Clinical characteristics, antimicrobial resistance and capsular types of community-acquired, healthcare-associated, and nosocomial *Klebsiella pneumoniae* bacteremia

Chih-Han Juan¹, Chien Chuang¹, Chi-Han Chen², Lo Li² and Yi-Tsung Lin¹,3*

**Abstract**

**Background:** *Klebsiella pneumoniae* bacteremia is a major cause of morbidity and mortality worldwide. We aimed to compare the clinical characteristics, distribution of capsular types, and antimicrobial resistance of *K. pneumoniae* bacteremia among community-acquired (CA), healthcare-associated (HCA), and nosocomial infections.

**Methods:** This retrospective study of patients with *K. pneumoniae* bacteremia was conducted at Taipei Veterans General Hospital from January to December 2015. Clinical characteristics of *K. pneumoniae* bacteremia were collected. The *K. pneumoniae* isolates were subjected to antimicrobial susceptibility testing and capsular genotyping.

**Results:** In total, 337 patients with *K. pneumoniae* bacteremia were identified: 70 (20.8%), 102 (30.3%), and 165 (48.9%) presented with CA, HCA, and nosocomial infection, respectively. The 28-day mortality of HCA bacteremia was lower than that of nosocomial bacteremia (17.6% versus 30.9%, *p* = 0.016); however, that of the HCA and CA bacteremia was similar (17.6% versus 14.3%, *p* = 0.557). CA isolates had the highest prevalence of virulent capsular types (51.4%), followed by HCA (36.3%) and nosocomial isolates (19.4%). The proportion of multidrug-resistant (MDR) isolates was highest in nosocomial infections (41.8%), followed by HCA (23.5%) and CA infections (5.7%).

**Conclusion:** CA, HCA and nosocomial *K. pneumoniae* are distinct entities, as evidenced by the differences in clinical characteristics, antimicrobial resistance, and capsular types found in this study.

**Keywords:** *Klebsiella pneumoniae*, Bacteremia, Community-acquired, Healthcare-associated, Nosocomial, Antimicrobial resistance, Capsular type

*Correspondence:* ytlin8@vghtpe.gov.tw

¹Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, Number 201, Section 2, Shih-Pai Road, Beitou District, Taipei 11217, Taiwan

²Institute of Emergency and Critical Care Medicine, National Yang-Ming University, Taipei, Taiwan

Full list of author information is available at the end of the article

© The Author(s). 2019 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

**Background**

*Klebsiella pneumoniae* bacteremia is a major cause of morbidity and mortality worldwide [1]. It is the second leading cause of gram-negative bacteremia, and its case fatality rate was 20% in a population-based study in Canada [2]. Community-acquired (CA) invasive syndromes encompass a variety of clinical presentations associated with *K. pneumoniae* bacteremia, including liver abscess and distant septic metastasis, which are seen more commonly in Taiwan and the Asian companies in comparison with Western countries. However, these syndromes were rarely reported in western countries [3]. Nosocomial *K. pneumoniae* bacteremia has been associated with a higher mortality rate than CA bacteremia [4–6], and these isolates are known for harboring resistance genes encoding expanded-spectrum β-lactams or carbapenems [7], which is less reported in CA isolates.
The presence of polysaccharide capsule is one of the most important virulence factors associated with *K. pneumoniae* [8]. Capsular types K1 and K2 are the most frequently observed virulent types and are usually associated with community-onset pyogenic infections in Asian countries [9]. Other capsular types, such as K3, K20, K54, and K57, were recently identified in individuals with community-onset pyogenic *K. pneumoniae* infections in Asian countries [10]. The capsular type K1 isolates were more common in community-onset infection than in nosocomial infection, whereas non-typeable isolates were more common in nosocomial infection than in community-onset infection in a previous study conducted in Taiwan [4]. *rmpA*, a regulator of the mucoid phenotype, and a gene known as an extracapsular polysaccharide synthesis regulator, can positively control the mucoid phenotype of *K. pneumoniae*, and it is also considered as an important virulence factor [11].

Community-onset bacteremia is classified into healthcare-associated (HCA) infections for patients who recently received healthcare services and underwent medical procedures, and CA infections for the remaining patients [12] because HCA infections were more similar to nosocomial infections in terms of clinical features and antimicrobial resistance [12]. The clinical characteristic and distribution of the capsular type of HCA *K. pneumoniae* bacteremia have been rarely reported in the literature [13–15]. Moreover, the capsular types of *K. pneumoniae* isolates among CA, HCA, and nosocomial bacteremia have never been compared.

Thus, this study aimed to compare the clinical characteristics, antimicrobial resistance, and distribution of the capsular types among CA, HCA, and nosocomial *K. pneumoniae* bacteremia. Moreover, the question of whether HCA bacteremia is a category distinct from CA and nosocomial bacteremia was also addressed.

**Methods**

**Study design and population**

This descriptive, retrospective study of consecutive patients with *K. pneumoniae* bacteremia was conducted at Taipei Veterans General Hospital, a 2900-bed tertiary-care teaching hospital in Taiwan, from January to December 2015. The study protocol was approved by the institutional review board of Taipei Veterans General Hospital.

The medical records of patients with positive blood culture for *K. pneumoniae* were reviewed, and their clinical information was obtained. CA *K. pneumoniae* bacteremia is defined as *K. pneumoniae*-positive isolates identified in patients upon admission or within 48 h of admission who did not fit the criteria for HCA bacteremia. HCA *K. pneumoniae* bacteremia is defined as *K. pneumoniae*-positive isolates identified in patients upon admission or within 48 h of admission meeting any of the following criteria [12]: having received intravenous therapy at home or in an outpatient clinic within the last 30 days; having received renal dialysis in a hospital or clinic within the last 30 days; having been hospitalized for 2 or more days within the last 90 days; or having resided in a nursing home or long-term care facility. Nosocomial *K. pneumoniae* bacteremia is defined as *K. pneumoniae*-positive isolates identified in patients more than 48 h after admission. The first blood culture of patients with two or more positive blood cultures was included, for the duration of their hospital admission. Patients < 20 years of age and those with incomplete medical records were excluded.

**Data collection**

We collected clinical information on the demographic characteristics of the patients, location at the time of culture, source of bacteremia, co-morbidities, immunosuppression, surgeries, invasive procedures or devices, surgical drainage, mechanical ventilation, antimicrobial therapy, severity of illness, outcome, and mortality. Appropriate empirical antimicrobial therapy is defined as the administration of at least one antimicrobial agent to which the causative pathogen is susceptible within 24 h of the onset of clinical sepsis at the approved route and dosage for the affected target organ(s). Appropriate definite antimicrobial therapy is defined as the administration of at least one antimicrobial agent to which the causative pathogen is susceptible after obtaining the result of the antimicrobial susceptibility test within 24 h at the approved route and dosage for the affected target organ(s). Prior antibiotic exposure is defined as at least 2 days of therapy within 30 days prior to acquiring bacteremia. We used the Pitt bacteremia score and the Acute Physiology and Chronic and Prevention Evaluation (APACHE) II score to determine the severity of illness within 24 h of the onset of bacteremia [16, 17].

**Microbiological studies**

All *K. pneumoniae* isolates were identified using matrix-assisted laser desorption-ionisation time-of-flight mass spectrometry (bioMérieux SA, Marcy l’Etoile, France). Antimicrobial susceptibility to this bacterium was determined using the VITEK2 system (bioMérieux, Marcy l’Etoile, France) and interpreted according to the guidelines of the Clinical and Laboratory Standards Institute 2017 [18]. Multidrug-resistant (MDR) *K. pneumoniae* isolate is defined as non-susceptibility to at least one agent in three or more antimicrobial categories [19].

To detect the capsular genotypes of *K. pneumoniae* isolates, we performed *cps* genotyping using the polymerase chain reaction of K-serotype-specific alleles at the *wzy* loci, including serotypes K1, K2, K5, K20, K54,
and K57 [10]. The detection of rmpA and rmpA2 genes was performed as described previously [20].

Statistical analyses
Categorical variables were compared using the chi-square or Fisher’s exact test. The analyses of continuous variables were conducted using the Student’s t test and Mann–Whitney U test (Wilcoxon rank-sum test). A two-tailed p value < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences software, version 17.0 (SPSS Inc., Chicago, IL, the USA).

Results
Clinical characteristics of the patients with CA, HCA, and nosocomial K. pneumoniae bacteremia
In total, 339 consecutive patients with K. pneumoniae bacteremia were identified and 2 (0.6%) patients were excluded due to missing data of treatment. Of which, 70 (20.8%), 102 (30.3%), and 165 (48.9%) presented with CA, HCA, and nosocomial infections, respectively. The mean age of the patients was 69.9 ± 15.3 years, and there was male predominance (n = 202, 59.9%). Among them, 67 (19.9%) had polymicrobial bacteremia. The crude 28-day mortality rate was 23.4%.

The clinical characteristics of the patients with CA, HCA, and nosocomial K. pneumoniae bacteremia are shown in Table 1. With regard to infection source, the prevalence of pneumonia (19.6% versus 5.7%, p = 0.013) and primary bacteremia (20.6% versus 7.1%, p = 0.016) was significantly higher in the HCA group than in the CA group, and that of urinary tract infection was also significantly higher in the HCA group than in the nosocomial group (17.6% versus 9.1%, p = 0.039). The prevalence of intraabdominal infection was higher in the CA group than in the nosocomial group (37.1% versus 21.8%, p = 0.015). The prevalence of liver abscess as a primary site of infection was similar between the HCA and nosocomial groups (4.9% versus 1.2%, p = 0.110), but it was lower in the HCA group than in the CA group (4.9% versus 20.0%, p = 0.002).

With regard to co-morbidities, malignancy and immunosuppression were both observed more frequently in the HCA group and nosocomial group as opposed to the CA group (48.0% versus 17.1%, p < 0.001; 40.2% versus 7.1%, p < 0.001, respectively). The prevalence of diabetes was higher among patients with HCA bacteremia than those with nosocomial bacteremia (40.2% versus 27.9%, p = 0.037). The proportion of performing invasive procedures and using medical devices was similar between the HCA and CA bacteremia groups (29.4% versus 20.0%, p = 0.165). However, a higher proportion was observed in the nosocomial bacteremia group than in the HCA bacteremia group (59.4% versus 29.4%, p < 0.001).

Prior antibiotic exposure was less common in the HCA group than the nosocomial group (29.4% versus 66.1%, p < 0.001). The low prevalence of prior antibiotic exposure was notably in the CA group (0.0%). Patients with HCA bacteremia had a higher disease severity than those with CA bacteremia, as indicated by the median APACHE II score (17.0 versus 11.0, p < 0.001), but a lower severity than those with nosocomial bacteremia (17.0 versus 19.0, p = 0.016) (Table 1).

Clinical outcomes of patients with CA, HCA, and nosocomial K. pneumoniae bacteremia
The proportion of appropriate empirical antimicrobials in the HCA group was lower than that in the CA group (89.2% versus 97.1%, p = 0.077), but higher than that in the nosocomial group (89.2% versus 80.6%, p = 0.063) with borderline statistical significance (Table 2).

The prevalence of respiratory failure requiring mechanical ventilation was higher in the HCA group than in the nosocomial group (13.7% versus 5.5%, p = 0.019). The 28-day mortality of the HCA group was significantly lower than that of the nosocomial group (17.6% versus 30.9%, p = 0.016), whereas that of the HCA and CA groups was similar (17.6% versus 14.3%, p = 0.557). The in-hospital mortality of the three groups had a similar trend.

Microbiological characteristics of the clinical isolates of CA, HCA, and nosocomial K. pneumoniae bacteremia
Table 3 depicts the antimicrobial resistance of K. pneumoniae isolates among the three groups. K. pneumoniae isolates from HCA bacteremia had a higher proportion of wild-type antibiotic susceptibility (isolates that are susceptible to several classes of antibiotics but ampicillin) than those from nosocomial bacteremia (65.7% versus 47.3%, p = 0.003). However, the proportion of wild-type antibiotic susceptibility was lower in the HCA isolates than CA isolates (65.7% versus 85.7%, p = 0.003). The proportion of MDR isolates from nosocomial infection was the highest (41.8%), followed by isolates from HCA infection (23.5%) and CA infection (5.7%) (Table 3). Similar trend among the three categories could be identified in isolates resistant to ceftriaxone, ciprofloxacin, levofloxacin, and ertapenem.

The distribution of capsular types and the presence of rmpA1/rmpA2 genes among all K. pneumoniae isolates are shown in Table 4. Of the 337 isolates of K. pneumoniae bacteremia, 105 (31.2%) belonged to the six virulent capsular types (K1, K2, K5, K20, K54, and K57), which was more common in the HCA isolates than in nosocomial isolates (36.3% versus 19.4%, p = 0.002) but less common in the HCA than in CA isolates (36.3% versus
Table 1 Clinical characteristics of patients with community-acquired (CA), healthcare-associated (HCA), and nosocomial *K. pneumoniae* bacteremia

| Variable                                      | CA (n = 70) | HCA (n = 102) | Nosocomial (n = 165) | p value CA vs. HCA | HCA vs. Nosocomial | CA vs. Nosocomial |
|-----------------------------------------------|-------------|---------------|----------------------|--------------------|--------------------|------------------|
| **Demographics**                              |             |               |                      |                    |                    |                  |
| Age, (Mean ± SD), years                       | 71.43 ± 13.64 | 72.37 ± 14.39 | 67.71 ± 16.32        | 0.696              | 0.031              | 0.122            |
| Gender, male                                  | 37 (52.9)   | 70 (68.6)     | 95 (57.6)            | 0.036              | 0.071              | 0.505            |
| Days of hospitalization prior to culture, median (IQR), days | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 14.0 (6.0–25.0)      | N/A                | < 0.001            | < 0.001          |
| Polymicrobial infection                       | 12 (17.1)   | 16 (15.7)     | 40 (24.2)            | 0.799              | 0.095              | 0.231            |
| Primary site of infection                     |             |               |                      |                    |                    |                  |
| Pneumonia                                     | 4 (5.7)     | 20 (19.6)     | 36 (21.8)            | 0.013              | 0.666              | 0.002            |
| Urinary tract                                 | 14 (20.0)   | 18 (17.6)     | 15 (9.1)             | 0.697              | 0.039              | 0.200            |
| Intra-abdomen^a                               | 26 (37.1)   | 32 (31.4)     | 36 (21.8)            | 0.432              | 0.082              | 0.015            |
| Liver abscess                                 | 14 (20.0)   | 5 (4.9)       | 2 (1.2)              | 0.002              | 0.110              | < 0.001          |
| Skin and soft tissue                          | 2 (2.9)     | 1 (1.0)       | 4 (2.4)              | 0.567              | 0.652              | 1.000            |
| Intravenous catheter                          | 0 (0.0)     | 1 (1.0)       | 8 (4.8)              | 1.000              | 0.160              | 0.109            |
| Primary bacteremia                            | 5 (7.1)     | 21 (20.6)     | 60 (36.4)            | 0.016              | 0.006              | < 0.001          |
| Disseminated infection                        | 4 (5.7)     | 4 (3.9)       | 2 (1.2)              | 0.717              | 0.206              | 0.066            |
| **Underlying disease**                        |             |               |                      |                    |                    |                  |
| Malignancy                                    | 12 (17.1)   | 49 (48.0)     | 95 (57.6)            | < 0.001            | 0.129              | < 0.001          |
| Diabetes mellitus                             | 27 (38.6)   | 41 (40.2)     | 46 (27.9)            | 0.830              | 0.037              | 0.105            |
| Chronic kidney disease                        | 28 (40.0)   | 35 (34.3)     | 57 (34.5)            | 0.447              | 0.969              | 0.426            |
| Hemodialysis                                  | 0 (0.0)     | 5 (4.9)       | 15 (9.1)             | 0.081              | 0.206              | 0.007            |
| Congestive heart failure                      | 4 (5.7)     | 13 (12.7)     | 14 (8.5)             | 0.193              | 0.262              | 0.597            |
| Liver cirrhosis                               | 6 (8.6)     | 10 (9.8)      | 14 (8.5)             | 0.785              | 0.714              | 0.983            |
| Cerebral vascular disease                     | 7 (10.0)    | 15 (14.7)     | 28 (17.0)            | 0.364              | 0.625              | 0.170            |
| Chronic obstructive lung disease              | 2 (2.9)     | 7 (6.9)       | 6 (3.6)              | 0.313              | 0.234              | 1.000            |
| Collagen vascular disease                     | 2 (2.9)     | 3 (2.9)       | 6 (3.6)              | 1.000              | 1.000              | 1.000            |
| Transplantation                               | 1 (1.4)     | 4 (3.9)       | 5 (3.0)              | 0.649              | 0.735              | 0.672            |
| Immunosuppression^b                           | 5 (7.1)     | 41 (40.2)     | 69 (41.8)            | < 0.001            | 0.794              | < 0.001          |
| **Invasive procedures and devices at onset of bacteremia** | 14 (20.0) | 30 (29.4) | 98 (59.4) | 0.165 | < 0.001 | < 0.001 |
| Central venous catheter                       | 1 (1.4)     | 3 (2.9)       | 45 (27.3)            | 0.647              | < 0.001            | < 0.001          |
| Nasogastric/Nasojejunal tube                  | 9 (12.9)    | 21 (20.6)     | 72 (43.6)            | 0.189              | < 0.001            | < 0.001          |
| Urinary catheter                              | 8 (11.4)    | 16 (15.7)     | 53 (32.1)            | 0.429              | 0.003              | 0.001            |
| Endotracheal tube^c                           | 1 (1.4)     | 2 (2.0)       | 24 (14.5)            | 1.000              | < 0.001            | 0.002            |
| Tracheostomy                                  | 1 (1.4)     | 0 (0.0)       | 18 (10.9)            | 0.407              | < 0.001            | 0.016            |
| Surgical drainage                             | 0 (0.0)     | 0 (0.0)       | 16 (9.7)             | N/A                | < 0.001            | 0.004            |
| Surgery within 2 weeks                        | 0 (0.0)     | 5 (4.9)       | 32 (19.4)            | 0.081              | 0.001              | < 0.001          |
| **Prior antibiotic exposure**                 |             |               |                      |                    |                    |                  |
| Any antibiotic                                | 0 (0.0)     | 30 (29.4)     | 109 (66.1)           | < 0.001            | < 0.001            | < 0.001          |
| 1st or 2nd generation cephalosporin^d         | 0 (0.0)     | 16 (15.7)     | 46 (27.9)            | < 0.001            | 0.022              | < 0.001          |
| 3rd or 4th generation cephalosporin^e         | 0 (0.0)     | 4 (3.9)       | 25 (15.2)            | 0.147              | 0.004              | < 0.001          |
| β-lactam and β-lactamase inhibitor^f          | 0 (0.0)     | 11 (10.8)     | 55 (33.3)            | 0.003              | < 0.001            | < 0.001          |
| Carbapenem^g                                  | 0 (0.0)     | 5 (4.9)       | 31 (18.8)            | 0.081              | 0.001              | < 0.001          |
| Fluoroquinolone^h                             | 0 (0.0)     | 4 (3.9)       | 23 (13.9)            | 0.147              | 0.011              | < 0.001          |
The distribution of capsular type K1/K2 among the three groups had a similar trend. The rate of rmpA and rmpA2 genes was higher in the HCA isolates than in the nosocomial isolates (38.2% versus 21.8%, \( p = 0.004 \), 36.3% versus 21.2%, \( p = 0.007 \), respectively), but lower in the CA isolates (38.2% versus 60.0%, \( p = 0.005 \), 36.3% versus 58.6%, \( p = 0.004 \), respectively). Moreover, several MDR isolates \((n = 12, 3.5\%)\) also belonged to the virulent capsular types and they were similarly distributed among the three categories \(n = 2 (2.9\%)\) in the CA bacteremia group, \(n = 3 (2.9\%)\) in the HCA bacteremia group, and \(n = 7 (4.2\%)\) in the nosocomial bacteremia group.

**Discussion**

The mortality of HCA *K. pneumoniae* bacteremia was comparable to that of CA bacteremia but significantly lower than that of nosocomial bacteremia. The rate of MDR phenotype, virulent capsular types and rmpA/rmpA2 genes in the isolates from HCA bacteremia was between those from CA and nosocomial bacteremia. The rate of isolates with virulent capsular types

---

### Table 1 Clinical characteristics of patients with community-acquired (CA), healthcare-associated (HCA), and nosocomial *K. pneumoniae* bacteremia (Continued)

| Variable                        | CA (n = 70) | HCA (n = 102) | Nosocomial (n = 165) | \( p \) value |
|---------------------------------|-------------|---------------|----------------------|--------------|
|                                 |             |               |                      | CA vs. HCA   | HCA vs. Nosocomial | CA vs. Nosocomial |
| Aminoglycoside                  | 0 (0.0)     | 1 (1.0)       | 9 (5.5)              | 1.000        | 0.095              | 0.061              |
| Tigecycline                     | 0 (0.0)     | 1 (1.0)       | 12 (7.3)             | 1.000        | 0.020              | 0.020              |
| Glycopeptide                    | 0 (0.0)     | 1 (1.0)       | 20 (12.1)            | 1.000        | 0.001              | 0.001              |
| Metronidazole                   | 0 (0.0)     | 2 (2.0)       | 11 (6.7)             | 0.514        | 0.140              | 0.037              |
| Pitt bacteremia score, median (IQR) | 1.0 (0.0–2.0) | 1.0 (0.0–3.0) | 2.0 (0.0–4.0)      | 0.517        | 0.054              | 0.012              |
| APACHE II score, median (IQR)   | 11.0 (9.0–16.0) | 17.0 (11.0–22.0) | 19.0 (14.0–24.0)     | < 0.001     | 0.016              | < 0.001             |

Data are presented as number (%) of patients, unless stated otherwise

SD standard deviation, IQR interquartile range, APACHE Acute Physiology And Chronic Health Evaluation, N/A not applicable

\( ^{a} \)Intra-abdominal infection was defined as infections of single organs of abdomen with or without extension into the peritoneal space with exclusion of liver abscess

\( ^{b} \)Immunosuppression was defined as meeting one of the following criteria: neutropenia, use of corticosteroids, or receiving chemotherapy

\( ^{c} \)Endotracheal tube was defined as patient being intubated at the onset of bacteremia

\( ^{d} \)Including cefazolin and cefuroxime

\( ^{e} \)Including cefoperazone, cefotaxime, cefepime, and ceftiraxone

\( ^{f} \)Including amoxicillin/clavulanate, ampicillin/sublactam, piperacillin/tazobactam, and ticarcillin/clavulanate

\( ^{g} \)Including etrapenem, imipenem, meropenem, and doripenem

\( ^{h} \)Including ciprofloxacin, levofloxacin, and moxifloxacin

\( ^{i} \)Including amikacin, gentamicin and isepamicin

\( ^{j} \)Including vancomycin and teicoplanin

---

### Table 2 Clinical outcomes of patients with community-acquired (CA), healthcare-associated (HCA), and nosocomial *K. pneumoniae* bacteremia

| Variable                                   | CA (n = 70) | HCA (n = 102) | Nosocomial (n = 165) | \( p \) value |
|--------------------------------------------|-------------|---------------|----------------------|--------------|
|                                            |             |               |                      | CA vs. HCA   | HCA vs. Nosocomial | CA vs. Nosocomial |
| Appropriate empirical antimicrobial therapy | 68 (97.1)   | 91 (89.2)     | 133 (80.6)           | 0.077        | 0.063              | < 0.001             |
| Appropriate definite antimicrobial therapy | 65 (92.9)   | 93 (91.2)     | 138 (83.6)           | 0.692        | 0.080              | 0.059              |
| Length of stay after bacteremia, median (IQR), days | 14.0 (8.0–23.8) | 16.0 (9.8–28.0) | 17.0 (7.0–30.5)     | 0.191        | 0.685              | 0.406              |
| Septic shock when bacteremia              | 15 (21.4)   | 35 (34.3)     | 58 (35.2)            | 0.068        | 0.889              | 0.038              |
| Respiratory failure requiring mechanical ventilation | 6 (8.6) | 14 (13.7)     | 9 (5.5)              | 0.300        | 0.019              | 0.371              |
| Mortality                                  |             |               |                      |              |                    |                    |
| In-hospital mortality                      | 12 (17.1)   | 25 (24.5)     | 67 (40.6)            | 0.248        | 0.007              | < 0.001             |
| Crude 28-day mortality                    | 10 (14.3)   | 18 (17.6)     | 51 (30.9)            | 0.557        | 0.016              | 0.008              |

Data are presented as number (%) of patients, unless stated otherwise

IQR interquartile range, ICU intensive care unit
capsular types in HCA infection was comparable to that in CA infection. However, the rate of MDR phenotype in HCA infection was higher than that in CA infection. Our findings support that HCA bacteremia is a category distinct from CA and nosocomial bacteremia in terms of the clinical and microbiological features, which was addressed in the previous study [12].

The clinical characteristics of CA, HCA, and nosocomial K. pneumoniae bacteremia have rarely been compared [2]. Meatherall et al. have found that among the 640 cases of K. pneumoniae bacteremia in Canada, 43, 30, and 27% were HCA, CA, and nosocomial infections, respectively [2]. Meatherall et al. only compared the primary source of infection among the three groups. The comparison of antimicrobial resistance and capsular types among the three groups were lacking. In the current study, we used similar definition to define HCA bacteremia, and 30.3% were classified as HCA infection. With regard to the foci of infection, the rates of liver abscess were 2.3% among all patients with bacteremia in Canada [2], and 6.2% among all patients with bacteremia in our study. Moreover, it was higher in the CA group (20.0%) than in the other two groups (4.9% in the HCA group, 1.2% in the nosocomial group).

### Table 3

| Variable                      | CA (n = 70) | HCA (n = 102) | Nosocomial (n = 165) | p value |
|-------------------------------|-------------|--------------|---------------------|---------|
|                               |             |              |                     | CA vs. HCA | HCA vs. Nosocomial | CA vs. Nosocomial |
| Amikacin                      | 0 (0.0)     | 1 (1.0)      | 7 (4.2)             | 1.000     | 0.160             | 0.107             |
| Gentamicin                    | 1 (1.4)     | 15 (14.7)    | 35 (21.2)           | < 0.001   | 0.003             | < 0.001           |
| Cefuroxime                    | 2 (2.9)     | 23 (22.5)    | 67 (40.6)           | < 0.001   | 0.002             | < 0.001           |
| Ceftriaxone                   | 1 (1.4)     | 12 (11.8)    | 52 (31.5)           | 0.016     | < 0.001           | < 0.001           |
| Cefepime                      | 0 (0.0)     | 6 (5.9)      | 24 (14.5)           | 0.082     | 0.029             | < 0.001           |
| Ciprofloxacin                 | 1 (1.4)     | 11 (10.8)    | 49 (29.7)           | 0.029     | < 0.001           | < 0.001           |
| Levofloxacin                  | 1 (1.4)     | 11 (10.8)    | 48 (29.1)           | 0.029     | < 0.001           | < 0.001           |
| Ertapenem                     | 0 (0.0)     | 7 (6.9)      | 27 (16.4)           | 0.042     | 0.024             | < 0.001           |
| Imipenem                      | 0 (0.0)     | 1 (1.0)      | 14 (8.5)            | 1.000     | 0.011             | 0.012             |
| Tigecycline                   | 2 (2.9)     | 3 (2.9)      | 5 (3.0)             | 1.000     | 1.000             | 1.000             |
| Trimethoprim-sulfamethoxazole | 5 (7.1)     | 25 (24.5)    | 61 (37.0)           | 0.003     | 0.034             | < 0.001           |
| Wild-type antibiotic susceptibilitya | 60 (85.7) | 67 (65.7)    | 78 (47.3)           | 0.003     | 0.003             | < 0.001           |
| Multidrug resistanceb         | 4 (5.7)     | 24 (23.5)    | 69 (41.8)           | 0.002     | 0.002             | < 0.001           |

Data are presented as number (%) of isolates resistant to the antibiotic indicated, unless stated otherwise.

aWild-type antibiotic susceptibility was defined in the isolates as susceptibility to all antibiotics except for ampicillin.
bMultidrug resistance was defined in the isolates as nonsusceptibility to at least one agent in three or more antimicrobial categories.

### Table 4

| Microbiological characteristic                      | CA (n = 70) | HCA (n = 102) | Nosocomial (n = 165) | p value |
|-----------------------------------------------------|-------------|--------------|---------------------|---------|
|                                                     |             |              |                     | CA vs. HCA | HCA vs. Nosocomial | CA vs. Nosocomial |
| Capsular type K1                                    | 12 (17.1)   | 10 (9.8)     | 8 (4.8)             | 0.157     | 0.117             | 0.002             |
| Capsular type K2                                    | 13 (18.6)   | 12 (11.8)    | 9 (5.5)             | 0.213     | 0.063             | 0.002             |
| Capsular type K1 and K2                             | 25 (35.7)   | 22 (21.6)    | 17 (10.3)           | 0.041     | 0.011             | < 0.001           |
| Capsular type K1, K2, K5, K20, K54, and K57        | 36 (51.4)   | 37 (36.3)    | 32 (19.4)           | 0.048     | 0.002             | < 0.001           |
| Isolates with both antimicrobial resistancea and capsular type K1, K2, K5, K20, K54, and K57 | 2 (2.9)     | 6 (5.9)      | 9 (5.5)             | 0.475     | 0.883             | 0.513             |
| Isolated with both multidrug resistanceb and capsular type K1, K2, K5, K20, K54, and K57 | 2 (2.9)     | 3 (2.9)      | 7 (4.2)             | 1.000     | 0.746             | 1.000             |
| Presence of plasmid rmpA                            | 42 (60.0)   | 39 (38.2)    | 36 (21.8)           | 0.005     | 0.004             | < 0.001           |
| Presence of plasmid rmpA2                           | 41 (58.6)   | 37 (36.3)    | 35 (21.2)           | 0.004     | 0.007             | < 0.001           |

aAntimicrobial resistance is defined as non-susceptibility to at least one antimicrobial agent in addition to ampicillin.
bMultidrug resistance is defined as non-susceptibility to at least one agent in three or more antimicrobial categories.
abscess was more common in East Asia than western countries. Our results underscored the endemic nature of K. pneumoniae liver abscess in Taiwan [9, 21, 22].

Our previous study conducted from 2007 to 2010 showed that patients with HCA K. pneumoniae bacteremia had a higher infection-related mortality than CA K. pneumoniae bacteremia (31.7% versus 13.5%, p < 0.001) [13]. In a study conducted in Korea from 2003 to 2008, the 30-day mortality rate of HCA K. pneumoniae bacteremia was higher than that of CA K. pneumoniae bacteremia (22.4% versus 11.3%, p = 0.001) [14]. However, HCA bacteremia was not associated with a significantly higher 28-day mortality than CA bacteremia in the current study (17.6% versus 14.3%, p = 0.557). HCA bacteremia is rising in prominence and physicians are becoming more familiar with this category, which may contribute to a lower threshold for investigation and detection bias resulting in improved prognosis. Furthermore, the mortality of patients with HCA bacteremia was significantly lower than those with nosocomial bacteremia. In the literature, nosocomial K. pneumoniae bacteremia is usually associated with a higher mortality than community-onset K. pneumoniae bacteremia [4].

Our study re-emphasized the severity and grave prognosis of nosocomial K. pneumoniae bacteremia.

In the present study, nosocomial isolates are still notorious for the highest rate of resistance (52.7%). The proportion of CA isolates that did not display wild-type susceptibility (14.2%) was similar to that (14.9%) in our previous study conducted from 2007 to 2010 [13]. However, HCA isolates also had a higher rate of antimicrobial resistance that is indicated by non-wild-type susceptibility (34.3%) than HCA isolates (20.7%) in our previous study [13]. It might be caused by the increased exposure to antimicrobials in the hospital environments that would promote the selection pressure for antimicrobial resistance. It may also suggest that more drug-resistant K. pneumoniae have spread to the community or the wild-type strains have evolved and became resistant. The characterization of HCA bacteremia isolates might be helpful in choosing an empirical antimicrobial therapy, as supported by the original intention. Moreover, the surveillance of the resistance pattern of HCA isolates can help in monitoring the development of drug-resistant K. pneumoniae in the community.

Tsay et al. have previously compared the serotypes of community-onset and nosocomial K. pneumoniae bacteremia strains [4]. The serotype K1 strain was more frequently observed in community-onset infections than in nosocomial infections (29.7% versus 14.0%, p = 0.02), and the non-typeable strains were more prevalent in nosocomial infections than in community-onset infections (75.0% versus 55.3%, p = 0.01) [4]. Cubero et al. have recently investigated the molecular epidemiology of CA, HCA, and nosocomial K. pneumoniae bacteremia via multi-locus sequence typing and pulsed-field gel electrophoresis in Spain [23]. However, data on the capsular types were lacking. This study first showed that CA K. pneumoniae isolates had the highest rate of virulent capsular types (K1, K2, K5, K20, K54, and K57), followed by the HCA isolates, whereas the nosocomial isolates had the lowest rate of virulent capsular types among the three categories. The distribution of K. pneumoniae isolates with rmpA/rmpA2 genes among CA, HCA, and nosocomial bacteremia was similar to that of the virulent capsular types. Classic K. pneumoniae and hypervirulent K. pneumoniae strains were proposed as the two different pathotypes of K. pneumoniae recently [24]. Hypervirulent K. pneumoniae were primarily responsible for community-onset pyogenic infections in Taiwan, and classic K. pneumoniae with antimicrobial resistance usually involved in nosocomial infections. The presence of rmpA/rmpA2 genes and virulent capsular types were usually associated with hypervirulent strains. The current findings support the unique microbiological features between nosocomial versus CA strains. Notably, approximately 19.4% of the nosocomial strains belonged to these virulent capsular types. This is of concern that these virulent strains are spreading and no longer restricted in the community. The virulent strains in hospitals must be monitored to prevent fatal outcomes among susceptible patients. The occurrence of virulent strains in HCA bacteremia might indicate the transmission between community and hospital. The active molecular screening of capsular genotypes and rmpA in K. pneumoniae isolates in hospitals might be an effective strategy in controlling and preventing the spread of infection.

The present study had several limitations. First, incomplete medical records excluded a certain proportion of the total population that should have been included. However, only 2 patients were excluded accounting for very low proportion (0.6%) of the total population. Second, the absence of evidence pertaining to prior antibiotic exposure does not equate to evidence of absence, especially in the CA and HCA K. pneumoniae bacteremia patients. Third, the difference of mortality rates among the three categories might be related to confounding variables that differed significantly and multivariate analysis was not performed to investigate mortality rates further. Fourth, we did not perform multilocus sequence typing of K. pneumoniae isolates to delineate the clonal distribution and genetic diversity among CA, HCA, and nosocomial bacteremia. Finally, our study was conducted in a single tertiary-care teaching hospital where the patient populations, clinical practice, and treatment outcome may differ from those in other non-tertiary-care hospitals. Thus, the results may not be generalizable.
Conclusions

HCA *K. pneumoniae* bacteremia is a category distinct from CA and nosocomial infections in terms of clinical and microbiological features. The characterization of the clinical characteristics of CA, HCA, and nosocomial bacteremia will help professionals to better manage patients. Further studies on the microbiological characteristics of HCA strains must be conducted to accurately identify the transmission of virulent or antimicrobial-resistant strains between community and hospital. We also encourage further studies from different geographical locations to assess the global distribution and trends in this research topic.

Abbreviations

APACHE: Acute physiology and chronic and prevention evaluation; CA: Community-acquired; HCA: Healthcare-associated; MDR: Multidrug-resistant; SPSS: Statistical package for the social sciences

Acknowledgements

We thank the Medical Science and Technology Building of Taipei Veterans General Hospital for providing experimental space and facilities. This study was presented in part at the 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) in Vienna, Austria, 22-25 April, 2017 (Abstract number: 2653).

Funding

This study was partly supported by grants from the Ministry of Science and Technology in Taiwan (MOST 105–2628-B-010-015-MY3), the Taipei Veterans General Hospital (V107C-081), Taipei Veterans General Hospital-National Yang-Ming University Excellent Physician Scientists Cultivation Program (106-V-B-027), and the Szu-Yuan Research Foundation of Internal Medicine.

Availability of data and materials

All materials and data analyzed during this study are contained within the manuscript.

Authors’ contributions

C-HJ and Y-TRL participated in the design, analysis of data, and writing of the manuscript. Y-TRL participated in the laboratory experiment. C-HJ, C-HC, CC, LL, and Y-TRL participated in the data collection. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital (protocol number 2016–05-009CC). No written informed consent was acquired due to the retrospective nature of the study and the information was de-linked.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

1Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, Number 201, Section 2, Shih-Pai Road, Beitou District, Taipei 11217, Taiwan. 2Department of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan. 3Institute of Emergency and Critical Care Medicine, National Yang-Ming University, Taipei, Taiwan.

Received: 24 August 2018 Accepted: 25 October 2018
Published online: 03 January 2019

References

1. Juan CH, Huang YW, Lin YT, Yang TC, Wang FD. Rok factors, outcomes, and mechanisms of tigecycline-nonsusceptible *Klebsiella pneumoniae* bacteremia. Antimicrob Agents Chemother. 2016;60:7357–63.
2. Matherill BL, Gregson D, Ross T, Pitout JD, Laupland KB. Incidence, risk factors, and outcomes of *Klebsiella pneumoniae* bacteremia. Am J Med. 2009;122:866–73.
3. Ko WC, Paterson DL, Sagnimeni AJ, Hansen DS, Von Gottberg A, Mohapatra S, et al. Community-acquired *Klebsiella pneumoniae* bacteremia: global differences in clinical patterns. Emerg Infect Dis. 2002;8:160–6.
4. Tsay RW, Su LK, Fung CP, Chang FY. Characteristic of bacteremia between community-acquired and nosocomial *Klebsiella pneumoniae* infection. Arch Intern Med. 2002;162:1021–7.
5. Yinnon AM, Butnaru A, Raveh D, Jerassy Z, Rudensky B. *Klebsiella* bacteremia: community versus nosocomial infection. JIM. 1996;89:933–41.
6. Watanakunakorn C, Jura J. *Klebsiella* bacteremia: a review of 196 episodes during a decade (1980–1989). Scand J Infect Dis. 1991;13:399–405.
7. Navon-Venezia S, Kondratevya K, Carattoli A. *Klebsiella* spp: a major worldwide source and shutsle for antibiotic resistance. FEMS Microbiol Rev. 2017;41:252–75.
8. Podschan R, Ullmann U. *Klebsiella* spp. as nosocomial pathogens: epidemiology, taxonomy, typing methods, and pathogenicity factors. Clin Microbiol Rev. 1998;11:589–603.
9. Siu LK, Yeh KM, Lin JC, Fung CP, Chang FY. *Klebsiella pneumoniae* liver abscess: a new invasive syndrome. Lancet Infect Dis. 2012;12:881–7.
10. Fang CT, Lai SY, Yi WC, Hsueh PR, Liu KL, Chang SC. *Klebsiella pneumoniae* genotype K1: an emerging pathogen that causes septic ocular or central nervous system complications from pyogenic liver abscess. Clin Infect Dis. 2007;45:284–93.
11. Yu WL, Ko WC, Cheng KC, Lee HC, Ke DS, Lee CC, et al. Association between *rmpA* and *mga* genes and clinical syndromes caused by *Klebsiella pneumoniae* bacteremia. Clin Infect Dis. 2006;42:1351–8.
12. Friedman MD, Kaye KS, Stout JE, McGary SA, Trivette SL, Briggs JP, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med. 2002;137:791–7.
13. Wu HS, Wang FD, Tseng CP, Wu TH, Lin YT, Fung CP. Characteristics of healthcare-associated and community-acquired *Klebsiella pneumoniae* bacteremia in Taiwan. J Inf Secur. 2012;64:162–8.
14. Jung Y, Lee MJ, Sin HY, Kim NH, Hwang JH, Park J, et al. Differences in characteristics between healthcare-associated and community-acquired infection in community-onset *Klebsiella pneumoniae* bloodstream infection in Korea. BMC Infect Dis. 2012;12:239.
15. Lin YT, Wang YP, Wang FD, Fung CP. Community-onset *Klebsiella pneumoniae* pneumonia in Taiwan: clinical features of the disease and associated microbiological characteristics of isolates from pneumonia and nasopharynx. Front Microbiol. 2015;6:1222.
16. Paterson DL, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, et al. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial infections. Ann Intern Med. 2004;140:26–32.
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13:818–29.
18. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: 27th informational supplement. CLSI document M100-S27. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.
19. Magiorakos AP, Srinivasan A, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18:268–81.
20. Hsu CR, Lin TL, Chen YC, Chou HC, Wang JT. The role of *Klebsiella pneumoniae* *rmpA* in capsular polysaccharide synthesis and virulence revisited. Microbiology. 2011;157:3446–57.
21. Tsai FC, Huang YT, Chang LY, Wang JT. Pyogenic liver abscess as endemic disease, Taiwan. Emerg Infect Dis. 2008;14:1592–600.
22. Fung CP, Chang FY, Lee SC, Hu BS, Kuo Bi, Liu CY, et al. A global emerging disease of Klebsiella pneumoniae liver abscess: is serotype K1 an important factor for complicated endophthalmitis? Gut. 2002;50:420–4.
23. Cubero M, Grau I, Tubau F, Pallarés R, Domínguez MA, Liñares J, et al. Molecular epidemiology of Klebsiella pneumoniae strains causing bloodstream infections in adults. Microb Drug Resist. 2018;24:949–57.
24. Sellick JA, Russo TA. Getting hypervirulent Klebsiella pneumoniae on the radar screen. Curr Opin Infect Dis. 2018;31:341–6.