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A 62-month retrospective epidemiological survey of anaerobic bacteraemia in a university hospital

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ABSTRACT

The incidence of anaerobic bacteraemia was studied retrospectively over 62 months at Mont-Godinne University Hospital, Yvoir, Belgium. The distribution of organisms, clinical presentations, choice of antimicrobial therapy and clinical outcome were analysed. The proportion of positive blood cultures yielding obligate anaerobes was 3.3%. The overall incidence of clinically significant anaerobic bacteraemia was 0.51 cases/1000 patient admissions (0.61 cases/10 000 hospital-days), but was significantly higher in patients with active haematological malignancies than in other groups (5.97/10 000 vs. 0.33/10 000 hospital-days; $p < 0.05$). The *Bacteroides fragilis* group accounted for 61% of isolates, followed by *Clostridium* spp. (12.2%), *Peptostreptococcus* spp. and *Leptotrichia* spp. (7.3% each) and *Fusobacterium* spp. (4.8%). The most common risk-factors were gastrointestinal surgery (49%) and active haematological malignancies with chemotherapy and/or bone marrow graft (47%). One or more co-morbidities were present in 30 (77%) of 39 patients. The lower gastrointestinal tract (41%) and the oropharynx (23%) were the two most frequent presumed or proven sources for bacteraemia, with the origin remaining unknown in eight (20.5%) cases. The overall mortality rate (evaluated 7 days after the occurrence of bacteraemia) was 13%. Fatal outcome correlated with the severity of underlying diseases and the immunosuppressed status of the patients rather than with the causative pathogen or the effectiveness of antimicrobial therapy. Likewise, there was no difference in the mortality rate between patients with monomicrobial and polymicrobial bacteraemia. Overall, the data re-emphasise the importance of anaerobic bacteraemia, especially in patients with haematological malignancies.

Keywords Anaerobes, bacteraemia, co-morbidities, haematological malignancies, neutropenia, origin

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INTRODUCTION

Anaerobic bacteraemia is uncommon, accounting for 0.5–13% of all positive blood cultures [1–4]. This rate corresponds to an incidence of 0.5–1.0 cases/1000 hospital admissions [1,3]. The need for objective microbiological diagnosis of anaerobic bacteraemia still remains controversial. It has been proposed that the clinical characteristics of anaerobic infections should guide the empirical choice of antimicrobial therapy [4–6], and the value of performing anaerobic blood cultures routinely has been questioned in several recent studies [5,7,8]. However, other studies have shown that anaerobic bacteraemia often remains unsuspected on clinical grounds, and that a substantial proportion of patients with anaerobic bacteraemia do not receive appropriate antimicrobial treatment on an empirical basis alone [2,4].

Despite its low incidence, anaerobic bacteraemia remains associated with significant mortality [2–4,9]. Fatal outcome has often been correlated with age and underlying diseases [9], as well as with inappropriate antimicrobial treatment or a delay in starting appropriate treatment [2,4,10]. The aim of the present study was to evaluate retrospectively the incidence and clinical significance of anaerobic bacteraemia in a cohort of hospitalised patients, and to establish whether a shift in frequency and distribution had occurred.

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METHODS AND MATERIALS

Setting

The Mont-Godinne University Hospital, Yvoir, Belgium, is a 380-bed tertiary-care teaching hospital with several specialised medical and surgical clinics, including cardiovascular, thoracic, orthopaedic, abdominal and neurosurgical wards. Facilities include a large pulmonary diseases unit (55 beds), a geriatric ward (30 beds), three medical-surgical intensive care units (24 beds), and a large oncology and haematology department that serves as a reference centre for haematological diseases in southern Belgium (provinces of Namur and Luxembourg). The haematology unit comprises 20 beds, six rooms with laminar flow, and ten rooms with positive pressure. Approximately 45 bone marrow transplants are performed annually.

Patients

Patients with blood cultures positive for anaerobic bacteria in the 62-month period between 21 January 1999 and 15 March 2004 were identified retrospectively from laboratory records. The hospital records of these patients were reviewed by a microbiologist, an infectious disease physician and a haematologist. Data were collected concerning age, gender, underlying diseases, empirical antimicrobial treatment and eventual changes in therapy when bacteriological results became available, proven or presumed foci of anaerobic bacteraemia, and outcome.

Bacteraemia was deemed to be clinically significant when the patient had one or more blood cultures positive for anaerobes and met one of the following criteria: leukocyte count $<100/mm^3$ or $>10\,000/mm^3$; temperature $>38°C$; or a physical examination or pathological or surgical evidence consistent with infection (e.g., isolation of anaerobes from a source other than blood, or evidence of barrier compromise). Potential contaminants (e.g., *Propionibacterium* spp.) that grew in only one of several blood cultures were discarded.

The source of infection was determined by radiological, surgical or microbiological evidence of barrier compromise, or an infectious pathology, such as abscess or necrosis. A bacteraemic episode was considered to be polymicrobial if two or more non-contaminant species were isolated from blood simultaneously or within 1 week of the initial blood culture positive for anaerobes. Based on National Nosocomial Infection Surveillance System guidelines, infections were deemed nosocomial if the positive blood culture was drawn >48 h after admission to the hospital [11].

Antimicrobial treatment was considered to be appropriate if the agents used for therapy had a spectrum of activity providing coverage for anaerobes and were found to be effective by in-vitro susceptibility testing.

Mortality was attributed to anaerobic bacteraemia when a patient died from uncontrolled sepsis within 7 days of the onset of the episode, in the absence of other non-infectious co-morbidities.

Cultures

Blood cultures were analysed with a BacT/Alert 240 system (bioMérieux, Marcy l'Etoile, France) following inoculation of 5–10 mL of blood into aerobic and anaerobic vials (BacT/Alert FA and SN bottles; bioMérieux). Blood culture bottles were incubated for a maximum of 5 days at 37°C with constant shaking. Positive anaerobic bottles were subcultured on tryptic soya agar containing sheep blood 5% v/v, and on Schaedler agar containing horse blood 5% v/v, and were incubated in an anaerobic atmosphere with an Anoxomat WS 80 device (Mart BV, Lichtenvoorde, The Netherlands). Bacterial colonies were identified by standard methods [12] and with an API 20A system (bioMérieux). Antibiotic susceptibility testing was performed by disk-diffusion [13] or Etest (AB Biodisk, Solna, Sweden) on Brucella blood agar supplemented with haemin 5 mg/L and vitamin K_1 1 mg/L) [14]. Disk inhibition zones were interpreted according to the guidelines of the Comité Français de l'Antibiogramme [13], and MIC values were interpreted according to CLSI (formerly NCCLS) guidelines [15].

Blood culture results were entered into a computerised laboratory database that allowed ward personnel to read the results as they became available. Information concerning positive blood culture results was also telephoned to clinicians as soon as the positive culture was identified, with simultaneous transmission to a consultant infectious diseases physician.

RESULTS

Overall, 4857 of 51 782 blood cultures were positive during the study period. Of the microorganisms isolated, 98.1% were bacteria (facultative anaerobes, 88.6%; Gram-negative non-fermentative bacteria, 6.2%; strict anaerobes, 3.3%) and 1.9% were fungi. The contamination rate was 2.5%. Blood cultures from 47 patients yielded 49 strict anaerobes (representing 3.3% of all episodes of bacteraemia). After review of the medical records, anaerobic bacteraemia was considered clinically significant in 39 patients (0.51 cases/1000 admissions). Blood cultures from two patients yielded mixed growth of two different organisms, so that 41 obligate anaerobes were isolated in total. Two major groups of patients presenting with anaerobic bacteraemia were identified: (1) patients with active haematological malignancies (n = 18); and (2) patients with various other clinical conditions (n = 21), including patients with a history of solid neoplasm (Table 1).

The mean incidence rate of anaerobic bacteraemia between 1999 and 2003 was 5.87/10 000 days of hospitalisation (95% CI, 2.54–9.20) for patients with haematological malignancies, compared with 0.33/10 000 days of hospitalisation (95% CI, 0.08–0.57) for other patient groups (p 0.0077 with T-test; Fig. 1). The total number of annual admissions, as well as the number of blood cultures obtained between 1999 and 2003, remained unchanged, while there was a linear trend towards an increased incidence of anaerobic bacteraemia during the study period

Table 1. Characteristics of patients with anaerobic bloodstream infections, stratified by group of patients

	Haematological group (n = 18)	Non-haematological group (n = 21)
Male, n	11	13
Female, n	7	8
Gender ratio, male/female	1.57:1	1.62:1
Age, years, mean ± SD (min.–max.)	56.8 ± 13.9 (23.5–80.9)	64.9 ± 15.7 (35.1–85.7)
Nosocomial infection, n (%)	15 (83)	12 (57)
Community infection, n (%)	3 (17)	9 (43)
Non-survivors, n (%)	3 (17)	2 (9.5)
ICU stay, n	2	4
Haematological disease, n		
Acute myeloid leukaemia	6	–
Myeloma	3	–
Myelodysplastic syndrome	3	–
Acute lymphoid leukaemia	2	–
Chronic lymphoid leukaemia	1	–
Lymphoma	3	–
Chemotherapy, n	17	0
Bone marrow transplant, n	5	–
Autograft	4	–
Allograft	1	–
Neutropenia, n	13	0
Portal of entry/focus, n		
Not found	6	2
Decubitus ulcer	1	3
Sacrum decubitus bedsore	1	2
Vertebral osteomyelitis		1
Amygdalitis	1	1
Mucositis, necrotic gingivitis	4	–
Dental abscess, dental care	1	1
Post-operative cervical wound infection	–	1
Abdominal gunshot wound	–	1
Appendicitis	–	2
Biliary tract infection	–	3
Gut haemorrhage	2	–
Gut ischaemia	–	1
Diverticulitis	–	2
Sigmoiditis	1	–
Neutropenic enterocolitis	1	–
Peritonitis	1	1
Days between admission and positivity, median (95% CI; min.–max.)	13 (5.00–21.32; 0–63)	4 (0.02–13.98; 0–204)
Pure anaerobic culture, n (%)	9 (50)	16 (76)
Mixed aerobic–anaerobic culture, n (%)	9 (50)	5 (24)
Enterobacteriaceae	22 (4)	4 (19)
Streptococcus/Enterococcus	22 (4)	2 (10)
Other	2 (11)	–

ICU, intensive care unit.

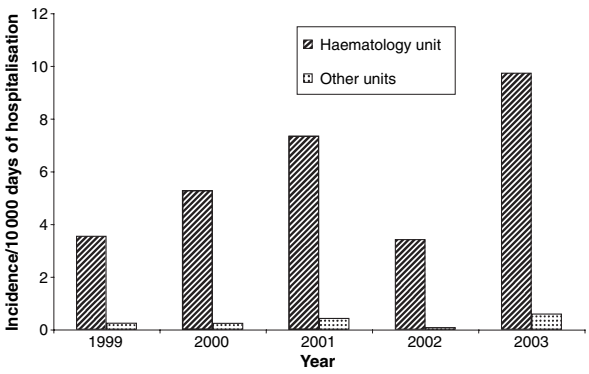

Fig. 1. Incidence of anaerobic bacteraemia, stratified by hospital unit.

(0.92/1000 patients in 2003 vs. 0.37/1000 patients in 1999; p 0.057). The mean age of the patients was 61.2 years (SD 15.3 years; range 23–85 years), and the male to female ratio was 1.6 (24 males).

Twenty-five (64%) of the 39 patients presented with at least one co-morbidity, and 12 (31%) patients had two or more underlying diseases. The most frequent co-morbidities were cardiovascular or respiratory disease (59%), haematological malignancy (46%), solid neoplasms (15.4%), diabetes mellitus (5%), and others (8%). Nineteen (48.7%) patients had gastrointestinal disorders or recent surgery of the digestive tract. Episodes of anaerobic bacteraemia were deemed nosocomial for 15 (83.3%) patients with haematological malignancies, and for 12 (57.1%) patients from the other groups. For 13 haematological patients, the elapsed time between the onset of neutropenia (< 100 white blood cells/mm^3) and the episode of bacteraemia was 0–161 days (median 11 days; 95% CI, 2–47.8 days). The different groups and species of organisms, arranged according to patient category and by presumed or proven sources of infection, are shown in Table 2. Overall, *Bacteroides* spp. and *Clostridium* spp. accounted for 75% of all reported cases of anaerobic bacteraemia. Episodes of anaerobic bacteraemia caused by *Clostridium tertium*, *Fusobacterium* spp. and *Leptotrichia* spp. were found exclusively among neutropenic patients with haematological dyscrasias, and were associated essentially with an oral or orodental portal of entry.

Altogether, the lower gastrointestinal tract (17/39 patients; 43.6%) was the most common proven or presumed portal of entry, and was associated with widely diverse clinical conditions, such as biliary tract infections, gut ischaemia, sigmoiditis, appendicitis, diverticulitis, peritonitis and neutropenic colitis (Table 1). The oropharynx and orodental systems (n = 9; 23%) constituted the second most frequent origins of anaerobic bacteraemia, especially in patients with haematological malignancies. In particular, necrotic gingivitis, mucositis or dental abscesses were documented frequently in this group of patients (Table 1). Episodes of anaerobic bacteraemia associated with infected wounds and decubitus ulcers were also quite common and were documented in eight patients. In one patient, the source of bacteraemia was a lumbo-sacral spondylodiscitis following vertebral surgery. No primary focus of infection could be detected for eight (20.5%)

Table 2. Anaerobic microorganisms isolated from episodes of bloodstream infections occurring among haematological and non-haematological patients

Bacteria	*n* (%)	Haematological patients	Non-haematological patients	Focus	Associated bacteria
Bacteroides fragilis group	25 (61)	9	16	OR, D, V	*Streptococcus anginosus*,
Bacteroides fragilis	19	7	12	D	*Streptococcus sanguis*,
Bacteroides diastonis	2	1	2	D	*Enterococcus faecium*,
Bacteroides ovatus	1	1	1	D	coagulase-negative
Bacteroides uniformis	1		1		staphylococci,
Bacteroides vulgatus	1				*Enterobacter aerogenes*,
Bacteroides stercoris	1				*Escherichia coli*,
					Clostridium perfringens
Bacteroides ureolyticus	1 (2.4)		1	OR	*Escherichia coli*,
					Streptococcus constellatus,
					Peptostreptococcus
Prevotella intermedia	1 (2.4)	1		D	*Streptococcus mitis*
Leptotrichia spp.	3 (7.3)	3		OR	None
Fusobacterium spp.	2 (4.9)	2		OR	*Klebsiella pneumoniae*
Clostridium spp.	5 (12.2)				None
Clostridium perfringens	2		2	D	*Proteus vulgaris*,
					Escherichia coli,
					Bacteroides fragilis
Clostridium tertium	3	3		OR, D	*Streptococcus mitis*,
					Klebsiella oxytoca,
					Escherichia coli
Peptostreptococcus spp.	3 (7.3)		3	D, OR	*Escherichia coli*,
					Morganella morganii,
					Bacteroides ureolyticus
Bifidobacterium spp.	1 (2.4)		1	D	None
Total	41 (100)	18	23		

OR, oropharynx or dental; D, digestive; V, various others.

patients (six (33%) in the haematological group and two (10%) in the other groups of patients).

Fourteen (36%) of all episodes of anaerobic bacteraemia presented as polymicrobial infections, with Enterobacteriaceae, streptococci and enterococci being the pathogens involved most frequently (Table 1). Polymicrobial mixed infections were found more frequently among patients with haematological disorders (n = 9; 50%) than among the other patient groups (n = 5; 23.8%).

Overall, most patients were receiving broad-spectrum antibiotics as empirical therapy at the onset of the episode of anaerobic bacteraemia. Antibiotic therapy was documented for 37 patients, of whom 24 received appropriate effective broad-spectrum antimicrobial therapy with coverage for anaerobes before the results of blood cultures were known. Initial empirical antibiotic therapy was changed for ten (27%) patients following the blood culture results. Two patients did not receive any antibiotics, but nevertheless had a favourable clinical outcome following surgical drainage. One patient with a bacteraemia caused by *Bacteroides fragilis* and an infected decubitus ulcer recovered uneventfully despite the administration of cefepime, an antibiotic with impaired coverage for anaerobes.

Five patients died during hospitalisation (a crude mortality rate of 13%). There was no difference in the mortality rate between patients with monomicrobial or polymicrobial bacteraemia (2/14, 14.3% vs. 3/25, 12%). None of the fatal cases could be linked directly to the anaerobic bacteraemia or to an inappropriate choice of antibiotic therapy. Three of the patients with a fatal outcome had severe uncontrolled active haematological disease (two patients with acute-phase leukaemia; one patient with aggressive lymphoma). One patient with chronic renal failure had a ruptured abdominal aortic aneurysm, and died from ischaemic colitis with anaerobic-related sepsis. The last non-survivor was a comatose geriatric patient with multiple organ failure, ionic disorders, and a sacral decubitus abscess as the probable source of bacteraemia.

DISCUSSION

Underlying diseases are reported frequently as risk-factors for anaerobic bacteraemia, particularly malignancies, liver failure, diabetes mellitus or previous gastrointestinal surgery [3,4,8,9]. In the present study, gastrointestinal pathologies or recent bowel surgery were confirmed as potential risk-factors, while diabetes mellitus and hepatic diseases were encountered rarely. A striking feature was that almost half of the patients with an episode of anaerobic bacteraemia presented with an active haematological disease at the time of infection.

The crude mortality rate associated with anaerobic bacteraemia has been shown to range between 13% and 45% [2–4,9,16,17], and is usually found to correlate closely with the age of the patients and the severity of co-morbidities [2–4,9]. It is also acknowledged that bloodstream infections caused by the *B. fragilis* group are associated with a higher rate of mortality, probably reflecting the higher virulence of these organisms [9,17,18]. In the present series, mortality could not be attributed directly to the bacteraemia in any of the five fatal cases, since each patient died from well-documented non-infectious causes.

In contrast with previous reports [10,17,19], a higher mortality rate was not found among patients who were treated inadequately. However, this may relate to the fact that most patients in the present study received effective empirical therapy with anaerobic coverage at the onset of their infection. Moreover, antimicrobial regimens were modified rapidly by the attending infectious diseases physicians, according to bacteriological results, for those patients who were not receiving effective empirical therapy.

Although several studies have reported a marked decline in the incidence of anaerobic bacteraemia and have questioned the value of routine anaerobic blood cultures [1,5,7,20], the present study observed a rising trend in the number of episodes of anaerobic bacteraemia and/or septicaemia, increasing from 0.37/1000 patients in 1999 to 0.92/1000 patients in 2003 (p 0.057). The total number of blood cultures assessed did not change significantly during this period, and the culture media and blood culture system used remained the same. Moreover, the overall population profile and patient-mix did not change and, in particular, the number of bone marrow transplant recipients remained stable. In a similar study, Lark *et al*. [16] also reported a rising incidence of anaerobic bacteraemia among patients with bone marrow transplants, with episodes of anaerobic bacteraemia occurring at a high frequency of 4/100 bone marrow transplant procedures, accounting for 17% of all episodes of bacteraemia during the study period.

The present retrospective study observed some significant differences between episodes of anaerobic bacteraemia in patients with active haematological malignancies compared with non-haematological patients. First, the incidence of anaerobic bloodstream infections was significantly higher in patients with haematological malignancies. Second, the oropharynx was shown to be the most frequent primary source of anaerobic bacteraemia in neutropenic patients with acute haematological malignancies while, as reported previously [3,4,9], the lower gastrointestinal tract represented the most common portal of entry for bacteraemia in the general population. Overall, *B. fragilis* was the most common pathogen causing anaerobic bacteraemia (61%), and was found mainly in association with gastrointestinal tract infections or in the context of infected decubitus ulcers. In contrast, episodes of bacteraemia involving specific anaerobic organisms, e.g., *Fusobacterium* spp., *Leptotrichia* spp. and *C. tertium*, were found exclusively among neutropenic bone marrow transplant recipients who had good evidence of barrier compromise (severe oral mucositis (grade II or III) and/or enterocolitis).

Almost half of the episodes of anaerobic bacteraemia occurring in haematological patients were polymicrobial and were associated with non-anaerobic bacteria, originating mostly from the oral or intestinal flora. This observation is in line with previous reports showing that polymicrobial mixed infections involving anaerobic bacteria occur at a higher frequency than monomicrobial episodes in neutropenic patients [16].

In summary, a trend towards a rising incidence of anaerobic bacteraemia was identified in the present study. Almost half of the affected individuals were patients with haematological dyscrasia (acute leukaemia or lymphoma) who had received bone marrow transplants and/or high doses of chemotherapy at or before the time of the infection. In this group of severely immunocompromised patients with neutropenia, the oral cavity (mucositis, gingivitis) was the most frequent putative source of anaerobic bacteraemia, while the gastrointestinal tract was the most common portal of entry in the general non-haematological population. As a consequence, the distribution of the causative pathogens differed substantially between the two groups of patients. Moreover, haematological patients had bacteraemia caused by mixed anaerobic and facultative oral or intestinal bacteria more frequently, suggesting erosions in the mucosal barriers. Finally, no correlation could be established between the appropriateness of the antimicrobial

treatment of the bacteraemia and the clinical outcome, thereby emphasising the primary importance of patients' co-morbidities and/or immune status in the outcome of these infections.

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