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Original Article

High mortality and antimicrobial resistance of *Klebsiella pneumoniae* bacteremia in northern Taiwan

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Abstract

Introduction: *Klebsiella pneumoniae*, a common hospital- and community-acquired pathogen, is notorious for multidrug resistance. This study aimed to better understand the correlation of clinical presentation and microbiological characteristics of the isolates causing bloodstream infections (BSIs) in Taiwan.

Methodology: We retrospectively collected 150 isolates derived from *K. pneumoniae* bacteremia patients in Taiwan in both 2014 and 2016. Clinical data, bacterial serotyping and drug susceptibility tests were comparatively analyzed.

Results: Demographic data showed that diabetes mellitus (DM) was the most common underlying disease (44.0%). The overall 30-day mortality rate was 19.3%, and higher mortality was found in patients with malignancy than others (P = 0.023). Serotype distribution was diverse. The major isolates belonged to non-PCR-typeable serotypes (58.7%) associated with hospital-acquired infections (P = 0.007) and in non-DM patients (P < 0.001), while K2 and K20 significantly caused infections and in DM patients (P = 0.046 and P = 0.006, respectively); however, only K2 showed more community-acquired infection (P = 0.022) than other typeable serotypes. Resistance to antibiotics in clinical isolates in the year 2016 was > 24%, including cefazolin (54%), ampicillin-sulbactam (25%) and cefuroxime (25%). Susceptibility to gentamicin, flomoxef, and tigecycline reduced between the two time periods (2014 and 2016). However, the isolates remained highly susceptible to amikacin and ertapenem (> 95%).

Conclusions: Patients with cancer had a higher 30-day mortality rate than others. Amikacin and ertapenem are the drugs of choice for the treatment of multidrug-resistant *K. pneumoniae* BSIs in Taiwan.

Key words: *Klebsiella pneumoniae*; bloodstream infection; serotype; multidrug resistance; mortality.

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Introduction

Klebsiella pneumoniae is an important hospital- and community-acquired pathogen that causes various diseases, such as pyogenic liver abscesses, pneumonia, urinary tract infections, endogenous endophthalmitis, and bacteremia in humans [1,2]. The incidence rates of these *K. pneumoniae*-associated infections are much higher in Taiwan than in other Asian countries. *K. pneumoniae*-induced pyogenic liver abscess was first reported in Taiwan in the 1980s [3,4], and additional strains have been subsequently isolated in Taiwan [5,6].

In several studies, various risk factors have been shown to be correlated with an increased mortality rate in *K. pneumoniae* infection, especially for hospitalized patients and those with diabetes mellitus [7,8]. *K. pneumoniae* virulence factors have been investigated, and several have been reported, including factors related to its capsular serotype and hypermucoviscosity phenotype [9,10]. *K. pneumoniae* serotypes show specific geographical distributions, and many Asian strains are hypervirulent [10,11]. Most hypervirulent *K. pneumoniae* isolates are capsule serotypes K1 and K2 [12], and in Taiwan, most *K. pneumoniae* isolates are from K1 serotype.[6] Genes *magA*, and *rmpA* are thought to be possible virulence factors [13]. Serotypes K1, K2,

K54, and K57 have been reported to be associated with community-acquired pyogenic liver abscesses [14].

Recently, the prevalence of multidrug-resistant *K. pneumoniae* isolates is increasing, and resistance to even the last-line antibiotic carbapenem has become a severe problem in *K. pneumoniae* [15]. However, the studies related to the correlations between the microbiological characteristics of *K. pneumoniae* and the clinical features of *K. pneumoniae* infections are limited. In this study, we collected 150 *K. pneumoniae* isolates from patients with bloodstream *K. pneumoniae* infections (bacteremia) at Chang Gung Memorial Hospital (CGMH), Taiwan in 2014 and 2016. We analyzed the demographic data, underlying diseases, infection foci, and mortality rates, to look for correlations between clinical findings and serotypes and other microbial characteristics.

Methodology

Study subjects and clinical data collection

This retrospective study of clinical data was approved by the Institutional Review Board (IRB: 201601455B0) of CGMH, Linkou Branch, a major medical center in northern Taiwan with 3,500 beds. Charts were reviewed for patients who were treated in CGMH between October, 2014 and December, 2016 and had ≥ 1 positive blood culture for *K. pneumoniae*, and symptoms and signs of infection. For patients with multiple episodes, only the first episode was included. Clinical data of the patients, including symptoms, signs of infection, underlying diseases, infection foci, susceptibility testing of blood isolates, and 30-day mortality were retrospectively collected. Patients with incomplete medical records were excluded from the analysis of mortality.

Definitions

The underlying diseases included malignancy, renal insufficiency (defined as a serum creatinine ≥ 1.4 mg/dL or the requirement for hemodialysis), diabetes mellitus, and liver cirrhosis.

The sources of bacteremia, including pneumonia, liver abscess, cholecystitis or cholangitis (biliary tract infection), and urinary tract infection, were determined by medical records, imaging studies, surgical findings, and microbiological evidence. Pneumonia probably caused by *K. pneumoniae* was defined as *K. pneumoniae* bacteremia with concurrent pulmonary findings: (1) the presence of lower respiratory tract symptoms, such as cough, dyspnea or tachypnea (respiratory rate ≥ 30 breaths/min), crackles or bronchial breathing sounds on auscultation, pleuritic chest pain, purulent sputum, hypoxemia or respiratory failure requiring mechanical ventilation, (2) new onset of abnormal radiographic findings without other significant bacteria isolated from the sputum, and (3) no evidence of other infection. Nosocomial bacteremia was defined as bacteremia onset after 48 hours of hospitalization. The *K. pneumoniae* isolates were identified and analyzed using the Bruker LT microflex MALDI-TOF mass spectrometer (Bruker Daltonics, Bremen, Germany), Department of Laboratory Medicine of CGMH, Linkou Branch [16].

Capsular serotyping and antimicrobial susceptibility testing

All isolates were cultured in Luria-Bertani medium (Difco, Becton Dickinson, Sparks, USA). All isolates were serotyped by multiplex polymerase chain reaction (PCR) using specific primers to detect the K1, K2, K5, K20, K54, and K57 serotypes, which are associated with community-acquired pyogenic liver abscess [12,13]. The primers used are listed [12,13]**.**

Antimicrobial susceptibility was determined by the disk diffusion method according to Clinical and Laboratory Standards Institute standards [17]. The 12 antimicrobial agents tested were amikacin, ceftazidime, ciprofloxacin, ceftriaxone, cefuroxime, cefazolin, ertapenem, cefepime, gentamicin, levofloxacin, ampicillin-sulbactam, and piperacillin-tazobactam. Additional testing for susceptibility to flomoxef and tigecycline was performed if the isolate was resistant to any third or fourth generation cephalosporin (i.e., ceftazidime, ceftriaxone, or cefepime). The resistance rate was calculated as follows: the total number of the isolates/the number of isolates showing resistance and intermediate resistance.

Statistical analysis

Statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous data were analyzed by Student's *t*-test. Student's *t*-test and the Chi-square test were performed to compare proportions in the two different time periods. *P* values less than 0.05 were considered statistically significant.

Results

Demographic data and clinical presentations of the patients

The clinical presentations of the patients at CGMH-Linkou from which the 150 blood isolates of *K. pneumoniae* were collected during the two different time periods, October–December, 2014 and July–

December, 2016 were compared (Table 1). However, the charts of three patients were lost due to mortality. Therefore, the data from only 147 patients were collected for the mortality analysis. There were no significant differences in the demographic data and clinical characteristics of the patients between these two time periods. The overall mortality rate was 19.7%.

In this study, diabetes mellitus was the most common underlying disease (44.0%, 66/150), closely followed by malignancy (41.3%, 62/150). The most common source of *K. pneumoniae* bacteremia was pneumonia (39/150, 26%), followed by primary bacteremia (38/150, 25.3%).

Analysis of survival according to demographics and clinical presentations

Comparison of the clinical characteristics between the surviving and non-surviving groups of patients suggested that patients with malignancies had a higher 30-day mortality rate (62.1%, 18/29; P = 0.023). However, other demographic data and underlying diseases, including diabetes mellitus, were not significantly related to 30-day mortality (Table 2).

Capsular serotypes

Among the 150 isolates, the major serotype was K1 (28/150, 18.7%), followed by K2 (14/150, 9.3%). However, 58.7% (88/150) of the isolates were of other non-PCR-typeable serotypes. Therefore, the majority of the *K. pneumoniae* infections in this study were caused by undetectable serotypes (Table 3). The serotyping did not differ according to time period.

We compared the mortality rate and capsular serotype distribution between healthcare-associated and community-acquired infections (Table 3). There was a higher percentage of K2 isolates in the community-acquired infection group and a higher percentage of non-detectable serotype isolates in the hospital-acquired infection group.

The K1 type was the most commonly detected serotype in both the diabetic and non-diabetic groups. However, the patients in the diabetic group had a significantly higher percentage of K2 (15.2%, 10/66) and K20 (9.1%, 6/66) serotype *K. pneumoniae* infections, compared to 4.8% (4/84) and 0% (0/84), respectively, in the non-diabetic group. In contrast, non-diabetic patients had a higher percentage of undetectable serotype isolates. There was no detectable relationship between serotype and mortality.

Table 1. Period comparison. Clinical characteristics of *K. pneumoniae*-infected patients enrolled between October–December 2014 and July–December 2016 were compared.

	Total N = 150 (%)	**2014 N = 50 (%)**	**2016 N = 100 (%)**	**P value**
Gender				
Female	58 (38.7)	17 (34.0)	41 (41.0)	0.478
Male	92 (61.3)	33 (66.0)	59 (59.0)	
Age, years, mean ± SD		62.4 ± 14.9	59.1 ± 20.5	0.27
≤ 18	7 (4.7)	1 (2.0)/0.0	6 (6.0)/3.0 ± 5.1	0.607
19-64	81 (54.0)	31 (62.0)/55.9 ± 6.5	50 (50.0)/51.4 ± 9.4	0.014*
≥ 65	62 (41.3)	18 (36.0)/77.1 ± 5.5	44 (44.0)/75.6 ± 8.7	0.412
Underlying disease				
Diabetes Mellitus	66 (44.0)	19 (38.0)	47 (47.0)	0.383
Cancer	62 (41.3)	22 (44.0)	40 (40.0)	0.726
Hemodialysis	12 (8.0)	7 (14.0)	5 (5.0)	0.106
Cirrhosis	23 (15.3)	10 (20.0)	13 (13.0)	0.336
Immunosuppressive agents use	26 (17.3)	6 (12.0)	20 (20.0)	0.260
Primary bacteremia	38 (25.3)	14 (28.0)	24 (24.0)	0.691
Secondary bacteremia				
Pneumonia	39 (26.0)	13 (26.0)	26 (26.0)	1.000
Liver abscess	12 (8.0)	5 (10.0)	7 (7.0)	0.535
Biliary tract infection	23 (15.3)	10 (20.0)	13 (13.0)	0.336
Urinary tract infection	22 (14.7)	5 (10.0)	17 (17.0)	0.331
Mortality	29 (19.7) (n = 147)†	13 (27.1) (n = 48)†	16 (16.2) (n = 99)†	0.128

*: Statistical significance is defined as P value < 0.05; †: Patients with incomplete medical records were excluded from the analysis of mortality; N: total; n: sub-total in this section.

Table 2. Risk factor. Clinical characteristics of *K. pneumoniae*-infected patients between surviving and non-surviving groups were compared.

	Patients number	Survival N = 118 (%)	Non-survival† N = 29 (%)	P value
Gender				
Female	58	48 (40.7)	10 (34.5)	0.672
Male	89	70 (59.3)	19 (65.5)	
Age/year, mean ± SD		59.7 ± 20.0	61.0 ± 13.6	0.734
≤ 18	7	7 (5.9) 2.6 ± 4.8	0 (0)	--
19-64	81	64 (54.2) 53.5 ± 9.0	17 (58.6) 51.5 ± 7.2	0.384
≥ 65	59	47 (39.8) 76.6 ± 8.1	12 (41.4) 74.6 ± 7.6	0.444
Underlying disease				
Diabetes Mellitus	65	53 (44.9)	12 (41.4)	0.836
Cancer	62	44 (37.3)	18 (62.1)	0.023*
Hemodialysis	12	8 (6.8)	4 (13.8)	0.254
Cirrhosis	23	17 (14.4)	6 (20.7)	0.401
Immunosuppressive agents use	26	17 (14.4)	9 (31.0)	0.054

*: Statistical significance is defined as P value < 0.05; †: 30-day mortality.

Table 3. Specific serotypes of *K. pneumoniae* associated with community-acquired and diabetes mellitus (DM). Bacteremic inpatients infected with different serotypes of K. pneumoniae were compared in terms of time period, community-acquired infection, diabetes mellitus (DM), and survival outcomes.

Serotype	Oct-Dec 2014 N = 50 (%)	Jul-Dec 2016 N = 100 (%)	P value	Community-acquired N = 62 (%)	Hospital - acquired N = 88 (%)	*P* value	DM N = 66 (%)	Non-DM N = 84 (%)	P value	Mortality# N = 29 (%)	Survival N = 118 (%)	P value
K1 N = 28	13 (26.0%)	15 (15.0%)	0.122	11 (17.7%)	17 (19.3%)	0.835	14 (21.2%)	14 (16.7%)	0.675	7 (24.1%)	21 (17.8%)	0.429
K2 N = 14	3 (6.0%)	11 (11.0%)	0.387	10 (16.1%)	4 (4.5%)	0.022*	10 (15.2%)	4 (4.8%)	0.046*	2 (6.9%)	12 (10.2%)	0.738
K20 N = 6	2 (4.0%)	4 (4.0%)	1.000	2 (3.2%)	4 (4.5%)	1.000	6 (9.1%)	0 (0%)	0.006**	1 (3.4%)	5 (4.2%)	1.000
K5 *N* = 6	1 (2.0%)	5 (5.0%)	0.664	5 (8.1%)	1 (1.1%)	0.082	4 (6.1%)	2 (2.4%)	0.406	1 (3.4%)	5 (4.2%)	1.000
K54 N = 4	3 (6.0%)	1 (1.0%)	0.108	3 (4.8%)	1 (1.1%)	0.307	1 (1.5%)	3 (3.6%)	0.631	0 (0%)	3 (2.5%)	1.000
K57 N = 4	1 (2.0%)	3 (3.0%)	1.000	3 (4.8%)	1 (1.1%)	0.307	2 (3.0%)	2 (2.4%)	1.000	1 (3.4%)	3 (2.5%)	1.000
Others N = 88	27 (54.0%)	61 (61.0%)	0.483	28 (45.2%)	60 (68.2%)	0.007**	29 (43.9%)	59 (70.2%)	< 0.001***	17 (58.6%)	69 (58.5%)	1.000

Mortality: death within 30 days of admission; *: Statistical significance is defined as *P* value < 0.05; **: *P* value < 0.01; ***: *P* value < 0.001.

Table 4. *Antimicrobial susceptibility rate.* Antibiogram patterns of *K. pneumoniae* strains isolated between October–December 2014 and July–December 2016 were compared.

Antimicrobials	Resistance		P value
	2014, N = 50 (%)	2016, N = 100 (%)	
Amikacin	1 (2.0)	4 (4.0)	0.665
Ampicillin-sulbactam	8 (16.0)	25 (25.0)	0.296
Cefazolin	21 (42.0)	54 (54.0)	0.225
Cefepime	9 (18.0)	17 (17.0)	1.000
Ceftazidime	12 (24.0)	20 (20.0)	0.673
Ceftriaxone	12 (24.0)	15 (15.0)	0.184
Cefuroxime	12 (24.0)	25 (25.0)	1.000
Ciprofloxacin	11 (22.0)	17 (17.0)	0.508
Ertapenem	0 (0)	1 (1.0)	1.000
Gentamicin	3 (6.0)	19 (19.0)	0.048*
Levofloxacin	7 (14.0)	11 (11.0)	0.602
Piperacillin-tazobactam	6 (12.0)	18 (18.0)	0.479
Flomoxef	1 (8.3) (*n* = 12)	8 (34.8) (*n* = 23)	0.121
Tigecycline	4 (33.3) (*n* = 12)	10 (43.5) (*n* = 23)	0.721

*: Statistical significance is defined as *P* value < 0.05. *N*: total; *n*: sub-total in this.

Antimicrobial resistance

The antibiograms of the *K. pneumoniae* isolates collected from the two different periods (October–December, 2014 and July–December, 2016) were analyzed and compared (Table 4). The rates of resistance to most antibiotics did not differ significantly between these two time periods. The isolates in both time periods (2014 and 2016) showed the highest rates of resistance to cefazolin (42% and 54%, respectively), and the lowest rates of resistance to ertapenem (0% and 1%, respectively), followed by amikacin (2% and 4%, respectively). Our results also demonstrated that the rate of carbapenem-resistant *K. pneumoniae* is low (1/150) in patients with bacteremia. However, significantly increasing resistance rates were noted for three antibiotics: gentamicin, flomoxef, and tigecycline, with respective increases from 6.0% to 19.0%, 8.3% to 34.8%, and 33.3% to 43.5%.

Discussion

Patients with *K. pneumoniae* bacteremia, one of the most common causes of Gram-negative bloodstream infections (BSIs) [18], are associated with high mortality rates (from 20% to 40%) [19].

Carbapenem-resistant *K. pneumoniae* (CRKP) isolates are resistant to most antibiotics resulting in few effective antibiotic options and high mortality [20,21]. Patients with bacteremia due to CRE (carbapenem-resistant *Enterobacteriaceae*) were associated with a 2-fold higher risk of fatal outcome compared to those with carbapenem-susceptible *Enterobacteriaceae* [22]. Proposed hypotheses for this increased mortality include (1) increased virulence of carbapenemase-producing isolates, (2) more severe underlying comorbidities among patients with CRE, (3) lower probability of receiving appropriate initial antibiotic therapy (IAT) in patients infected with CRE, and (4) lower effectiveness and higher toxicity of antibiotics used for treatment of these infections [23-26]. In several countries including the United States, Greece, Italy, and Israel, the rate of infections with *K. pneumoniae* resistant to all commercially available antibiotics is growing at an alarming rate [27-31]. Most of these isolates are resistant to all β-lactams due to the production of a class A carbapenemase named KPC and can also be resistant to other antibiotics of last resort such as tigecycline and colistin [32,33].

Previous hospital-based studies have suggested several comorbidities as risk factors for the development of *K. pneumoniae* bacteremia, including diabetes mellitus, cancer, chronic liver disease, and biliary disease [34]. We also found that diabetes mellitus and malignancy were the most common comorbidities. However, only malignancy was associated with the 30-day mortality rate (62.1%, 18/29; P = 0.023).

A seroepidemiological study of 1000 non-repetitive *K. pneumoniae* isolates collected by a medical center in Taiwan during 1993–1997 showed that 630 isolates (63%) were from community-acquired infections [35], and 77% of the serotypes were detectable. Serotypes K1 and K2 accounted for 21.7% and 9.3% of the isolates, respectively. The frequency of serotype K1 among bacteremic isolates (30.8%) far exceeded that reported by other investigators worldwide. In contrast, in another study of the capsular serotypes of 225 *K. pneumonia* isolates by PCR, the numbers of K1 serotypes (41 isolates) were higher among patients with community-onset bacteremia, nonfatal diseases, and liver abscesses [36]. In our study, among the serotype-detectable strains, K1 was also the predominant serotype, followed by K2, K5, and K20. An increasing percentage of K2 serotype isolates was observed among community-acquired infections. Noteworthily, 58.7% of the bacteremic isolates were untypeable in this study. The high percentage of non-detectable serotypes suggests that many new PCR-untypeable serotype isolates are emerging to cause nosocomial infections in a hospital, even to non-diabetic patients. In comparison of the clinical characteristics with serotyping in this study, it indicates that different serotype plays a unique role in specifically clinical characteristics. For example, the K2 serotype isolates tended to cause community-acquired infections and in diabetic patients, while the K20 may significantly cause infections in diabetic patients, but no correlation of community- or hospital-acquired infection was observed.

In our study, antibiotic susceptibility testing revealed that the antibiotics used for the treatment of multidrug-resistant bacterial infections should be much more carefully selected due to the recent increases in the rates of resistance to flomoxef and tigecycline. In a previous study, tigecycline-non-susceptible *K. pneumoniae* bacteremia was associated with high mortality, and the overexpression of AcrAB and/or OqxAB contributed to tigecycline non-susceptibility in *K. pneumonia* [37].

There were some limitations in this study. First, the case number was limited, as only 150 cases were collected. Second, the capsular types we detected are those that were previously detected in cases of invasive pyogenic liver abscess. These strains are not necessarily the same as those causing bacteremia, which may be the

reason for the high percentage of undetectable capsular serotypes. Lastly, this was a retrospective study.

Conclusion

Our results showed that the bacteremic K1 serotype was still the most common among the detected serotypes. Patients with *K. pneumoniae* bacteremia and cancer had a higher 30-day mortality rate than those with other comorbidities. Lastly, susceptibility to gentamicin, flomoxef, and tigecycline decreased significantly between the two time periods (2014 and 2016). This is important because flomoxef and tigecycline are mainly used for the treatment of more resistant strains and troublesome infections. Amikacin and ertapenem showing more than 96% susceptibility are the best drugs of choice to treat *K. pneumoniae* BSIs in Taiwan in contrast to high antibiotic resistance rates found in many countries in the world.

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Authors' contribution

Conception and design (PCH, YTW, CLC, CCY); acquisition of data (PCH, YTW, CLC, YLZ); analysis of data (PCH, YTW, CLC, HYL, YLZ, TSW); drafting the work (PCH, YTW, CLC, HYL, RPJ, CCY); critical revision of the work (all authors); final approval of the manuscript (all authors).

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Ethical approval

This retrospective study of clinical data was approved by the Institutional Review Board (IRB: 201601455B0) of CGMH, Linkou Branch, Taiwan.

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