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Community-acquired anaerobic bacteremia in adults: one-year experience in a medical center

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A prospective observational study was conducted to evaluate the clinical characteristics and outcome of community-acquired anaerobic bacteremia. From June 1 2001 through May 31 2002, 52 patients with community-acquired anaerobic bacteremia were enrolled at the emergency department in a teaching hospital. There were 19 patients (34%) with polymicrobial bacteremia and *Escherichia coli* was the most common copathogen (n = 6). Of 62 anaerobic isolates, species of the *Bacteroides fragilis* group were the most common isolates (n = 28, 45%), followed by *Clostridium* spp. (n = 11, 18%). Among the 52 patients enrolled, up to 27% had underlying malignancy and the gastrointestinal tract accounted for 48% of the sources of infection. Clinical manifestations suggesting anaerobic infections were common and three-quarters (n = 39) of 52 patients received adequate empirical antimicrobial treatment. Documentation of anaerobic bacteremia seldom influenced antimicrobial treatment. The 30-day mortality was 25%. Although univariate analysis revealed that underlying malignancy (p=0.003), leukopenia (p=0.044) and absence of fever (p=0.047) were associated with mortality, only malignancy (p=0.007) was an independent risk factor in the multivariate analysis.

Key words: Anaerobic bacteremia, community-acquired infections, mortality, neoplasms

Bacteremia due to anaerobic pathogens has a low incidence and a relatively minor clinical impact [1-5]. Infection due to antibiotic-resistant anaerobic bacteria, however, is an emerging problem [6-10], the magnitude of which may be masked by the increasingly frequent use of potent, broad-spectrum antibiotics as empirical therapy.

In Taiwan, studies of anaerobic bacteremia and data on susceptibilities of anaerobes remain limited [6,7,11, 12]. We conducted the present study to evaluate the clinical characteristics and outcome of patients with anaerobic bacteremia. The distributions of bacterial species and antibiotic susceptibilities of anaerobic isolates were also analyzed. To eliminate the influence of nosocomial infections, only patients with community-acquired bacteremia were enrolled.

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Materials and Methods

Hospital setting and patients

National Taiwan University Hospital is a university hospital comprising 2200 beds and provides both primary and tertiary care. The annual emergency room (ER) census recorded more than 100,000 visits. A central microbiology laboratory is responsible for management of all clinical specimens. A positive finding of microbial growth in blood culture is reported to the attending physicians before the results of antimicrobial susceptibility tests are known and organism identification is established. From June 1, 2001 through May 31, 2002, a prospective observational study was conducted in adult patients (age >16 years old) who had positive anaerobic blood cultures from specimens collected within 48 h of their arrival at the emergency department. All patients were evaluated using a structured form. A patient interview was undertaken as soon as possible after the notification of a positive blood culture result. Family members or caregivers were interviewed if the patient

could not complete the interview. Demographic data, clinical features, antibiotic regimen, clinical outcome and microbiological data were recorded. Health care-associated conditions within 1 year prior to the present ER visit, including recent hospitalization, residence in a chronic care facility, medication use (such as chemotherapy, steroids or antibiotics), and application of hemodialysis were also recorded. In addition, the response of physicians to notification of positive anaerobic blood cultures in their patients was evaluated based on subsequent changes in antimicrobial treatment.

Definitions

An episode of true anaerobic bacteremia was defined as isolation of anaerobic bacteria alone or in combination with other microorganisms from a specimen obtained in a patient with clinical symptoms and signs of infection. Community-acquired bacteremia was defined as infection occurring within 48 h of hospitalization or prior to admission [13]. All of the patients had blood samples taken at our ER and fulfilled the definition of community-acquired bacteremia. Patients transferred from other hospitals were excluded. Bacteremia was categorized as monomicrobial when only 1 species of anaerobic bacteria was isolated and polymicrobial when 1 or more additional species, whether aerobes or not, were isolated. The source of infection was determined based on radiological, surgical or microbiological evidence of barrier compromise or infectious pathology, such as an abscess or necrosis. Antimicrobial therapy was considered adequate when the empirical antibiotic, which had been used for at least 3 days, was shown to be effective against the causative agents by in vitro susceptibility testing. Crude mortality was determined based on the all-cause fatality rate within 30 days of hospitalization.

Microbiology

Blood samples were inoculated into both aerobic and anaerobic broth media for processing with the BACTEC 9240 blood culture system (Becton Dickinson Diagnostic Instruments, Sparks, MD, USA). Bacteria were identified from the colonies using a standard algorithm [14] followed by definitive identification with Vitek ANI cards (bioMérieux, Durham, NC, USA). The antimicrobial susceptibility of anaerobes was tested using the agar dilution method, in accordance with guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) [15]. An inoculum of 10^5 colony-forming units per well was applied with a Steers replicator onto Brucella agar plates supplemented with vitamin K_1 and 5% pooled sheep blood. Plates were incubated in an anaerobic chamber for 48 h at 35°C. The antimicrobial agents used for susceptibility testing of anaerobic bacteria were as follows: penicillin G, ampicillin-sulbactam, clindamycin, metronidazole and chloramphenicol (Sigma Chemical Co., St. Louis, MO, USA), cefoxitin (Merck Sharp and Dohme, West Point, PA, USA) and cefmetazole (Sankyo, Tokyo, Japan). The proportions of susceptible, intermediate, and resistant isolates were determined using NCCLS breakpoints [15]. Reference strains of *Bacteroides fragilis* American Type Culture Collection [ATCC] 25285 and *Bacteroides thetaiotaomicron* ATCC 29741 were used for quality control of the susceptibility tests.

Table 1. Distribution of 62 anaerobic bacterial isolates from 56 patients with anaerobic bacteremia

Anaerobic bacteria species	No. of isolates (%)
Bacteroides fragilis group	28 (45)
B. fragilis	16
B. thetaiotaomicron	7
B. ovatus	2
B. vulgatus	1
B. uniformis	1
B. capillosus	1
Clostridium spp.	11 (18)
C. perfringens	4
C. septicum	2
C. sordelii	2
C. tertium	1
C. barati	1
C. clostridiforme	1
Peptostreptococcus spp.	6 (10)
P. micros	2
P. asacchacrolyticus	2
P. anaaerobius	1
Peptostreptococcus spp.	1
Fusobacterium spp.	5 (8)
F. nucleatum	2
F. varium	2
F. mortiferum	1
Lactobacillus spp.[a]	3
Gemella spp.[b]	3
Prevotella spp.[c]	3
Veillonella parvula	1
Bilophila wardsworthia	1
Anaerobic (Gram-positive bacilli)[d]	1
Total	62

[a]Included *L. jensenii, L. catenaforme, Lactobacillus* spp.
[b]Included *G. morbillorum, G. haemolysans.*
[c]Included *P. melaninogenicus, P. oris.*
[d]No further identification of the species.

Table 2. Susceptibility rates of anaerobic isolates by agar dilution method

Bacterium (no. of isolates)	Susceptibility to antimicrobial agents (%)						
	P	CC	C	CMZ	FOX	SAM	MET
Bacteroides fragilis group (28)							
B. fragilis (16)	0	62	100	75	94	94	100
B. thetaiotaiomicron (7)	0	14	100	0	14	86	100
Other species (5)	0	20	100	40	60	80	100
Clostridium spp. (11)							
C. perfringens (4)	100	100	100	100	100	100	100
Other species (7)	100	86	100	100	100	100	100
Peptostreptococcus spp. (6)	100	67	100	100	100	100	100
Fusobacterium spp. (5)	60	60	100	100	100	80	100
Other species[a] (5)	73	100	100	91	91	100	100

Abbreviations: P = penicillin; CC = clindamycin; C = chloramphenicol; CMZ = cefmetazole; FOX = cefoxitin; SAM = ampicillin/sulbactam; MET = metronidazole

[a]Only included *Prevotella* spp., anaerobic Gram-positive bacteria, and *Bilophila wardsworthia.*

Statistical analyses

All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS), version 10.0 for Windows (SPSS, Chicago, IL, USA). Categorical variables were analyzed using chi-squared or Fisher's exact test as appropriate. All *p* values were 2 tailed and a *p* value <0.05 was considered statistically significant.

Results

Of the 56 patients, 4 were excluded from further analysis either due to loss to follow-up (n = 1) or transfer to other hospitals (n = 3). Among the remaining 52 patients enrolled in the study, 26 (50%) were men and the median age was 67.5 years (range, 16-92 years). Polymicrobial bacteremia was found in 19 patients (34%), 15 of whom had concomitant aerobic bacteremia. *Escherichia coli* was the most common aerobic organism isolated (n = 6).

Of 62 anaerobic isolates detected, the most common genus was *Bacteroides* (n = 28), among which *B. fragilis* (n = 16) was the most common species. The second most common genus was *Clostridium* (n = 11), among which *C. perfringens* was the most common species (n = 4). Other detected genera included genus *Peptostreptococcus* (n = 6) and *Fusobacterium* (n = 5) [Table 1].

All *B. fragilis* isolates were resistant to penicillin G and displayed variable resistance to other antibiotics. In contrast, the 4 *C. perfringens* isolates were susceptible to all antimicrobial agents tested. All anaerobic isolates included in the present study were susceptible to chloramphenicol or metronidazole (Table 2).

The median duration of hospitalization was 14.5 days (range, 1-118 days). Malignancy was the most common underlying disease (n = 14), followed by diabetes mellitus (n = 12), cerebrovascular accident (n = 6), liver cirrhosis (n = 2), and end-stage renal disease (n = 1). Health care-associated conditions included recent hospitalization (n = 22), antibiotic use (n = 16), residence in a chronic care facility (n = 5), chemotherapy (n = 4), pressure sores (n = 3), steroid use (n = 1), and hemodialysis (n = 1). Fever (n = 33, 63%) was the most common presenting symptom. Clinical manifestations suggesting anaerobic infections were common and included the following: abdominal discomfort presenting as either abdominal pain (n = 19), abdominal fullness (n = 2) or accompanied by diarrhea (n = 2); soft tissue infection with purulent discharge (n = 5); and choking history with aspiration (n = 2). The gastrointestinal tract was the most common source of anaerobic bacteremia

Table 3. Infection sources of 52 patients with anaerobic bacteremia

Source	No. of patients (%)
Gastrointestinal tract[a]	25 (48)
Bone and soft tissue	9 (17)
Respiratory tract	7 (13)
Unknown	5 (10)
Gynecologic infections	3 (6)
Others[b]	3 (6)

[a]Biliary tract infection (n = 9), appendicitis (n = 7), colon perforation (n = 4), perirectal abscess (n = 2), diverticulitis (n = 1), liver abscess (n = 1), cholecystitis (n = 1).

[b]Spontaneous bacterial peritonitis (n = 2), catheter infection (n = 1).

Table 4. Clinical characteristics and survival analysis of 52 patients with anaerobic bacteremia

Factor	No. of patients (%)	Mortality (%)	*p*
Gender			
Male	26 (50)	27	
Female	26 (50)	22	1.00
Age			
>65 years	29 (56)	31	
<65 years	23 (44)	17	0.34
Type of bacteremia			
Monomicrobial	35 (67)	17	
Polymicrobial	17 (33)	41	0.13
Concomitant aerobic bacteremia	14 (27)	43	0.15
Underlying disease			
Cerebrovascular accident	6 (12)	0	0.32
End-stage renal disease	1 (2)	100	0.25
Diabetes mellitus	12 (23)	25	1.00
Malignancy	14 (27)	57	0.003
Liver cirrhosis	2 (4)	50	0.44
Pressure sore	3 (6)	0	0.56
Presentation with			
Fever (>38°C)	33 (63)	15	
No fever	19 (37)	42	0.047
Chills	31 (60)	16	
No chills	21 (40)	38	0.11
Hypothermia (<36°C)	5 (10)	20	
No hypothermia	47 (90)	26	1.00
Tachycardia (>90/min)	46 (88)	28	
No tachycardia	6 (12)	0	0.32
Laboratory findings			
Anemia[a]	40 (77)	28	
No anemia	12 (23)	17	0.71
Leukocytosis (>12,000/μL)	26 (50)	23	
No leukocytosis	26 (50)	27	1.00
Leukopenia (<4000/μL)	4 (8)	75	
No leukopenia	48 (92)	21	0.04
Thrombocytopenia (<100 × 10^3/μL)	4 (8)	50	
No thrombocytopenia	48 (92)	23	0.26
Treatment			
Inadequate antibiotic to anaerobe[b]	9 (26)	22	
Adequate antibiotic to anaerobe	26 (74)	15	0.64
Surgical intervention	18 (35)	17	
Without surgery	34 (65)	29	0.50

[a]Hemoglobin <13 g/dL in males, <12 g/dL in females.
[b]Included only monomicrobial anaerobic bacteremia.

(n = 25, 48%), followed by bone and soft tissue (n = 9) and respiratory tract (n = 7) [Table 3].

Microbiological results were not available in 12 patients until after discharge (n = 6) or death (n = 6), and 10 of them had received adequate empirical antimicrobial treatment. Attending physicians modified the antimicrobial regimen according to the microbiological results in 7 of the remaining 40 patients. Empirical regimens were not changed in 33 patients because the regimen was appropriate (n = 29), clinical conditions had improved despite inappropriate therapy (n = 3), or the result indication for changing inappropriate therapy was neglected (n = 1).

Thirteen patients died (crude mortality, 25%) within 30 days of hospitalization and the median duration from onset of bacteremia to death was 7 days (range, 1-24 days). Among the 35 patients with monomicrobial anaerobic bacteremia, 26 (74%) received adequate

Table 5. Summary of various studies of anaerobic bacteremia

Authors [reference]	Study period	Most common isolates (%)	No.of patients	Mean age, years (range)	M/F
Brook [16]	1973-6~1985-6	*B. fragilis* group (42)	296	40	228/68
Bouza et al [40]	1978~1981	*B. fragilis* group (32)	103[b]	56 (0.2-86)	66/37
Vazquez et al [17]	1981-1~1985-12	*B. fragilis* group (30)	63[d]	54 (0.1-90)	41/22
Kornowski et al [18]	1984~1988	*Clostridium* (50), *Bacteroides* spp. (50)	32[e]	72 (37-88)	24/8
Lombardi and Engleberg [2]	1987-7~1988-12	*B. fragilis* group (33)	40	54 (7-82)	24/16
Gomez et al [5]	1988-1~1992-4	*B.fragilis* group (59)	61[f]	54 (2-82)	31/30
Peraino et al [19]	1991-1~1991-12	*B. fragilis* group (33)	16	69[h] (32-84)	6/10
Salonen et al [20]	1991~1996	*B .fragilis* group (44)	57	53 (0.1-83)	38/19
Wilson and Limaye [21]	1998-9~2000-4	*Bacteroides* spp. (26)	73[i]	53 (18-89)	44/29
Saito et al [3]	1999-1~2000-12	*B. fragilis* group (51)	57	63 (0.3-86)	36/21
Hung et al [PR]	2001-6~2002-6	*B. fragilis* group (45)	52	64 (16-92)	26/26

Abbreviations: M = male; F = female; GI = gastrointestinal; PR = present report; NA = not available; ICU = intensive care unit

[a]Only included factors with statistical significance.

[b]Community-acquired: n = 36.

[c]Severe underlying disease, nosocomial acquisition, shock, metastatic sepsis, absence of surgery.

[d]Community-acquired: n = 27.

[e]Community-acquired: n = 13.

[f]Community-acquired: n = 25.

[g]Surgical ward hospitalization, nosocomial acquisition, previous surgery, critical initial illness, presence of complications including shock,

[h]Median value.

[i]Community-acquired: n = 34.

empirical antimicrobial treatment. Of these 26 patients, 4 died and 22 (85%) survived. Among the 9 patients who received inadequate empirical antimicrobial therapy, only 2 died and 7 (78%) survived. Univariate analysis revealed malignancy (p=0.003), leukopenia (p=0.044) and absence of fever (p=0.047) were associated with mortality. In addition, there was a trend towards higher fatality rates for patients older than 65 years (31% vs 17%, p=0.341) and those with polymicrobial bacteremia (41% vs 17%, p=0.125). Multivariate analysis identified malignancy (p=0.007) as the only independent predictor of 30-day mortality (Table 4).

Discussion

This is the first prospective study to evaluate the clinical characteristics and outcome of adult patients with community-acquired anaerobic bacteremia in Taiwan. In addition, most previous studies of anaerobic bacteremia in Taiwan and other countries either involved nosocomial isolates or analyzed a limited number of strains [2,3,5,12,16-29] and thus do not provide adequate perspective for clinicians encountering patients with community-acquired infections.

In both the present and previously published series, the most frequently occurring anaerobic pathogens were members of the *B. fragilis* group, with *B. fragilis* being the most prevalent species [2,3,5,16-18,20,22,30,31]. The growing resistance of some *Bacteroides* isolates to penicillin-derived antibiotics in the last decade has been described [6,7,32,33]; our study confirms this trend and suggests the need for continued monitoring of antibiotic susceptibility patterns of clinically important anaerobes.

Specific clinical situations predisposing patients to anaerobic infections include malignancy [34], chemotherapy-induced mucositis or other types of oral lesions [35,36], necrotizing soft tissue infections [37], dental extraction [38], and aspiration pneumonia [39]. In our study, 27% of patients had an underlying malignancy and clinical manifestations suggesting anaerobic infections were common, which might explain why most of our patients (n = 39, 75%) received effective empirical antimicrobial treatment. However, there are conflicting reports concerning the success rate of empirical antimicrobial treatment [2,5,17,19, 20,40,41]. The cause of these discrepancies might be related to variation in the characteristics of study populations, available antimicrobial agents, and bacterial susceptibility.

There were 12 patients whose microbiological results were available only after their death or discharge. For these patients, adjustment of therapy in light of the

GI tract as focus (%)	Malignancy (%)	Adequacy of antibiotic (%)	Surgical intervention (%)	Mortality (%)	Risk factors associated with mortality[a]
42	NA	NA	NA	25	NA
50	29	61	40	32	See note[c]
40	41	57	51	25	Age >60 years, lack of surgery
28	56	NA	NA	25	Inadequate antibiotics
63	48	75	NA	38	NA
26	NA	80	23	38	See note[g]
56	31	50	NA	44	NA
46	21	49	39	25	Ineffective antibiotics, ICU care
62	23	NA	NA	25	Age, underlying liver disease
47	49	NA	NA	NA	NA
48	27	75	35	25	Malignancy

septic metastasis.

susceptibility data was impossible. Among the remaining 40 patients, 33 continued with their initial antibiotic regimens even after culture results were available. In other words, the blood culture results rarely led to a change of antibiotic regimen, which supports the conclusion [2,4] that documentation of anaerobic bacteremia seldom influences a physician's clinical options.

In previous studies, the mortality rate of patients with anaerobic bactermia ranged from 25% to 44% [2, 5,16-21]. The patient characteristics, treatment, clinical course, outcome and risk factors identified in previous studies of anaerobic bacteremia are summarized in Table 5. Mortality in the current study is reported as crude mortality, rather than attributable mortality, since the relative contribution of anaerobic bacteremia to the overall mortality could not be reliably ascertained, especially when polymicrobial infections occurred. This study found that malignancy was the only independent factor associated with the 30-day hospital mortality in adult patients with community-acquired anaerobic bacteremia. Previous studies found that inadequate early antimicrobial therapy [17,19] and old age [16,20] were poor prognostic factors. Because of the different study populations and inconsistent methodology for determining mortality estimates in previous studies, comparisons are difficult, although inclusion of only patients with community-acquired bacteremia might partially explain the low mortality rate in our series.

There were some limitations in this prospective observational study. First, as only ER patients were enrolled, patients with positive anaerobic blood cultures collected at the ward within 48 h of hospitalization were not represented, although such patients meet the conventional definition of community-acquired bacteremia [13]. Second, unlike this study, a recently proposed reappraisal of the definition of community-acquired bacteremia does not include patients from health care facilities [42,43]. Further studies are needed to evaluate the impact of health care on the development of anaerobic bacteremia. Third, because empirical antibiotics are subject to frequent change in the ER, only the antimicrobial agents used for at least 3 days were included in the analysis of adequacy. The impact of other antibiotics used for less than 72 h in the same patient remains unclear.

In conclusion, our findings suggest that *B. fragilis* group spp. are the most common isolates of community-acquired anaerobic bacteremia. The clinical manifestations of anaerobic bacteremia are highly suggestive and gastrointestinal tract infections affected most of the study population. The majority of patients received adequate empirical antibiotics and physicians rarely changed empirical regimens after documentation of anaerobic

bacteremia. Although resistant anaerobic pathogens are common, inadequate empiric therapy was not associated with a worse prognosis. Finally, this study demonstrated that underlying malignancy is an independent contributor to mortality in patients with anaerobic bacteremia.

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