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Characteristics of patients with *Burkholderia cepacia* bacteremia

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Burkholderia cepacia has become an important pathogen of infections in immunocompromised and nosocomial patients. The characteristics of 42 episodes of *B. cepacia* bacteremia in 40 patients admitted to the Taipei Veterans General Hospital between January 1997 and December 1999 were retrospectively analyzed. Factors that adversely influenced the mortality rate included respiratory failure, an unknown infection source, a period in an intensive care unit, and shock. Most of the patients had serious underlying diseases, such as diabetes mellitus, malignancy, congestive heart failure, and chronic obstructive pulmonary disease. The mean time for a positive blood culture was 45 days after admission. The overall mortality rate was 28.6% (12/42), and 44.4% (12/27) of all deaths were directly related to *B. cepacia* bacteremia. Polymicrobial bacteremia was found in 5 patients. Ceftazidime was the most effective antimicrobial agent *in vitro*, whereas chloramphenicol, imipenem, and trimethoprim/sulfamethoxazole were less effective alternatives. Appropriate antibiotic therapy was given to 30 patients, most of whom responded to the therapy except for 5 who died despite receiving appropriate treatment. Although *B. cepacia* infection develops in a relatively small proportion of hospitalized individuals, it has a major impact on morbidity and mortality. In view of the fact that *B. cepacia* develops resistance to a wide range of antimicrobial agents, ceftazidime and/or trimethoprim/sulfamethoxazole should be the drug of choice for empiric therapy.

Key words: Bacteremia, *Burkholderia cepacia*, nosocomial infection

Burkholderia cepacia (formerly *Pseudomonas cepacia*), a phytopathogen first described in the 1950s as the causative agent of onion rot [1], is increasingly recognized as an important pathogen associated with infections in immunocompromised and nosocomial patients [2,3]. The bacterium is an aerobic, gram-negative, glucose-nonfermenting bacillus that proliferates under conditions of minimal nutrition, and can survive even in the presence of certain disinfectants. This bacterium is ubiquitous [4,5].

B. cepacia bacteremia is uncommon and is found mainly in cystic fibrosis, immunocompromised, or hospitalized patients [6]. Nosocomial infection can arise from anesthetics, disinfectants, disposable catheters, ventilator nebulizers, temperature probes, antiseptics, saline solutions, human serum albumin, or bath water used for warming blood before blood infusion becoming contaminated with *B. cepacia*, and by pseudobacteremia caused by this organism [7,8].

B. cepacia bacteremia is not uncommon in the Taipei Veterans General Hospital, a 2700-bed teaching hospital in Taiwan. This study reviewed the clinical and laboratory characteristics of all patients who have a diagnosis of *B. cepacia* bacteremia in the Taipei Veterans General Hospital from January 1, 1997 through December 31, 1999. The epidemiology, demography, clinical features, laboratory results, treatment, and outcome were analyzed.

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Patients and Methods

Blood culture systems

Blood culture was performed whenever septicemia was suspected. Blood samples were inoculated into both aerobic and anaerobic broth media for processing with the BACTEC NR 860 nonradiometric blood culture system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, US).

Case definition

All cases with a blood culture positive for *B. cepacia* from January 1, 1997 through December 31, 1999 were included in the analysis. *B. cepacia* bacteremia was defined as the isolation of *B. cepacia* in 1 or more blood

cultures by the clinical microbiology laboratory. The ID 32 GN system (Automatic Identification System for Gram-negative Rods, bioMerieux Vitek, France) was used to identify all positive organisms. Antibiotic susceptibility tests of the organisms were performed in the clinical microbiology laboratory by using the standard disc diffusion method, according to the recommendations of the National Committee for Clinical Laboratory Standards [9].

Clinical parameters

The medical records of the patients were reviewed, and the following data were collected: age, sex, underlying diseases, laboratory data, presence of a central venous or arterial catheter, recent surgical or other invasive procedures, possible sources of bacteremia, risk factors, results of antimicrobial susceptibility tests, responses to therapy, and outcomes.

A bacteremic episode was defined as the isolation of 1 or more organisms from the same patient in 1 or more positive blood cultures. Positive blood culture was defined on the basis of clinical features of septicemia such as fever and leukocytosis, the number of sets of positive blood cultures, the results of positive cultures from other sites, the clinical course, and the treatment. Positive cultures were considered not to be contaminants if the patient had 2 or more of the symptoms and signs of systemic inflammatory response syndrome. Nosocomial bacteremia was defined as a positive blood culture taken from patients who show clinical evidence of infection no sooner than 48 h after admission. A body site was considered to be the source of bacteremia if *B. cepacia* was isolated from that site around the time of the bacteremic episode. Bacteremia was considered to be intravascular catheter-related when a culture of the tip of the catheter grew *B. cepacia* during the same period of blood culture. If *B. cepacia* was not isolated from any culture of clinical materials other than the blood, the source was considered to be unknown.

Appropriate antimicrobial therapy was defined as one or more antimicrobial agents being administered, which include at least 1 effective agent with *in vitro* activity against the isolate, and that the dosage, route of administration, and duration of the treatment were in accordance with current medical standards. Death was considered related to bacteremia if the patient died within 14 days after receiving treatment for bacteremia, unless clear clinical data suggested that death was due to another cause.

Statistical analysis

Comparisons of the groups were performed by using the Fisher's exact test; p values were determined based on 2-tailed tests. A p value of less than 0.05 was considered statistically significant.

Results

A total of 140 591 blood cultures were performed at the hospital from January 1, 1997 through December 31, 1999, and 6900 of these cultures were positive. Forty-nine (0.7%) of the positive blood cultures grew *B. cepacia*, 7 of which were considered contaminated. A total of 42 *B. cepacia* bacteremia was identified in 40 patients. Of the 42 cases, 37 (88.1%) were men and 5 (11.9%) were women; the ages ranged from 2 to 92 years (median, 70 years). On average, a positive blood culture result was obtained 45 days after admission. The lower proportion of women was likely to have been influenced by the patient population of this hospital, which is predominantly men. Half (21/42) of the episodes occurred in patients who have underwent surgery, and 14 episodes occurred in patients in intensive care units (ICU).

Of the 42 episodes of bacteremia, 37 (88.1%) were monomicrobial, whereas the remaining 5 (11.9%) were polymicrobial. The accompanying microorganisms in the polymicrobial cases were other gram-negative rod type bacteria such as *Stenotrophomonas maltophilia*, *Chryseobacterium menigosepticum*, *Enterobacter aerogenes*, and *Acinetobacter* spp. Forty (95.2%) of the cases were nosocomial, whereas the remaining 2 community-acquired cases were both found in patients with infective endocarditis.

Of the 42 cases, 27 (64.3%) died during hospitalization; 12 (28.6%) of the deaths were directly caused by *B. cepacia* bacteremia, whereas the remaining 15 deaths were caused by underlying diseases. Factors that may have been associated with mortality are listed in Table 1. Most of the patients had intravascular catheters, respiratory failure with intubation, or undergone tracheotomy. Half of the episodes occurred in patients who had undergone surgical intervention during the preceding month. Factors associated with a higher mortality included an entry portal at the respiratory tract, an unknown origin, respiratory failure, a bacteremia that occurred after admission to the ICU, septic shock, and an inappropriate antimicrobial therapy. Patients who received antimicrobial therapy with ceftazidime, or with a combined treatment of ceftazidime and aminoglycoside had a lower mortality rate.

The entry portal of *B. cepacia* bacteremia was determined in 32 episodes, and was unknown in 10 episodes. The most frequent route of infection was the respiratory tract, whereas the second most common

Table 1. Risk factors of mortality in patients with *Burkholderia cepacia* bacteremia

Factor	No. of cases	Case fatality (%)	*p*
Sex			NS
Male	37	11 (29.7)	
Female	5	1 (20.0)	
Age			NS
<70 years	17	5 (29.4)	
>70 years	25	7 (28.0)	
Means of acquiring the bacteremia			NS
Hospital-acquired	40	11 (27.5)	
Community-acquired	2	1 (50.0)	
Type of bacteremia			NS
Polymicrobial	5	3 (60.0)	
Monomicrobial	37	9 (27.2)	
Stay in intensive care unit			0.0002
Yes	14	9 (64.2)	
No	28	3 (10.7)	
Portal of entry			
Lower respiratory tract	20	5 (30.0)	NS
Urinary tract	1	0	NS
Intravascular lines	8	0	NS
Others	3	1 (33.3)	NS
Unknown	10	6 (50.0)	0.0264
Underlying condition			
Malignancy	11	5 (45.4)	NS
Congestive heart failure	8	3 (37.5)	NS
Diabetes mellitus	15	6 (40.0)	NS
COPD	7	1 (14.2)	NS
Respiratory failure	26	11 (35.7)	0.0120
Arterial catheter	6	3 (50.0)	NS
Central line catheter	36	9 (25.0)	NS
Major surgery (<30 days)	21	7 (33.3)	NS
Clinical manifestation			
Fever >38°C	30	7 (23.3)	NS
Hypothermia <36°C	3	2 (66.7)	NS
Shock	20	9 (45.0)	0.0246
Respiratory failure	23	8 (34.7)	NS
Antibiotic therapy			
Appropriate	30	5 (16.7)	NS
Ceftazidime	13	2 (15.3)	NS
Ceftazidime + aminoglycoside	5	0	NS
Ciprofloxacin	6	2 (33.3)	NS
Imipenem	6	1 (16.7)	NS
Inappropriate	12	7 (58.3)	0.0069

Abbreviations: COPD = chronic obstructive pulmonary disease; NS= not significant

route was infection via an intravascular catheter. Patients who had *B. cepacia* bacteremia with an unknown infection source had a higher mortality rate.

Table 2 summarizes the *in vitro* antimicrobial susceptibility of the blood isolates of *B. cepacia*. In general, isolates of *B. cepacia* were susceptible to third-generation cephalosporins, trimethoprim/sulfamethoxazole, quinolones, imipenem, and most susceptible to ceftazidime. In contrast, most isolates were resistant to ampicillin, aminoglycosides, piperacillin, ticarcillin, latamoxef, flomoxef, as well as first- and second-generation cephalosporins. The isolates from ICU and non-ICU patient show no specific difference in their susceptibility patterns. Appropriate antimicrobial therapy was given in 30 (71.4%) cases, with a mortality rate of 16.7%. Inappropriate antimicrobial therapy was given in 12 (28.6%) cases, with a mortality rate of 58.3%.

The clinical manifestations of *B. cepacia* bacteremia were similar to those found in other types

Table 2. *In vitro* susceptibilities of *Burkholderia cepacia* by disk diffusion method

Antimicrobial agent	No. of susceptible isolates n = 42 (%)
Gentamicin	0
Tobramycin	1 (2.38)
Amikacin	2 (4.76)
Ampicillin	0
Ticarcillin	2 (4.76)
Tetracycline	2 (4.76)
Cefazolin	0
Cefonicid	2 (4.76)
Cefoperazone	19 (45.2)
Aztreonam	26 (61.9)
Cefotaxime	27 (64.2)
Ceftriaxone	28 (66.6)
Ceftazidime	40 (95.2)
Ciprofloxacin	30 (71.4)
Imipenem	32 (76.2)
Chloramphenicol	34 (80.9)
Trimethoprim/sulfamethoxazole	36 (85.7)

of gram-negative rod bacteremia (Table 3). The most common symptoms were fever and leukocytosis. Septic shock was present in 20 (47.6%) episodes. At the onset of bacteremia, 30 cases had hyperthermia (body temperature >38°C) and 3 cases had hypothermia (body temperature <36°C). Of the 42 cases, 23 had tachycardia, 21 had tachypnea, and 6 had neutropenia. Patients who presented with shock or hypothermia had a higher mortality rate than those who did not.

Discussion

B. cepacia is being increasingly recognized as an important pathogen of humans in both immunocompromised and immune-competent patients who are infected by contact with contaminated equipment during hospitalization [4,6]. Although cystic fibrosis patients are often heavily infected with *B. cepacia* and might have a sputum colony counts of 10^8 CFU/mL, a direct pathogenic role of the organism has not been proven. It has been shown that person-to-person transmission of *B. cepacia* is possible among individuals with cystic fibrosis [10], and recent observations suggest that the environment also serves as a source of acquiring this bacterium [11]. *B. cepacia* bacteremia should be considered in febrile patients with nosocomial infections, especially in those who have an indwelling catheter, who receive ventilation, have cystic fibrosis, or have immune dysfunction.

Table 3. Case-fatality rate by clinical findings at the onset of *Burkholderia cepacia* bacteremia

Clinical finding	No. of cases	No. of fatal cases (%)
Fever	30	7 (23.3)
Hypothermia	3	2 (66.7)
Leukocytosis	28	7 (25.0)
Neutropenia	6	1 (16.6)
Tachypnea	21	6 (28.6)
Tachycardia	23	6 (26.1)
Shock	20	9 (45.0)
Respiratory failure	23	8 (34.7)

Nosocomial infections of *B. cepacia* included bacteremia, meningitis, endocarditis, pneumonia, surgical wound infection, and urinary tract infection in immunocompromised patients [2,6,12]. Community-acquired *B. cepacia* bacteremia is rare, but it has been reported in a case of infective endocarditis [13]. Two patients in this study had infections of *B. cepacia*, which were community-acquired. The first patient had native valve endocarditis, and blood culture on admission yielded *B. cepacia*. He was successfully treated with a combined therapy of ceftazidime and amikacin for 14 days. The other case of community-acquired infection was a 56-year-old diabetic patient with intravenous drug abuse (heroin). Following a dog bite, fever developed and blood culture yielded *B. cepacia* 10 days later. He died on the 18th day of admission despite receiving antimicrobial therapy with ceftazidime and clindamycin.

Several predisposing factors have been suggested as the major determinants for developing *B. cepacia* bacteremia. These factors include staying in an ICU, having undergoing major surgery, and having an intravascular catheter [14]. The significant predisposing factors found in this study were staying in an ICU, having major surgery in the past, and contracting an unknown source of infection ($p<0.05$). Fever and leukocytosis are common, unspecific clinical manifestations of *B. cepacia* bacteremia. The most common portals of entry for *B. cepacia* bacteremia were the lower respiratory tract and intravascular catheters. Most (26/42) of the patients in this study had undergone intubation or tracheotomy with ventilator support.

B. cepacia exhibits broad-range resistance to many antimicrobial agents *in vitro*. The high level of antibiotic resistance demonstrated by most strains of *B. cepacia* severely limits the therapeutic options, and this may be considered an important determinant of virulence. *B. cepacia* is intrinsically resistant to antimicrobial agents such as polymyxin, aminoglycosides, first-and second-generation cephalosporins, and traditional anti-pseudomonal penicillins [15,16]. The species also possess several mechanisms by which it may become resistant to a variety of other agents. Some antibiotics such as ceftazidime, carbapenem, and ciprofloxacin

display some *in vitro* activities against this bacterium. Combinations that have shown synergy *in vitro* include ciprofloxacin and piperacillin, tobramycin and piperacillin, trimethoprim/sulfamethoxazole and ceftazidime, ciprofloxacin and carbapenem, ceftazidime and amikacin, and ceftazidime and ciprofloxacin [14, 17,18]. Ceftazidime combined with amikacin has been shown to have the best synergistic antimicrobial activities. Removal of intravascular catheter may be helpful in treating *B. cepacia* bacteremia [14]. In this study, ceftazidime treatment with or without other effective antimicrobials resulted in a lower mortality than other effective agents such as imipenem, chloramphenicol, trimethoprim/sulfamethoxazole, ciprofloxacin, and other β-lactams. For empiric therapy of *B. cepacia* infection, ceftazidime and/or trimethoprim/sulfamethoxazole should be the drug of choice.

In summary, *B. cepacia* bacteremia is a nosocomial disease most commonly found in patients with respiratory failure and infection in the lower respiratory tract. In this study, mortality rate was positively associated with infections of an unknown origin, respiratory failure, shock, an inappropriate antimicrobial therapy, and a period in the intensive care unit. Although *B. cepacia* affects a relatively small proportion of the population, it is associated with high morbidity and mortality. Treatment of *B. cepacia* is a challenge as isolates are often resistant to most commonly used antibiotics. Early use of effective antimicrobial therapy can nevertheless decrease the morbidity and mortality of *B. cepacia* bacteremia.

References

1. Burkholder WH. Sour skin, a bacterial rot of onion bulbs. Phytopathology 1950;50:115-7.
2. Pegues DA, Carson LA, Anderson RL, Norgard MJ, Argent TA, Jarvis WR, Woernle CH. Outbreak of *Pseudomonas cepacia* bacteremia in oncology patients. Clin Infect Dis 1993;16:407-11.
3. Conly JM, Klass L, Larson L, Kennedy J, Low DE, Harding GK. *Pseudomonas cepacia* colonization and infection in intensive care units. Can Med Assoc J 1986;134:363-6.
4. Mortensen JE, Fisher MC, LiPuma JJ. Recovery of *Pseudomonas cepacia* and other *Pseudomonas* species from the environment. Infect Control Hosp Epidemiol 1995;16:30-2.
5. Govan JR, Huges JE, Vandamme P. *Burkholderia cepacia*: medical, taxonomic and ecological issues. J Med Microbiol 1996;45:395-407.
6. Goldman DA, Klinger JD. *Pseudomonas cepacia*: biology, mechanisms of virulence, epidemiology. J Pediatr 1986; 108:806-12.
7. Jumma PA, Chattopadhyay B. Pseudobacteremia. J Hosp Infect 1994;27:167-77.
8. Mangram A, Jarvis WR. Nosocomial *Burkhoderia cepacia* outbreaks and pseudo-outbreaks. Infect Control Hosp Epidemiol 1996;17:718-20.
9. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests. 3rd ed; approved standard. Villanova, PA: National Committee for Clinical Laboratory Standards; 1984. NCCLS document M2-A3.
10. LiPuma JJ, Dasen SE, Nielson DW, Stern RC, Stull TL. Person-to-person transmission of *Pseudomonas cepacia* between patients with cystic fibrosis. Lancet 1990; 336:1094-6.
11. Fisher MC, LiPuma JJ, Dasen SE, Caputo GC, Mortensen JE, McGowan KL, Stull TL. Source of *Pseudomonas cepacia* ribotyping of isolates from patients and from the environmental sources. J Pediatr 1993;123:745-7.
12. Holmes B. The identification of *Pseudomonas cepacia* and its occurrence in clinical material. J Appl Bacteriol 1986;61:299-314.
13. Noriega ER, Rubinstein E, Simberkoff MS, Rahal JJ. Subacute and acute endocarditis due to *Pseudomonas cepacia* in heroin addicts. Am J Med 1975;59:29-36.
14. Lu DC, Chang SC, Chen YC, Luh KT, Lee CY, Hsieh WC. *Burkholderia cepacia* bacteremia: a retrospective analysis of 70 episodes. J Formos Med Assoc 1997;96:972-8.
15. Nord CE, Wadstrom T, Wretlind B. Synergistic effect of colonization of sulfamethoxazole, trimethoprim and colistin against *Pseudomonas maltophilia* and *Pseudomonas cepacia*. Antimicrob Agents Chemother 1974;6:521-3.
16. Lewin C, Doherty C, Govan J. *In vitro* activities of meropenem, PD 127391, PD 131628, ceftazidime, chloramphenicol, co-trimoxazole and ciprofloxacin against *Pseudomonas cepacia*. Antimicrob Agents Chemother 1993;37:123-5.
17. Lu DC, Chang SC, Chen YC, Luh KT, Hsieh WC. *In vitro* activities of antimicrobial agents, alone and in combinations, against *Burkholderia cepacia* isolated from blood. Diagn Microbiol Infect Dis 1997;28:187-91.
18. Bonacorsi S, Fitoussi F, Lhopital S, Bingen E. Comparative *in vitro* activities of meropenem, imipenem, temocillin, piperacillin, and ceftazidime in combination with tobramycin, rifampin, or ciprofloxacin against *Burkholderia cepacia* isolates from patients with cystic fibrosis. Antimicrob Agents Chemother 1999;43:213-7.