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Anaerobic bacteremia in a cancer center

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Abstract. Seventy-five episodes of clinically relevant anaerobic bacterial bacteremia observed in cancer patients were reviewed. Gastrointestinal (22.7%), hematological (22.7%) and female genital tract (18.6%) cancers were the most common underlying malignant diseases. Among 84 strains of strict anaerobic bacteria recovered in the 75 patients, gram-negative rods were isolated in 49 patients (58.3%), gram-positive rods in 29 patients (34.5%) and gram-positive cocci in 6 patients (8%). *Bacteroides* spp. and *Clostridium* spp. were the most frequent pathogens (85.7%). Twenty-one episodes of bacteremia were polymicrobial, aerobic gram-positive cocci being the most frequently associated pathogens. When identified, the primary sites were the gastrointestinal tract (40%), the female genital tract (17.3%), skin and soft tissue (14.6%), the oropharynx (12%) and the lower respiratory tract (6.7%). The source remained unknown in 7 cases (9.3%). The overall survival (evaluated 10 days after the occurrence of bacteremia) was 82.5%. There was no difference in mortality between patients with monomicrobial and polymicrobial bacteremia. Pulmonary complications were more frequent in patients with fatal outcome in comparison to patients who survived. The mortality rate of the patients adequately treated was 10.3% compared to 41% for the patients not treated or treated inadequately ($P=0.016$, χ_2).

Key words: Anaerobes – Bacteremia – Cancer – Bacteroides – Clostridium

Introduction

Anaerobic bacteria account for an important part of the endogenous human microflora and are recognized as relatively common causes of infection. Upper airways and the gastrointestinal and female genital tracts harbor a large number of these bacteria, and therefore are considered as the most frequent portals of entry for anaerobic infections.

Tissue necrosis and breaches of the mucotaneous barriers are two features frequently encountered in cancer patients producing an appropriate environmental milieu that will permit anaerobic bacteria to invade the host.

Despite these considerations, anaerobic bacteremia in cancer patients is a fairly infrequent event. The recovery of anaerobic bacteria ranges between 5% and 12% of positive blood cultures among unselected non-cancer patients with clinically significant bacteremia [2, 3, 7, 13, 14, 20]. Bacteremia due to strict anaerobes is particularly unusual in granulocytopenic patients representing less fewer 1% of all the bacteremic isolates [7, 8, 15]. From the comparison between previous studies published in the 1970s and early 1980s [11, 14, 17, 22] and those published more recently [7, 13], the incidence of anaerobic bacteremia seems to have declined.

In this study we are reviewing the episodes of anaerobic bacteremia occurring in a cancer hospital over 10 years. Clinical characteristics of the patients and microbiological data are analyzed.

Materials and methods

All records of blood cultures performed between 1979 and 1989 in the microbiology laboratory of the Institut Jules Bordet were reviewed. Over this period, 142 episodes of anaerobic bacteria bacteremia were documented, corresponding to 7% of all bacteremic episodes.

Eighty-four charts were available for review from the medical archives and were analyzed. Four patients were excluded because they had no cancer and 5 because bacteremia was caused by *Propionibacterium acnes*, which was considered to be clinically insignificant.

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Patients who had a strict anaerobic organism, alone or in association with other organisms, isolated from one or more blood-culture sets, were included and considered as significant providing they had clinical manifestations of bacteremia including fever, chills or septic chock, or an evident source of infection.

Multiple isolations of an identical organisms were considered to be single episodes. Brain/heart infusion (BHI) broth (Gibco) was used for anaerobic blood cultures. Specimens were inoculated on Columbia blood agar and incubated anaerobically using a Gaspack anaerobic system (BBL, Cockeyville). Pathogens recovered from blood cultures were identified according to standard procedures.

For susceptibility testing, we used the Neo-sensitabs agar-disk diffusion method (Rosco Diagnostic Teastrup, Denmark). The inoculum was prepared directly by picking up several colonies from a fresh agar plate and suspending them in the BHI medium to a final concentration of 10^7–10^8 colony-forming units/ml.

After adjustement, the strains were applied with cotton swabs to the surface of Columbia blood agar. Neo-sensitabs were applied and the plates were incubated in anaerobic conditions. Zones of inhibition were measured after 24–48 h of incubation at 37° C and compared with two different interpretative zone standards, one for the fast-growing and another for the slow-growing anaerobic bacteria according to the manufacturer [4].

The underlying cancer disease, age, sex, predisposing factors, clinical characteristics, occurrence of granulocytopenia (polymorphonuclear neutrophils, PMN $<1000/\mu l$), primary site, types of associated pathogens, in vitro susceptibility, treatment and outcome were recorded.

Cancer disease was considered to be evolutive if rapid clinical or laboratory progression was evident within 2 weeks and not evolutive if only localized or no progressive disease was detected.

Only systemic cancer chemotherapy (including steroid treatment) and surgical treatment performed within 30 days before the onset of anaerobic bacteremia were considered as predisposing factors.

The determination of the primary source of bacteremic isolates was mainly based on clinical data and, whenever available, confirmed by microbiological data.

Bacteremia was considered polymicrobial if two or more bacterial species were isolated from blood cultures within a 24-h period [16].

Breakthrough bacteremia was defined as persistent isolation of organisms for 5 days or recurrent bacteremia within 10 days of treatment end that occurred despite appropriate antimicrobial therapy [21].

Patients were considered to be in septic shock when they had signs and symptoms of hemodynamic instability with systolic blood pressure below 90 mm Hg (12 kPa) or a decrease of at least 40 mm Hg (5.3 kPa) from baseline despite adequate fluid infusion and without evidence of hemorrhage.

Antimicrobial therapy that includes at least one antibiotic proven to be active in vitro against the anaerobic organism was considered to be adequate. In 12 cases where no sensitive tests were performed, appropriateness of therapy was judged on the sensitivity pattern of various anaerobic species isolated at the Institut Jules Bordet.

Death was considered to be related to bacteremia if occurring within 10 days of the onset of bacteremia unless clinical and pathological data clearly suggested another reason.

Results

The mean incidence of anaerobic bacteremia during this study was 3/1000 admissions (range: 1.5–5.6/1000). Anaerobic bacteremia represented 7% of all bacteremic episodes in our hospital.

The characteristics of the patients are shown in Table 1, stratified according to the granulocyte count at the time of bacteremia.

As indicated in Table 1, among 75 patients studied, 51% were female and 49% were male. Their age ranged from 20 to 84 years (mean age 54.4 years).

Thirty-three patients (44%) received chemotherapy and 27 patients (36%) had surgery during the last month preceeding anaerobic bacteremia.

Seventeen patients (23%) were profoundly granulocytopenic (PMN $\leq 100/ml$) on the day of onset of bacteremia. In 16 patients, granulocytopenia was secondary to systemic antineoplastic chemotherapy and in 1 patient it was consequence of the underlying malignancy.

Three patients (4%) were receiving immunotherapy and 6 patients (8%) corticosteroids. The most common underlying malignancies were gastrointestinal (22.7%), genital (18.7%) and hematological (22.7%). Cancers of the head and neck, lung, urinary tract, breast, skin and soft tissue and miscellaneous cancers accounted for the other 36%.

Malignant disease was considered to be evolutive in 81.3% of the patients and not evolutive in 18.7%.

Among clinical manifestations of bacteremia, fever (T $>38°$ C) was documented in 61 patients (81.3%) and chills in 20 patients (26.7%). Septic chock occurred in 11 patients (14.7%).

The most probable sources of bacteremia are shown in Table 1. The gastrointestinal tract was predominant (40%), followed by the female genital tract (17.3%), skin and soft tissue (14.7%), the oropharynx (12%) and the lower respiratory tract (6.7%). Only 7 patients (9.3%), all with hematological malignancy, had no source identified.

The site of malignancy correlated well with the source of bacteremia in 80% of patients.

Breakthrough bacteremia was found in 8 patients (10.7%). Among the 17 patients with profound granulocytopenia, 7 (41.2%) had polymicrobial bacteremia. As expected, most granulocytopenic patients (97%) had hematological malignancy. The source of bacteremia remained unknown in 42% of them.

Microbiological documentation of the offending pathogen at a potential portal of entry was obtained in 18 patients (24%) and negative or not feasible in 57 patients (76%).

The distribution of the pathogens identified is shown in Table 2.

Eighty-three strains of anaerobic bacteria were isolated in 75 patients. Gram-negative bacilli were found in 49 episodes (58.3%), gram-positive bacilli in 29 episodes (34.5%) and gram-positive cocci in 6 episodes (7.2%).

Bacteroides spp. occurred in 51.2% of the 75 episodes and *Clostridium* spp. in 31%. A similar distribution was seen in gastrointestinal, breast and genitourinary cancer while, in patients with female genital tract malignancy, the *Bacteroides* group accounted for 87% of the cases and the *Clostridium* group for only 6.7%. *Bacteroides* spp. and *Clostridium* spp. accounted for

Table 1. Characteristics of the patients

Characteristic	No granulocytopenia	Granulocytopenia[a]	Total
No. of patients	58	17	75
Male/female	26/32	11/7	37/38
Mean age (years)	55.7	50.3	54.4
Range	22–80	20–67	20–80
Predisposing factors			
Antineoplastic chemotherapy	17 (29.3)[b]	16 (94.0)	33 (44.0)
Surgery	27 (46.6)		27 (36.0)
Corticosteroids	2 (3.5)	4 (23.5)	6 (8.0)
Underlying malignancy			
Gastrointestinal	17 (29.3)		17 (22.7)
Hematological malignancy	1 (1.7)	16 (94.0)	17 (22.7)
Female genital tract	13 (22.4)	1 (6.0)	14 (18.6)
Breast	7 (12.0)		7 (9.3)
Head and neck	7 (12.0)		7 (9.3)
Urinary tract	5 (8.6)		5 (6.7)
Miscellaneous[c]	4 (6.9)		4 (5.3)
Skin and soft tissue	2 (3.5)		2 (2.7)
Lung	2 (3.5)		2 (2.7)
Clinical data			
Fever (>38°C)	47 (81.0)	14 (82.4)	61 (81.3)
Chills	14 (24.1)	6 (35.3)	20 (26.6)
Shock	8 (13.8)	3 (17.6)	11 (14.6)
Breakthrough bacteremia	5 (8.6)	3 (17.6)	8 (10.7)
Source of bacteremia			
Gastrointestinal	25 (43.1)	5 (29.4)	30 (40.0)
Female genital tract	13 (22.4)		13 (17.3)
Skin and soft tissue	10 (17.2)	1 (5.9)	11 (14.6)
Oropharynx	6 (10.3)	3 (17.6)	9 (12.0)
Lower respiratory tract	4 (6.9)	1 (5.9)	5 (6.7)
Unknown		7 (41.2)	7 (9.3)

[a] On the day when positive blood cultures were drawn
[b] Percentages given in parentheses
[c] Seminoma, retroperitoneal Schwanoma, thymoma, pancreas cancer

Table 2. Pathogens identified in 75 episodes of anaerobic bacteremia

Single anaerobic isolates (53 episodes)	
Bacteroides group	29
Clostridium group	18
Peptostreptococcus spp.	3
Fusobacterium sp.	1
Capnocytophaga sp.	1
Propionibacterium sp.	1
Polymicrobial anaerobic isolates (1 episode)	
Clostridium perfringens + *Bacteroides* species	
Mixed bacteremia (22 episodes)	
Bacteroides group	14
Clostridium group	7
Peptostreptococcus sp.	1
Propionibacterium spp.	2
Leptotrichia spp.	3
Fusobacterium sp.	1
Staphylococcus aureus	3
Coagulase-negative *Staphylococcus*	6
Escherichia coli	5
Streptococcus spp.	8
Enterococcus faecalis	3

30% and 50% respectively in head and neck malignancies, and for 38.9% and 38.9% respectively in hematological malignancies.

Among the 75 episodes, 22 (29%) were polymicrobial and 53 (71%) were caused by a single organism. Among the polymicrobial infections 2 or more anaerobic bacteria during the same episode occurred in 6 patients (8%). Of those, 3 had 2 anaerobic organisms and 3 had more than 2 anaerobic bacteria. Only 1 patient had positive blood cultures for 2 anaerobic organisms without aerobic pathogens. In 4 patients, more than one aerobic bacterium was recovered from the blood cultures. As shown in Table 2, gram-positive cocci accounted for 80% of associated aerobic pathogens and gram-negative rods for 20%. Among the 22 polymicrobial bacteremias, three episodes were associated with two simultaneous infections at different sites (catheter-related infection and intraabdominal abscess).

Fourteen episodes (18.7%) occurred within 72 h of admission while 61 episodes (81.3%) occurred after 72 h and were considered to be nosocomial.

Granulocytopenia occured in 18% of patients with monomicrobial bacteremia and 31.8% of patients with polymicrobial bacteremia.

The in vitro antibiotic suspectibility of 117 blood isolates is shown in Table 3. All gram-negative bacilli

Table 3. Susceptibility of 117 bacteremic anaerobes

Strain	No. tested	Susceptibility to antibiotic (% of strains susceptible)			
		Penicillin	Chloramphenicol	Clindamycin	Metronidazole
Bacteroides fragilis	36	0	100	86.1	100
Other *Bacteroides* spp.	24	12.5	100	75	100
Leptotrichia buccalis	3	100	100	100	100
Capnocytophaga ochracea	1	100	100	100	100
Fusobacterium spp.	5	100	100	100	100
Propionibacterium acnes	12	100	100	100	0
Clostridium perfringens	18	94.5	94.5	100	88.9
Other *Clostridium* spp.	10	80	90	50	100
Peptostreptococcus spp.	8	87.5	87.5	87.5	75

Table 4. Outcome of patients with anaerobic bacteremia. P by χ^2 test with Yates correction: *$P=0.0016$; **$P=0.016$; ***$P=0.025$; ****not significant

Characteristics	Patients who died[a]	Patients who survived
Overall	13 (17.3)[b]	62 (82.7)
Granulocytopenia	4 (23.5)	13 (76.5)
Non-granulocytopenia	9 (15.5)	49 (84.5)
Male/female	6/7	31/31
Mean age and range (years)	57.8 (30–84)	53.5 (20–80)
Predisposing factors		
Chemotherapy	8 (61.5)	25 (40.0)
Surgical treatment	4 (30.8)	23 (37.0)
PMN <100 µl (day 0)	4 (30.8)	13 (21.0)
Corticosteroids	2 (15.4)	4 (6.5)
Clinical data		
$T>38°C$	7 (53.8)	54 (87.0)**
Shock	5 (38.5)	6 (9.7)***
Pulmonary complication	4 (30.8)	3 (4.8)**
Mono/polymicrobial	10 (77.0)/3 (23.0)	43 (71.0)/19 (29.0)****
Breakthrough bacteremia	0 (0)	8 (12.9)
Associated malignancy		
Female genital tract	6 (46.5)	8 (12.9)*
Gastrointestinal	2 (15.7)	15 (24.2)
Hematological malignancy	4 (30.8)	13 (21.0)
Lung	1 (7.7)	1 (1.6)
Source of bacteremia		
Gastrointestinal	6 (46.2)	24 (38.7)
Pelvic	3 (23.0)	10 (16.1)
Unknown	2 (15.4)	5 (8.0)
Lungs	1 (7.7)	7 (6.5)
Skin and soft tissue	1 (7.7)	10 (16.1)

[a] Within 10 days after bacteremia
[b] Number of patients (%)

were susceptible to chloramphenicol and metronidazole.

As shown in Table 4, the overall mortality within 10 days after bacteremia was 17.3% (13 patients). Among these, 10 patients (77%) had monomicrobial bacteremia and 3 patients (23%) had polymicrobial bacteremia.

Pulmonary complications were observed in 7 patients (9.3%). Mortality was 14% for polymicrobial bacteremia (3/22) and 19% for monomicrobial bacteremia (10/53), a non-statistically significant difference.

There was no significant difference in predisposing factors between the patients who died and those who survived, although the patients who died had significantly less fever and a higher rate of septic shock and pulmonary complications compared to surviving patients ($P<0.05$).

Female genital tract cancer was associated with a significantly higher mortality rate compared to other neoplasias ($P<0.05$).

Among the 75 patients, 9 were not treated, of whom 4 died within 48 h of bacteremia and 5 survived. Fifty-eight patients had received adequate treatment; 52 of them (89.7%) survived and 6 patients (10.3%) died.

Antimicrobial treatment was not adequate in 8 patients, of whom 2 died from infection.

Discussion

Our data show that the frequency of anaerobic bacteremia in cancer patients is similar to that reported from general hospitals: 3.7–12% of the episodes of bacteremia [3, 7, 13, 14, 20] or 0.5–4/1000 admissions [7, 9, 13, 14, 20]. The most common microorganisms causing bacteremia in cancer patients are facultative gram-negative bacilli and gram-positive cocci [8]. Few studies have focused on bacteremia due to strict anaerobes in such patients [4, 11, 17, 19]. As mentioned in the Introduction, cancer patients have several predisposing conditions for anaerobic infections (tissue necrosis, chemotherapy, breach in mucocutaneus barriers), but bacteremia is still infrequent under these conditions [12]. There is evidence that humoral immunity protects against anaerobic bacteremia, whereas T-cell-mediated immunity is important in the formation of abcesses caused by *Bacteroides fragilis* [18]. However, patients with granulocytopenia secondary to antineoplastic chemotherapy and corticosteroids and those with acquired defects in humoral immunity rarely develop anaerobic infections unless the underlying disease is associated with other recognized predisposing factors (obstruction, perforation and necrosis) [1].

In our patients, antineoplastic chemotherapy (44%) and surgery (36%) were the more frequent predisposing factors besides the underlying malignant disease. The most frequent types of cancer identified in our institute are breast, head and neck, lung cancers and hematological malignancies. Gastrointestinal, pelvic and hematological malignancy accounted for 60% of the underlying malignancies in our series, which is similar to the observations of Fainstein et al. [9] although these authors only reported bacteremia due to non-sporulating anaerobic bacteria (Table 5).

The mean duration of hospital stay in our center is comparable whether or not anaerobic bacteremia occurred. In addition, there was no difference between the length of stay of the patients who survived and those who died. The most frequent cause of anaerobic bacteremia (*Bacteroides* spp.) represented 48% of all blood anaerobic isolates. *Clostridium* spp. represented 28% of all anaerobic organisms isolated in blood cultures. The proportion of aerobic gram-negative rods and gram-positive cocci varies among the published reports. The susceptibility pattern of the strains isolated in our study was similar to the one published by Finegold [10].

The mortality rate was similar for the non-sporulating and sporulating pathogens. No significant difference between polymicrobial and monomicrobial bacteremia could be observed. The mortality of the patients undergoing chemotherapy and/or surgery was

Table 5. Bacteremia with non-sporulating anaerobes: comparison between series of cancer patients

Characteristics	Present study	M. D. Anderson [9]
No. episodes	53 (51 patients)	315 (300 patients)
Episodes/1000 admissions (range)	2.33 (1–3)	4 (2–6)
Underlying disease		
Hematological	19%	29%
Solid tumor	81%	71%
Urology, gynecology	30.2%	33%
Gastrointestinal	20.8%	12%
Head and neck	7.6%	3%
Breast	9.4%	—
Lung	3.8%	3%
Sarcoma	—	6%
Others	9.4%	14%
Cancer chemotherapy	44%	40%
Surgery	36%	29%
Granulocytes $<100/\mu l$	19%	12%
Septic shock	13.2%	32%
Polymicrobial bacteremia	34%	22%
Polymicrobial bacteremia (non-sporulating) in number of patients		
Two organisms	10	47
Two anaerobes	1	13
Anaerobes + gram-negative facultative	0	17
Anaerobes + gram-positive facultative	9	16
Anaerobes + yeast	0	1
Three organisms	4	18
Four or more organisms	4	4
Mortality		
Overall (15 days)	18%	30%
Shock present	45%	43%
Pulmonary complications present	57%	46%
When treated adequately	10%	20%
Not or inadequately treated	57%	46%

not different from the mortality of the other patients. Granulocytopenia and corticosteroid use were not associated with unfavorable clinical evolution.

The high mortality rate of patients with cancer of the female genital tract reflects the extension and the severity of the underlying disease.

Adequate treatment is an important factor in outcome in our series, while this is still controversial in various series reported in the literature [2, 5, 9, 13, 14].

Two recent studies suggest that the incidence of anaerobic bacteremia has probably decreased in recent years [7, 13] although their clinical features and prognosis have remained the same. Several factors may have played a role in this decrease over 20 years: (a) a major increase in the prophylactic and empiric use of antibiotics such as clindamycin and metronidazole, which is indirectly supported by a decrease in the rate of post-surgical wound infection in gastrointestinal surgery; (b) a better diagnosis of deep-seated abscesses through the use of new imaging techniques such as ^{111}In-labelled neutrophil scans, echography and computed tomography scanning; (c) a more rapid intervention with non-surgical drainage under the visual control of these imaging methods. However, one cannot exclude secular epidemiological changes unrelated to medical practices. During this period, the practice of anaerobic blood culturing has increased both in quality (better media are commercially available) and quantity (at least during the 1980s). As discussed by Coullioud et al. [7], this low prevalence of strict anaerobic bacteremia questions the systematic use of a specific bottle. In most recent reviews of anaerobic bacteremia in cancer centers [7, 9, 11] (the present study), most episodes were associated with cancer of the gastrointestinal and female reproductive tracts and of the head and neck. A more targetted approach would most probably be more cost-effective, by restricting the use of a specific anaerobic bottle in febrile patients with such tumors. This would decrease their use by 50%–70%.

In conclusion, our study shows that anaerobic bacteremia in cancer patients was more frequently associated with intraabdominal and hematological malignancies. Pathogen distribution is the same as in non-cancer patients. The most important predictor of mortality seems to be the type and extension of cancer, the presence of septic shock and development of pulmonary complications following anaerobic bacteremia.

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