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Note

Bacteraemia Caused by Non-Glucose-Fermenting Gram-Negative Bacilli and *Aeromonas* Species in Patients with Haematological Malignancies and Solid Tumours

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Abstract The clinical characteristics and outcome of bacteraemia caused by non-glucose-fermenting gram-negative bacilli and *Aeromonas* spp. were examined in 115 adults with haematological malignancies or solid tumours. The most aggressive pathogens were *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Aeromonas* spp., *Acinetobacter* spp. and *Burkholderia cepacia*, all of which caused either septic syndrome or pneumonia in more than 40% of cases. *Pseudomonas aeruginosa* was involved less often in catheter-related bacteraemia than other species. Polymicrobial bacteraemia ($n=28$) was more often catheter-related than monomicrobial bacteraemia and more often required catheter removal for definitive cure. The most important predictors of catheter-related bacteraemia and its outcome were polymicrobial infection, the presence of pneumonia or septic syndrome and the species involved.

Introduction

Patients receiving intensive chemotherapy for leukaemia or lymphoma and patients undergoing autologous or allogeneic stem cell transplant suffer frequent episodes of bacteraemia caused by gram-positive and gram-negative bacteria. The most frequent pathogens are facultative gram-negative bacilli (GNB) of the *Enterobacteriaceae* family (mainly *Escherichia coli* and *Klebsiella* spp.), followed by *Pseudomonas aeruginosa,* which is an aerobic non-glucose-fermenting gram-negative bacillus (NGFGNB). Over the past 15 years bacteraemia caused by previously unknown or rare GNB has increasingly been reported [1–5]. In this study we compared the clinical characteristics of bacteraemia caused by aerobic NGFGNB and *Aeromonas* spp. in cancer patients observed in two institutions over a 6-year period.

Materials and Methods

From January 1993 until December 1998, 115 consecutively diagnosed patients with bacteraemia caused by NGFGNB or *Aeromonas* spp. in the Haematology and Oncology Departments of two tertiary hospitals in Barcelona, Spain, were enrolled in this prospective study. The medical records were reviewed to retrieve any relevant data lacking. All patients had at least one positive blood culture plus signs and symptoms of infection (fever and/or signs of tissue infection) not considered to be attributable to either colonisation or blood culture contamination. Table 1 summarises the patient characteristics.

Blood cultures were performed by an automatic method (BacT/Alert; Organon Teknika, USA). The species were identified by standard methods using conventional media [6] and classified according to recent taxonomic classifications [7]. If a central venous catheter was removed, a quantitative and semiquantitative culture of the tip was done [8]. Antimicrobial susceptibility was tested in a routine microbiology laboratory using disk diffusion and microdilution tests (Sensititre; AccuMed, USA).

Patients who developed fever and bacteraemia more than 72 h after admission were considered to have a hospital-acquired infection. Neutropenia was defined as $<0.5\times10^9$/l neutrophils. Septic syndrome was defined as the presence of at least two of the following features: systolic blood pressure <90 mmHg in a previously normotensive patient, heart rate ≥120 per minute and respiratory rate ≥28 per minute. Complications of bacteraemia included deep-organ involvement (pneumonia or enterocolitis), soft-tissue involvement and/or septic syndrome [1]. Patients

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Table 1 Characteristics of the 115 patients included in the study

Total no. of patients	115
Median age in years (range)	49 (16–86)
Gender (M/F)	62/52
Underlying disease	
Acute myelogenous leukaemia (%)	31 (27)
Acute lymphoblastic leukaemia (%)	10 (9)
Non-Hodgkin's lymphoma (%)	28 (24)
Hodgkin's disease (%)	7 (6)
Multiple myeloma	7
Chronic myelogenous leukaemia	7
Breast cancer (%)	16 (14)
Other (%)	9 (8)
Therapy prior to infection	
Conventional chemotherapy (%)	56 (49)
ASCT [APBSCT/ABMT] (%)	35 [29/6] (30)
AlloSCT [AlloPBSCT/AlloBMT] (%)	7 [3/4] (6)
Outpatients off therapy (%)	17 (15)
Neutropenia with <0.5 cells $\times 10^9$/l (%)	77 (67)
No. of nosocomial infections (%)	71 (62)
Central venous catheter	
No. of patients with catheter (%)	90 (78)
Tunnelled (Hickman)/non-tunnelled CVC	57/33
Median time in days from insertion (range)	48 (8–470)
Polymicrobial infection[a] (%)	28 (24)
Gram-positive cocci[b] (% of all patients)	14 (12)
Enterobacteria[c] (% of all patients)	6 (5)
Other NGFGNB (% of all patients)	13 (11)
Candida spp. (% of all patients)	2 (2)
No. of NGFGNB isolated	128
Antibiotic therapy before infection	
None (%)	82 (71)
Prophylactic fluoroquinolones[d] (%)	24 (21)
On broad-spectrum antibiotics at infection (breakthrough bacteraemia)[e] (%)	9 (8)

ASCT, autologous haematopoietic stem cell transplantation; APBSCT, autologous peripheral blood stem cell transplantation; ABMT, autologous bone marrow transplantation; AlloSCT, allogeneic SCT; AlloPBSCT, allogeneic PBSCT; AlloBMT, allogeneic BMT; NGFGNB, non-glucose fermenting gram negative bacilli

[a] 7 patients with 3 different species; 21 patients with 2 different species

[b] 10 coagulase-negative staphylococci, 3 *Enterococcus* spp., 1 *Micrococcus* sp.

[c] *Escherichia coli*, 1 *Enterobacter cloacae*, 1 *Klebsiella* sp.

[d] 10 norfloxacin,14 ciprofloxacin

[e] 5 patients on imipenem (4 *Stenotrophomonas maltophilia*, 1 *Pseudomonas putida*), 2 on ceftazidime (1 *Stenotrophomonas maltophilia*, 1 *Pseudomonas aeruginosa*), 2 on cefepime (1 *Burkholderia cepacia,* 1 *Acinetobacter sp.*)

without these complications were considered to have non-complicated bacteraemia. Bacteraemia was considered to be polymicrobial if more than one organism was isolated from one or more concurrent blood cultures. Catheter-related bacteraemia was diagnosed according to the following criteria: (i) isolation of the same microorganism from blood and exudate from the catheter exit site or specimens from the catheter lumen in the presence of signs of inflammation; (ii) isolation of the same microorganism from blood and the catheter tip on removal of the catheter. No quantitative blood cultures of peripheral blood or catheter-drawn blood were performed.

A response to antibiotic therapy was defined as complete resolution of all clinical and microbiological signs of infection. In the case of pneumonia a response was defined as resolution of signs and symptoms and improvement of the findings on chest radiograph. The response was assessed at the end of antibiotic therapy. In the case of patients with prolonged illness who eventually responded to antibiotic therapy alone, this was rated as a response.

Differences between categorical variables were tested for univariate significance using two-tailed chi-square tests (or Fisher's exact test when appropriate), while Mann-Whitney's U test was used for continuous variables. Stepwise logistic regression with the use of maximum likelihood estimates was used to measure the unique contribution of various variables in a response to primary therapy, with a significance level of $P \leq 0.05$.

Results and Discussion

One hundred fifteen patients with bacteraemia were diagnosed during the study period. Table 1 gives details of the pathogens isolated. Thirteen patients had more than one NGFGNB isolate so that the total number of isolates was 128.

More than 20 species of NGFGNB and *Aeromonas* spp. were isolated. Table 2 shows the main characteristics of infections with these species. As expected, *Pseudomonas aeruginosa* was by far the most frequent species isolated (46 cases) followed by *Stenotrophomonas maltophilia* (19 cases). The most aggressive pathogens were *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Aeromonas* spp., *Acinetobacter* spp. and *Burkholderia cepacia*, all of which were associated with either sepsis or pneumonia in >40% of cases with a mortality of 8–29%. Other species, on the other hand, were involved in catheter-related infections in 50–80% of cases with no mortality, and were rarely associated with sepsis, pneumonia or metastatic skin lesions.

Fifty-four (47%) patients had bacteraemia with complications, 40 septic syndrome, 22 pneumonia, 4 enterocolitis and 4 soft-tissue infections, consisting of 2 cases each of acute rhabdomyolysis and myonecrosis in patients with bacteraemia caused by *Aeromonas* spp. Six (16%) other patients with monomicrobial *Pseudomonas aeruginosa* bacteraemia developed ecthyma gangrenosum.

There were 28 cases of polymicrobial bacteraemia and 87 cases of monomicrobial bacteraemia. Since the risk factors, clinical characteristics and outcome of polymicrobial bacteraemia may differ from those of monomicrobial bacteraemia, we compared the two types of infection. There were no differences in the frequency of septic syndrome (32% vs 36%), pneumonia (18% vs 20%), neutropenia at onset (64% vs 68%), presence of a central venous catheter (89% vs 75%), catheter duration or nosocomial infection (57% vs 63%). However, polymicrobial infection was associated with catheter-related infection (88% vs 44%, $P<0.001$), a decreased frequency of *Pseudomonas aeruginosa* as pathogen (20% vs 44%, $P=0.05$) and a poor response to antibiotic therapy without catheter removal (32% vs 72%, $P=0.003$).

Table 2 Number of isolates and characteristics of bacteraemia caused by non-glucose fermenting gram-negative bacilli and *Aeromonas* spp.

Species (n)	No. of isolates								
	Poly-microbial infection	Catheter related infection	Septic syn-drome	Pneum-onia	Primary treatment antibiotics	Primary treatment catheter removal (±ATB)	Response to primary treatment	Catheter removal as secondary treatment	Death from infec-tion
Pseudomonas aeruginosa (46)	8	8	18	11	43	3	32	1	6
Stenotrophomonas maltophilia (19)	9	11	8	5	14	6	7	4	3
Pseudomonas putida (9)	5	8	0	1	6	6	6	2	none
Alcaligenes xylosoxidans (8)	2	7	1	0	8	1	2	4	none
Sphingomonas paucimobilis (4)	1	4	1	0	4	0	0	3	none
Aeromonas spp.[a] (7)	2	2	3	0	7	1	2	1	2
Acinetobacter spp.[b] (13)	8	12	5	1	13	5	5	6	1
CDC IV-C2 (4)	0	2	0	0	4	0	2	2	0
Burkholderia cepacia (5)	1	3	2	2	3	3	3	0	1
Roseomonas spp. (3)	2	3	1	0	3	0	0	2	0
Pseudomonas spp. (8)	2	4	2	2	6	4	7	1	0
Alcaligenes faecalis (1)	0	0	0	0	1	0	1	0	0
Oligella ureolytica (1)	1	1	0	0	1	0	0	1	0

[a] *Aeromonas caviae*, 2 *A. veronii* biovar *sobria,* 1 *A. hydrophila*
[b] 3 *Acinetobacter baumanii*, 2 *A. lwoffii*, 1 *A. calcoaceticus*, 7 *Acinetobacter* sp
[c] 3 *Pseudomonas alcaligenes*, 1 *P. stutzeri*, 4 *Pseudomonas* sp., ATB, antibiotic

This was a prospective observational study in which treatment decisions were made by the attending physician and not based on a controlled protocol so that conclusions regarding treatment efficacy must be interpreted with caution. In 26 patients with catheter-related infection the central venous catheter was removed within 48 hours of onset of bacteraemia with ($n=16$) or without ($n=10$) antibiotic treatment, all but one patient responding. Eighty-four patients initially received empirically based therapy with a broad-spectrum beta-lactam (imipenem, meropenem, piperacillin/tazobactam, cefepime or ceftazidime) plus amikacin in most cases; additional agents such as ciprofloxacin or trimethoprim/sulfamethoxazole being given as necessary.

To identify factors associated with an improved response to antibiotic therapy, logistic regression analysis was performed in these 84 patients. In multivariate stepwise logistic regression, only two variables were predictive of a higher rate of response to antibiotics: bacteraemia caused by *Pseudomonas aeruginosa* ($P=0.002$, OR 7, 95% CI 1.8–26.3) and monomicrobial bacteraemia ($P=0.02$, OR 4.2, 95% CI 1.4–18.5).

Over the past decade there has been a substantial change in the pattern of bacteraemia caused by GNB in neutropenic patients and cancer patients in many institutions world-wide. Although enteric bacilli and *Pseudomonas aeruginosa* are still the predominant pathogens, several species of GNB have emerged as significant opportunistic pathogens. A wide range of species of GNB are implicated in bacteraemia in cancer patients, and there is considerable variation between institutions in the relative frequency of these infections and in the predominating species. The highest frequency of bacteraemia is usually reported in conjunction with the use of central venous catheters [2, 4, 5, 9, 10]. NGFGNB frequently cause catheter-related infections [2–5, 9, 11, 12], which is consistent with their ubiquitous distribution in the hospital environment and their tendency to contaminate fluids, instruments and material used for patient care.

Elting and Bodey [2] reported on 149 cases of bacteraemia caused by NGFGNB in cancer patients nearly a decade ago. They found that 43% of infections (52% in patients with a central venous catheter) were catheter-related and that catheter removal was the most effective approach in the management of such infections. Furthermore, polymicrobial infections (16%) were always catheter-related and some differences observed in the clinical presentation were species related. Similar findings have been reported in smaller patient groups [4, 5, 11–13]. In previous studies in our institution with smaller groups of patients, most episodes of bacteraemia caused by species other than *Pseudomonas aeruginosa* were catheter-related, whereas the more frequent episodes of bacteraemia caused by enteric bacilli were usually without complications and had no identifiable source [3, 9].

Our study reveals two different clinical entities in cancer patients with bacteraemia due to NGFGNB and *Aeromonas* spp. Polymicrobial bacteraemia was typically catheter-related and usually without complications. However, the infection was often not eradicated by therapy with the appropriate antibiotics, catheter

removal usually being necessary to cure the infection. In the absence of neutropenia or infection at other sites, removal of the catheter is probably the optimal approach in managing patients with non-complicated bacteraemia.

On the other hand, bacteraemia accompanied by complications was usually monomicrobial and rarely catheter-related. The organisms most frequently involved were *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter* spp., *Aeromonas* spp. and *Burkholderia cepacia*, these organisms accounting for all 16 deaths (13 directly related to the infection and 3 with other major contributing factors). In these infections therapy with antibiotic combinations was the most effective initial management, catheter removal only being resorted to in cases of persistent or recurrent bacteraemia.

In summary, bacteraemia caused by NGFGNB in cancer patients differs somewhat in the clinical presentation, source of infection and outcome according to the species involved, but there are many features in common. The most important factors indicating the origin of bacteraemia (i.e. infected catheter) and predicting its outcome in this patient population are the monomicrobial or polymicrobial nature of the infection, the presence of pneumonia or septic syndrome and the species involved. *Pseudomonas aeruginosa* and other aerobic GNB (*Stenotrophomonas maltophilia*, *Acinetobacter* spp., *Aeromonas* spp. and *Burkholderia cepacia* in our patients) appear to be the most virulent species.

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