Clinical features and prognostic factors of anaerobic infections

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Abstract

CLINICAL FEATURES AND PROGNOSTIC FACTORS OF ANAEROBIC INFECTIONS

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A total of 1,050 patients with anaerobic infection at the Severance Hospital, Yonsei University College of Medicine in Seoul, Korea, were reviewed. Mean age of the patients was 54.1 years (SD 16.8). 57.7% of patients were male.

Overall, 320 (30.5%) of persons with case-defined illness experienced pain on affected site, and 230 (21.9%) experienced pus from the lesion. 10 (1.4%) patients were presented as shock state.

In view of the results, 80.3% of all clinically significant cases were polymicrobial anaerobic infections. The number of pathogens including aerobe and anaerobe was 3.69±0.968 (minimum; 1, maximum; 5) and the number of anaerobic organism was 1.03±0.259 in each specimens. The rank order of the major pathogens was that *Bacteroides fragilis* group accounted for 41.8% of anaerobic infections, followed in rank *Clostridium* species (11.8%), *Prevotella* species, (9.4%) and *Peptostreptococcus* species (8.4%). *Escherichia* coli (17.5% of episodes), *Staphylococcus aureus* (7.5%) and *Klebsillea pneumoniae* (7.5%), were common concomitant aerobic organisms.

Overall crude mortality of anaerobic infection was 29.7%, with much higher crude mortality among patients with nosocomial versus community-onset infections. Among

the determining factors associated with mortality with $p<0.05$, liver disease ($p=0.003$) and increasing age ($p<0.005$) were statistically significant in multivariate analysis.

Key Words: anaerobe, anaerobic infections, clinical features, prognostic factors

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I. INTRODUCTION

Anaerobic bacteria can cause a variety of endogenous infections.[1] Because of their fastidious nature, they are difficult to isolate from infectious sites, and are often overlooked.[2]

It is becoming clear that anaerobes play a key role in maintaining the balance between the host and its colonizing organisms. Anaerobic infections occur when the harmonious relationship between the host and the bacteria is disrupted. Such mixed infections are seen in the head and neck (chronic sinusitis, chronic otitis media, Ludwig's angina, and periodontal abscesses).[3] Brain abscesses and subdural empyema are the most common anaerobic infections of the central nervous system[4,5]. Anaerobes are responsible for pleuropulmonary diseases such as aspiration pneumonia, necrotizing pneumonia, lung abscess, and empyema[6]. These organisms also play an important role in various intraabdominal infections, such as peritonitis and intraabdominal and liver abscesses. They are isolated frequently in female genital tract infections, such as salpingitis, pelvic peritonitis, tuboovarian abscess, vulvovaginal abscess, septic abortion, and endometritis. Anaerobic bacteria are also found often in infections of the skin,

soft tissues, and bones and in bacteremia[1,2].

Their isolation requires appropriate methods of collection, transportation and cultivation of specimens[7]. Treatment is complicated by their slow growth, their polymicrobial nature and their growing resistance to antimicrobials. Antimicrobial therapy is often the only form of therapy required, whereas in others it is an important adjunct to a surgical approach. Because anaerobes are generally recovered mixed with aerobic organisms, the choice of antimicrobial agents should provide coverage of both types of pathogens[8].

Despite the relatively low incidence of anaerobic infections, it remains associated with significant mortality. Recent estimates of case fatality rates in patients with clinically significant anaerobic bacteremia range from 25% to 44%[9].

The aims of the present study were to determine the clinical feature for a broad range of obligate anaerobic organisms isolated from blood, cerebrospinal fluid, peritoneal fluid, pleural fluid etc, and to define the factors independently associated with mortality.

II. MATERIALS AND METHODS

1. Materials

The present study was conducted at Severance hospital, Yonsei University College of Medicine, Seoul, Korea that is a 1544-bed tertiary care referral center with large hematopoietic stem cell and solid organ transplant specialty services, from January 1996 to December 2003.

Consecutive 1,050 adult patients (>17 years old) with 3,169 results of sterile fluid and abscess cultures for anaerobic bacteria were retrospectively identified from clinical microbiology records. Following the first positive anaerobic culture, outcome data were collected from the patient medical records and clinical microbiology laboratory records for 30 days or discharge or until death, whichever came first.

2. Methods

The primary endpoint was mortality, recorded as the number of days after the positive results of culture positive for anaerobic bacteria. The following variables were assessed: personal information (i.e., age, sex of the patient), dates of admission and discharge, mode of acquisition (nosocomial or community acquired), type of infection (polymicrobial or monomicrobial), source of infection, results of cultures, types of surgeries and procedures performed during hospitalization, diagnosis at discharge and presence of concurrent underlying diseases (i.e., heart, liver, lung, or kidney disease, hypertension, diabetes, malignancy, immunosuppression, etc.).

The presence of an underlying disease was based on the description made by the physician. Each disease variable was similarly defined; a patient was only considered to have a disease if it was documented as ongoing at the time of the positive culture results. Immunosuppression was said to be present if the patient had a history of solid organ transplant, had AIDS, was pregnant, or was undergoing high-dose steroid

therapy.

The source of infection was determined by radiological, surgical or microbiological evidence of barrier compromise or infectious pathology, such as abscess or necrosis. Based on National Nosocomial Infection Surveillance system guidelines, infections were deemed nosocomial if the positive culture was drawn more than 48h after admission to the hospital[10].

The results were expressed as the mean ±SD or as a proportion of the total number of patients or isolates. For continuous variables, mean values were compared using 2 sample *t* test for independent samples. Differences in proportions were compared using a x^2 test. Mean values are reported with standard deviations. All tests of significance are 2-tailed; *a* was set at 0.05. Mortality was evaluated using univariate and multivariate Cox proportional hazards models. All statistical analyses were done using SPSS software.

III. RESULTS

1. Study population and patient characteristics

Total 3,169 anaerobic organisms from 1,050 patients were reported. Patients with clinically anaerobic infections ranged in age between 18 and 88 years (median, 58.0 years; mean, 54.1 years; standard deviation, 16.8 years). 57.7% of patients were male.

The most frequent underlying conditions (recorded as diagnoses at admission) were malignancy, in 343 patients (32.7%); diabetes mellitus, in 132 patients (12.6%); renal diseases, in 123 patients (11.7%); and liver diseases, in 88 patients (8.4%) (Table 1).

Table 1. Patients Characteristics

Parameter (N = 1,050)		
Age (yr)		54.1±16.8
Sex	M : F	1 : 0.733
Underlying diseases	Malignancy	343 (32.7%)
	Diabetes mellitus	132 (12.6%)
	Renal allograft or end-stage renal disease	123 (11.7%)
	Liver disease	88 (8.4%)

2. Clinical features

Symptoms as information on anaerobic infections was available for 1,008 (96%) of 1,050 cases. Overall, 320 (30.5%) of persons with case-defined illness experienced pain on affected site, and 230 (21.9%) experienced pus from the lesion. 10 (1.4%) patients were presented as shock state (Table 2). Mean duration of illness was 20.0 days (SD 23.8).

Table 2. Presenting symptoms and signs (N=1,050)

Symptoms and signs	Number (%)
Pain on affected site	320 (30.5%)
Pus from the lesion	230 (21.9%)
Fever	189 (18.0%)
Symptoms involving CNS*	70 (6.7%)
General weakness	40 (3.8%)
Mass	19 (1.9%)

*CNS; central nervous system

There were various kinds of diagnosis derived from anaerobic infections (Table 3). 157 patients having predisposing surgery were identified and more than half (56%) of them resulted from abdominal surgery.

Table 3. Diagnosis derived from anaerobic infections (N = 1,050)

Anatomical site	Diagnosis	Number (%)
Head and Neck	Sinusitis	38 (3.6%)
	Otitis media	63 (6.0%)
	Retropharyngeal abscess	14 (1.3%)
Lung and Thorax	Lung abscess or empyema	80 (7.6%)
Abdomen*		156 (14.9%)
Soft tissue and extremities	Burn	4 (0.4%)
	DM foot	79 (7.5%)
	Necrotizing fasciitis	20 (1.9%)
	Septic arthritis	16 (1.5%)
	Pressure sore	123 (11.7%)
Bacteremia		284 (27.0%)
Catheter related	CAPD† peritonitis	13 (1.2%)
	V-P‡ shunt infection	3 (0.3%)
Predisposing surgery due to cancer or accidents		157 (15.0%)

*Abdomen included liver abscess, gall bladder stone or biliary tract infection, bowel obstruction, periappendiceal abscess or intra-abdominal abscess

†CAPD=Continuous ambulatory peritoneal dialysis

‡V-P=Ventriculo-peritoneal

3. Microbiological features

From these results, 80.3% of all clinically significant cases were polymicrobial anaerobic infections. The number of pathogens including aerobe and anaerobe was 3.69± 0.968 (minimum; 1, maximum; 5) and the number of anaerobic organism was 1.03± 0.259 in each specimens. The rank order of the major pathogens shows that *Bacteroides fragilis* accounted for 41.8% of anaerobic infections, followed in rank *Clostridium* species (11.8%), *Prevotella* species (9.4%) and *Peptostreptococcus* species (8.4%). *Escherichia coli* (17.5% of episodes), *Staphylococcus aureus* (7.5%) and *Klebsillea pneumoniae* (7.5%), were common concomitant aerobic organisms (Table 4).

Table 4. Isolated bacterial strains

Anaerobic bacteria	Number of anaerobe (%)
Bacteroides fragilis	1,325 (41.8%)
Clostridium species	374 (11.8%)
Prevotella species	298 (9.4%)
Peptostreptococcus species	266(8.4%)
Bacteroides species	247(7.8%)
Peptostreptococcus asaccharolyticus	193(6.1%)
Peptostreptococcus magnus	193(6.1%)
Propionibacterium acnes	171(5.4%)
Fusobacterium species	76(2.4%)
Bifidobacterium species	63(2.0%)
Clostridium perfringens	54(1.7%)
Total	3,169 organisms
Concomitant isolation of aerobic bacteria	Number of aerobe (%)
Escherichia coli	401(17.5%)
Staphylococcus aureus	172(7.5%)
Klebsiella pneumoniae	172(7.5%)
Coagulase negative staphylococci	144(6.3%)
Enterococcus faecalis	114(5.0%)
Streptococcus species	87(3.8%)
Total	2,295 organisms

4. Mortality and prognostic factors

A few simple abscesses and otitis media even needed no antibiotics and some cases could only recover by surgical intervention such as aspiration or drainage. Consequently, complete resection of infected source could make cure even though no additional antimicrobials. But, despite of sufficient therapy, half of the patients suffering from pressure sore passed away. In view of their underlying disease, most of them (60%) had malignancy treated with chemotherapy and radiation therapy and the rest was bed-ridden state due to cerebrovascular accidents. In anaerobic bacteremia patients, adequate surgical intervention induced higher survival (81.8% vs 57.1%, $p<0.05$) than not.

Overall crude mortality was 29.7% and among patients who died, the mean and median time to death was 10.7 and 3.5 days, respectively (range, 0.4 to 37 days).

Each variable was evaluated using a Cox proportional hazards model to determine factors associated with mortality. Four discrete factors with $p<0.05$ were increasing age per year over 18 ($p=0.011$), inappropriate prescription of antibiotics at diagnosis and no postoperative antibiotics use ($p=0.014$, $p=0.019$), and underlying liver disease ($p=0.0006$) disease.

The four significant factors were examined using multivariate Cox proportional hazards analysis to determine which variables were acting independently. Liver disease ($p=0.003$) and increasing age ($p=0.005$) were statistically significant in this analysis. (Table 5)

Table 5. Prognostic factors associated with mortality(p<0.05)

		Univariate analysis(P)	Multivariate analysis(P)
Age		*0.011	*0.005
Sex		0.4	
Inappropriate antibiotics prescription	at diagnosis	*0.014	0.45
No antibiotics use for anaerobe	postoperative	*0.019	0.7
Polymicrobial infections		0.05	
Nosocomial acquisition		0.34	
Underlying diseases	Liver disease	*0.0006	*0.003
	Immunosuppression	0.8	
	Diabetes mellitus	0.8	
	Malignancy	0.4	

*significant statistically

IV. DISCUSSION

It is well known that the factors predisposing to infections due to anaerobes include neoplasms, hematologic disorders, organ transplant, recent surgery, diabetes mellitus, and the use of cytotoxic agents or corticosteroid[2].

Many of the patients expressed their pain and pus on affected site and few patients were presented as shock state in this study. But, in view of bacteremia patients, most common clinical symptom and sign was fever (70%) as like previous study in 1989[11,12].

This study showed the average number of anaerobes per specimen was 1.03 and most common pathogen was *Bacteroides fragilis* (41.8%). And total average number of organisms per specimen was 3.69±0.968. Shin et al. reported that most frequently isolated was *B. fragilis* and *Peptostreptococcus magnus*[13]. Most common concomitant isolation of aerobic bacteria was *E.coli* and that reason was deemed that had affected by each underlying disease. Anaerobic infections in the skin and soft tissue might be most often caused by contamination with fecal or oral flora[14]. Also, it could be noted that there is a strong correlation between the development of carcinoma of the bowel and intra-abdominal infection despite of no significance of statistics.

Among many important lessons, it is prominent that the proper management of anaerobic infection depends on suspicion and appropriate documentation of the bacteria causing infection. In this study, we had some significant statistics on the antibiotics use; inappropriate anaerobic antibiotics prescription at diagnosis (p=0.014) and no post-toperative antibiotics use (p=0.019) as prognostic factors with mortality. In relation to antibiotics use, Hecht said antibiotic-resistant anaerobic bacteria have become increasingly recognized as a confounding factor in the selection of therapeutic agents.[15] Although appropriate therapy for anaerobic infections has been associated with significant reductions in mortality[16], most clinical laboratories still do not perform routine anaerobic susceptibility testing[17]. Among the 913 clinical isolate of *B. fragilis* group organisms isolated during an 8-year period in Severance hospital, the resistances to

antimicrobial agents such as piperacilliin, third-generation cephalosporins, and clindamycin were not uncommon, and antimicrobial susceptibility testing of these drug was necessary before using them[18,19]. So, we should always concentrate on appropriate narrow-spectrum antibiotics for prescription in fields.

And, surgery is important adjunct to a medical approach, such as draining abscesses, debriding necrotic tissues, decompressing closed-space infections. However this study could not show correlation of surgical intervention with mortality by Pearson x^2 test.

The current study of patients with infections due to a broad range of anaerobic pathogens, demonstrated that age and liver disease is strong, independent risk factor for mortality in multivariate analysis. Mortality in the current study is reported as crude mortality, rather than attributable mortality, since the relative contribution of anaerobic infection to the overall mortality rate could not be reliably ascertained. Our data demonstrate a 29.7% crude mortality rate for clinically significant anaerobic infections. The majority of previous studies of patients with anaerobic infections also reported mortality rates as crude mortality, with recently published estimates ranging between 25% and 44% in studies that included a broad range of anaerobic pathogens[9]. In several cases, mortality was assessed with reference to discharge from the hospital or to the interval of antibiotic treatment[22]. Our figures were based on mortality within 30 days following the first positive blood culture.

The present study provides an updated perspective on the clinical significance of infections due to each of a broad range of anaerobic species. This information may be helpful (when combined with careful clinical assessment) in determining the clinical significance of cultures with anaerobic organisms. However, given changes in the available antimicrobial therapy and bacterial susceptibility, these studies are difficult to apply to current circumstances; additionally, they failed to include multivariate statistical analysis. The strengths of the present study are the diversity of the study population and the relatively large sample size. We were able to study a varied study population with a broad range of underlying conditions and clinical presentations. The

distribution of pathogens was similarly diverse, with the proportions of clinically significant pathogens similar to those reported recently.

There are some limitations to the present study. First, as with any retrospective review, there is the potential for selection bias and data omissions. Second, not all analyzed variables were necessarily included in the present study. Thus, both liver disease and severity of illness measures should be included as independent variables in further studies, in order to confirm their association with mortality.

In conclusions, by means of multivariate analysis we have demonstrated a strong and independent association between age, underlying liver disease and mortality.

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국문 요약

혐기성 세균 감염의 임상 양상 및 예후 인자

최근 중증의 기저 질환이나 면역기능이 심하게 저하된 환자의 증가에 따라 혐기성 세균 감염의 빈도가 증가하고 있는 추세로 본 연세대학교 의과대학 세브란스병원에서 1996년 1월부터 2003년 12월까지 혐기성 세균이 분리된 환자 1,050명을 분석하였다. 평균 연령은 54.1±16.8세이며 남녀비는 1:0.7이었다. 320명(30.5%)의 환자들은 내원 당시 병변 부위의 통증을 호소하였고, 230명(21.9%)의 환자는 병변 부위의 분비물이나 농을 주소로 내원하였다.

혐기성 세균과의 복합 감염은 80.3%이었다. *Bacteroides* spp. (41.8%)가 가장 흔한 균종이며, 다음으로 *Peptostreptococcus* (20.6%), *Clostridium* (11.8%), *Prevotella* (9.4%), *Propionibacterium* (5.4%), *Lactobacillus* (3.3%), *Fusobacterium* (2.4%), *Bifidobacterium* (2.0%), *Actinomyces* (1.7%), *Gemella* (1.2%)으로 빈도를 보였다. 혐기성 균주와 동반된 호기성 균주는 *Escherichia coli* (17.5%), *Staphylococcus aureus* (7.5%), *Klebsillea pneumoniae* (7.5%)의 순서로 빈도가 높았다. 1,050명에서 치료 중 사망한 환자는 312명으로 사망에 기여한 위험 인자는 나이 (p=0.011) 및 간질환 (p=0.0006)이었다. 적극적인 수술적 처치를 받은 환자는 항생제 투여만으로 보존적 치료를 받은 군에 비해 생존율이 높았으며, 혐기성 세균을 대상으로 적절한 항생제를 투여한 경우에 상대적으로 치료 성적이 우수하였다.

핵심되는 말: 혐기성 세균, 혐기성 세균 감염, 임상 양상, 예후 인자