Anaerobe 39 (2016) 45–50

Contents lists available at ScienceDirect

Anaerobe

journal homepage: www.elsevier.com/locate/anaerobe

Clinical characteristics associated with mortality of patients with anaerobic bacteremia

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ARTICLE INFO

Article history:
Received 17 March 2015
Received in revised form
15 February 2016
Accepted 18 February 2016
Available online 20 February 2016

Handling Editor: Elisabeth Nagy

Keywords:
Anaerobe
Anaerobic bacteremia
Blood stream infection
Prognostic factor
Clindamycin

ABSTRACT

The presence of anaerobes in the blood stream is known to be associated with a higher rate of mortality. However, few prognostic risk factor analyses examining whether a patient's background characteristics are associated with the prognosis have been reported. We performed a retrospective case-controlled study to assess the prognostic factors associated with death from anaerobic bacteremia. Seventy-four patients with anaerobic bacteremia were treated between January 2005 and December 2014 at Aichi Medical University Hospital. The clinical information included drug susceptibility was used for analysis of prognostic factors for 30-day mortality. Multivariate logistic analyses revealed an association between the 30-day mortality rate and malignancy (OR: 3.64, 95% CI: 1.08–12.31) and clindamycin resistance (OR: 7.93, 95% CI: 2.33–27.94). The result of Kaplan–Meier analysis of mortality showed that the 30-day survival rate was 83% in clindamycin susceptible and 38.1% in clindamycin resistant anaerobes causing bacteremia. The result of log-rank test also showed that susceptibility to clindamycin affected mortality ($P < 0.001$). Our results indicated that malignancy and clindamycin susceptibility could be used to identify subgroups of patients with anaerobic bacteremia with a higher risk of 30-day mortality. The results of this study are important for the early and appropriate management of patients with anaerobic bacteremia.

1. Introduction

An overall increase in the number of immunocompromised patients with various types of disease has reflected some of the changes in patient demographics over recent years. In addition to this phenomenon, an increase in the frequency of the isolation of anaerobic bacteria has been noted, with special emphasis on *Bacteroides* species from blood cultures [1,2]. It is important to recognize the risk factors of anaerobic bacteremia in order to enable quick and appropriate actions. Anaerobic bacteremia has been associated with associated with higher mortality, thus requiring appropriate therapy [3,4]. Risk factors for anaerobic bacteremia include an underlying malignancy, diseases of the gastrointestinal and genitourinary tracts, diabetes, and a history of gastrointestinal surgery [2,5–10].

The presence of anaerobes in the blood stream is known to be associated with mortality [11,12]. However, few risk factor analyses have been performed with the goal of investigating whether a patient's background characteristics are correlated with the prognosis. Therefore, we performed a retrospective case-controlled study to assess the risk factors associated with death from anaerobic bacteremia.

2. Materials and methods

2.1. Setting

This study was conducted from January 2005 to December 2014 at Aichi Medical University Hospital (1014 beds). For blood culture, BD rezun bottles (Becton Dickinson, Tokyo, Japan) were used, and the BD Bactec™ FX blood culture system (Becton Dickinson, Tokyo, Japan) was utilized for the growth and detection of

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http://dx.doi.org/10.1016/j.anaerobe.2016.02.007
1075-9964/

anaerobes. Each pair of aerobic and anaerobic bottles was incubated for a week. Anaerobic bacteria were identified using the RapID-ANA II system (Remel, Kansas, USA) and additional biochemical tests. All the patient identifiers were removed before analysis. This study was approved by the ethical committee of Aichi Medical University.

2.2. Definition of patients with anaerobic bacteremia

Patients with blood cultures positive for anaerobic bacteria were retrospectively identified using bacterial data included in electronic health records. 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 and > 12,000/μL; temperature >38 °C; or physical, pathological, or surgical evidence consistent with infection (e.g., isolation of anaerobic bacteria from a source other than blood) [12,13]. Patients with *Propionibacterium* species isolated from blood cultures were defined as clinically significant using previously cited criteria [12,14].

2.3. Variables

The following data were obtained for the analysis of prognostic factors for 30-day mortality: age, sex, white blood cell count, C-reactive protein, diabetes mellitus and malignancy as underlying diseases, intensive care unit (ICU) admission, primary disease, current administration of steroids or immunosuppressants for >4 weeks, clear source of bacteremia, initial inappropriate therapy, *Bacteroides* bacteremia, and multibacterial (or monobacterial) bacteremia, with drug resistance defined as intermediate or resistant based on drug susceptibility testing. Inappropriate therapy was defined as failure to administer anti-anaerobic drug therapy when a blood culture was submitted. Anti-anaerobic drugs were defined as beta-lactam/beta-lactamase inhibitor combinations, oxacephem, carbapenem, clindamycin, and other drugs identified by susceptibility testing.

2.4. Antibiotic susceptibility testing

Antibiotic susceptibility testing for clindamycin, amoxicillin-clavulanic acid, cefmetazole, imipenem, and moxifloxacin complied with the standards of Clinical and Laboratory Standards Institute (CLSI). The final inoculum for anaerobic bacteremia was 10^6 colony forming units (CFU) per mL. Brucella broth was supplemented with hemin (5 μg/mL), vitamin K_1 (1 μg/mL) and lysed horse blood. All the analyses were performed in anaerobic chambers. Cultures were incubated in an anaerobic atmosphere at 37 °C for 48 h. The strains were considered resistant according to break points defined by the CLSI.

2.5. Statistical analysis

Qualitative and stratified continuous variables were compared using the Fisher exact or Pearson χ^2 test. Continuous variables were compared using the Student *t*-test or the Mann–Whitney U test, as appropriate. Multivariate logistic analyses were used for the logistic regression models. Variables achieving a probability (*P*) value of <0.2 in the univariate logistic analyses were included in the multivariate analysis [15]. Survival was analyzed using the Kaplan–Meier method. Plots were compared using the log-rank test. Predictive values are presented as the odds ratios (ORs) with respective 95% confidence intervals (CI). Two-tailed *P* values < 0.05 were considered statistically significant. Analyses were performed using IBM SPSS Statistics 19 (IBM®).

3. Results

Seventy-four patients with anaerobic bacteremia were eligible for this study. Besides patients with monobacterial anaerobic bacteremia, also those were included who had multibacterial bacteremia caused by two different anaerobic species or an anaerobic and an aerobic bacteria were isolated from the blood culture at the same time. Table 1 shows the anaerobic bacteria detected in blood cultures and the results from drug susceptibility testing. The most frequently isolates anaerobic bacteria were *Bacteroides*, followed by *Clostridium*, *Prevotella*, and *Peptoniphilus*. Some anaerobes remained unidentified because the identification of anaerobic bacteria was not routinely performed. Only one deceased patient had multibacterial bacteremia involving *Bacteroides distasonis* and *Bacteroides thetaiotaomicron*. Unfortunately, not all the anaerobic blood culture isolates were tested for all anti-anaerobic drugs during the routine procedures in the laboratory (Table 1). However, we noticed that more resistant isolates among the *Bacteroides* strains to clindamycin, amoxicillin/clavulanic acid, cefmetazole, and moxifloxacin than among other anaerobic blood culture isolates. Out of 13 *Bacteroides fragilis* isolates, 5 isolates (38.4%) were susceptible to clindamycin, whereas 8 isolates (61.6%) were resistant. Among the non-fragilis *Bacteroides* isolates, 4 (33.3%) strains were susceptible to clindamycin and 8 (66.7%) showed resistance. Among the *Bacteroides* strains, which had resistance data for amoxicillin/clavulanic acid were available, 10 (55.6%) were susceptible and 8 (44.4%) were resistant. The same tendency was seen for cefmetazole and moxifloxacin. All the tested *Bacteroides* blood culture isolates were fully susceptible to imipenem. We found only one anaerobic Gram-negative bacillus (unidentified) which showed resistance to imipenem.

Table 2 shows the possible sources of the anaerobic bacteremia of the patients according to whether they survived or died within 30 days, according to their other clinical data. In general, a gastrointestinal origin of infection led to anaerobic bacteremia in both patients group was dominating. Regarding the origin of the bacteremia, the incidence of the intra-abdominal foci were significantly higher in the deceased patient group than in the survivors ($P = 0.030$), while no other source of anaerobic bacteremia was significantly linked to unfavorable patients outcome (Table 2).

Table 3 shows the results of univariate analyses of the included patient characteristics. Variables with *P* values < 0.2 included malignancy ($P = 0.017$), a history of ICU admission ($P = 0.060$), inappropriate therapy ($P = 0.174$), and clindamycin resistance ($P < 0.001$). Univariate analysis was carried out only for clindamycin and imipenem resistance. Susceptibility testing was not consistently conducted for other drugs.

Table 4 shows the results of a multivariate logistic regression analysis of prognostic factors associated with the mortality of anaerobic bacteremia. No statistically significant differences in ICU admission ($P = 0.266$) or inappropriate therapy ($P = 0.287$) were observed between the groups. Independent prognostic factors were malignancy (OR: 3.64, 95% CI: 1.08–12.31) and clindamycin resistance (OR: 8.06, 95% CI: 2.33–27.94). Table 5 shows the antimicrobial agents that were administered to all patients with anaerobic bacteremia. In the survival group, the antibiotic therapy of two patients was changed from ceftriaxone to carbapenem and piperacillin/tazobactam, respectively, according to the positive anaerobic blood culture results.

Fig. 1 shows the Kaplan–Meier survival analysis of mortality at 30 days of follow up according to clindamycin susceptibility. The 30-day survival rates were 83% for patients with clindamycin-sensitive isolates and 38.1% for patients with clindamycin-resistant isolates. A log-rank test showed that clindamycin susceptibility affected the mortality rate ($P < 0.001$).