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Original Article

Clinical characteristics and risk factors for attributable mortality in *Enterobacter cloacae* bacteremia

Yi-Chun Lin[1], Te-Li Chen[2], Huang-Ling Ju[2], Huan-Shen Chen[3], Fu-Der Wang[2], Kwok-Woon Yu[4], Chen Yi Liu[2]

[1]Department of Medicine, Taichung Hospital, Department of Health, The Executive Yuan, Taichung; [2]Section of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital and National Yang-Ming University, Taipei; [3]Department of Medicine, Li Shin Hospital, Taoyuan; and [4]Department Pathology and Laboratory Medicine, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan

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Background and Purpose: *Enterobacter* spp. have emerged as an important cause of nosocomial bacteremia. The purpose of this study was to delineate the clinical, laboratory and microbiologic features that may influence prognosis of *Enterobacter cloacae* and enable a stratification of those patients at high risk of mortality.
Methods: This retrospective study reviewed 108 episodes of *E. cloacae* bacteremia occurring over a 2-year period (November 2001 to October 2003) at Taipei Veterans General Hospital. Univariate analysis were performed to demonstrate the relation of possible risk factors to death attributable to *E. cloacae* bacteremia.
Results: Ninety-three episodes (86.1%) were hospital-acquired. The most common portal of entry was the genitourinary tract (17.9%) followed by the gastrointestinal tract (15.1%). Underlying diseases associated with *E. cloacae* bacteremia were neoplastic diseases (42 episodes, 38.9%), diabetes mellitus (20 episodes, 18.5%) and chronic renal failure (18 episodes, 16.7%). The overall mortality rate was 42.6%, and *E. cloacae* bacteremia-attributable mortality occurred in 22 patients (20.9%). Factors significantly correlated with death attributable to bacteremia were older age, a higher medium number of underlying diseases, hemoglobin <10 g/dL, serum C-reactive protein >10 mg/dL, hypoalbuminemia, disseminated intravascular coagulation, septic shock, respiratory failure, renal failure (creatinine >2 mg/dL) and delayed clinical response after initiation of antibiotic therapy.
Conclusions: Antibiotic-resistant isolates and appropriate empirical antibiotic use were not independent predictors of mortality in this study. The condition of patients at onset of symptoms and presence of underlying diseases appear to be important predictors mortality from *E. cloacae* bacteremia.

Key words: Bacteremia, comorbidity, *Enterobacter cloacae*, prognosis, risk factors

Introduction

Enterobacter cloacae is a Gram-negative bacillus, which is a member of the family *Enterobacteriaceae*. The genus *Enterobacter* is composed of *Enterobacter aerogenes*, *E. cloacae*, *Enterobacter agglomerans*, *Enterobacter gergoviae* and *Enterobacter sakasakii*. *E. cloacae* is responsible for 65-75% of all *Enterobacter* infections [1,2]. *E. cloacae* has been shown to account for 5-10% of all cases of Gram-negative sepsis and has emerged as an important cause of hospital-acquired infection in recent years [3-5]. Common endogenous reservoirs for *E. cloacae* include the gastrointestinal tract in healthy adults, the urinary and respiratory tracts, as well as surgical sites and burn wounds [6]. The purpose of this study was to delineate the clinical, laboratory and microbiologic features that may influence prognosis of *E. cloacae* bacteremia and enable a stratification of those patients at high risk of mortality.

Corresponding author: Fu-Der Wang, Section of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan.
E-mail: fdwang@vghtpe.gov.tw

Methods

Case definition

Patients with episodes of *E. cloacae* bacteremia were identified from the microbiological and medical records

at Taipei Veterans General Hospital over a 2-year period from November 2001 to October 2003. The medical records of all 108 patients identified were retrospectively reviewed. There was no apparent outbreak of *E. cloacae* bacteremia during the period of study.

E. cloacae bacteremia was defined as the presence of *E. cloacae* in 1 or more positive blood cultures collected during the presentation of infectious symptoms (e.g., fever, leukocytosis, chills or rigor). Shock was defined as a systolic blood pressure below 90 mm Hg in previously normotensive patients or a decrease of more than 40 mm Hg in previously hypertensive patients. Nosocomial infection was defined as an infection occurring after 72 h of hospitalization. Polymicrobial bacteremia was defined as isolation of additional bacterial species in a blood culture within 48 h of the diagnosis of *E. cloacae.*

The portal of entry was designated as 1 of the following: lower respiratory tract, surgical wound, soft tissue, bone and joint, abdomen, urinary tract, intravascular catheter or unknown, based on clinical signs and symptoms of infection and organisms cultured from these possible portals. Bacteremia was considered to have originated from the respiratory tract when clinical or radiologic evidence of new-onset or progressing pneumonia was found with concomitant isolation of *E. cloacae* from blood, or when strains with an antibiotic susceptibility pattern identical to those isolated from blood were recovered from sputum, bronchial secretion or other respiratory specimens. Bacteremia of unknown origin was defined as bacteremia for which there was no documented distal source.

Empirical treatment was classified as appropriate when all isolated pathogens were susceptible to at least 1 of the administered agents. Empiric therapy was considered inappropriate when the isolate was non-susceptible to the antimicrobial agent(s) administered, or when the patient received no antimicrobial agent on the day of the onset of bacteremia [7]. Being afebrile and vital-sign stable after initiation of antibiotic therapy was considered to indicate clinical response. Mortality was considered directly related to bacteremia if it occurred in the phase of active infection without evidence of any other attributable cause [8].

The correlation of mortality with several diverse factors was assessed, including age, underlying diseases, clinical characteristics, place of acquisition of bacteremia, septic shock, disseminated intravascular coagulation, portal of entry, appropriateness of empirical treatment, clinical response, median numbers of antibiotics to which the *E. cloacae* isolate was resistant and laboratory data.

Microbiology

Blood culture samples were processed by the BACTEC NR-660 system (Becton Dickinson Diagnostic Instrument Systems, Spark, MD, USA). An automatic identification system for Gram-negative rods (ID 32 GN; bioMérieux Vitek, France) was used for species identification. Antibiotic susceptibility was tested by the disk diffusion method as recommended by the National Committee on Clinical Laboratory Standards [9].

Statistical analysis

Univariate analysis was performed to demonstrate the relation of possible risk factors to death attributable to *E. cloacae* bacteremia. Mann-Whitney rank sum test, Student's *t* test and chi-squared tests were used as appropriate. Continuous variables are expressed as mean ± standard deviation or median (interquartile range). All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 12·0 software (SPSS Inc., Chicago. IL, USA). A p value of less than 0.05 was considered statistically significant.

Results

During the study period, 5542 positive blood cultures were obtained in the clinical laboratory. Among them, 108 were positive for *E. cloacae*, accounting for 1.95% of all bacteremias. Ninety-three episodes (86.1%) were hospital-acquired. Only 1 patient had 2 episodes of *E. cloacae* bacteremia, and the second episode in this patient was regarded as a separate case in the analysis. The age of patients ranged from 11 to 90 years (mean ± standard deviation, 61.89 ± 16.45 years). The proportion of male to female patients in these episodes was approximately 2.1:1 (72 vs 35).

The most common underlying diseases in patients with *E. cloacae* bacteremia were neoplastic diseases (42 episodes, 38.9%), diabetes mellitus (20, 18.5%), chronic renal failure (18, 16.7%), and gastric ulcer (17, 15.9%).

The source of infection could be identified in 63% of patients (Table 1). Genitourinary tract (17.9%) and gastrointestinal tract (15.1%) were the major sources of bacteremia. Other sources of bacteremia included intravascular catheters (11.3%), respiratory tract (9.4%) and surgical wound (9.4%). One patient had concomitant joint infection during the bacteremic episode.

Table 1. Underlying diseases and portal of entry in 108 episodes of *Enterobacter cloacae* bacteremia

	No. of episodes (%)
Underlying diseases	
Autoimmune disease	4 (3.7)
Chronic obstructive pulmonary disease	7 (6.5)
Congestive heart failure	8 (7.4)
Liver cirrhosis	9 (8.3)
Cerebrovascular accident	12 (11.1)
Gastric ulcer	17 (15.9)
Chronic renal failure	18 (16.7)
Diabetes mellitus	20 (18.5)
Neoplastic disease	42 (38.9)
Portal of entry	
Intravenous catheter	12 (11.3)
Respiratory tract	10 (9.4)
Urinary tract	19 (17.9)
Gastrointestinal tract	16 (15.1)
Wound	10 (9.4)
Soft tissue, bone and joint	1 (0.9)
Unknown	40 (37.04)

The overall mortality rate was 42.6% (46/108). Death was attributed to *E. cloacae* bacteremia in 22 patients (20.4%), and 24 patients (22.2%) died of underlying diseases. The clinical and laboratory factors potentially related to death attributable to bacteremia in patients with *E. cloacae* bacteremia are shown in Tables 2 and 3. Factors that were correlated significantly with a poor prognosis in the univariate analysis were older age, median number of underlying diseases, presence of disseminated intravascular coagulation, septic shock, respiratory failure, renal failure (creatinine >2mg/dL), and delayed clinical response after initiation of antibiotic therapy. Among these clinical and laboratory factors, only respiratory failure (odds ratio, 46.50; 95% confidence interval, 7.6-286.2; $p<0.001$) was an independent risk factor for mortality in the multivariate analysis.

The correlation between death attributable to bacteremia and other laboratory variables including hemoglobin, platelets, C-reactive protein (CRP), and creatinine was also analyzed. Analysis of cut-off values for hemoglobin and CRP revealed that hemoglobin ≤10 g/dL ($p=0.04$) and CRP >10 mg/dL ($p<0.001$) were correlated with poor prognosis (Table 3).

The antimicrobial susceptibility of the 108 bacteremic isolates of *E. cloacae* is summarized in Table 4. Ampicillin and cefazolin exhibited little in vitro antibacterial activity against *E. cloacae*, with a susceptible rate of 4.8% and 2.8%, respectively. The most effective antibiotics were imipenem (98.1%) and cefepime (97.2%).

Discussion

Little attention was given to *E. cloacae* as a pathogen until 1965 when *E. cloacae* bacteremia was first reported in studies at Boston City Hospital [10]. Initially, *E. cloacae* bacteremia accounted for only 2.8% of Gram-negative rod bacteremias, but this incidence has increased gradually [7], accounting for 10.9% of nosocomial infections in a study from Taiwan reported in 1999 [11].

In the present study, the most common portal of entry was the genitourinary tract, which is similar to most other Gram-negative bacteremias [7,12,13]. The portal of entry was unknown in approximately one-third of *E. cloacae* bacteremic episodes in this study, a lower percentage than in other reports (usually at least 50%) [14,15]. The gastrointestinal tract is a common endogenous reservoir for *E. cloacae* [6] and origination of infection from the gastrointestinal tract is difficult to

Table 2. Laboratory variables associated with mortality in patients with *Enterobacter cloacae* bacteremia

Variable[a,b]	Survivors (n = 61)	Attributable deaths (n = 22)	*p*
Leukocyte count (/mm^3)	7000 (7220)	7850 (11,950)	0.845
Hemoglobin (g/dL)	10.7 (2.7)	9.5 (2.4)	0.010
Platelet count (mm^3)	132,000 (163,500)	80,000 (125,000)	0.011
C-reactive protein (mg/dL)	6.25 (8.41)	16.82 (13.05)	<0.001
Albumin (g/dL)	3.1 (0.8)	2.5 (0.7)	0.020
Creatinine (mg/dL)	1.0 (0.7)	1.9 (1.8)	0.003
GPT (U/L)	36.5 (54.0)	56.5 (107.0)	0.320
Glucose (mg/dL)	115.5 (64.0)	169.5 (135.0)	0.061

Abbreviation: GPT = glutamate pyruvate transaminase (alanine aminotransferase)

[a]Median (interquartile range).

[b]Variables were measured at the time of positive blood culture.

Table 3. Prognostic factors associated with mortality in patients with *Enterobacter cloacae* bacteremia

Variable	Survival n = 61 (%)	Death attributed to bacteremia n = 22 (%)	*p*
Length of hospital stay >1 week	4 (6.7)	4 (19.0)	0.195
Median no. of underlying diseases (interquartile range)	2.0 (2.0)	3.5 (1.0)	0.002
Septic shock	10 (16.4)	13 (59)	0.001
Respiratory failure	2 (3.3)	14 (63.6)	0.001
Renal failure (creatinine >2 mg/dL)	10 (16.4)	10 (45.5)	0.018
Hemoglobin ≤10 g/dL	21 (34.4)	14 (63.6)	0.04
C-reactive protein >10 mg/dL	14 (23.0)	14 (63.6)	<0.001
Period between start of antibiotics and clinical response (day)			<0.001
1-3	5 (8.2)	1 (4.5)	
3-7	10 (16.39)	0 (0)	
8-14	28 (45.9)	3 (13.6)	
15-21	12 (19.35)	15 (68.2)	
>21	6 (9.8)	3 (13.6)	
Inappropriate empirical therapy	29 (47.5)	12 (54.5)	0.806
Polymicrobial bacterermia	14 (23.0)	4 (18.2)	0.769

ascertain. This may explain why the portal of entry often cannot be identified. Chow et al reported that the most common portal of entry was the gastrointestinal tract (39%); the percentage bacteremia of unknown origin was only 19% in their series [16]. No significant difference in mortality was noted among patients who acquired bacteremia from different routes in this study.

In the present study, the most common underlying disease associated with *E. cloacae* bacteremia was neoplastic disease, followed by diabetes mellitus. Although no single underlying disease was associated with a poor prognosis, a higher median number of underlying diseases was correlated with a higher mortality rate in patients with *E. cloacae* bacteremia. The numbers of underlying diseases should be considered as a major factor influencing prognosis.

It is not surprising that septic shock was significantly correlated to mortality in this study, since the development of septic shock has been shown to be associated with fatal outcome in Gram-negative bacteremia [11,17-19]. The presence of disseminated intravascular coagulation, respiratory failure or renal failure was correlated to bacteremia-attributable mortality. Episodes of bacteremia with defeverscence occurring more than 1 week after initiation of antibiotic therapy showed a tendency towards correlation with bacteremia-attributable mortality. However, this mortality was not affected by the inappropriateness

Table 4. Antimicrobial susceptibility[a] of 108 blood isolates of *Enterobacter cloacae*

Antibiotic	Isolates [no. (%)]		
	Susceptible	Intermediate	Resistant
Ampicillin	5 (4.8)	2 (1.9)	98 (93.3)
Piperacillin/tazobactam	95 (88.8)	6 (5.6)	6 (5.6)
Cefazolin	3 (2.8)	2 (1.9)	103 (95.4)
Cefuroxime	69 (63.9)	2 (1.9)	37 (34.3)
Ceftriaxone	75 (69.4)	5 (4.6)	28 (25.9)
Ceftazidime	75 (69.4)	1 (0.9	32 (29.6)
Cefepime	105 (97.2)	1 (0.9)	2 (1.9)
Imipenem	106 (98.1)	0 (0)	2 (1.9)
Aztreonam	74 (68.5)	1 (0.9)	33 (30.6)
Ciprofloxacin	101 (93.5)	2 (1.9)	5 (4.6)
Amikacin	91 (84.3)	7 (6.5)	10 (9.3)
Gentamicin	81 (75.7)	1 (0.9)	25 (23.4)
TMP/SMX	79 (73.1)	2 (1.9)	27 (25.0)

Abbreviation: TMP/SMX = trimethoprim/sulfamethoxazole

[a]Disk diffusion method.

of empirical antibiotics (p=0.806). Thus, the severity and type of underlying disease of patients at onset of bacteremia might play the more important role in the clinical outcome of affected patients.

Widespread antimicrobial resistance now exists among *Enterobacter* strains. *E. cloacae* isolates in this study had high rates of resistance to cefazolin and ampicillin. *Enterobacter* readily develop resistance to second- and third-generation cephalosporins owing to an inducible beta-lactamase [5,20], and this is associated with previous use of extended-spectrum cephalosporins [2,16,21-23].

The emergence of antibiotic resistance in *Enterobacter* has impacted the clinical outcome of affected patients in some studies which showed that infection with multi-resistant *Enterobacter* spp. was associated with a higher mortality rate [16,21,24]. However, Liu et al showed that excluding patients infected by the predominant clone, multi-resistant *E. cloacae*, was not associated with a higher mortality rate [24]. Different clones of *E. cloacae* in different studies might explain the discrepancies in findings.

In summary, *E. cloacae* is an emerging nosocomial pathogen with increasing antimicrobial resistance. Multiple predisposing and prognostic factors for *E. cloacae* bacteremia were identified in this study. Infection with drug-resistant isolates or inappropriate use of antibiotic was not associated with mortality, whereas disease severity and number of underlying diseases at presentation of bacteremia were significantly associated with mortality due to *E. cloacae* bacteremia.

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