American Journal of Biomedicine and Pharmacy
https://biojournals.us/index.php/AJBP
ISSN: 2997-7177

Clinical Epidemiology of the Global Expansion of Klebsiella Pneumonia

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Received: 2024 15, Nov
Accepted: 2024 21, Nov
Published: 2024 20, Dec

Annotation: Klebsiella pneumoniae BSIs are associated with high mortality rates worldwide. The emergence of antibiotic-resistant K. pneumoniae complicates the management of infections caused by these bacteria. This study aimed to evaluate the epidemiology, resistance profiles, and clinical outcomes of K. pneumoniae BSIs. The infection rate was slightly higher in females (52%) than in males (48%). The ICU and ER had the highest prevalence of K. pneumoniae BSI. ICUs are considered factories that create, amplify, and disseminate antibiotic resistance [20, 21]. The high prevalence of antibiotic resistance in ICUs might be due to multiple infections, frequent application of antimicrobials, or the frequent use of invasive procedures. In our study, Klebsiella pneumoniae BSIs in patients admitted to the ICU were significantly associated with multiple risk factors including carbapenem resistance, mechanical ventilation, respiratory infection, multi-organ dysfunction, ischemic heart disease, and septic shock were significantly higher among ICU patients than non-ICU patients. In a recent study by Wang et al. (2023), age over 70 years, admission to ICU, and urinary tract infection were found to be the risk factors for Carbapenem-resistant and ESBL-KP-resistance.

INTRODUCTION

First discovered in the USA in 1996,1 Klebsiella pneumoniae carbapenemases (KPCs) are β-lactamases produced by Gram-negative bacteria. They efficiently hydrolyse penicillins, all cephalosporins, monobactams, carbapenems, and even β- lactamase inhibitors. Since their first description, KPC enzymes have spread across countries and continents , although the exact epidemiology of their expansion varies by geographical location. Bacteria producing these enzymes are generally only susceptible to a few antibiotics, and there is high mortality among patients with bloodstream infections caused by these organisms. Many bacteria with these enzymes remain susceptible to colistin, tigecycline, and one or more aminoglycoside, but some are resistant even to these drugs. Moreover, only a few drugs are in development against KPC-positive bacteria. K. pneumoniae is gram- negative, non-motile, encapsulation-fermenting, optional anaerobic bacteria that are rod-shaped, established in normal mouth, skin, and intestines flora and feces of about 5% of people. It triggers tiny bacterial pneumonias. It may cause substantial hemorrhagic necrotizing lung consolidation. Occasionally, it induces urinary tract infection and focal lesion bacteremia in compromised patients . K. pneumoniae is often linked to hospital infection. Some underlying diseases including malignantness, cirrhosis, biliary diseases, urinary and Infections of biliary tract, diabetes mellitus osteomas and bacteremia and alcoholism can impair the defenses of the person and increase the risk of K. pneumoniae infection. This species is a second most common cause of GNB after Escherichia coli. K. pneumoniae bacteremia in general populations are responsible for significant morbidity and mortality. The most important features of k. pneumoniae infections are metastatic infections – for example, pyogenic brain abcess, meningitis, and endophthalmitis .

K. pneumoniae has been shown to develop in vitro as a biofilm since the late 1981s, but only in 1992 did Reid and his colleagues scan the bladder epithelial cells of a patient with spinal cord K. pneumoniae infection. In vitro studies subsequently showed that approximately 41% of K. pneumoniae was capable of developing biofilms not only from urine but also from sputum, blood and wound swabs.

Etiology

Klebsiella pneumoniae belongs to the Enterobacteriaceae family and is described as a gram-negative, encapsulate, and non-motile bacterium. Virulence of the bacterium is provided by a wide array of factors that can lead to infection and antibiotic resistance. The polysaccharide capsule of the organism is the most important virulence factor and allows the bacteria to evade opsonophagocytosis and serum killing by the host organism. To date, 77 different capsular types have been studied, and those Klebsiella species without a capsule tend to be less virulent. A second virulence factor is lipopolysaccharides that coat the outer surface of a gram-negative bacteria. The sensing of lipopolysaccharides releases an inflammatory cascade in the host organism and has been a major culprit of the sequela in sepsis and septic shock. Another virulence factor, fimbriae, allows the organism to attach itself to host cells. Siderophores are another virulence factor that is needed by the organism to cause infection in hosts. Siderophores acquire iron from the host to allow propagation of the infecting organism. Klebsiella pneumoniae is one of a handful of bacteria that are now experiencing a high rate of antibiotic resistance secondary to alterations in the core genome of the organism. Alexander Fleming first discovered resistance to beta-lactam antibiotics in 1929 in gram-negative organisms. Since that time, K. pneumoniae has been well studied and has been shown to produce a beta-lactamase that causes hydrolysis of the beta- lactam ring in antibiotics. Extended-spectrum beta-lactamase (ESBL) K. pneumoniae was seen in Europe in 1983 and the United States in 1989. ESBLs can hydrolyze oxyimino cephalosporins rendering third-generation cephalosporins ineffective against treatment. Due to this resistance, carbapenems became a treatment option for ESBL. However, of the 9000 infections reported to the Centers for Disease Control and Prevention (CDC) due to carbapenem-resistant Enterobacteriaceae in 2013, approximately 80% were due to K. pneumoniae. Carbapenem resistance has been linked to an up-

regulation in efflux pumps, alteration of the outer membrane, and increased production of ESBL enzymes in the organism.

Pathophysiology

Host protection from bacterial invasion mainly depends on two things: polymorphonuclear granulocytes, which phagocytose the bacteria, and serum complement proteins, which are bactericidal. The alternate pathway of complement activation is more active in Klebsiella pneumoniae infection. Neutrophil myeloperoxidase and lipopolysaccharide-binding protein facilitate in defense against Klebsiella pneumoniae infection. Bacteria have a polysaccharide capsule made up of complex acidic polysaccharides and determine their pathogenicity. The capsule protects bacteria from phagocytosis and serum bactericidal proteins. It adheres to host cells with many fimbrial and non-fimbrial adhesions, which is critical to the infectious process.

Biochemical identification

Phenotypic identification of each isolate was performed based on conventional biochemical tests: TSI (triple sugar-iron, Bioxon, México), LIA (lysine-iron agar, Bioxon), MIO (motility medium-indole-ornithine, Bioxon®, urea in Christensen base (Bioxon), Simmons citrate (Bioxon), methyl red, and Voges-Proskauer (Bioxon).

GENUS KLEBSIELLA

Klebsiella, a genus that is belongs to the Enterobacteriaceae family. It is so- called after the German microbiologist Edwin Klebs (1834–1913) . Klebsiella are found throughout nature. This is due to different sub-lineages, which evolve unique niche versions with associated biochemical adaptations, making them more appropriate for a given climate. It is present in water, soil, plants, insects, animals and humans . Typically, they are straight rods with circular or slightly pointing ends. It is found individually in pairs or small chains and produces colonies with a little or fewer dome-shaped, glossy form with varying degrees of stubbornness, contingent on the medium's pressure and structure . In the human nose, throat and gastrointestinal tract, Klebesiella species are generally known as the natural flora; however, they may also serve as opportunistic human pathogens.

EPIDEMIOLOGY

Persons serve as K.pneumoniae 's primary reservoir. In the general community, 5-38% of persons bear the organism in their stool and 1-6% in the nasopharynx. The major sources of infection are gastrointestinal tract and hospital worker's hands. It can cause nosocomial eruption. Though, Chinese ethnicity and those experiencing chronic alcoholism have reported higher colonization rates. In hospitalized patients, K.pneumoniae carrier prevalence is ample higher than in the population. In a single sample, carriers' levels of up to 75% in the stool of those hospitalized can be seen and felt to be consistent with the amounts of antibiotics given .

Materials and methods

Study design and setting

This retrospective study was conducted over one year (January 2019 to January 2020) at KFMC, which has a capacity of 1200 beds. A total of 152 Klebsiella pneumoniae isolates from blood clinical samples were analysed. The clinical history of 152 patients was included in this study.

Data collection

In total, 152 samples of Klebsiella pneumoniae were collected from blood (central and peripheral line blood). The following were the included collection categories:

A. age (paediatric or adult).

B. Ward or clinic to which the patient was admitted (emergency, ICU, ward, or outpatient clinic).

C. blood sample source and location or site; and (D) bacterial-resistance category (susceptible, Extended-spectrum β-lactamases (ESBL), and Carbapenem-Resistant strains).

Any growth other than that of K. pneumoniae was excluded from the study. Clinical history was collected from the KFMC database for paediatric and adult patients admitted to ICU.

The clinical history collected for ICU patients included different criteria: (1) if present, the type of co-infection;

(2) exposure to carbapenem or other antibiotics in the past 14–30 days;

(3) renal dialysis at isolation or not;

(4) mechanical ventilation or not;

(5) chronic diseases such as diabetes mellitus (DM), hypertension, renal disease, or malignancy;

(6) presence of clinical symptoms such as fever, gastrointestinal tract (GIT) symptoms, or respiratory symptoms;

(7) presence of wound or urinary tract infection;

(8) presence of bacteraemia or septicaemia; and

(9) clinical outcomes and additional notes, if available.

Klebsiella pneumoniae identification and antimicrobial susceptibility testing

All isolates were presumptively identified as Klebsiella species, using a Phoenix BD instrument (Becton Dickinson Diagnostic Systems, Sparks, MD, USA) for full identification and sensitivity testing.

We included only patients whose isolates were definitively identified as K. pneumoniae. Antimicrobial sensitivity testing (AST) was performed for the following antibiotics:

ampicillin (AMP), amoxicillin-clavulanate (AMC), piperacillin-tazobactam (TZP), imipenem (IPM), meropenem (MER), ertapenem (ETP), cephalothin (CEF), cefuroxime (CXM), ceftazidime (CTZ), cefoxitin (FOX), cefepime (CFPM), cefotaxime (CTX), ceftriaxone (CRO), ciprofloxacin (CIP), levofloxacin (LVX), gentamicin (GM), amikacin (AMK), tigecycline (TGC), colistin (COL), and trimethoprim-sulfamethoxazole (TMP-SMX).

Susceptibility was classified as follows: susceptible, intermediate, or resistant. Confirmation of resistant isolates was performed using Microbroth dilution.

Additional tests of disc diffusion or gradient diffusion (Etest) methods were performed using Mueller-Hinton agar which were then incubated in ambient air at 35 ℃ for 16–20 h. For interpretation, CLSI M100 Interpretive Document for Enterobacterales. EUCAST was used for the interpretation of tigecycline activity.

Statistical analysis

The data were analysed using GraphPad Prism version 9.3.1. Descriptive analysis, using contingency tables and graphs, was used to illustrate the following data: age divisions, sex, ward/clinic, sample source, and sample site. The descriptive data are expressed as absolute numbers (n) and percentages. $P < 0.05$ was considered statistically significant. Relative risk (RR) was computed to demonstrate how much the risk variables raised the risk of mortality following a study by Hafiz et al. (2022) [19].

Ethical approval

This project was approved by the institutional review board (IRB) of KFMC. Consent was obtained from KFMC according to the ICH GCP ethical code (IRB approval number 20-164E). Informed consent was obtained from all the participants and from the legal guardians of the participants who were below 16 years of age.

Results

Demographic and clinical characteristics of patients infected with K. pneumoniae BSI

During the study period, 152 incident BSI cases were identified as caused by K. pneumoniae isolated from the central or peripheral venous catheter. Approximately two-thirds (66%) of the study population were aged > 15 years. Females were fairly probable as males to be infected with K. pneumoniae BSI. Among the incident K. pneumonia bloodstream infections, 53 isolates were classified as ESBL strains, 55 as Carbapenem-Resistant strains, and 44 as susceptible strains.

More than half of the K. pneumoniae isolates originated from critical care wards, such as ER and ICU wards (Table 1).

Table 1 Demographic and clinical characteristics of patients with Klebsiella pneumoniae bloodstream infection

Data are presented as number of patients (n), with the corresponding percentage in parentheses (%). [1]ESBL, Extended-spectrum β- lactamases; [2]ICU, Intensive care unit; [3]ER, Emergency ward .

Characteristic	Patients (n = 152)
Gender, n (%)	
Male	73 (48)
Female	79 (52)
Age group, n (%)	
Paediatric patient	51 (33.6)
Adult patients	101 (66.4)
Blood specimen source, n (%)	
Peripheral line	77 (50.7)
Central venous line	75 (49.3)
Category of multi-drug resistance, n (%)	
ESBL[1] strains	53 (34.87)
Carbapenem-Resistant strains	55 (36.18)
Susceptible strains, n (%)	44 (28.95)
Type of ward/ clinic, n (%)	
ICU[2]	63 (41.5)
ER[3]	23 (15.1)
Other	66 (43.4)

Clinical manifestations among adult and paediatric patients infected with K. pneumoniae BSI

Univariate analysis was conducted to compare clinical manifestations between paediatric and adult patients with K. pneumoniae bloodstream infections (Table 2).

Paediatric patients were substantially more likely to develop septicaemia than adults ($P < 0.0001$, 56.9% vs. 21.8%, respectively). However, septic shock was significantly more frequent in adult patients ($P = 0.0092$). In adult patients, K. pneumoniae BSI and comorbidities, such as diabetes mellitus, hypertension, malignancy, chronic kidney disease, and ischaemic heart disease, were significantly associated ($P < 0.0001$, $P < 0.0001$, $P = 0.0078$, $P = 0.0021$, and $P = 0.0004$, respectively). Notably, paediatric patients with acute respiratory distress syndrome were slightly more vulnerable to K. pneumoniae BSI than adult patient.

Clinical outcome of patients infected with K. pneumoniae BSI

We conducted a univariate analysis to compare the outcome of all patients with K. pneumoniae bloodstream infection. Table 3 shows the relative risks (RRs) of mortality and 95% confidence intervals, demonstrating the strength of the associations between the risk factors and mortality. To

ensure an accurate comparison between patients, we excluded four patients because they were transferred to another medical facility. Of the total patients with K. pneumoniae BSI (n = 148), the overall mortality rate was 32.4% (48/148 patients). Univariate analysis revealed many risk factors associated with mortality (ranked from highest to lowest significance): mechanical ventilation, multi-organ dysfunction, septic shock, gastrointestinal infection, chronic kidney disease, carbapenem resistance, age > 15 years, ischaemic heart disease, and hypertension (P < 0.0001, P = 0.0005, P = 0.0007, P = 0.0061, P = 0.0087, P = 0.0029, P = 0.0169, P = 0.0170 and

P = 0.0462, respectively). The risk of mortality was 34% higher in adult patients and approximately 50% lower in paediatric patients (RR = 1.342; 95% CI: 1.063–

1.669 vs. RR = 0.508; 95% CI: 0.275–0.889). Patients with multi-organ dysfunction were at a substantially high risk of death from K. pneumoniae BSI (RR = 16.67; 95% CI: 2.801–101.1 Septic shock and chronic kidney disease raised the RR three-fold, whereas ischaemic heart disease, mechanical ventilation, gastrointestinal infection, and carbapenem resistance raised it two-fold (Table 3).

Characteristics	**Outcome**				
	Deceased(n = 48)	**Alive(n = 100)**	**RR**	**CI 95%**	***P* value**
Age group, n (%)					
Paediatric	10 (20.8%)	41 (41.0%)	0.5081	0.275 to 0.889	0.0169*
Adult	38 (79. 2%)	59 (59.0%)	1.342	1.063 to 1.669	0.0169*
Category of multidrug resistance, n (%)					
ESBL[1] strains	16 (33.3%)	37 (37.0%)			0.7168
Carbapenem-Resistant strains	25 (52.1%)	26 (26.0%)	2.003	1.299 to 3.059	0.0029**
Susceptible strains, n (%)	7 (14.6%)	37 (37.0%)	0.394	0.188 to 0.778	0.0067**
Invasive procedure, n (%)					
CVC[2]	24 (50.0%)	49 (49.0%)			> 0.9999
MV[3]	29 (60.4%)	23 (23.0%)	2.627	1.719 to 4.024	< 0.0001****
Dialysis	5 (10.4%)	11 (11.0%)			> 0.9999
Clinical presentation / complication, n (%)					
Respiratory infection	21 (43.8%)	34 (34.0%)			0.2786
Gastrointestinal infection	18 (37.5%)	16 (16.0%)	2.344	1.315 to 4.142	0.0061**
Wound infection	2 (4.2%)	6 (6.0%)			> 0.9999
Urinary tract infection	7 (14.6%)	18 (18.0%)			0.8151
Septicaemia	12 (24. 5%)	38 (38.0%)			0.1392
Septic shock	17 (35.4%)	11 (11.0%)	3.220	1.655 to 6.262	0.0007***
Multi-organ dysfunction	8 (16.7%)	1 (1.0%)	16.67	2.801 to 101.1	0.0005***

Underlying disease, n (%)					
Diabetes	21 (43.8%)	35 (35.0%)			0.3660
Hypertension	24 (50.0%)	32 (32.0%)	1.563	1.034 to 2.316	0.0462*
Malignancy	18 (37.5%)	35 (35.0%)			0.8550
CKD[4]	12 (25.0%)	8 (8.0%)	3.125	1.394 to 6.982	0.0087**
ARDS[5]	6 (12.51%)	9 (9.0%)			0.5648
IHD[6]	11 (22.9%)	8 (8.0%)	2.865	1.256 to 6.496	0.0170*

Data are presented as a number of patients (n) with the corresponding percentage in parentheses (%). * $P < 0.05$; The statistical significance was indicated by a (*) symbol and the number of * represents the strength of the significance difference. [1]ESBL, Extended-spectrum β-lactamases; [2]CVC, Central venous catheter; [3]MV, Mechanical ventilation ; [4]CKD, Chronic kidney disease; [5]ARDS, Acute respiratory distress syndrome ; [6]IHD, Ischemic heart disease; RR, Relative risk; CI, Confidence interval.

Discussion

Klebsiella pneumoniae BSIs are associated with high mortality rates worldwide. The emergence of antibiotic-resistant K. pneumoniae complicates the management of infections caused by these bacteria. This study aimed to evaluate the epidemiology, resistance profiles, and clinical outcomes of K. pneumoniae BSIs. The infection rate was slightly higher in females (52%) than in males (48%). The ICU and ER had the highest prevalence of K. pneumoniae BSI. ICUs are considered factories that create, amplify, and disseminate antibiotic resistance [20, 21]. The high prevalence of antibiotic resistance in ICUs might be due to multiple infections, frequent application of antimicrobials, or the frequent use of invasive procedures. In our study, Klebsiella pneumoniae BSIs in patients admitted to the ICU were significantly associated with multiple risk factors including carbapenem resistance, mechanical ventilation, respiratory infection, multi-organ dysfunction, ischemic heart disease, and septic shock were significantly higher among ICU patients than non-ICU patients. In a recent study by Wang et al. (2023), age over 70 years, admission to ICU, and urinary tract infection were found to be the risk factors for Carbapenem-resistant and ESBL-KP-resistance [22]. In another study by Huang et al. (2023), the risk factors for resistance to carbapenems in K. pneumoniae were ICU admission, respiratory failure, admission from the Emergency, and imipenem use [23]. In addition, the mortality rate was higher among ICU patients and contributed to 45.9% of the death rate. This finding is supportive of the EUROBACT-2 international cohort study on epidemiology and outcomes of hospital-acquired bloodstream infections in ICU patients which revealed predominant Klebsiella spp. (27.9%) bloodstream infection in ICU patients with poor outcomes [24]. Various hospital-based studies have suggested multiple comorbidities, including DM, biliary disease, and liver disease, as risk factors for K. pneumoniae BSI development [25, 26]. Here, we found that neurological disorders were the primary underlying conditions in both age groups, whereas DM was a main risk factor in adults. This conflicts with another study [28], which reported a lower risk associated with DM than with chronic liver disease and cancer. This contrast may reflect differences in the selected populations studied. Increasing age is associated with an increased risk of comorbidities [27, 28]. Here, the risk factors were associated with a 32.4% mortality rate. The risk of dying from K. pneumoniae BSIs was greater for adults than paediatric patients and was high for those with multi-organ failure. The higher mortality rate can be attributed to the greater virulence of the carbapenemase- producing strains, inappropriate antibiotic therapy, the greater toxicity and reduced effectiveness of antibiotics, and severe underlying diseases such as DM and chronic kidney disease [29].Antimicrobial resistance is one of the most urgent public health concerns worldwide. Based on a comprehensive global analysis, it caused 1.27 million deaths in 2019, more

than those caused by HIV/AIDS or malaria [30], and it could lead to 10 million deaths by 2050 unless a global effort to control it is implemented [31]. Increased prescription rates, and the extensive use of antibiotics, have led to the emergence of resistance against last-resort drugs, including carbapenems and colistin, especially among medically important bacteria such as E. coli and K. pneumoniae. It has been estimated that resistance to fluoroquinolones and β-lactam antibiotics, including carbapenems, cephalosporins, and penicillins, is responsible for more than 70% of deaths attributable to antimicrobial resistance [30]. The emergence and spread of MDR K. pneumoniae pose a global public health concern. In Saudi Arabia, the rate of K. pneumoniae resistance has increased substantially in the last few years, reaching 100% resistance in some regions [32]. We believe that the local pattern of antibiotic prescription is comparable to the national pattern of the Hafiz et al. (2023) study, which looks at the impact of improper antibiotic therapy on drug-resistant Gram- negative bacteria and indicates that it is strongly associated with poor outcomes [33]. Furthermore, according to worldwide research, inappropriate treatment is related to poor outcomes [34, 35]. ESBLs, produced primarily by gram-negative bacteria, mediate resistance to a wide range of β-lactam antibiotics, including extended-spectrum cephalosporins and the monobactam aztreonam. Most ESBL- encoding genes are carried by mobile genetic elements, facilitating the spread of resistance genes among bacteria. Several national and international studies have reported an increase in the prevalence of ESBL production among clinical isolates, reaching approximately 74% in some countries [36,37,38]. A study conducted in Saudi Arabia [39].

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