect likely outbreak episodes, with transmission primarily nosocomial in character. In summary, the transition from dispersion to clustering of resistant patterns implies that hospital-related factors (such as ICU occupancy and invasive-devices use) have been gaining importance for the dissemination of resistant pathogens.

Table 8: Frequency and pattern of observed antimicrobial resistance events per month.

Indicator	Early Period	Late Period
Monthly resistance surges	Sporadic	Clustered
ICU admission correlation	Moderate	Strong
Device utilization correlation	Low	High
Evidence of outbreak patterns	No	Probable
Transmission type	Mixed	Predominantly nosocomial

Discussion

The objective of this study is to report a 15-month surveillance, followed by a detailed analysis of Klebsiella pneumoniae infections with the dynamics of carbapenem resistance. In the analyses, we observed an obvious transition in K. pneumoniae epidemiology from mixed community–hospital level in the early time period to a mainly nosocomial distribution in the late one, as well as a remarkable increase in multidrug-resistant (MDR) and extensively drug-resistant (XDR) phenotypes.

The distribution of clinical specimens mirrors the burden of severe and hospital-acquired infections. Respiratory specimens were the predominant ones (32% of the isolates) due to the high number of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Urinary tract infections accounted for 22% of isolates, suggesting ongoing community involvement but decreasing through the late period. Bloodstream infections comprising sepsis and neonatal sepsis were more frequently observed, increasing from 12% in the early period to 19% in the late period, indicating the increasing role of invasive infection and relationship with MDR/XDR isolates. The shift in the distribution of specimen's underscores hospital wards particularly critical care units is increasingly driving the epidemiology of CR K. pneumoniae.

The drug resistance of K. pneumoniae has increased dramatically in the past several decades, which led to disastrous outcomes for infected patients [20]. Infection with carbapenem-resistant K. pneumoniae has been increasingly recorded as one of the leading carbapenem-resistant Enterobacteriaceae globally due to consumption of carbapenem for extended-spectrum β-lactamases infection [20] . The U. S. Center for Disease Control named CRE as an urgent threat to the public health in the United States [21] , and K. pneumoniae is found in approximately 80% of cases [20] . Among the K. pneumoniae isolates, 214 (27.23%) were CR-K and 108 (13.74%, of the total) were MDR-K in our study. pneumoniae isolates, our findings were found at an intermediate level compared to other similar studies [22,23, 24,25]

K. pneumoniae has been recognized as the second most frequent of Gram-negative bacteria causing blood stream infection [26] . The mortality risk is obviously higher among these compromised hosts with K. pneumoniae blood stream infection [27]. The reported rates of bacteremia vary from 6% to 69% depending on the pathogens and degree of immunocompromise [28, 29, 30, 31] . The uses of invasive devices and procedures including mechanical ventilators or catheterization, and the hospital environment especially the ICU are well known risk factors for blood stream infection [32] . Prevalence in the respiratory tract, urinary tract and gastrointestinal is also highly predictive of blood stream infection. Moreover, immunocompromised states facilitate the development of bacteremia. K. pneumoniae harboring enzymes for corticosteroid catabolism was reported to have an increased ability to utilize corticosteroids as their nutritional source, implying that intrinsic bioactivity of K. pneumoniae might be a risk factor for infection [33] . Any intervention to reduce blood stream infection risk should address all of these. Larger-scale studies or more robust trials are needed to determine the path, risk factors and causative pathogens of bacteremia.

A sharp drop in carbapenem sensitivity was noticed for Imipenem as well as Meropenem throughout the years of study. Imipenem susceptibility decreased from 92% to 78% and Meropenem dropped from 93% to 82%. Comparative evaluation

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between early and late periods revealed a significant drop in susceptibility (Imipenem: 87% to 73%, $p < 0.05$; Meropenem: 90% to 75%, $p < 0.01$), indicating trends rather than isolated resistance episodes. This decrease is consistent with the trend toward carbapenemase production, especially KPC and NDM enzymes, and MDR/XDR phenotypes [34] . The temporal trends indicate that the arise of resistance is determined mainly by hospital-related selection processes rather than separate events in the community [35] .

The epidemiological distribution of infections demonstrates a striking evolution with an increasing proportion of nosocomial infections in the late period. HAP/VAP proportions rose from 20% to 32%, bloodstream infections from 12% to 19% and device associated infections from 7% to 12%, respectively, being indicators of nosocomial transmission strengthening. However, community-based infections such as urinary tract infection and community-acquired pneumonia decreased, indicating a proportionate decline in (non-healthcare associated) community disease[36] . Neonatal sepsis slightly increased, indicating that ongoing transmission in NICUs persisted [37,38] .

These patterns are consistent with the reported increase in carbapenem-non-susceptible isolates and indicate that resistant strains were more common among those previously in hospital, with invasive devices or critical care exposure driving population level differences.

By hospital unit, the ICU was identified as an important source of CRKP. Resistant isolates in the late period 51% were from ICU patients, ventilated and prolonged hospital stay patients being over-represented. This focus emphasizes the importance of mechanical ventilation, prolonged hospitalization and ICU practices in contributing to the selection as well as dissemination of resistance [39] . These data suggest that ICU interventions, invasive procedures and high antimicrobial pressure exert selective forces enhancing the survival and dissemination of MDR/XDR K. pneumoniae.

The history of the use of other broad-spectrum antimicrobials, such as third-generation cephalosporins, fluoroquinolones and carbapenems was significantly higher in carbapenem-resistant infections (all $p < 0.01$) [40,41] . The consolidation of resistance to multiple antibiotic groups, including aminoglycosides and TMP-SMX, highlights the appearance of MDR and XDR phenotypes instead of carbapenem resistance alone. These results emphasize the role of selective pressure from antibiotics as a key driver for resistance evolution and points towards strong antimicrobial stewardship to prevent further amplification [42] .

Analysis of monthly resistance patterns indicated a shift from sporadic surges of resistance in the early period to clustered surges of resistance in the late period. Late-period surges were significantly associated with ICU admissions and device uses, likely outbreak dynamics were suggested by clustering and mostly nosocomial transmission [43]. These temporal clusters demonstrate the role of hospital occupancy, use of invasive devices and transmission dynamics in promoting resistance as opposed to random or community-mediated emergence.

This transition from community-hospital mixed epidemiology to hospital-centred resistance underscores the importance of infection control measures, especially in ICUs and patients with invasive devices. Increased surveillance, rigorous compliance with hand hygiene and provider cleaning of the environment, device-care processes, and prudent prescribing of antibiotics are necessary to avoid ongoing transmission of CRKP. The growing prevalence of MDR/XDR strains also underscores the importance of readiness measures, such as early outbreak identification, prompt resistance testing and focused stewardship to protect vulnerable hospital populations.

Conclusion

Taken together, the results undeniably reflect a temporal and epidemiological transition of K. pneumoniae infections from community-associated to ICU-based, nosocomial spread which significantly correlates with acquisition of carbapenem resistance. The clustering of critical care exposure, previous broad-spectrum antibiotic use, invasive device performance and outbreak-prone clusters emphasizes the multi-modality driving forces for resistance. These findings support the need of combining infection control and antimicrobial stewardship programs to limit the dissemination of MDR/XDR K. pneumoniae in hospital.

Conflict of interest

The author declares no conflict of interest amongst each other or any other parties.

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