

## Characteristics of *Klebsiella pneumoniae* Bacteremia in Community-acquired and Nosocomial Infections in Diabetic Patients

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**Background:** Although diabetes mellitus is known as a major risk factor for *Klebsiella pneumoniae* infection, the differences in clinical characteristics between community-acquired and nosocomial *K. pneumoniae* bacteremia in diabetic patients have been rarely reported.

**Methods:** This retrospective analysis enrolled 193 adult diabetic patients with *K. pneumoniae* bacteremia hospitalized between January 2005 and December 2006. The chi-squared test, analysis of variance (ANOVA), Student's *t* test, Fisher exact test, and Cox regression model were used for statistical analysis.

**Results:** Of the enrolled patients, 147 had community-acquired infections and 46 had nosocomial infections. Compared with the community group, the nosocomial group had higher rates of in-hospital mortality (41.3% vs. 18.4%,  $p = 0.001$ ), malignancy (50.0% vs. 19.0%,  $p < 0.001$ ), and leukopenia (21.7% vs. 5.4%,  $p = 0.001$ ) but had lower levels of serum C-reactive protein (124.3 mg/L vs. 188.7 mg/L,  $p = 0.018$ ) and HbA<sub>1c</sub> (8.1% vs. 9.5%,  $p = 0.025$ ). The rate of infection with the extended-spectrum  $\beta$ -lactamase-producing strain (ESBL infection) in the nosocomial group was 11 times higher than that in the community group (45.7% vs. 4.1%,  $p < 0.001$ ). ESBL infection accounted for 53% of mortality in the nosocomial group. Pneumonia was more common in the nosocomial group, while local abscess was more common in the community group. The risk factors for mortality were pneumonia, leukopenia, cirrhosis, and a high serum creatinine ratio (creatinine level at admission/baseline).

**Conclusions:** The nosocomial group had more ESBL infections which might account for the higher mortality. The HbA<sub>1c</sub> level during the course of infection did not affect the outcome. Pneumonia, leukopenia, cirrhosis, and a high serum creatinine ratio at admission were the risk factors for poor outcome.

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**Key words:** *Klebsiella pneumoniae*, diabetes mellitus, community-acquired bacteremia, nosocomial bacteremia

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*Klebsiella pneumoniae* (*K. pneumniae*), a member of the human intestine flora, is frequently associated with hospital-acquired infection. Certain underlying diseases such as malignancy, cirrhosis, biliary tract disorders, diabetes mellitus (DM), and alcoholism may impair an individual's defenses and increase the risk of *K. pneumoniae* infection.<sup>(1-4)</sup> *K. pneumoniae* is the second most common cause of gram-negative bacteremia after *Escherichia coli*.<sup>(5,6)</sup> *K. pneumoniae* bacteremia causes significant morbidity and mortality in general populations.<sup>(3,4)</sup> Metastatic infections—such as pyogenic brain abscess, meningitis, and endophthalmitis—are the most important characteristics of *K. pneumoniae* infections.<sup>(7-15)</sup>

Previous reports in East Asia revealed that DM is the major underlying disease, accounting for 34–36% of cases of *K. pneumoniae* bacteremia.<sup>(3,4)</sup> In this study, we analyzed the characteristics, risk factors, and outcomes of diabetic patients with community- vs. hospital-acquired *K. pneumoniae* bacteremia.

## METHODS

We retrospectively reviewed the medical and microbiological records in a 3,700-bed medical center in northern Taiwan to identify diabetic patients with *K. pneumoniae* bacteremia between January 2005 and December 2006.

*K. pneumoniae* bacteremia was defined as the isolation of *K. pneumoniae* from one or more sets of blood cultures associated with the clinical features of bacteremia. Nosocomial bacteremia was defined as at least one set of positive blood cultures obtained 48 hours or more after admission; otherwise, the bacteremia was considered community-acquired. Underlying conditions associated with *K. pneumoniae* bacteremia included biliary tract disease, malignancy, cirrhosis, chronic kidney disease, end-stage renal disease (ESRD), glucocorticoid or immunosuppressive therapy given within 14 days before the positive blood culture, and chronic obstructive pulmonary disease. Biliary tract disease included biliary tract stones or surgical history, hepatobiliary or pancreatic malignancy or metastasis, and structural abnormality of the gall bladder. The primary sites of infection related to bacteremia were defined as sources of the *K. pneumoniae* isolation other than

blood when the blood culture was positive for *K. pneumoniae*. Pneumonia was diagnosed when an abnormal infiltration or patch in the lung was seen on the chest radiograph. In-hospital mortality was defined as death or critical discharge against medical advice during hospitalization; otherwise, the discharge was considered as survival. The serum HbA<sub>1c</sub> levels were obtained within three months before or during hospitalization, while the baseline serum creatinine levels were obtained within six months before admission.

The creatinine ratio was defined as the ratio of the serum creatinine level at admission to the baseline before admission. Leukopenia was arbitrarily defined as a white blood cell (WBC) count < 3,500/ $\mu$ L, while leukocytosis was defined as a WBC count > 11,000/ $\mu$ L.

Statistical analysis was performed using Statistical Products and Service Solutions for Windows (Version 17.0; SPSS Chicago, IL, U.S.A.). The continuous variables were presented as mean  $\pm$  standard deviation. Student's *t* test and analysis of variance (ANOVA) were used for comparison of continuous variables. The categorical variables were calculated as a frequency and expressed as a percentage; the chi-squared test and Fisher exact test were performed for comparisons between subgroups. Cox regression analysis was used to identify the possible affective predictors of mortality and calculate the odds ratios (OR); the survival subgroup was used as a baseline. For all tests, statistical significance was set at  $p < 0.05$ .

## RESULTS

A total of 193 diabetic patients with *K. pneumoniae* bacteremia were enrolled in this study. Most of them (190 out of 193) had type 2 DM. The male gender was predominant (109, 56.5%); the mean age was 63.5 years (range, 20–101 years). The diabetic duration was  $7.0 \pm 7.4$  years; the mean HbA<sub>1c</sub> level was 9.2% (range, 4.7–18.0%) and the mean baseline serum creatinine level was 1.3 mg/dL (range, 0.3–9.6 mg/dL). Concurrent underlying diseases included biliary tract disease (79 cases), malignancy (51), cirrhosis (32), chronic kidney disease (28, including 9 cases of ESRD), immunosuppressive therapy (23, including 13 cases with glucocorticoid treatment, 8 with chemotherapy, 3 of rheumatic disease, 1 with

kidney transplantation, and 1 with liver transplantation), and chronic obstructive pulmonary disease (7). Some patients had two or more underlying conditions.

Of these 193 cases, 147 (76.2%) had community-acquired infections while the remaining 46 (23.8%) had nosocomial infections (Table 1). Compared with the community-acquired group, the nosocomial group was older ( $67.3 \pm 12.8$  vs.  $62.3 \pm 15.2$  years,  $p = 0.045$ ) and had higher rates of malignancy (50.0% vs. 19.0%,  $p < 0.001$ ), leukopenia (21.7% vs. 5.4%,  $p = 0.001$ ), infection with the extended-spectrum  $\beta$ -lactamase-producing strain (ESBL infection) (45.7% vs. 4.1%,  $p < 0.001$ ), and mortality (41.3% vs. 18.4%,  $p = 0.001$ ). There were 109 (74.1%) and 26 (56.5%) cases with accessible HbA<sub>1c</sub> levels in the community-acquired and nosocomial groups, respectively. The community-acquired group had higher serum HbA<sub>1c</sub> ( $9.5 \pm 2.8\%$  vs.  $8.1 \pm 2.3\%$ ,  $p = 0.025$ ) and C-reactive protein levels ( $188.7 \pm 116.6$  mg/L vs.  $124.3 \pm 105.8$

mg/L,  $p = 0.018$ ) than the nosocomial one.

The overall in-hospital mortality rate was 23.8% (46/193)—27 in the community-acquired group and 19 in the nosocomial group. There were 27 cases (14.0%, 27/193) of ESBL infection in this study—6 (4.1%) in the community-acquired group and 21 (45.7%) in the nosocomial group (Table 1). The rate of ESBL infection in the nosocomial group was eleven times higher than that in the community-acquired group while the mortality rate in the nosocomial group was more than two times that in the community-acquired group (41.3% vs. 18.4%). The mortality rates of patients with ESBL infection were also different in the community-acquired (1/6, 17%) and nosocomial groups (10/21, 48%).

Some patients had more than one infection site. Intra-abdominal infections, including pyogenic liver abscess formation, were the most common type of infection (37%) in the community-acquired group (Table 2), followed by urinary tract infection (24%) and pneumonia (13%). In contrast, lung infections,

**Table 1.** Comparison of Clinical Characteristics in Diabetic Patients with Community-acquired and Nosocomial *K. pneumoniae* Bacteremia

Variable	Community-acquired infections (n = 147)	Nosocomial infections (n = 46)	p value
Age (years)	62.3 ± 15.2	67.3 ± 12.8	0.045
Gender, male	56.5%	56.5%	0.994
Diabetic duration (years)	6.8 ± 7.5 (n = 135)	7.6 ± 7.1 (n = 44)	0.526
Biliary tract disease*	50.9% (n = 116)	66.7% (30)	0.458
Malignancy	19.0%	50.0%	< 0.001
Cirrhosis	16.3%	17.4%	0.405
HbA <sub>1c</sub> (%)	9.5 ± 2.8 (n = 109)	8.1 ± 2.3 (n = 26)	0.025
Baseline Cr (mg/dL)	1.2 ± 1.4	1.4 ± 1.4	0.572
Cr (mg/dL) at admission	1.9 ± 1.7	2.1 ± 2.3	0.430
Cr ratio <sup>†</sup>	1.7 ± 1.0	1.6 ± 1.1	0.770
WBC (/μL)	13,223.8 ± 6,910.0	12,415.2 ± 10,315.1	0.543
Leukopenia	5.4%	21.7%	0.001
CRP (mg/L)	188.7 ± 116.6 (n = 105)	124.3 ± 105.8 (n = 22)	0.018
ESBL-KP	4.1%	45.7%	< 0.001
Polymicrobial bacteremia	17.7%	26.1%	0.211
Overall mortality	18.4%	41.3%	0.001

**Abbreviations:** HbA<sub>1c</sub>: hemoglobin A<sub>1c</sub>; WBC: white blood cells; CRP: C-reactive protein; ESBL-KP: extended-spectrum  $\beta$ -lactamase-producing *K. pneumoniae*; \*: Biliary tract diseases included biliary tract stones, hepatocellular carcinoma, metastatic carcinoma, pancreatic carcinoma, and gallbladder polyps. †: Ratio of the serum creatinine (Cr) level at admission to the baseline. The numbers in parentheses are the numbers of patients whose records were available.

**Table 2.** Comparison of Infection Sites between Community-Acquired and Nosocomial *K. pneumoniae* Bacteremia Groups

Infection sites	Community-acquired infections (n = 174)	Nosocomial infections (n = 58)	<i>p</i> value
Undetectable	12 (7%)	6 (10%)	0.395
Intra-abdominal	64 (37%)	6 (10%)	< 0.001
Liver abscess	43 (25%)	2 (3%)	< 0.001
Others*	21 (12%)	4 (7%)	–
Lung	31 (18%)	29 (50%)	< 0.001
Pneumonia	22 (13%)	27 (47%)	< 0.001
Septic pulmonary embolism	5 (3%)	0	0.192
Others†	4 (2%)	2 (3%)	–
Urinary tract	41 (24%)	13 (22%)	0.790
Meningitis/brain abscess	6 (3%)	0	0.192
Endophthalmitis	4 (2%)	0	0.314
Intravascular catheter-related	0	3 (5%)	0.003
Others‡	16 (9%)	1 (2%)	–
Abscess formation§	63 (36%)	4 (7%)	< 0.001

\*: Community-acquired vs. nosocomial infections: biliary tract infection - 7% vs. 3%, *p* = 0.283; spontaneous bacterial peritonitis - 2% vs. 2%, *p* = 0.739; anal abscess and acute appendicitis - 3% vs. 2%, *p* = 1; †: Community-acquired vs. nosocomial infections: empyema - 2% vs. 2%, *p* = 1; lung abscess - 0 vs. 2%, *p* = 0.083; ‡: Community-acquired vs. nosocomial infections: soft tissue infections - 7% vs. 2%, *p* = 0.214; combination of arthritis, osteomyelitis, and parotiditis - 2% vs. 0, *p* = 0.316; §: Community-acquired abscess: liver (n = 43), deep neck (n = 5), perirenal (n = 3), kidney (n = 2), perianal (n = 2), prostate (n = 2), spine (n = 1), brain (n = 1), uterine (n = 1), hip joint (n = 1), back (n = 1), paraureteral (n = 1); nosocomial abscess: liver (n = 2), lung (n = 1), perianal (n = 1).

including pneumonia, were the most common infection (50%) in the nosocomial group, followed by urinary tract infection (22%). Community-acquired infections included local abscess formation (36%), meningitis, endophthalmitis, and septic pulmonary embolism. Intravascular catheter-related infections occurred only in the nosocomial group.

The polymicrobial bacteremia rate was 17.7% in the community-acquired group and 26.1% in the nosocomial group. It is notable that the most commonly encountered pathogens were almost the same in the two groups: *E. coli* (6.8% vs. 8.7%), coagulase-negative staphylococci (2.7% vs. 6.5%), and *Enterobacter cloacae* (2.0% vs. 4.3%).

A comparison of risk factors for mortality between the deceased and survival groups was as follows (Table 3): malignancy (41.3% vs. 21.8%, *p* = 0.009), cirrhosis (26.1% vs. 13.6%, *p* = 0.047), nosocomial infections (41.3% vs. 18.4%, *p* < 0.001), pneumonia (54.3% vs. 16.3%, *p* < 0.001), ESBL infection (23.9% vs. 10.9%, *p* = 0.026), inappropri-

ate antimicrobial therapy within three days after a positive blood culture (19.6% vs. 5.4%, *p* = 0.003), older age (67.7 ± 12.6 vs. 62.2 ± 15.2 years, *p* = 0.028), leukopenia (23.9% vs. 4.8%, *p* < 0.001), high serum creatinine level (2.6 ± 2.0 mg/dL vs. 1.7 ± 1.6 mg/dL, *p* = 0.008), and high creatinine ratio (2.1 ± 1.5 vs. 1.5 ± 0.8, *p* < 0.001).

Cox regression analysis was introduced to examine the influential variables in Table 3. As shown in Table 4, the four foremost risks for mortality in diabetic patients with *K. pneumoniae* bacteremia were pneumonia (adjusted OR: 4.138, 95% CI [2.260, 7.575], *p* < 0.001), leukopenia (adjusted OR: 3.457, 95% CI [1.512, 7.907], *p* = 0.003), cirrhosis (adjusted OR: 2.106, 95% CI [1.059, 4.188], *p* = 0.034), and creatinine ratio at admission (adjusted OR: 1.342, 95% CI [1.091, 1.651], *p* = 0.005). For the 49 cases with pneumonia in both groups, multiple lobar involvement was exclusively observed in 100% of cases in the deceased group (n = 25) while single lobar involvement was observed in 45.8% of cases in

**Table 3.** Risk Factors Associated with In-hospital Mortality in Diabetic Patients with *K. pneumoniae* Bacteremia

Variables	Survival (n = 147)	Deceased (n = 46)	p value
Age (years)	62.2 ± 15.2	67.7 ± 12.6	0.028
Gender, male	53.7%	65.2%	0.172
Diabetic duration (years)	6.9 ± 7.4 (n = 136)	7.4 ± 7.6 (n = 43)	0.713
Biliary tract disease*	51.8% (n = 114)	62.5% (n = 32)	0.196
Malignancy	21.8%	41.3%	0.009
Cirrhosis	13.6%	26.1%	0.047
Immunosuppressive therapy	9.5%	19.6%	0.067
Nosocomial infection	18.4%	41.3%	< 0.001
Metastatic infection	10.9%	21.7%	0.06
Pneumonia	16.3%	54.3%	< 0.001
ESBL-KP	10.9%	23.9%	0.026
Polymicrobial bacteremia	17.7%	26.1%	0.211
Inappropriate antimicrobial therapy within the first three days	5.4%	19.6%	0.003
HbA <sub>1c</sub> (%)	9.3 ± 2.8 (n = 111)	8.8 ± 2.8 (n = 24)	0.436
WBC (/μL)	12,830.6 ± 6,659.2	13,671.7 ± 10,835.2	0.526
Leukopenia	4.8%	23.9%	< 0.001
Leukocytosis	55.1%	58.7%	0.804
CRP (mg/L)	181.2 ± 113.0 (n = 97)	165.7 ± 130.3 (n = 30)	0.527
Baseline Cr (mg/dL)	1.2 ± 1.5	1.4 ± 1.1	0.581
Cr (mg/dL)	1.7 ± 1.6	2.6 ± 2.0	0.008
Cr ratio <sup>†</sup>	1.5 ± 0.8	2.1 ± 1.5	< 0.001

**Abbreviations:** HbA<sub>1c</sub>: hemoglobin A<sub>1c</sub>; WBC: white blood cells; CRP: C-reactive protein; ESBL-KP: extended-spectrum β-lactamase-producing *K. pneumoniae*; \*: Biliary tract diseases included biliary tract stones, hepatocellular carcinoma, metastatic carcinoma, pancreatic carcinoma, and gallbladder polyps. †: Ratio of the serum creatinine (Cr) level at admission to the baseline. The numbers in parentheses are the numbers of patients whose records were available.

**Table 4.** Multivariate Stepwise Cox Regression Analysis of Risk Factors for Mortality in Diabetic Patients with *K. pneumoniae* Bacteremia

Variable	Adjusted OR	95% CI	p value
Pneumonia	4.138	(2.260, 7.575)	< 0.001
Leukopenia	3.457	(1.512, 7.907)	0.003
Cirrhosis	2.106	(1.059, 4.188)	0.034
Cr ratio	1.342	(1.091, 1.651)	0.005

**Abbreviations:** OR: odds ratio; CI: confidence interval; Cr ratio: Ratio of the serum creatinine (Cr) level at admission to the baseline. p value from the Wald statistic.

the survival group (n = 24). There were 32 subjects with coexisting liver cirrhosis, of which 20 survived and 12 died. There was no statistical difference in mortality according to the severity of Child's classification.

## DISCUSSION

Diabetic patients with *K. pneumoniae* bacteremia tend to be older than the general population.<sup>(3,4)</sup> Tsay et al. reported that the common underlying diseases in patients with *K. pneumoniae* bacteremia were DM (34.2%), neoplastic disease (29.7%), cirrhosis (16.5%), and biliary tract disease (8.2%).<sup>(4)</sup> In this study, the common concurrent underlying diseases in diabetic patients with *K. pneumoniae* bacteremia were biliary tract disease (54.1%), malignancy (26.4%), and cirrhosis (16.6%). The rates of underlying malignancy and liver cirrhosis in diabetic patients with *K. pneumoniae* bacteremia were similar to those in a previous report.<sup>(4)</sup> The high incidence of biliary tract disease might reflect the high incidence of gall stones and hepatobiliary abnormalities in diabetic patients.<sup>(16,17)</sup>

The abdominal cavity (37%), urinary tract (24%), and lung (18%) were the most common infection sites in the community-acquired group.

This might be attributed in part to the fact that carrier rates of *K. pneumoniae* in humans are significantly higher in the gastrointestinal tract than nasopharynx.<sup>(18)</sup> In the nosocomial group, the most common infection sites in descending order were the lung (50%), urinary tract (22%), and abdominal cavity (10%). This might be attributed to the increased nasopharyngeal carrier rate of *K. pneumoniae* following antibiotic use.<sup>(18)</sup> Similar to the observations for *K. pneumoniae* bacteremia in the general population,<sup>(3,4)</sup> the community-acquired infections in our diabetic patients were also characterized by abscess formation (36% vs. 7%,  $p < 0.001$ ), most commonly pyogenic liver abscess.

Although serotyping of *K. pneumoniae* isolates was not performed in this study, a local study demonstrated a higher rate of capsular serotype K1 in a community-acquired group compared with a higher rate of non-typeable serotypes in nosocomial infections.<sup>(4)</sup> The capsular serotype K1 and hypermucoviscosity phenotype were associated with a higher frequency of pyogenic liver abscesses in community-acquired isolates.<sup>(4,7,15,19,20)</sup> Similarly, meningitis, brain abscess, endophthalmitis, and septic pulmonary embolism occurred only in the community-acquired group in our diabetic patients as they do in the general population.<sup>(7-15)</sup>

The in-hospital mortality rate was 23.8% among our diabetic patients with *K. pneumoniae* bacteremia, which was similar to that observed in the general population (22.8% to 32%).<sup>(3,4,6)</sup> It is well known that diabetic patients with poor glycemic control are prone to *K. pneumoniae* infection through impairment of phagocytosis and humoral immunity.<sup>(21,22)</sup> Our data demonstrated that serum HbA<sub>1c</sub> levels during the course of infection did not correlate with the mortality rate (Table 3). Although only 26 of 45 patients (54.5%) in the nosocomial group had accessible data, the mean HbA<sub>1c</sub> level was lower in the nosocomial group than the community-acquired group. Since subjects in the nosocomial group had a higher incidence of concurrent malignancy and other immune compromised states, it is feasible to speculate that both poor glycemic control and concurrent underlying disease impair the host defense system and lead to *K. pneumoniae* infection in diabetic patients.

Mortality in diabetic patients in this study was caused by factors similar to those in previous

studies,<sup>(4)</sup> including nosocomial infections, pneumonia, leukopenia, ESBL infection, and inappropriate antimicrobial therapy within the first three days. However, following a Cox regression adjustment, the major mortality causes for *K. pneumoniae* bacteremia in the diabetic patients were pneumonia, leukopenia, cirrhosis, and high creatinine ratio. Half (25 out of 49) of our patients with pneumonia died. We identified that multiple lobar involvement was exclusively in the deceased group, but only 54% in the survival group. There was no statistical difference in mortality according to the severity of Child's classification because of the relatively small sample size. The creatinine ratio was used as a marker for acute kidney injury based on the RIFLE criteria.<sup>(23)</sup> The ratio is easily accessible and might be a good indicator for predicting the outcome of diabetic patients with *K. pneumoniae* infections at admission.

In conclusion, this study showed significant differences in risk factors, infection sites, ESBL infections, and mortality rates between community-acquired and nosocomial infections in diabetic patients with *K. pneumoniae* bacteremia. Although DM is a major risk factor for *K. pneumoniae* infection, the HbA<sub>1c</sub> level during the course of infection did not affect the outcome. The foremost factors for mortality were pneumonia, leukopenia, cirrhosis, and a high creatinine ratio.

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## 比較社區感染與醫院感染克雷白氏肺炎菌血症在糖尿病患的差異

蔡松昇 黃瑞助 陳思達 孫瑞鴻 王誌慶 林樹福 許瑞旭 林仁德  
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- 背景：** 糖尿病是感染克雷白氏肺炎菌血症重要危險因子。本研究為針對糖尿病族群感染克雷白氏肺炎菌血症的回溯性研究，並探討社區與院內感染臨床特性的差異。
- 方法：** 自民國九十四年一月至九十五年十二月，收集 193 例克雷白氏肺炎菌血症的糖尿病病患的臨床與微生物資料。統計分析方法使用了 ANOVA、Chi-Square test、Student's *t*-test、Cox regression analysis 與 Fisher exact test。
- 結果：** 百分之七十六糖尿病患者是社區感染，百分之二十四為院內感染。相對於社區感染，院內感染常伴隨惡性腫瘤及白血球缺少、較高粗死亡率 (41.3% vs. 18.4%)、較低的 CRP 值與 HbA<sub>1c</sub>。ESBL 細菌抗藥性菌株在院內感染為社區感染的十一倍 (45.7% vs. 4.1%)，且在院內感染死亡率高達 53%。院內感染好發部位位於肺部 (50%) 而社區感染則以膿瘍的產生為其特色 (36%)。Cox 回歸統計分析後顯示肺炎感染，白血球減少，肝硬化，與到院時高肌酐酸比為影響粗死亡的主要因子。
- 結論：** 對糖尿病病人來說，克雷白氏肺炎菌血症的社區感染與院內感染確實有著顯著的差異，包括危險因子、感染部位與膿瘍產生、死亡率及 ESBL 細菌抗藥性菌株感染。雖然高血糖為克雷白氏肺炎菌感染的因素，糖尿病病人到院時的 HbA<sub>1c</sub> 值並不影響感染的死亡率。病患有肺炎感染，白血球減少，肝硬化，與到院時高肌酐酸比有較差的預後。
- (長庚醫誌 2010;33:532-9)

**關鍵詞：** 克雷白氏肺炎菌，糖尿病，社區感染菌血症，院內感染菌血症

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