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ORIGINAL ARTICLE

Occult *Klebsiella pneumoniae* bacteremia at emergency department: A single center experience

Eileen Kevyn Chang [a], Kai-Liang Kao [b], Mao-Song Tsai [a], Chia-Jui Yang [a,c], Yu-Tsung Huang [a], Chia-Ying Liu [a], Chun-Hsing Liao [b,c,*]

[a] *Department of Infectious Diseases, Internal Medicine, Far Eastern Memorial Hospital, New Taipei City, Taiwan*
[b] *Department of Pediatrics, Far Eastern Memorial Hospital, New Taipei City, Taiwan*
[c] *College of Medicine, Yang-Ming University, Taipei, Taiwan*

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Abstract *Background/Purpose:* Patients with undetected bacteremia when discharged from a hospital are considered to have occult bacteremia. *Klebsiella pneumoniae* bacteremia (KPB) is endemic to Taiwan. Our purpose was to study the impact of occult KPB.
Methods: We retrospectively reviewed the records of patients who were discharged from our emergency department (ED) and subsequently diagnosed with KPB (occult bacteremia), from January 2008 to March 2014. All patients are followed for at least 3 months after the index ED visit. The study group was compared to KPB patients who were directly hospitalized (DH) from ED in 2008. Thirty-day mortality was the primary endpoint.
Results: A total of 913 patients were admitted to our ED with KPB, and 88 of these patients (9.6%) had occult KPB. Among them, 43 had second ED visit and 41 were admitted. The overall 30-day mortality was 2.3%. Relative to patients with occult KPB, DH patients had more respiratory tract infections ($p < 0.001$) but fewer other intra-abdominal infections ($p = 0.015$). Liver abscess was the major diagnosis for the second ED visit (37.2%). DH patients had significantly greater 30-day mortality than that of overall patients with KPB (19.2% vs.2.3%, $p < 0.001$).

* Corresponding author. Department of Internal Medicine, Far Eastern Memorial Hospital, 21 Nan-Ya South Road, Section 2, Banchiao, New Taipei City, Taiwan.
E-mail address: liaochunhsing@gmail.com (C.-H. Liao).

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Conclusion: Most patients with occult KPB had favorable outcomes, but about half of them required a second ED visit. Clinicians should aggressively follow patients with occult KPB and should seek to identify the focus of infection in this endemic area.

Introduction

Fever is one of the most common symptoms of patients admitted to emergency departments (EDs). Blood cultures are essential for investigation of febrile illnesses[1] because the results can identify the infectious species and guide treatment protocol. Moreover, a positive blood culture may indicate severe disease.[2]

Blood culture is performed by taking samples and inoculation into bottles with culture media.[3] It takes time to detect microorganism growth, and also the further processing and identification of microorganisms is time consuming. However, physicians face decisions regarding admission or discharge of ED patients based on clinical observations. Patients with undetected bacteremia who are discharged are considered to have occult bacteremia.[4–6]

Previous studies have examined the frequency of occult bacteremia at EDs,[2,4–6] and the outcomes of discharged pediatric patients with *Streptococcus pneumoniae* bacteremia.[7–10] Other studies have reported cases of occult *Staphylococcus aureus* bacteremia, and indicated that such patients have an increased 30-day mortality rate.[11] Additional studies have reported cases of occult *Escherichia coli* bacteremia.[2,4,6,12,13] However, little is known about the foci of infection and prognosis of occult bacteremia from *Klebsiella pneumoniae*. Although uncommon in English literature, community-acquired *K. pneumoniae* bacteremia (KPB) is endemic in Taiwan.[1,3,14–16] It can cause severe metastatic infections, such as endophthalmitis, osteomyelitis, and brain abscess, that may have severe consequences and long-term sequelae. *K, pneumoniae*-related liver abscess is also endemic in Taiwan, and this can be a source of distal metastatic infections. Two studies have described the economic consequences of *K. pneumoniae* liver abscesses in the endemic area that lead to prolonged hospitalization.[17,18]

Little is known about occult KPB, but there are concerns about the increasing morbidity and mortality due to its delayed diagnosis and treatment at EDs. We conducted a retrospective study to evaluate the impact of occult KPB on ED patients at a single ED in Taiwan.

Methods

Setting and patients

We conducted a retrospective study by reviewing the records of all patients who presented to the ED of the Far Eastern Memorial Hospital (New Taipei City, Taiwan) with KPB from January 2008 to March 2014. The ED of this hospital provides a range of services including medical, surgical, pediatric, and other care in diverse specialties. This ED has 38 temporary beds and admits an average of more than 300 patients per day. The attending physician at the ED decides whether collection of a blood sample for culture is necessary. All microbiology samples were processed in a central laboratory. The BACTEC 9240 automated detection blood culture system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA) was used for blood culturing. All bottles with positive results were examined by Gram's staining, and then subcultured. Species identification was performed using biochemical methods.[19] Susceptibility of isolates to different antibiotics was determined by the disk diffusion method, according to the criteria of the Clinical and Laboratory Standards Institute.[20,21]

We obtained a complete list of cases of bacteremia from the hospitals microbiology database. All enrolled patients had occult KPB, defined as positive blood cultures for *K. pneumoniae* at the ED, but no direct hospitalization (DH).[6] Patients with short ED stay due to critical conditions and discharged and those who died within 24 hours at ED were excluded.

Clinical parameters and definitions

Underlying diseases, initial diagnoses, etiology of bacteremia, presence and duration of antibiotic use, tubular or surgical drainage, morbidities,[13] long-term complications, and survival were determined from chart review. In basic surveillance, we identified demographic features and possible risk factors for KPB, including presence or poor control of type-2 diabetes mellitus (DM; random glucose $>$ 200 mg/dL or HbA1c $>$ 8%), gastrointestinal tract abnormalities, and urinary tract abnormalities. Initial symptoms and diagnosis, antibiotic prescriptions, and time since the first ED visit were also recorded. Pittsburgh bacteremia score was obtained from the index ED event. The duration between the first and second ED visits was documented; if there was no second ED visit, the next outpatient department visit was documented. The following were recorded at the second visit: vital signs, presentations, diagnosis; presence of organ failure during the ED stay (acute kidney injury: serum creatinine concentration $>$ 30% above baseline; hepatic damage: bilirubin $>$ 2 mg/dL if it was normal at baseline, or a rise of the absolute level $>$ 0.5 mg/dL; respiratory failure: requirement for mechanical ventilation; hemodynamic failure: documented shock status or requirement for vasopressors; and central nervous system failure: new-onset altered mental status); and the transfer to a regular ward or an intensive care unit (ICU). Further

examinations that determined the focus of infection, presence of persistent bacteremia, and antibiotic resistance pattern were documented. The focus of infection was determined retrospectively for patients who were not hospitalized according to all available evidence. When a clear focus of infection was not identified, it was classified as primary bacteremia.

Total hospitalization time, ICU admission (if applicable), and invasive procedures were documented for morbidity analysis.[13,14] We also performed follow-ups at least 3 months after admission to determine the presence of recurrent bacteremia. The primary endpoint was the crude mortality at 30 days after the index bacteremia onset. Patients who were lost to follow-up for KPB but followed for other illnesses were included in the analysis. A metastatic infection[15] was defined as an abscess in a site other than the primary site, as indicated by imaging or isolation of *K. pneumoniae*.

For comparison of patients with occult KPB, information of patients who were hospitalized for KPB (DH) was collected from January 2008 to December 2008. Patients who had at least one discharge from the ED within 3 months prior to admission were excluded, and the remaining patients were considered to have received DH from the ED.

Statistical analysis

Patients with occult bacteremia were compared to patients given DH. Among patients with occult bacteremia, we compared patients with and without second ED visits. We also compared patients with two ED visits to patients given DH to study the possible effect of delayed hospitalization, hospitalization duration, need for an invasive procedure, and 30-day mortality. Continuous data, such as age and duration of hospitalization, were compared with an independent *t* test. The foci of infection, invasive procedures, and ICU hospitalization were compared with a Chi-square test. Risk factors of occult bacteremia were analyzed using multivariate analysis. The 30-day survival was compared with Kaplan—Meier method. Data were analyzed using SPSS software for Windows (version 17.0; SPSS Inc., Chicago, IL, USA).

Results

Incidence of occult *K. pneumoniae* bacteremia

There were 16,137 positive blood cultures at the ED during the 6-year study period (2 sets with the same pathogen on the same day were calculated as 1 bacteremia event). There were 1393 KPB events in 1349 patients in the entire hospital, and this included 950 events in 913 patients admitted to the ED. KPB accounted for 8.6% of all cases of bacteremia in the ED. We retrospectively reviewed the charts of all 913 ED patients with KPB, and identified 93 patients (10.2%) who were directly discharged after short ER stays, before preliminary blood culture results were available. Five of these patients were excluded because of death at the ED, critical discharge, or missing chart data. We classified the remaining 88 patients (9.6%) as having occult KPB (Figure 1).

Demography of patients with occult KPB

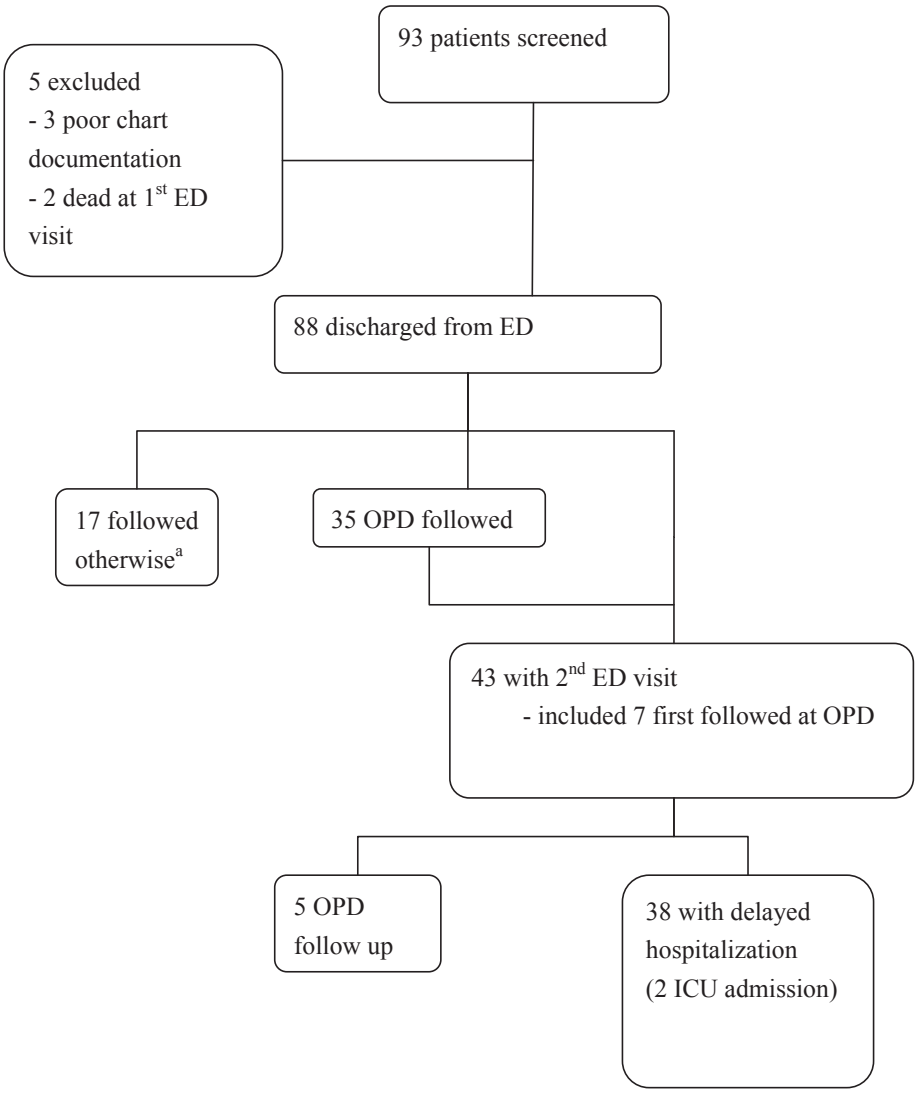
The mean age of these 88 patients was 60.4 ± 16.9 years, and 65.9% were male (Table 1). Sixty-two patients (70%) were community-origin. DM was the most common underlying illness ($n = 44$, 50%), and 18 patients had newly diagnosed or poorly controlled DM. The other underlying illnesses were GI tract disorder other than liver cirrhosis ($n = 20$, 23%), genitourinary tract disorder ($n = 17$, 20%), including urinary tract stones or recipients of genitourinary tract procedures, liver cirrhosis ($n = 14$, 16%), and malignancy ($n = 14$, 15.9%). Urinary tract infection was the most common first impression of the first ED visit ($n = 26$, 29.5%), followed by the respiratory tract infection ($n = 21$, 23.9%).

A total of 49 of these patients (55.7%) were prescribed oral antibiotics after discharge from ED (Table 1). Analysis of the antimicrobial susceptibility of isolates from the initial visits indicated that 74 (84%) were wild-type (only ampicillin-resistant), seven were cefazolin-resistant, and three had multiple-drug resistance (resistance to 3rd generation cephalosporins and fluoroquinolone; data not shown). The median duration of postdischarge oral antibiotic use was 3 days [mean, 5.3 days; range: 1—24 days; interquartile range (IQR), 1—3 days]. The antibiotics administered to these 49 patients were a first generation cephalosporin ($n = 18$, 37%), a fluoroquinolone ($n = 11$, 22%), amoxicillin/clavulanate ($n = 9$, 18%), a second generation cephalosporin ($n = 6$, 12%), and a third generation cephalosporin ($n = 5$, 10%).

Thirty-five patients were followed at outpatient clinics and 17 patients were followed from clinical visitations for reasons other than infection (Figure 1). Forty-three patients had two ED visits (including 7 patients who were initially followed at the outpatient department) and 38 patients (88%) were hospitalized. The mean time between the first and second ED visits was 5.4 days (range, 0—26 days; IQR, 1—7 days). Six patients (7%) had metastatic infections, and this included lung abscess ($n = 2$), psoas muscle abscess ($n = 1$), brain abscess ($n = 1$), mediastinitis ($n = 1$), and peritonitis ($n = 1$). There were no cases of osteomyelitis or endophthalamitis. The overall mean hospitalization time was 17.2 days (median, 11 days; range, 1—107 days; IQR, 8—22 days) and the mean follow-up time was 797 days (range, 30—2193 days). Three of the 43 patients (7%) who had two ED visits experienced in-hospital mortality. Overall, nine patients (12%) died during the follow-up period.

Patients with second ED visit

Among the 43 patients with two ER visits, blood cultures were performed in 30 patients (70%), and 19 blood cultures (63%) were positive. Patients who did not take oral antibiotics after their first ED discharge were more likely to have two ED visits (30.2% vs. 57.8%, $p = 0.009$). Thirty-eight patients (88%) were admitted and five were discharged to the outpatient clinic. Liver abscess was the most common diagnosis ($n = 16$, 37%). The average diameter of the abscess was 6.7 cm (range, 1—14 cm). Percutaneous drainage, aspiration, or surgery was performed in 13 patients.



[a] Distant OPD follow up dates (> 6 weeks after 1st ED visit) at different specialties services.
ED = emergency department; ICU = intensive care unit; OPD = outpatient department.

Figure 1. Disposition of patients diagnosed with occult *Klebsiella pneumoniae* bacteremia.

Twenty-two patients (51%) presented with organ failure, 14 patients with single-organ failure, and eight patients with multiple-organ failure (no patients had organ failures at the first ED visit). Two patients required ICU admission, and one of them died in the hospital. Overall, three patients died in the hospital, and two of them had persisting KPB. One patient with a diagnosis of urosepsis and multiple organ failure died very shortly after the second ED visit. Other patients died from causes unrelated to KPB. The other in-hospital death was related to complications of prolonged hospitalization due to advanced-stage heart failure; this condition began several weeks after completion of the treatment of *K. pneumoniae*-related liver abscess, although there was persisting bacteremia at the beginning of hospitalization.

Comparison of patients with one and two ED visits

Among the 88 patients with occult KPB, 43 patients had returned to ED after the index event of occult bacteremia (2 ED visits). Comparison of patients with one and two ED visits indicated no significant differences in the prevalence of underlying illnesses, but there was a trend for more cases of end-stage renal disease (ESRD) in patients who had two ED visits (2.3% vs. 13.3%, $p = 0.09$). However, these two groups had a significant difference in the foci of infection. Liver abscesses were more common in patients with two ED visits than in those with 1 ED visit [16/43 (37.2%) vs. 3/45 (6.7%), $p < 0.001$]. The urinary tract was the most common site of infection for patients with only one ED visit, and it tended to be more common than in

Table 1 Basic demographic and clinical characteristics of patients diagnosed with occult *Klebisella pneumoniae* bacteremia ($n = 88$).

Characteristic		*n*	%
Age (y; mean ± SD)		60.4 ± 16.9	
Male sex		58	65.9
Underlying illness			
Diabetes mellitus		44	50.0
Well controlled		26	29.5
New onset/poorly controlled		18	20.5
Genitourinary		17	19.3
Gastrointestinal	Cirrhosis	14	15.9
	Other	20	22.7
End stage renal disease		7	8.0
Malignancy	Solid tumor	9	10.2
	Hematologic	5	5.7
Initial diagnosis			
Urinary tract infection		26	29.5
Respiratory tract infection		21	23.9
Biliary tract infection		13	14.8
Acute gastroenteritis		10	11.4
Noninfectious		6	6.8
Soft tissue infection		5	5.7
Viral infection		3	3.4
Liver abscess		2	2.3
Fever without diagnosis		2	2.3
Use of oral antibiotics		49	55.7

SD = standard deviation.

patients with two ED visits [15/43 (33.3%) vs. 8/43 (18.6%), $p = 0.058$].

Comparison of patients with occult bacteremia and direct hospitalization

Comparison of the characteristics of patients with occult KPB with those given DH is shown in Table 2. There were no significant differences in underlying demographics or underlying illnesses, including age (60.4 ± 16.9 years vs. 64.3 ± 14.9 years, $p = 0.12$), sex (male: 65.9% vs. 66.3%, $p = 0.96$), prevalence of DM (50% vs. 54.1%, $p = 0.58$), liver cirrhosis (15.9% vs. 8.4%, $p = 0.58$), ESRD (8% vs. 4.8%, $p = 0.40$), and malignancy (16.3% *vs.* 13.3%, $p = 0.58$). The foci of infection were diverse. There were significantly more respiratory tract infections in the DH group than in the occult KPB group (22.9% vs. 0%), and significantly more intra-abdominal infections (other than liver abscess and biliary tract infections) in the occult KPB group (18.2% vs. 6%, $p = 0.015$). The two groups had similar frequencies of liver abscess (21.6% vs. 22.9%, $p = 0.83$). The number of cases with Pittsburgh bacteremia score ≥ 3 was zero among the study group. Thirty-six cases in the direct hospitalization group had a score ≥ 3; 23 had a score ≥ 4. Kaplan–Meier survival analysis showed the 30-day mortality was significantly lower in the occult KPB group (2.3% vs. 19.2%, $p < 0.0001$; Figure 2).

Comparison of patients with second ED visit and direct hospitalization

Comparison of the characteristics of patients with a second ED visit with those given DH is shown in Table 3. There were no significant differences in age and sex, but a trend for more underlying liver cirrhosis ($p = 0.10$) and ESRD ($p = 0.07$) in patients given DH. Analysis of the foci of infection indicated that primary KPB was more common in patients given DH (12% vs. 0%, $p = 0.018$). Liver abscess tended to be more common in patients with two ED visits (37.2% vs. 22.9%, $p = 0.09$), but the two groups had similar durations of hospitalization (17.6 ± 18.9 days vs. 17.7 ± 14.8 days, $p = 0.72$). The 30-day mortality was significantly greater in the DH group (19% vs. 5%, $p < 0.01$). The two groups had similar frequencies of metastatic infection, but pooling of data from both groups indicated that metastatic infection was more common in patients admitted for liver abscesses (15/20 vs. 9/82, $p < 0.001$; data not shown). In the OB group, five metastatic infection was described: four in the thorax (3 lung abscesses and 1 mediastinal abscess), and one psoas muscle abscess. All five patients had primary focus in liver abscess.

Multivariate analysis for 30-day mortality among patients with occult KPB

A multivariate analysis for 30-day mortality was performed among patients with occult bacteremia (Table 4). Age [odds ratio (OR), 1.07], female (OR 0.20), cirrhosis (OR 11.15), and initial Pittsburgh bacteremia score (OR 19.69) were found to be significant factors related to mortality. Liver abscess was a protective factor but it did not reach statistical significance (OR 0.18).

Discussion

K. pneumoniae is a community-acquired pathogen that is endemic to Taiwan that causes a variety of deep-seated infections with significant morbidities. The focus may be obscure when a patient presents with a febrile disorder and no other major complaints. Liver abscess should always be considered in Taiwan. Our study showed that occult KPB accounted for 9.6% of all cases of KPB at our ED during the 6-year study period. This is equivalent to 1.2 cases of occult KPB per week.

Previous reports showed that *E. coli* is the most common cause of occult bacteremia.[6,11] An 1-year study of occult bacteremia at a tertiary institute in Taiwan indicated that *E. coli* accounted for most cases (37%), followed by *K. pneumoniae* (9.3%), and *S. aureus* (8.1%).[11] There have been more studies of occult bacteremia in pediatric populations, and *S. pneumoniae* may account over 80% of cases.[8] Alpern reported that serious adverse outcomes of occult bacteremia in children were rare, similar to occult bacteremia caused by *E. coli* in adults.[8,22] On the contrary, *S. aureus* bacteremia was associated with adverse impacts and poor outcomes.[11] In this study, patients with occult KPB were discharged due to low Pittsburgh bacteremia scores and obscure symptoms (largely due to liver abscess). Occult

Table 2 Comparison of patients with occult *Klebisella pneumoniae* bacteremia with those had direct hospitalization for *Klebisella pneumoniae* bacteremia.

Characteristic	Occult bacteremia, $n = 88$		Direct hospitalization, $n = 83$		
	n	%	*n*	%	*p*
Age (y; mean ± SD)	60.4 ± 16.9		64.3 ± 15.0		0.12
Male sex	58	65.9	55	66.3	0.96
Underlying illness					
Diabetes mellitus	44	50.0	45	54.2	0.58
Cirrhosis	14	15.9	7	8.4	0.14
End stage renal disease	7	8.0	4	4.8	0.40
Malignancy	7	16.3	11	13.3	0.58
Final diagnosis					
Urinary tract infection	23	26.1	13	15.7	0.09
Liver abscess	19	21.6	19	22.9	0.83
Respiratory tract infection	0	0.0	19	22.9	< 0.0001
Biliary tract infection	12	13.6	8	9.6	0.41
Other intra-abdominal infection	16	18.2	5	6.0	0.015
Primary	11	12.5	10	12.0	0.92
Soft tissue infection	6	6.8	2	2.4	0.17
Meningitis	0	0	2	2.4	
Pittsburgh bacteremia score ≥ 3[a]	0	0	36	43.3	< 0.0001
30-day mortality	2	2.3	16	19.2	< 0.0001

[a] Calculated at the index emergency department visit.
SD = standard deviation.

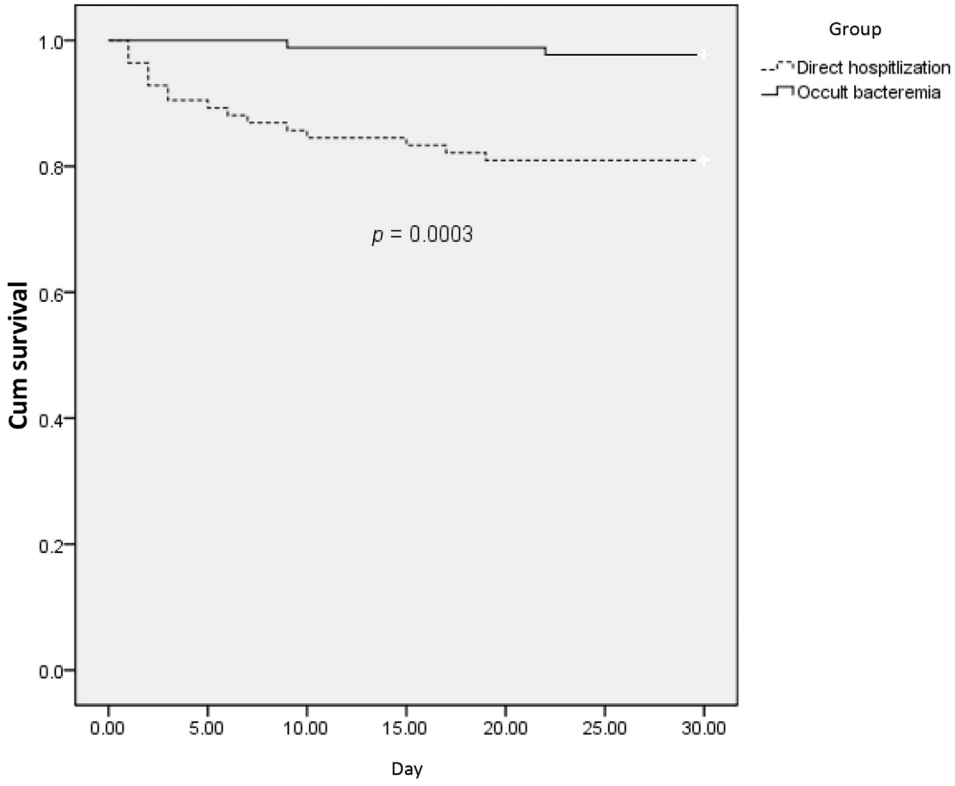


Figure 2. Kaplan—Meier survival curve comparing 30-day mortality of occult bacteremia (broken line) and direct hospitalization (solid line), Day 0 from the first emergency department visit.

Table 3 Comparison of patients with occult *Klebsiella pneumoniae* bacteremia who had two emergency department (ED) visits with those given direct hospitalization.

Characteristic	2nd ED visit, $n = 43$		Direct hospitalization, $n = 83$		
	n	%	*n*	%	*p*
Age (y; mean ± SD)	60.3 ± 16.2		64.3 ± 15.0		0.27
Male sex	29	67.4	55	66.3	0.89
Underlying illness					
Diabetes mellitus	23	53.5	45	54.2	0.93
Cirrhosis	8	18.6	7	8.4	0.095
End stage renal disease	6	14.0	4	4.8	0.07
Malignancy	7	16.3	15	18.1	0.64
Final diagnosis					
Urinary tract infection	8	18.6	13	15.7	0.67
Liver abscess	16	37.2	19	22.9	0.08
Respiratory tract infection	0	0.0	19	22.9	0.001
Biliary tract infection	7	16.3	8	9.6	0.26
Soft tissue infection	3	7.0	2	2.4	0.21
Other intra-abdominal infection	8	18.6	5	6.0	0.028
Meningitis	0	0	2	2.4	
Primary bacteremia	0	0	10	12.0	0.018
Intensive care unit admission	3	6.9	14	16.8	0.10
Admission duration (d; mean ± SD)	17.6 ± 18.9		17.7 ± 14.8		0.72
Pittsburgh bacteremia score ≥ 3[a]	12	27.9	36	43.3	0.090
30-day mortality	2	4.7	16	19.3	0.044

[a] Calculated at the second ED visit.
SD = standard deviation.

KPB did not significantly increase mortality, but half of the patients who had second ED visit presented with organ failure, which is possibly to be prevented if the bacteremia was identified at the initial visit or the patient was called back promptly and actively.

The foci of infection from KPB differed from those of occult *E. coli* bacteremia.[5,17] Among patients with *E. coli* occult bacteremia, urinary tract infection predominated, and patients with such infections can often improve without hospitalization. Intra-abdominal foci were the most common sites for occult KPB (61%), especially liver abscess. There were no significant differences between patients with and without a second ED visit except for liver abscess. An aggressive search for infectious focus other than the urinary tract should be performed at outpatient clinics, including an abdominal sonography. If no focus could be identified, close follow-up should be performed. Any patients with occult KPB should be treated as rapidly and carefully as possible.

Table 4 Multivariate analysis for 30-day mortality among patients with occult *Klebsiella pneumoniae* bacteremia.

	Odds ratio estimates			
Effect	Point estimate	95% Wald confidence limits		*p*
Age (y)	1.07	1.02	1.13	0.010
Female	0.20	0.05	0.76	0.018
Diabetes mellitus	0.61	0.17	2.20	0.450
Cirrhosis	11.15	1.89	65.88	0.008
Liver abscess	0.18	0.02	1.92	0.156
Initial PBS	19.69	4.85	79.99	< 0.0001

PBS = Pittsburgh bacteremia score.

Liver abscess was the most common focus of infection among patients who had a second ED visit. A specific *K. pneumoniae* strain is endemic in Taiwan (serotype K1) that can lead to severe and fatal necrotizing inflammation,[17–19,23] so timely and detailed examination is warranted. Repeated abdominal sonography or computed tomography scan sometimes is necessary. This reflects the importance of follow-up at clinic or a call-back system, as studied previously.[22] Monitoring bacteremic patients who are discharged, in addition to patient education, may help to reduce serious complications.[24] A monitoring system subjecting patients with occult KPB to adequate surveillance of infectious foci may help to improve patient safety in regions where *K. pneumoniae* is endemic, such as Taiwan.[18,19]

A limitation of this study is its retrospective design. We were unable to perform a case–control study due to lack of complete clinical information of all *K. pneumoniae* bacteremia. Moreover, some patients were lost to follow-up, with no second ED visit or any other out-patient visit. Although we are unaware of the outcome of these patients, only two patients never returned to our hospital. Second, the follow-up duration varied among the different patients. Outcomes and complications could not be fully assessed in patients with short follow-up because we did not perform telephone follow-ups after discharge. Although the comparison group (direct hospitalization) consisted of patients from a single year (2008), there were few changes in the treatment policies of KPB or pyogenic liver abscess during the study period. Therefore, we consider the different

timing of collecting data from the control group and the occult KPB group as insignificant. Last, it is difficult to assess the effect of appropriate antibiotic therapy due to many factors including different antibiotic uses (even no antibiotic), different sites of infection, and different duration of antibiotic use.

In conclusion, most patients with occult KPB had favorable outcomes and uncomplicated course of disease. Compared to patients with KPB who had DH, patients with occult KPB had lower 30-day mortality rate, which was possibly due to lower severity of illness. However, half of the patients with occult KPB presented with organ failure at their second ED visits. Any patient discovered to have occult KPB should be given aggressive treatment and the focus of infection must be identified promptly in Taiwan.

Conflicts of interests

All authors have no conflicts interest declare.

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