Investigation of the risk factors of anaerobic bacteremia in a case–control study

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Background: Many case series studies have reported risk factors of infection with anaerobic bacteria, but few factor analysis studies have been conducted.

Objective: We conducted a case–control study to identify the risk factors of anaerobic bacteremia.

Methods: We compared a number of characteristics of patients with anaerobic bacteremia with those with aerobic bacteremia. Clinical information for 71 patients of anaerobic bacteremia was collected from January 1999 to December 2012 in Aichi Medical University Hospital. For each case, we identified up to four controls matched by the time of the positive blood culture.

Results: Multivariate logistic analyses revealed an association between anaerobic bacteremia and malignancy (OR: 3.35, 95%CI: 1.85–6.09), Douglas' pouch drains (OR: 25.90, 95%CI: 2.90–25.00) and chest drains (OR: 3.35, 95%CI: 1.19–9.43) as the primary causative disease, as well as associations between anaerobic bacteremia and the gastrointestinal tract (OR: 3.29, 95%CI: 1.38–7.81) , genitourinary tract (OR: 4.98, 95%CI: 2.06–12.05), Douglas' pouch drains (OR: 16.95, 95%CI: 1.82–166.67) and chest drains (OR: 3.62, 95%CI: 1.29–10.20) as the primary causative organs. On the other hand, our study showed that having a central venous catheter was not associated with anaerobic bacteremia.

Conclusions: We demonstrated an association between anaerobic bacteremia and malignancy, gastrointestinal and genitourinary tracts, patients having a Douglas' pouch drains or chest drains. These findings may be useful for developing early appropriate management for anaerobic bacteremia.

Introduction

It is widely accepted that the presence of anaerobes in the blood stream is associated with mortality. The detection rate of anaerobes in blood cultures is 1–17%, depending on the institution[1~6]. Some studies report a decrease in the number of blood cultures testing positive for anaerobes[6~9]. The presence of *Bacteroides* in the blood of patients with bacteremia is increasing[9], and a greater proportion of patients with anaerobic bacteremia present with underlying malignancies, diabetes, and gastrointestinal surgery[2,10,11].

In addition, anaerobic bacteremia has been associated with a poor clinical outcome, necessitating appropriate therapy[12,13]. It remains uncertain whether the rates of anaerobic bacterial infection are increasing or decreasing, and the accurate detection of anaerobes depends on the clinical laboratory of specific institutions. Because of these factors, it is important to recognize the risk factors of anaerobic bacteremia in order to take quick and appropriate action. Many case series studies have reported risk factors of infection with anaerobic bacteria[5,14,15], but few factor analysis studies have been conducted. As such, we initiated a case–control study to identify these risk factors using a more valid methodology.

Material and Methods

Setting

This study was conducted from January 1999 to December 2012 in Aichi Medical University Hospital (1014 beds). For blood culture, BD rezun bottles (Becton, Dickinson & Co., Tokyo, Japan) were used, and the BD BACTEC™ FX blood culture system (Becton, Dickinson & Co., Tokyo, Japan) was employed for the growth and detection of anaerobes. Each pair of aerobic and anaerobic bottles was incubated for one week in this system. All patient identifies were removed before analysis. This study was approved by the ethical committee of Aichi Medical University Hospital.

Case–control study

Definition of cases and controls

Patients with blood cultures positive for anaerobic bacteria included as cases and were retrospectively identified using fjwing bacterial test systems (Fuji Techno Supply Co.).

Bacteremia was deemed clinically significant when the patient had one or more positive blood cultures and met one of the following criteria: white blood cell count <4000 or $>12{,}000/\mu$L; temperature >38°C; or physical, pathological, or surgical evidence consistent with infection (*e.g.*, isolation of anaerobic bacteria from a source other than blood)[16]. Patients with *Propionibacterium* species from blood culture were defined as clinically significant using previously cited criteria[16,17].

For each case, we identified up to four controls matched by the time of the positive blood culture (within one week)[18~20]. Clinical significance was determined using the same criteria as listed above, and controls with clinically insignificant bacteremia were excluded.

Variables

We recorded the sex, age [children (≤15 years) and the elderly (≥65 years)], body temperature (℃), over 48 hours after admission, abscess formation, necrosis, ICU admission history, steroid use within four weeks, anticancer agent use within four weeks, blood glucose level (≥140 mg/dL)[21], primary causative disease and primary causative organ classified according to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)[22], and type of catheter or drain used.

Statistical analysis

Qualitative and stratified continuous variables were compared using Fisher's exact test or Pearson's χ^2 test. Continuous variables were compared using Student's t-test or the Mann-Whitney U test as appropriate. Multivariate logistic analyses were used for logistic regression models. The variables that achieved a p value <0.1 in univariate logistic analyses were included in the multivariate analysis[23]. Predictive values are presented as odds ratios (ORs) with their 95% confidence intervals (CI). p values <0.05 were considered statistically significant. We separated primary disease groups and primary disease organs for multivariate logistic analyses to avoid duplicate risk factors. Analyses were performed using IBM SPSS Statistics 19 (IBM®).

Results

Table 1 shows blood culture yield at Aichi Medical University Hospital. In one year, 601–

Table 1. Blood culture yield at Aichi Medical University Hospital

	1999	2000	2001	2002	2003	2004	2005
No. of sets all blood cultures	601	1045	844	1153	869	1044	1302
No. of sets containing positive all bacteria (%)	106 (17.6)	183 (17.5)	169 (20.0)	191 (16.6)	183 (21.1)	251 (24.0)	250 (19.2)
No. of sets containing positive anaerobic bacteria(%)	4 (0.67)	6 (0.57)	5 (0.59)	3 (0.26)	8 (0.92)	7 (0.67)	9 (0.69)

	2006	2007	2008	2009	2010	2011	2012
No. of sets all blood cultures	1583	1744	2332	2151	2754	3315	3666
No. of sets containing positive all bacteria (%)	234 (14.8)	304 (17.4)	390 (16.7)	329 (15.3)	485 (17.6)	586 (17.7)	628 (17.1)
No. of sets containing positive anaerobic bacteria(%)	5 (0.32)	13 (0.75)	16 (0.69)	13 (0.60)	16 (0.58)	14 (0.42)	32 (0.87)

The data for No. of sets of blood cultures

Table 2. Anaerobic bacteria isolated from blood culture

Anaerobic bacteria	No. of isolates (%)
Bacteroides species	20 (28)
Clostridium species	9 (13)
Prevotella species	6 (8)
Peptostreptococcus species	4 (6)
Anaerobic bacillus Gram-positive	17 (24)
Anaerobic bacillus Gram-negative	9 (13)
Others	6 (8)
Total	71

The data for all anaerobic bacteria isolated from blood culture in case patients

3666 sets of aerobic and anaerobic blood cultures were performed. For each year, 14.8–24.0% samples tested positive for aerobic and anaerobic bacteria, and positive tests for anaerobes were 0.26–0.92% that increasing tendency.

Seventy-one anaerobic bacteremia and 262 aerobic bacteremia patients were eligible for this study. Table 2 shows the data for all anaerobic bacteria isolated from blood culture in bacteremia patients. The most common anaerobic organisms were *Bacteroides* sp., followed by *Clostridium* sp. and *Prevotella* sp. In this study, approximately half of the anaerobes were unidentified because anaerobic bacteria identification was not routinely conducted.

Univariate logistic analysis

Table 3 shows the baseline characteristics and univariate logistic regression analyses of patient histories. Each variable was evaluated using univariate logistic analysis. Variables with p value <0.1 were [malignancy], [injury], [diseases of the muscle] [peritoneum] [circulatory system], [gastrointestinal tract], [genitourinary tract], [Douglas' pouch drains], and [chest drains].

Multivariate logistic analysis

The variables with p value <0.1 were examined using multivariate logistic analysis. There were few anaerobic bacteremia patients with the classification of [injury] and [diseases of the muscle] as the primary causative disease or the [circulatory system] and [peritoneum] as the primary causative organ were thus excluded from multivariate logistic analyses.

Multivariate logistic regression analysis of primary causative disease and the type of catheter or drain used

Table 4 shows the results of multivariate logistic regression analysis of the primary causative disease and the type of catheter or drain used. Independent risk factors of anaerobic bacteremia were [malignancy] (OR: 3.35, 95%CI: 1.85–6.09), [Douglas' pouch drains] (OR: 25.90, 95%CI:

Table 3. Univariate logistic regression analyses of patients histories

Factors	Cases (n = 71)	Controls (n = 262)	Odds ratio	p value	95%CI		
Age (mean ± SD)	63.9 ± 19.9	62.8 ± 22.2	-	0.691	-	-	-
children(≤15 years)	5	17	1.09	0.868	0.42	-	2.84
aged (≥65 years)	46	158	1.07	0.492	0.48	-	1.31
Male	40	159	1.11	0.507	0.82	-	1.51
Body temperature (mean ± SD)	38.3 ± 0.80	38.4 ± 2.93	-	0.698	-	-	-
Over 48 hours after admission	59	200	0.68	0.271	0.34	-	1.36
Abscess formation	16	54	1.09	0.724	0.67	-	1.79
Necrosis	2	5	1.48	0.644	0.29	-	7.45
ICU admission history	10	38	0.97	0.920	0.51	-	1.84
Use of steroids (within 4 weeks)	11	32	1.27	0.465	0.67	-	1.59
Use of anticancer agent (within 4 weeks)	7	17	1.52	0.330	0.66	-	3.52
Blood glucose level (≥140 mg/dL)	23	108	0.96	0.177	0.55	-	1.133
Primary causative diseases							
Malignancy	27	44	2.26	0.001	1.52	-	3.38
(parts breakdown) genitourinary tract	10	6					
lymphatic vessels and lymph nodes	4	14					
liver, gallbladder and biliary tract	4	13					
gastrointestinal tract	9	4					
endocrine system	1	1					
respiratory system	1	2					
central nervous system	0	2					
breast	0	2					
Injury	3	1	11.07	0.032	1.17	-	104.82
Infectious diseases	17	79	0.79	0.306	0.50	-	1.25
Diseases of the liver, gallbladder, biliary tract, and pancreas	0	6	-	-	-	-	-
Diseases of the muscle	3	2	5.54	0.067	0.94	-	32.49
Diseases of the blood and blood-forming organs	1	4	0.92	1.000	0.11	-	8.13
Diseases of the respiratory system	0	9	-	-	-	-	-
Autoimmune disease	2	8	0.92	1.000	0.20	-	4.25
Diseases of the arteries, arterioles, and capillaries	2	16	0.46	0.382	0.11	-	1.96
Diseases of the gastrointestinal tract	1	9	0.41	0.695	0.53	-	3.18
Ischaemic heart diseases	4	20	0.74	0.80	0.26	-	2.09
Glomerular diseases and renal failure	4	16	0.92	1.000	0.32	-	2.67
Metabolic disorders	0	5	-	-	-	-	-
Diseases of the central nervous system	1	2	1.85	0.514	0.17	-	20.06
Cerebrovascular diseases	5	25	0.51	0.644	0.29	-	1.86
Diseases of genitourinary system	1	2	1.85	0.514	0.17	-	20.58
Diseases of the skin and subcutaneous tissue	0	13	-	-	-	-	-

Table 3. (continued)

Factors	Cases (n = 71)	Controls (n = 262)	Odds ratio	p value	95%CI
Primary causative organs					
Lymphatic vessels and lymph nodes	1	5	0.74	1.000	0.88 - 6.22
Liver, gallbladder, biliary tract, and pancreas	5	24	0.77	0.574	0.30 - 1.94
Musculoskeletal system and connective tissue	4	13	1.14	0.766	0.38 - 3.38
Blood and blood-forming organs	3	9	1.23	0.724	0.34 - 4.42
Respiratory system	7	30	0.86	0.705	0.40 - 1.88
Peritoneum	4	3	4.92	0.040	1.13 - 21.48
Circulatory system	4	40	0.37	0.031	0.14 - 1.00
Gastrointestinal tract	11	16	2.54	0.024	1.23 - 5.22
Glomerular and renal	4	27	0.55	0.355	0.20 - 1.51
Systemic	4	17	0.87	1.000	0.30 - 2.50
Central nervous system	2	6	1.23	0.680	0.25 - 5.96
Endocrine system	3	11	1.01	1.000	0.29 - 3.51
Head and cerebrovascular	6	29	0.76	0.523	0.33 - 1.77
Genitourinary tract	12	12	3.69	0.001	1.73 - 7.86
Skin	2	15	0.49	0.542	0.12 - 2.10
Treatment unit	0	5	-	-	- - -
Types of catheters and drains					
Douglas' pouch drains	5	1	18.45	0.002	2.19 - 155.41
Lower leg	1	5	0.74	1.000	0.88 - 6.22
Chest drains	7	10	3.03	0.040	1.02 - 6.54
Gastrointestinal	4	11	1.34	0.534	0.44 - 4.09
Head	0	2	-	-	- - -
Dorsal and lumbar region	0	1	-	-	- - -
Genitourinary organ	17	63	1.00	0.986	0.62 - 1.59
Central venous catheters	28	114	0.91	0.538	0.66 - 1.25
Percutaneous endoscopic gastrostomy	1	4	0.92	1.000	0.11 - 8.13
Nasogastric tube	8	39	0.76	0.437	0.37 0.00 1.55

SD: Standard deviation
CI: Confidence interval
The baseline characteristics and univariate logistic regression analysis of patient histories.
Each variable was evaluated using univariate logistic analysis

Table 4. Multivariate logistic regression analysis of primary causative diseases and types of catheters and drains

Factors		Cases (n = 71)	Controls (n = 262)	Odds ratio	p value	95%CI
Primary causative diseases	Malignancy	27	44	3.35	<0.001	1.85 - 6.09
Types of catheters and drains	Douglas' pouch	5	1	25.90	0.004	2.90 - 25.00
	Chest	7	10	3.35	0.022	1.19 - 9.43

CI: Confidence interval
The results of multivariate logistic regression analysis of the primary causative diseases and the type of catheter or drain used

Table 5. Multivariate logistic regression analysis of primary causative organs and types of catheters and drains

Factors		Cases (n = 71)	Controls (n = 262)	Odds ratio	p value	95%CI	
Primary causative organs	Gastrointestinal tract	11	16	3.29	0.01	1.38 -	7.81
	Genitourinary tract	12	12	4.98	<0.001	2.06 -	12.05
Types of catheters and drains	Douglas' pouch	5	1	16.95	0.013	1.82 -	166.67
	Chest	7	10	3.62	0.015	1.29 -	10.20

CI: Confidence interval

The results of multivariate logistic regression analysis of the primary causative organs and the type of catheter or drain used

2.90–25.00) and [chest drains] (OR: 3.35, 95%CI: 1.19–9.43).

Multivariate logistic regression analysis of primary causative organ and the type of catheter or drain used

Table 5 shows the results of multivariate logistic regression analysis of the primary causative organ and the type of catheter or drain used. Independent risk factors of anaerobic bacteremia were [gastrointestinal tract] (OR: 3.29, 95%CI: 1.38–7.81), [genitourinary tract] (OR: 4.98, 95%CI: 2.06–12.05), [Douglas' pouch drains] (OR: 16.95, 95%CI: 1.82–166.67) and [chest drains] (OR: 3.62, 95%CI: 1.29–10.20).

Discussion

In cases where anaerobic bacteremia is suspected, a quick and appropriate action is important[13]. However, few factor analysis studies have been reported, and no previous studies have compared patients with anaerobic bacteremia with those with aerobic bacteremia. This case–control study was conducted to identify the risk factors of anaerobic bacteremia using aerobic bacteremia patients as controls.

Results of the current study indicated that age [children (≤15 years) and the elderly (≥65 years)] was not associated with anaerobic bacteremia. Saito reported that the mean age of patients with clinically significant anaerobic bacteremia was 62.9 years in four universities and one community hospital case series study[24]; similarly, the mean age in the current study was 63.9 years. In addition, Oguri reported in a 41-year case series study that 50% patients with anaerobic bacteremia were over 60 years[25], and Finegold *et al.* reported that the elderly were at a higher risk of anaerobic bacteremia than infants[26]. However, our findings revealed that age was not a characteristic risk factor of anaerobic bacteremia because there was little difference between case and control patients (Table 3). High blood glucose levels is a risk factor of various types of infection[10,22,27], but our study showed it was not a unique risk factor of anaerobic bacteremia (Table 3).

In this study, multivariate logistic regression analysis of the primary causative disease and the type of catheter or drain revealed that malignancy increased the risk of anaerobic bacteremia (Table 4). This observation is consistent with that of previous reports. For example, Saito *et al.* reported that 49% patients with anaerobic bacteremia had malignancy[24]. Similarly, Oguri *et al.* reported that 77.2% anaerobic bacteremia patients had some type of malignancy[25], and multiple institutional and long-term case series studies reported that numerous patients with anaerobic bacteremia had malignancy as the primary causative disease[13,28]. Our findings indicated that patients with malignancy had a specific risk ratio (OR) of 3.35 for anaerobic bacteremia compared with patients with aerobic bacteremia. This result has some unknown reasons. It has been suggested that these are causal factors, and it is important to consider the presence of anaerobes in patients with malignancies who are suspected of having bacteremia.

In a multivariate logistic regression analysis of the primary causative organ and type of catheter or drain used, gastrointestinal tract as the primary causative organ increased the risk (OR: 3.29) of anaerobic bacteremia (Table 5). Anaerobic bacteria are indigenous flora of the intestinal tract[29], primarily consisting of *Clostridium* and *B. fragilis*[30], which is consistent with previous studies. Robert *et al.*[16] and Oguri *et al.*[25] reported that in 52% and 46.5% patients, respectively, anaerobic bacteremia originated from the digestive tract. Brook *et al.* subsequently reported that the primary portal of entry for bacteria was the gastrointestinal tract[28]. Frainstein *et al.* reported that one of the most common malignancies was gastrointestinal malignancy[31]. The results of our study corroborate these findings.

In addition, in a multivariate logistic regression analysis of the primary causative organ and type of catheter or drain used, disease of the genitourinary tract increased the risk (OR: 4.98) of anaerobic bacteremia (Table 5). Some studies have reported an increase in anaerobic bacteremia among patients with genitourinary malignancies. *Bacteroides* and *Clostridium* are often detected in anaerobic bacterial infections of the genitourinary tract, and these can cause severe infections[30]. In general, anaerobic genitourinary tract infection frequently occurs in females. In our study, nine of the 12 case patients were female (data was not shown), but only four females had genitourinary tract infection while the others had malignancies. In order to confirm this finding, additional long-term studies at multiple institutions are necessary.

In a multivariate logistic regression analysis, Douglas' pouch drains and the chest drains increased risk of anaerobic bacteremia (Tables 4 and 5). Douglas' pouch and the chest are sites where anaerobic bacteria are often detected by cultivation tests[30,32]. Drainage is performed when abscesses are present in these locations, and we suggest that abscess formation increases the risk of anaerobic bacteremia.

On the other hand, our study showed that having a central venous (CV) catheter was not associated with anaerobic bacteremia (Table 3), but this finding was not statistically significant. However, this finding may have been the result of not including any patients with *Propionibacte-*

rium infection, which is an indigenous bacterium of the skin, because coagulase-negative staphylococci (such as *Staphylococcus epidermidis*) frequently cause bacteremia when a CV catheter is present.

However, our study had some limitations. First, our results were based on a retrospective review of routine microbiology data. We may have missed additional risk factors since our data includes a small sample size. Second, our study is 14 years long term study but one institution study, so patients of anaerobic bacteremia are not enough. Additional long-term prospective studies at multiple institutions are required to investigate a larger number of patients and to identify those risk factors using multivariate logistic analyses.

In conclusion, by using multivariate logistic analysis, we demonstrated an association between anaerobic bacteremia and malignancy as the primary causative disease, as well as associations between anaerobic bacteremia and the gastrointestinal and genitourinary tracts as the primary causative organs. In addition, the study revealed associations between anaerobic bacteremia and having a Douglas' pouch drains or chest drains. The results of this study are important for early and appropriate management of anaerobic bacteremia.

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Conflict of interest

The authors state that they have no conflict of interest with the subject matter discussed in this article.

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