

Positive culture for *Klebsiella pneumoniae* in relevant sputum samples as a predictor of rapidly fatal outcome in septic patients at medical intensive care units

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Abstract Sixty-five patients with main diagnosis of sepsis, who were directly admitted to the emergency department (ED) and had fatal outcomes after transfer to the medical intensive care units (MICU), were included. Patients who died within 48 hours of MICU transfer were defined as having rapidly fatal outcomes (RFO). The following clinical variables, including diagnosis of infection source; results of blood, sputum, and urine cultures; management for sepsis in the ED and MICU and survival time, were analyzed. There were 30 (46%) patients with RFO. The median survival time in the RFO group was 22.6 hours in MICU. *Klebsiella pneumoniae* was the most common pathogen isolated from blood (7/65, 10.7%) and relevant sputum samples (7/45, 15.5%). Multivariate analysis revealed that age, gender and positive sputum culture for *K. pneumoniae* (hazard ratio, 11.898, $p < 0.001$) were independently associated with RFO in septic patients. The median survival times for patients with positive and negative *K. pneumoniae* sputum culture were 17 hours and 66.8 hours ($p < 0.001$, by the log rank test), respectively. This study found that positive sputum culture of *K.*

pneumoniae was an important independent predictive factor of RFO in septic patients admitted to the MICU.

Introduction

Sepsis is one of the main causes of death among hospitalized patients and has high mortality rates ranging from 20 to 40% in the United States [1]. Although current evidence suggests hospital mortality of sepsis can be reduced by the use of sepsis care bundles [2], few studies have investigated the risk factors for rapidly fatal outcome in septic patients. Alcoholic patients with bacteremic pneumonia due to *Klebsiella pneumoniae* were found to have high mortality, short onset of illness, and short survival before and after hospital admission [3]. Although increasing studies have shown the potential of biomarkers such as protein C and macrophage migration inhibitory factor (MIF) to predict early death in severe sepsis [4–6], a better understanding of the predicting host factors, pathogens and management in septic patients is crucial to prevent their rapidly fatal outcomes.

This study investigated the potential risk factors for rapidly fatal outcomes in septic patients including underlying conditions, pathogens, and management in the emergency department (ED) and medical intensive care unit (MICU).

Materials and methods

Setting and patients

The medical records of all patients with sepsis (including severe sepsis and septic shock) who were transferred to the

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MICU (23 beds in a 600-bed regional teaching hospital) after ED admission between July 2005 and June 2006 were reviewed. Only patients with a main diagnosis of sepsis, direct transfer from the ED and fatal outcomes in the MICU were included in this study. Patients who were transferred from other intensive care units or from a general ward were excluded. At least two sets of blood culture were obtained from all patients either in the ED or MICU. The gender, age, drinking habits, and underlying diseases of the patients were recorded. The following clinical variables during the patient's stay in the ED and MICU were also recorded: clinical diagnosis (including systemic inflammatory response syndrome (SIRS), sepsis, pneumonia, urinary tract infection (UTI), intra-abdominal infection (IAI), organ dysfunction, etc.); management (including obtaining cultures, antibiotic regimen, insertion of central venous catheter, amount of fluid resuscitation, mechanical ventilator requirement, PaO₂/FiO₂ ratio, vasopressor use, steroid use, and component therapy), hemogram, blood gas, blood chemistry, coagulation profile, results of blood, sputum, urine and other cultures; chest radiographic features and survival time. All chest radiographs were read and consensus on findings was reached by two of the authors.

Definitions

Rapidly fatal outcome (RFO) was defined as a septic patient who died within 48 hours after MICU admission. The late fatal outcome (LFO) group was defined as a septic patient who died more than 48 hours after MICU admission. A clinical diagnosis of pneumonia, UTI and IAI was made at the time of ED admission if the patients presented with associated symptoms, laboratory data or radiographic evidence [7]. Cultures of sputum, urine and other specimens were obtained according to the judgment of clinicians at the ED or MICU. All patients had at least two sets of blood cultures; sputum cultures were obtained in 45 patients and urine cultures were collected in 44 patients. The results of sputum culture were considered of clinical significance if they had good quality Gram stain showing numerous polymorphonuclear cells (>25 in a ×100 microscopic field) and few squamous cells (<10 in a ×100 microscopic field) [8]. Blood culture specimens were inoculated into BACTEC culture bottles using the BACTEC 9240 system (Becton Dickinson, Cockeysville, MD, USA). Sputum culture specimens were processed on blood agar, chocolate agar, and eosin methylene blue agar media. Antimicrobial susceptibility was determined by the disk diffusion method, as described by the Clinical and Laboratory Standards Institute (CLSI) [9]. Extended-spectrum β-lactamase (ESBL) production of *Escherichia coli* and *K. pneumoniae* was determined by the disk diffusion method using both cefotaxime and ceftazidime

alone and in combination with clavulanic acid as recommended by the CLSI [9].

The diagnosis of SIRS, sepsis and organ dysfunction was made according to 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference and Surviving Sepsis Campaign 2008 criteria [10, 11]. Empiric antibiotic treatment was considered appropriate if it included intravenous antimicrobials to which the specific isolate (or isolates, if polymicrobial) showed in vitro susceptibility [12].

Statistical analysis

The data were compiled and analyzed with the statistical package SPSS 13.0 (SPSS Inc., Chicago, IL). All continuous data were expressed as mean ± standard deviation (SD) and compared using a two-tailed Student's t-test. Categorical variables were reported as a percentage and compared using chi-square or Fisher's exact test when appropriate. Multivariate Cox regression analysis after adjustment for age and gender was used to identify independently significant factors in predicting rapidly fatal outcome. Survival curves were plotted using the Kaplan-Meier method and examined by log-rank test. A value of $p < 0.05$ was considered statistically significant.

Results

A total of 849 patients were admitted to the MICU during the study period. Among these patients, 168 were directly admitted to the ED and were transferred to the MICU for further management under the main diagnosis of sepsis and 65 of them died in the MICU during the study period. The overall mortality in the MICU was 21.9% and the in-ICU mortality was 38.6% in the study group. Forty seven of these patients were male and the mean age of all patients was 71 years, with a range of 28–95 years. Thirty patients (46%) had RFO. There was no significant difference between the RFO and LFO groups in age, gender, drinking habit, underlying diseases, diagnosis, organ dysfunction (not shown), laboratory data (not shown), treatment and the time spent in the ED (Table 1). However, the RFO group had a significantly lower incidence of IAI (3.33% vs. 25.7%, $p = 0.013$) and a significantly higher incidence of renal dysfunction (75.0% vs. 44.1%, $p = 0.041$) diagnosed in the MICU (Table 2). Only half of these patients received empirical antimicrobial therapy in the ED (Table 1). After admission to the MICU, all of them received empirical antibiotic treatment. The most commonly used antibiotics in the ED and the MICU were cefuroxime and ceftriaxone. There was no significant difference in the use of empirical antibiotics and appropriate antibiotic therapy in the ED and MICU between patients with RFO and LFO (data

Table 1 Demographic data, diagnosis and treatment on the day of ED admission

Variables	Rapidly fatal outcome group (n=30)	Late fatal outcome group (n=35)	p value
Age	69.4±17.6	71.7±16.2	0.586
Gender (male)	25 (83.3%)	22 (62.8%)	0.066
Underlying condition			
Alcohol intake	11 (36.6%)	10 (29.4%)	0.573
Diabetes mellitus	10 (33.3%)	14 (40.0%)	0.579
Liver cirrhosis	2 (6.66%)	7 (20.0%)	0.121
Uremia	0 (0.00%)	2 (5.71%)	0.495
Malignancy	6 (20.0%)	5 (14.2%)	0.540
Diagnosis in ED			
SIRS	2.47±0.77	2.46±0.95	0.965
Sepsis	22 (73.3%)	27 (77.1%)	0.722
Pneumonia	19 (63.3%)	14 (40.0%)	0.061
Urinary tract infection	3 (10.0%)	4 (11.4%)	0.853
Intra-abdominal infection	1 (3.33%)	6 (17.1%)	0.073
Specimens sent in ED			
Blood	20 (66.6%)	22 (62.8%)	0.749
Sputum	2 (6.66%)	2 (5.71%)	0.873
Urine	9 (30.0%)	7 (20.0%)	0.351
Treatment in ED			
Empirical antibiotics	16 (53.3%)	17 (48.5%)	0.702
CVC insertion	8 (26.6%)	10 (28.5%)	0.864
Fluid resuscitation (mL)	982 ± 764	1165±902	0.391
Intubation	12 (40.0%)	16 (45.7%)	0.643
Dopamine	14 (46.6%)	13 (37.1%)	0.437
Norepinephrine	1 (3.33%)	0 (0.00%)	0.276
Stay in ED (hours)	5.95±9.65	13.48±39.06	0.308

ED emergency department, SIRS systemic inflammatory response syndrome, CVC central venous catheter

Data are presented as mean (standard deviation) or number (percentage)

not shown). Other diagnoses, laboratory data (not shown), and management in the MICU were not significantly different between the two groups.

The positive rates of blood, sputum, and urine cultures were 53.8% (35/65), 40.0% (18/45), and 50.0% (22/44), respectively. Other positive culture results included wound (7/8) and body fluid (2/12). *K. pneumoniae* was the most common pathogen isolated from blood (10.7%, 7/65) and sputum (15.5%, 7/45) cultures. The RFO group had a significantly higher incidence of positive *K. pneumoniae* culture from both blood (23.3% vs. 0.00%, $p=0.002$) and sputum (27.3% vs. 4.34%, $p=0.034$) (Table 3). Four patients had multiple pathogens in blood cultures including *K. pneumoniae* and group D *Streptococcus*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus agalactiae*, methicillin resistant *S. epidermidis* (MRSE) and *Micrococcus* spp., and coagulase-negative staphylococci (CoNS) and *Bacteroides thetaiotaomicron*, respectively. All *K. pneumoniae* isolates recovered from sputum specimens were pure cultures but one

patient had multiple isolates from sputum culture including MSSA, *S. pyogenes*, and *Mycobacterium tuberculosis*. Two patients had multiple isolates from urine culture including *K. oxytoca* and ESBL-producing *E. coli*, and *K. pneumoniae* and *E. coli*, respectively.

The results of Cox regression analyses of factors associated with rapidly fatal outcome are summarized in Table 4. The univariate analysis identified four variables associated with rapidly fatal outcome in septic patients: intraabdominal infection (IAI) diagnosed in the MICU; positive blood culture for *K. pneumoniae*; renal dysfunction diagnosed in the MICU; and positive sputum culture for *K. pneumoniae*. In the multivariate analysis after adjustment for age and gender, three factors including age, gender and positive sputum culture for *K. pneumoniae* were independently associated with rapidly fatal outcome in septic patients. The hazard ratio estimate for patients with positive sputum culture for *K. pneumoniae* was 11.898 (95% confidence interval, 3.115–45.444; $p<0.001$).

Table 2 Diagnosis and treatment on the day of MICU admission

	Rapidly fatal outcome group (n=30)	Late fatal outcome group (n=35)	p value
Diagnosis in MICU			
Sepsis	29 (96.6%)	35 (100%)	0.276
Pneumonia	21 (70.0%)	17 (48.6%)	0.081
Urinary tract infection	6 (20.0%)	10 (28.6%)	0.424
Intra-abdominal infection	1 (3.33%)	9 (25.7%)	0.013*
APPACHE-II score	22.6±8.3	23.4±8.0	0.702
Glasgow coma scales	8.30±3.96	8.26±3.76	0.971
Cardiovascular dysfunction	25 (86.2%)	29 (85.3%)	0.918
Respiratory dysfunction	10 (58.8%)	21 (72.4%)	0.343
Renal dysfunction	12 (75.0%)	15 (44.1%)	0.041*
Hepatic dysfunction	3 (23.0%)	7 (38.9%)	0.353
Metabolic dysfunction	15 (78.9%)	16 (72.7%)	0.644
Hematologic dysfunction	6 (42.8%)	17 (50.0%)	0.653
Treatment in MICU			
CVP catheter insertion	27 (90.0%)	31 (88.5%)	0.853
Fluid resuscitation (mL)	1124±529	1338±821	0.244
Ventilator support	21 (70.0%)	28 (80.0%)	0.351
PaO ₂ /FiO ₂ ratio	203±137	203±145	0.996
Steroid	2 (6.66%)	2 (5.71%)	0.869
Component therapy	8 (26.6%)	17 (48.6%)	0.087
Median survival time	22.6 hours	5.4 days	n/a

MICU medical intensive care unit, SIRS systemic inflammatory response syndrome, n/a not available

Data are presented as mean (standard deviation) or number (percentage)

* Significant values

Table 3 Culture results obtained during admission to either the ED or MICU

Culture results	Rapidly fatal outcome group (n=30)	Late fatal outcome group (n=35)	p value
Positive blood culture	16/30 (53.3%)	19/35 (54.2%)	0.939
<i>Klebsiella pneumoniae</i>	7/30 (23.3%)	0/35 (0.00%)	0.002*
Coagulase-negative staphylococci	1/30 (3.33%)	4/35 (11.4%)	0.363
<i>Escherichia coli</i>	2/30 (6.66%)	1/35 (2.85%)	0.591
Positive sputum culture	10/22 (45.4%)	8/23 (34.8%)	0.627
<i>Klebsiella pneumoniae</i>	6/22 (27.3%)	1/23 (4.34%)	0.034*
Methicillin-resistant <i>Staphylococcus aureus</i>	2/22 (9.09%)	1/23 (4.34%)	0.524
<i>Acinetobacter baumannii</i>	0/22 (0.00%)	2/23 (8.69%)	0.157
β-hemolytic streptococci, non-group A, B, or D	1/22 (4.54%)	1/23 (4.34%)	0.974
<i>Mycobacterium tuberculosis</i>	0/22 (0.00%)	2/23 (8.69%)	0.157
Positive urine culture	10/20 (50%)	12/24 (50%)	1.000
<i>Escherichia coli</i>	4/20 (20%)	2/24 (8.3%)	0.261
<i>Klebsiella pneumoniae</i>	2/20 (10%)	3/24 (12.5%)	0.795
<i>Candida</i> spp.	1/20 (5.0%)	2/24 (8.3%)	0.662

ED emergency department, MICU medical intensive care unit

* Significant values

Table 4 Cox regression modeling of factors leading to rapidly fatal outcome in septic patients

Factor	Hazard ratio	95% CI	<i>p</i> value
Univariate analysis			
Intra-abdominal infection in MICU	0.1	0.012–0.841	0.034
Positive blood cultures of <i>Klebsiella pneumoniae</i>	0.397	0.289–0.545	see footnote ^a
Renal dysfunction in MICU	3.8	1.017–14.205	0.047
Positive sputum cultures of <i>Klebsiella pneumoniae</i>	8.250	0.903–75.414	0.062
Positive blood and sputum cultures of <i>Klebsiella pneumoniae</i>			
Multivariate analysis			
Age	1.025	1.002–1.049	0.036
Gender (male to female)	5.545	2.024–15.191	0.001
Positive sputum culture of <i>Klebsiella pneumoniae</i>	11.898	3.115–45.444	<0.001

CI confidence interval, MICU medical intensive care unit, RFO rapidly fatal outcome

^a Every stratum was such that the RFO group's second response (positive blood cultures of *Klebsiella pneumoniae*) was zero

All patients died during their stay in the MICU. The overall median survival time in MICU was 57 hours. Survival curves for all patients based on positive sputum culture of *K. pneumoniae* are presented in Fig. 1. The median survival time of patients with positive sputum culture for *K. pneumoniae* and the remaining patients were 17 hours and 66.8 hours, respectively ($p < 0.001$, by the log-rank test).

A total of 11 patients had positive sputum and/or blood cultures for *K. pneumoniae*. Ten of them died within 48 hours after admission to the MICU. Three of them had *K. pneumoniae* isolates from both sputum and blood. The mean age of the 11 patients was 61 years and ranged from 32 to 95 years. Their underlying conditions included alcohol intake (6/11), diabetes mellitus (3/11), liver cirrhosis (1/11), and malignancy (1/11). The initial radiographic finding of these

11 patients revealed no active lung lesion in two patients with *K. pneumoniae* isolated from blood culture. The initial radiographic findings of the remaining nine patients included unilateral lobar consolidation in six patients, bilateral lobar consolidation in two patients, and unilateral pleural effusion in three patients.

All isolates of *K. pneumoniae* from sputum and/or blood were susceptible to cefazolin, cefuroxime, ampicillin/sulbactam, ceftriaxone, and levofloxacin but resistant to ampicillin by the routine disk diffusion method. Five of the 11 patients received appropriate empirical antibiotics in the ED (two with piperacillin-tazobactam, one with ampicillin/sulbactam, one with levofloxacin and one with cefazolin), and all 11 patients received appropriate antibiotics in the MICU (two with cefuroxime, four with ceftriaxone, one with cefazolin, one with imipenem, two with levofloxacin and one with combination therapy of ceftriaxone and levofloxacin).

Discussion

Analysis of the clinical data of 65 patients with a main diagnosis of sepsis who were transferred from the ED to the MICU revealed that positive culture of *K. pneumoniae* in relevant sputum samples was an independent predictor of rapidly fatal outcome. *K. pneumoniae* was the most common cause of severe pneumonia in patients without response to initial empiric antibiotics who required mechanical ventilation [13]. Significantly elevated interleukin 10 (IL-10) level in the bronchoalveolar lavage (BAL) fluids and serum of patients with positive BAL culture for *K. pneumoniae* was found compared to other pathogens [13]. A previous study also showed that bacteremic *K. pneumoniae* pneumonia (BKPP) caused RFO in alcoholics despite management with adequate antibiotics and intensive care [3].

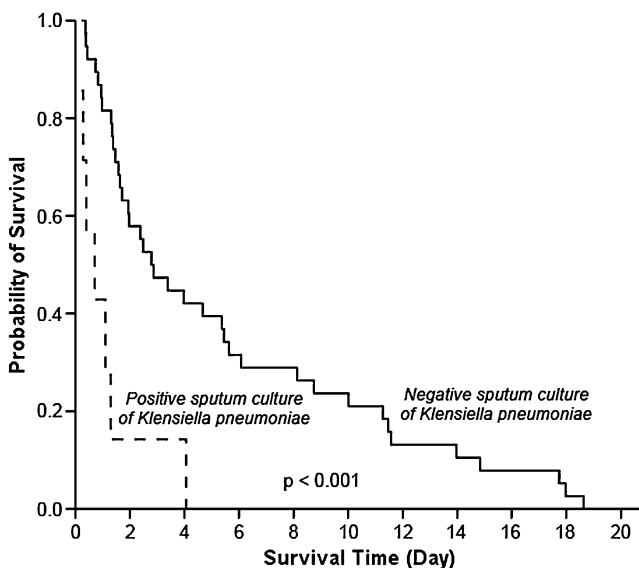


Fig. 1 Survival curves based on positive sputum culture and negative sputum culture of *Klebsiella pneumoniae* in septic patients with fatal outcomes at medical intensive care units

In Taiwan, community-acquired BKPP was due to mucoid phenotype (100%), aerobactin production (83%), and capsular K1 or K2 serotype (75%) in younger patients without serious underlying diseases [14]. All of these findings indicate the high virulence of *K. pneumoniae*, which induced a marked immune response compared to other pathogens and could lead to rapidly fatal outcome even in younger and previously healthy people.

Recent studies suggested that high serum MIF levels and inappropriate adrenal response were associated with early death in patients with severe sepsis [5, 6]. Intra-peritoneal injection of recombinant MIF in a rat model of sepsis induced disseminated intravascular coagulation (DIC) in plasma [15]. Continuously high levels of soluble fibrin and low protein C levels were also found in septic patients with DIC [16]. In a mouse model of systemic *K. pneumoniae* infection the elevation of plasma IL-10 was observed within 24 hours and peaked within 12 hours after infection. Rukavina et al. speculated that the dynamic of greater IL-10 production in infected animals during the early phase was responsible for inadequate inflammatory reaction and control of the infection [17]. All of these findings suggest a combination of high serum IL-10 and high MIF level could lead to RFO in septic patients with suppression of inflammatory response and development of DIC.

Surprisingly, there was no significant difference in the diagnosis and management at the ED between the RFO and LFO groups. There are two possible reasons which may explain this finding. First, the treatment for sepsis was not adequate to overcome rapidly fatal outcome and more effective therapy such as activated protein C and optimization of glycemic control was not available to these patients. Second, these similar results might indicate poor compliance with initial resuscitation and infection control measures in both ED groups of patients including low rates of obtaining blood cultures, prescribing empirical antibiotics, insertion of central venous catheter, and conservative fluid resuscitation [11]. Inadequate use of these measures seems to be a global issue in implementation of surviving sepsis campaign guidelines. De Miguel-Yanes et al. reported 15% of septic patients had no blood cultures drawn, and only two thirds of septic patients had received their first dose of antibiotics within 6 hours after admission [16]. In addition, 46.6% of their cases of severe sepsis or shock received aggressive fluid therapy and no patient had central venous pressure monitoring at the ED [16]. Ferrer et al. reported that the compliance with performing blood cultures and early administration of broad-spectrum antibiotics was only 54.4% and 66.5%, respectively, before an educational program to improve the process of care for severe sepsis [2]. Although earlier implementation of sepsis care bundles could reduce mortality and MICU stay, no study has demonstrated such management could prevent rapidly fatal

outcome [17, 18]. Further study is needed to determine whether implementation of the current 6-hour and 24-hour sepsis care bundles is reasonable to prevent rapidly fatal outcomes on the basis of cytokine intervention and administration of APC.

The empirical antibiotic treatments given in the ED and MICU seemed to be ineffective in our patients with positive sputum and blood culture of *K. pneumoniae* even though sensitivity testing showed the isolates were all sensitive to these empirical antibiotics. There are several possible causes which may explain this finding. First, only five patients (45.5%) received effective empirical antibiotics in the ED and there was a delay in receiving empirical antibiotics in the ED in another 6 patients (54.5%). Second, a retrospective study by Thom et al. found that appropriate empiric antimicrobial therapy for *K. pneumoniae* bacteremia was not associated with lower in-hospital mortality [12]. This suggests that the choice of empiric antimicrobial agents might not improve outcomes and that baseline severity of illness was a potential confounding factor of the association between mortality and antimicrobial therapy [12]. Third, Fang et al. reported that first line empirical antibiotics had at least 98% disk susceptibility in a retrospective cohort study involving 177 cases of *K. pneumoniae* pyogenic liver abscess [19]. The mortality rate (2.8%) in their study was low because most patients (94%) received a third-generation cephalosporin. Septic ocular or central nervous system complications developed in 23 of their patients (13.0%) and *K. pneumoniae* genotype K1 was the only significant risk factor for this type of septic complication, even with appropriate antimicrobial therapy. This finding suggests *K. pneumoniae* genotype K1 could be susceptible to empirical antibiotics but still have high virulence and result in serious complications or even mortality in patients with conditions other than pyogenic liver abscess. Further studies are needed to delineate the serial change of virulence of *K. pneumoniae* genotype K1 before and after the prescription of empirical antibiotics.

Several limitations of this study should be mentioned. First, the results should not be applied to regions other than Southeast Asia and South Africa because of geographic differences in the spectrum of disease caused by *K. pneumoniae* [14]. Second, the role of the most recent biomarkers which have been found to predict early mortality from sepsis, such as MIF and protein C, could not be determined in this analysis because of the retrospective study design. Third, the serotype and genotype of *K. pneumoniae* isolates from our patients could not be further evaluated because they were no longer available at the time of the study. Further prospective study is needed to explore the relationships among virulence of *K. pneumoniae*, cytokine intervention, current sepsis care bundles and the

early diagnosis and treatment of septic patients with rapidly fatal outcome.

In conclusion, this retrospective study identified positive sputum culture of *K. pneumoniae* as the most powerful predictor of rapidly fatal outcome in septic patients. Whether activated protein C is the medication of choice to avoid rapidly fatal outcome in sepsis care bundles will require further investigation.

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