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Original articles

Prospective multicentric study of the etiology of 1051 bacteremic episodes in 782 cancer patients

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Abstract. A total of 1051 bacteremic episodes (782 patients) were prospectively recorded in 10 cancer centers (9 French, 1 Belgian), with: patient's age (mean 53, range 1–89 years), underlying cancer, neutropenia (< 1000 neutrophils/μl; 233), signs and symptoms, type of i.v. line (percutaneous central: 534; peripheral: 228; central implanted: 304), treatment, blood culture system, number of positive blood culture bottles/total obtained, time to growth. Of all episodes, 23.2% occurred within 48 h of admission. The patients were receiving systemic antibiotics at sampling (on AB) in 34.6% of cases. The 1147 pathogens isolated (86 polymicrobial) were: *E. coli* (10.7%), *Klebsiella-Enterobacter-Serratia* (6.1%), other enterobacteriaceae (2.2%), *Pseudomonas aeruginosa* (4.8%), other nonfermenters (4.7%), coagulase-negative staphylococci (CNS, 40.8%), *Staphylococcus aureus* (9.9%), streptococci (5.4%), enterococci (2.2%), anaerobes (3.4%), yeasts (3.5%), and other bacteria (6.9%). The CDC (Centers for Disease Control) criteria (1988) were used to assess significance: group 1: pathogenic species (616 episodes; 59%); group 2: clinical signs and isolation of a "contaminant" species (47; 4.5%); group 3: as in group 2 with an i.v. line and empiric antibiotic treatment (181 episodes including 176 CNS; 17%); group 4: non-significant (207 episodes including 203 CNS; 20%). Groups 1–3, in which the episodes were considered to be significant (844 episodes; 80%) were compared with non-significant episodes (Fisher). Significant differences ($P \leq 0.05$) were seen in time to growth (median growth within 24 h vs 48 h), fever (86% vs 54%), chills (40% vs 3%), hypotension (10% vs 2%), septic shock (9% vs 1%), polymicrobial etiology (10% vs 0.5%), and initiation of empiric antibiotic treatment (71% vs 4%). Bacteremic episodes of CDC groups 1, 3 and 4 were further studied in episodes with a single isolate as a *doubtful clinical significance* (482 episodes) and episodes with ≥ 2 bottles positive of *probable clinical significance* (569 episodes; 54%). In group 1 (218 doubtful, 398 probably significant episodes) significant differences were seen in chills (36% vs 52%), shock (7% vs 13%), polymicrobial (8% vs 17%), initiation of empiric antibiotic treatment (60% vs 72%); in group 3 (87 doubtful, 94 probably significant) in time to growth delay; in group 4 (177 doubtful, 30 probably significant) in proportion with implanted catheter (26% vs 52%), fever (62% vs 10%), and time to growth. This study confirms the predominant role of Gram-positive cocci in bacteremia occurring in cancer patients.

Key words: Bacteremia in cancer patients – Clinical significance – Blood cultures – Nosocomial bacteremia – Diagnostic criteria for bacteremia

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Introduction

In patients with neoplastic diseases, whether or not they are neutropenic, bacteremia is the most frequent form of infection during a hospital stay or after specific anticancer treatment [3, 4, 13, 17, 30]. Bacteremia includes clinical sepsis and laboratory-confirmed bloodborne infections. The significance of positive blood cultures has been evaluated in previous studies to distinguish between exogenous contamination from the clinically significant positive samples, particularly in cancer patients with indwelling intravascular catheters [16, 18, 26, 27].

Bacteremia is the second most frequent nosocomial infection in cancer patients after respiratory tract infection [22], causing about one-fifth of all nosocomial infections in such patients [5, 22].

We have carried out a multicenter prospective study of bacteremic episodes in cancer patients, in order to assess the spectrum of presently occurring microorganisms with particular interest for Gram-positive bacteria which have recently become predominant over the Gram-negative aerobic bacilli in neutropenic patients. In addition, we were interested in correlated signs and symptoms with the delay of growth.

No such studies performed specifically in cancer patients have been published recently, with the exception of the numerous reports on neutropenic patients [4, 13, 17].

Materials and methods

Participating centers

One cancer center in Belgium (Institut Jules Bordet) and nine cancer centers in France took part in the study: Centre Antoine-Lacassagne, Nice; Centre Jean-Godinot, Reims; Centre Alexis-Vautrin, Nancy; Centre George-François Leclercq, Dijon; Fondation Bergognié, Bordeaux; Centre Oscar-Lambret, Lille; Centre Paul-Strauss, Strasbourg; Centre René-Gauducheau, Nantes; Centre Léon-Bérard, Lyons. These centers are comprehensive integrated cancer centers devoted mainly to the treatment of advanced disease. Most patients are referred to the centers from general hospitals.

Admission criteria

Blood cultures are performed whenever fever is present (>38° C) or when signs suggestive of infection are present (with or without fever): chills, hypotension, clinical deterioration, shock. In some of the centers, blood cultures are obtained as a routine procedure in high-risk patients (neutropenia or high-dose corticosteroids). In the course of the study, the possibility of a bacteremic episode was considered whenever a blood culture sample was found positive. Participating centers recorded all successive bacteremic episodes. The following data were recorded on a case report form: initials, birth date, type of tumor, day of enrollment on study, time since admission to hospital, hospital unit, clinical signs (fever, chills, blood pressure), current antimicrobial agents at sampling of the first positive blood culture, antimicrobial agents given for the actual episode, number of blood cultures, site of sampling, type of material, time to positivity for each blood sample that grew, microorganisms isolated, presence of an intravascular catheter and its type, number of neutrophils. The episode was considered to be acquired in the hospital when it started after 2 or more days of hospitalization.

Neither the source of bacteremia nor the death of the patient had to be recorded, the first because in most episodes of bacteremia in cancer patients the primary source is extremely difficult to assess and the second because the specific mortality attributable to infection is difficult to extract from the crude mortality in a given follow-up period.

The blood culture systems were selected at the participating centers: Hemoline (Bio-Mérieux, 101 episodes), Septicheck (Roche, 334 episodes) combined or not with Isolator (Dupont), Castaneda (Pasteur Production, 17 episodes), Bactec system with or without resin (330 episodes), or Signal (Oxoid; 269 episodes).

Definition of bacteremic episodes

The episodes were classified according to the definitions of the Center for Disease Control (CDC) [11] and consisted of: group 1: a "pathogenic" microorganism is isolated; group 2: the growing microorganism is a "contaminant" species ("diphteroids", *Bacillus* spp., *Micrococcus* spp., coagulase-negative staphylococci or CNS) but two samples (from different sets of blood cultures) at least are positive in the presence of a clinical sign (fever, chills or hypotension); group 3: bacteremia with a "contaminant" in the presence of a clinical sign and an intravascular catheter (suspected of being the cause of bacteremia) and an empiric antibiotic treatment administered; group 4: all other situations. According to the CDC [11], groups 1–3 are considered to be clinically significant.

We have used a second criterion based on the number of positive blood samples. The isolate was considered to be of possible clinical significance when it was isolated from more than one sample; other episodes were considered to be of doubtful clinical significance.

Antibiotic susceptibility testing

This was performed by the disk diffusion method using French (Comité Français de l'Antibiogramme, CFA, used in France; [1]) and US standards (National Committee for Clinical Laboratory Standards NCCLS, Villanova, Pa. 19085, USA; used at the Institut Jules Bordet, Belgium); 3 centers in France used ATB method (API, France), which has been correlated with the CFA standards. Staphylococci were tested at 30° C for oxacillin and other β-lactams.

Statistics

Fisher exact tests and Odds ratios were computed using GraphPAD InStat software v. 1.01 (H. J. Motulsky, 1989). A two-tailed probability of ≤ 0.05 was considered to be statistically significant. Kaplan–Meier statistics was used to compare the rate of growth in different categories of bacteremic episodes.

Results

Patients

During the period studied, the total number of admissions to the participating centers was 36398, and 1051 episodes were recorded, giving an incidence of 28.9/1000 admissions (range: 8.6–72.6). Using the CDC criteria [11], the incidence of significant episodes was 23.1/1000 admissions. Using our criterion of at least two positive samples, the incidence of clinically probably significant episodes was 15.6/1000 admissions.

The 1051 episodes occurred in 782 patients. Less than 4% of the data required were missing. The following items were missing (each out of a total of 1051 case re-

Table 1. Clinical and microbiological data of bacteremiac episodes reviewed in the present study

Characteristic	Total	Significant bacteremia[a]		Non-significant bacteremia[a]		*P*	Odds ratio
		n	%	*n*	%		
No. of episodes	1051	844		207			
Fever >38° C	834	723	85.7	111	53.6	<0.001	1.6
Chills	373	340	40.3	33	15.9	<0.001	2.5
Hypotension <90 mm	87	82	9.7	5	2.4	0.001	4.0
Shock	78	75	8.9	3	1.4	<0.001	6.1
≥1 clinical sign	863	748	88.6	115	55.5	<0.001	1.6
Empiric antibiotic treatment initiated	607	598	70.8	9	43.0	<0.001	1.6
Breakthrough bacteremia	364	281	33.3	83	40.1	0.15	
Neutropenia	233	195	23.1	38	18.3	0.26	
Central venous catheter	534	422	50.0	112	54.1	0.66	
Peripheral venous catheter	228	195	23.1	33	15.9	0.13	
Implantable catheter	304	245	29.0	59	28.5	0.80	
Duration of bacteremic episode (days)							
1	910	723	85.7	187	90.3		
2	89	77	9.1	12	5.8		
3	30	26	3.1	4	1.9		
4 or more	22	18	2.1	4	1.9		
Number with >1 organism	86	85		1		<0.001	20.8
Delay of positivity							
<10 h	59	56		3			
10–24 h	463	407		56			
25–48 h	243	199		44			
49–72 h	124	86		38			
>72 h	162	96		66			

[a] According to Centers for Disease Control (CDC) criteria

ports): presence of central catheter (42), peripheral catheter (42), implantable catheter (62), fever (6), chills (86), neutropenia (21), hypotension (36), shock (42), episode occurring during systemic antibiotic treatment (13), initiation of empiric antibiotic treatment (18).

Among the 1051 episodes, 474 occurred in a medical department (45.1%), 205 in a surgical department (19.5%), 101 in a radiotherapy department (9.6%), 146 in a hematology unit (13.8%), 111 in an intensive care unit (10.6%) and 25 elsewhere (2.4%). The sites of the tumors present in these patients were: oral cavity (34 patients), pharynx (67), larynx (15), esophagus and stomach (33), digestive tract and peritoneum (62), liver and pancreas (12), lung and mediastinum (62), malignant hemopathy (64), lymphoma (58), bone and joint (13), soft tissues and skin (34), breast (86), female genitalia (86), male genitalia (29), urinary tract (45), neurological tumors (36), thyroid and other endocrine glands (8), miscellaneous and unknown (38).

General characteristics of the episodes

Fever over 38° C was present in 79.3% of the episodes, chills in 35.4%, and hypotension (<90 mm Hg) in 8.2%; at least one of these signs was present in 82.1% of patients. Shock was observed and reported in 7.4%. Patients were already receiving antibiotics in 34.6%, and an appropriate empiric treatment was started immediately after blood sampling in 57.7%. Neutropenia (<500 polymorphonuclear cells/μl) was present in 22.1%. Catheters were present in all patients, including central venous catheter (50.8%), peripheral venous catheter (21.6%), implanted catheter (28.9%). Two patients had all three types of catheters simultaneously, 70 had both a peripheral and a central venous catheter, and 9 had both a central venous and an implanted catheter. The duration of positive blood cultures varied: 910 episodes lasted only 1 day (86.6%), 89 lasted 2 days (8.5%), 30 lasted 3 days (2.8%), and 22 lasted more than 3 days (2%).

Classification according to CDC criteria

The episodes were considered to be clinically nonsignificant in 19.7% of cases (Table 1), which, however, included 20 episodes (9.7%) that were recurrent, additional single positive blood cultures being obtained on the next day or later with the same organism.

Episodes that were considered to be clinically significant were associated significantly more frequently with clinical signs of infection, including fever >38° C, chills, hypotension, and shock (alone or in combination). Interestingly, only 9/207 (4.3%) clinically insignificant episodes were associated with empiric antimicrobial treatment, in contrast to 598/844 (70.8%) clinically significant episodes. The bacteremic episode occurred in patients receiving systemic antibiotics in similar proportions of the two groups to the presence of

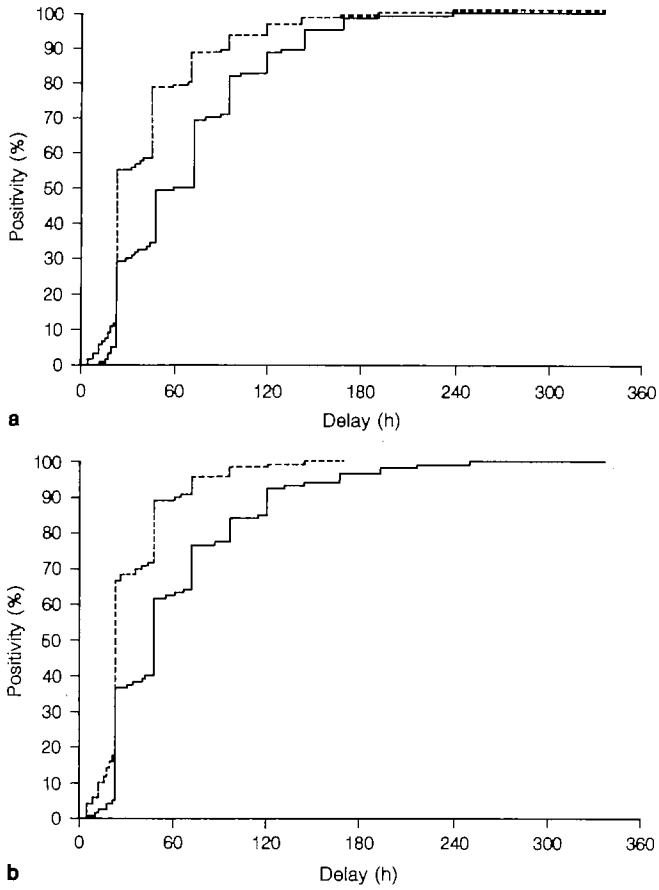

Fig. 1a, b. Cumulative positivity of blood cultures by type of bacteremic episode. **a** ------, 844 significant episodes according to CDC definitions (groups 1-3); ———, 207 non-significant episodes (group 4); $P<10^{-6}$, Kaplan-Meier. **b** ------, 492 episodes of probable clinical significance (≥2 positive samples); ———, 305 episodes of doubtful significance (single positive blood culture only); $P<10^{-6}$, Kaplan-Meier

neutropenia or the presence of a catheter. All polymicrobial episodes but one were considered to be clinically significant. As expected, the time to growth detection was significantly shorter in the group of clinically significant bacteremia (Fig. 1) [21].

Offending pathogens and blood culture methods

Table 2 shows that coagulase-negative staphylococci were the leading pathogens for both community- and hospital-acquired episodes, representing 40% and 41%, respectively. *Staphylococcus aureus* ranked second in the community-acquired episodes and *Escherichia coli* ranked second in the hospital-acquired episodes. Next came *E. coli*, *Pseudomonas aeruginosa*, streptococci and the *Klebsiella-Enterobacter-Serratia* group for the community-acquired episodes and *S. aureus*, the *Klebsiella-Enterobacter-Serratia* group, streptococci, yeasts, and *P. aeruginosa* for the hospital-acquired episodes. Strict anaerobes were seldom isolated (3.4%). All episodes with yeasts or which were polymicrobial were acquired in the hospital. All but one of the episodes due to enterococci were nosocomial. Surprisingly, 24% of the episodes caused by other nonfermenters than *P. aeruginosa* were acquired in the community.

For coagulase-negative staphylococci, growth to 50% recovery for each blood culture system occurred 1 day later in the Roche and 1–2 days later in the Bio-Mérieux system than in Bactec and Oxoid systems (Fig. 2). For Gram-negative bacilli, growth in the Roche system was slower than that in Bio-Mérieux, Oxoid or Bactec. Similar figures were observed for other microorganisms. However, interpretation of these results should take into account that each system was used in different hospitals and hence concerned different isolates.

Table 3 shows that in 257 episodes only one set of blood cultures was obtained (24.4%), whereas in 794 episodes more than one set was collected. Among the 257 episodes for which a single set collected, 122 (47.4%) were associated with a microorganism considered to be pathogenic and clinically significant (CDC group 1); on the other hand 38 (14.8%) corresponded to an opportunistic bacterium with signs of infection and for which an appropriate antimicrobial treatment was given.

In the present study, 33 episodes in which *Corynebacterium* spp. were isolated were considered significant according to CDC criteria [11]. Of these episodes, 5 were polymicrobial. In 6 episodes, the bacterium was identified as *C. jekeium*. In the each of the 24 other episodes (88%), there was at least one clinical sign of infection, or an empiric antibiotic treatment was started, or the patient had neutropenia and bone marrow transplant.

Strictly anaerobic bacteremia

Table 4 shows the characteristics of the 34 episodes attributed to strict anaerobes. The offending pathogens belonged mainly to the genus *Bacteroides* (24 isolates): *B. fragilis* (14), *B. thetaiotaomicron* (4), *B. vulgatus* (2), *B. ovatus* (1), *B. bivius* (1), and unspeciated (2). Nine isolates were due to *Clostridium* species: *C. perfringens* (7), *C. septicum* (1), and *C. inocuum* (1). Other strict anaerobes were: *Eubacterium limosum* (1), *Peptococcus saccharolyticus* (3), unspeciated Gram-negative bacilli (1), *Fusobacterium* species (1).

Among the clinical signs at the presentation of the episodes, none of their incidence was significantly different in episodes with anaerobes than in episodes without anaerobes. The only difference concerned the presence of implantable catheters, much more frequently associated with anaerobes.

Most episodes were associated with solid tumors of the digestive tract (9) or female reproductive tract (6), or with head and neck tumors (3). Some episodes (11 out of 34) were polymicrobial. The pathogens involved in polymicrobial episodes including strict anaerobes were: *E. coli* (3), CNS (5), *S. aureus* (1), *Candida albicans* (2).

Yeast fungemia

Table 4 shows the characteristics of the episodes due to yeasts. The offending species were: *Candida albicans*

Table 2. Offending pathogens isolated during bacteremic episodes reviewed in the present study. * $P<0.05$

Pathogen	No. of pathogens acquired					
	Total		Community		Hospital	
	n	(%)	*n*	(%)	*n*	(%)
E. coli	123	(10.7)	24	(9.0)	99	(11.2)
Klebsiella-Enterobacter-Serratia	71	(6.2)	15	(5.7)	56	(6.3)
Other Enterobacteriaceae	25	(2.2)	6	(2.2)	19	(2.1)
P. aeruginosa	55	(4.7)	19	(7.2)	36	(4.1)
Other non-fermenters	54	(4.7)	13	(4.9)	41	(4.7)
Coagulase-negative staphylococci	468	(40.8)	106	(40.0)	362	(41.0)
S. aureus	114	(9.9)	37	(13.4)	77	(8.7)
Streptococci	62	(5.4)	17	(6.4)	45	(5.1)
Enterococci	25	(2.2)	1	(0.4)	24*	(2.7)
Strict anaerobes[a]	39	(3.6)	10	(3.8)	29	(3.3)
Yeasts[a]	41	(3.6)	0		41*	(4.7)
Others	70	(6.1)	17	(6.4)	53	(6.0)
Achromobacter spp.	4					
Agrobacterium sp.	1					
Alcaligenes faecalis	2					
Bacillus spp.	7					
Campylobacter spp.	2					
Capnocytophaga spp.	2					
CDC group 4	1					
Corynebacterium spp.	33					
Fusarium sp.	1					
Lactobacillus sp.	1					
Listeria monocytogenes	4					
Micrococcus spp.	5					
Unidentified Enterobacteriae	2					
Unidentified bacteria	5					
Number with >1 organism	86	(7.5)			86*	(9.7)
Total	1147	(100)	265	(100)	882	(100)

[a] See Table 4

(30), *C. tropicalis* (1), *C. guillermondi* (1), *C. krusei* (2), *C. parakrusei* (1), other *Candida* species (5), and an unspeciated yeast (1).

None of the characteristics listed in Table 4 were different from those observed in patients with clinically significant bacteremia (CDC criteria), but more patients had multiple episodes. Only 7 out of the 41 episodes were associated with neutropenia. Most episodes occurred in patients with solid tumors (oral cavity, digestive tract and female reproductive tract).

Species of bacteria per CDC group

Table 5 shows the classification of the offending pathogens in each of the CDC groups and within these groups according to the clinical significance assessed by the number of positive samples. By definition most CNS were associated with CDC groups 2–4. The strains of CNS associated with group 1 were always associated with other bacteria (*Acinetobacter* spp.: 3; *Corynebacterium* spp.: 5; *Clostridium* spp.: 3; *Bacteroides* sp.: 1; *Candida* spp.: 2; *E. coli*: 4; *Enterococcus* spp.: 3; *Streptococcus* spp.: 9; unidentified enterobacteriaceae: 1; *P. aeruginosa*: 6; *Pseudomonas* spp.: 3; *S. aureus*: 1). As far as CDC group 1 is considered, the following species were more frequently associated with more than one positive blood culture: *E. coli*, *Klebsiella-Enterobacter-Serratia*, *S. aureus*, streptococci, yeasts and the group of other bacterial species. Most polymicrobial episodes fell in CDC group 1, most of them being associated with multiple isolates.

Analysis of episodes classified as CDC group 1

These 616 episodes were subclassified according to the number of positive blood culture samples considering the episodes with a single isolate of doubtful clinical significance (35.4%) (Table 6). Chills were more likely to occur in the subgroup with multiple isolates (Table 6). Of the probably clinically significant episodes, 6.5% were not associated with fever, or chills, or hypotension, despite the multiple isolates. Conversely, 80.7% of episodes with a single isolate were associated with at least one of the signs of bacteremia. Central venous catheters were used slightly more often in the group with probable clinical significance. Polymicrobial episodes were more likely to be associated with multiple positive blood cultures. Finally, growth was detected earlier in probably significant episodes than in episodes of doubtful significance (Kaplan–Meier; $P<0.001$) (Table 6, Fig. 1).

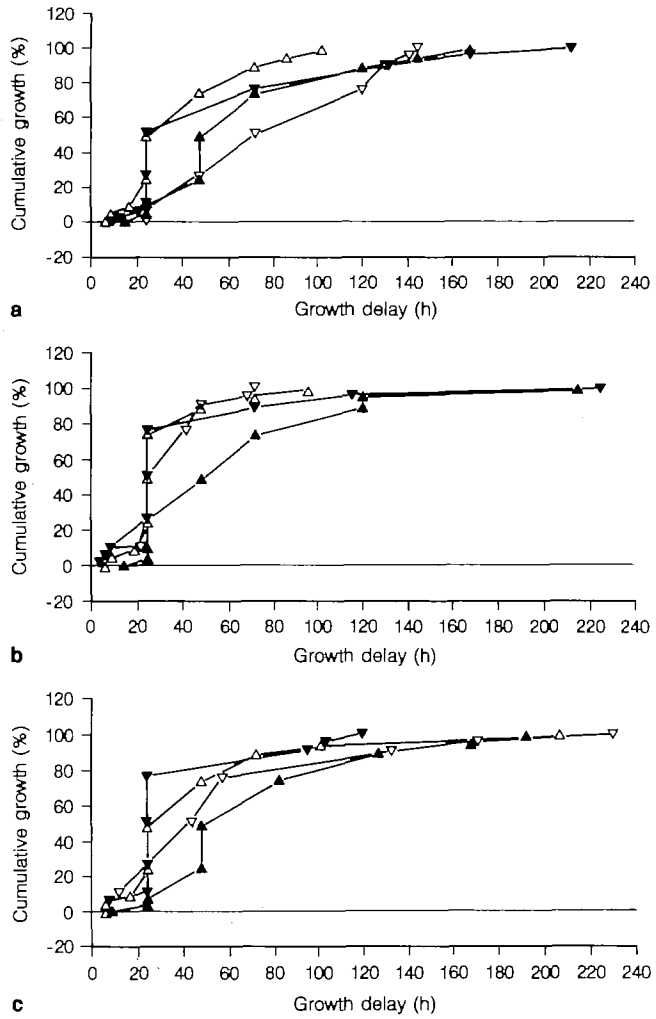

Fig. 2a–c. Cumulative positivity rate by type of bacteria (coagulase negative staphylococci or Gram-negative bacilli) and type of blood culture system. Number of episodes with **a** coagulase-negative staphylococci: Bio-Mérieux (24), Roche (146), Oxoid (154), Bactec (112); **b** Gram-negative bacilli: Bio-Mérieux (41), Roche (92), Oxoid (63), Bactec (109); and **c** other microorganisms: Bio-Mérieux (36), Roche (96), Oxoid (52), Bactec (109). In the case of polymicrobial bacteremia, only the delay to the growth of the first organism was recorded. ▽, Bio-Mérieux; ▲, Roche; ▼, Oxoid; △, Bactec

Analysis of episodes classified as CDC group 2

There were 47 episodes classifiable in CDC group 2. All were considered to be of clinical significance because at least two samples were positive and clinical signs were present. The episodes were due to CNS in 46 cases. Fever was observed in 98%, chills in 49%, hypotension in 10.6%, at least one sign in 100% and septic shock in 8.5%. Appropriate empiric antibiotic treatment was initiated in 12.8%; 28.2% of the patients were under antibiotic treatment at the time of blood sampling.

Analysis of episodes classified as CDC group 3

These 181 episodes were subclassified according to the number of positive blood culture samples (Table 7), and

Table 3. Number of positive blood culture and total obtained

CDC class	No. of episodes	With		
		1+/1	1+/≥2	≥2/≥2
1	616	122	96	398
2	47	0	0	47
3	181	38	49	94
4	207	97	80	30
Total (%)	1051 (100)	257[a] (24.4)	225[a] (21.4)	569[b] (54.1)

[a] 482 episodes of potentially doubtful clinical significance
[b] 569 episodes of probable clinical significance

Table 4. Episodes associated with strict anaerobes and yeasts

Characteristic	Anaerobes *n* (%)	Yeasts *n* (%)
No. of episodes	34	41
No. of isolates	39	41
Fever >38° C	29 (85.2)	35 (85.3)
Chills	14 (41.1)	18 (43.9)
Hypotension <90 mm	7 (5.8)	3 (7.3)
Shock	5 (14.7)	3 (7.3)
Empiric antibiotics initiated	26 (76.4)	26 (63.4)
Breakthrough bacteremia	13 (38.2)	27 (65.8)
Neutropenia	6 (17.6)	7 (17.0)
Central venous catheter	14 (41.1)	29 (70.7)
Peripheral venous catheter	8 (23.5)	6 (14.6)
Implantable catheter	21 (61.7)	23 (31.7)
Hospital-acquired	24 (70.5)	35 (85.3)
Positively delay ≤72 h	31 (79.4)	33 (80.4)
No. of patients	34	28
Tumors		
Oral cavity	1	5
Pharynx	1	1
Stomach/esophagus	1	1
Digestive tract/peritoneum	8	2
Liver/pancreas	1	2
Lung and mediastinum	1	2
Malignant hemopathy	3	1
Lymphoma	3	1
Bone and joint	0	1
Soft tissue and skin	0	2
Breast	4	3
Female reproductive tract	6	4
Urinary tract	2	2
Miscellaneous and unknown	3	1

87 (48.1%) were considered to be of doubtful clinical significance. However, the two subgroups (probably clinically significant and of doubtful clinical significance) did not differ significantly in the signs and symptoms of infection, with the exception of shock, which was observed almost exclusively in the most significant episodes. The most significant episodes (at least two positive blood samples) included 13.8% that were not associated with fever, chills, or hypotension. Conversely, signs of infection were observed in 82.7% of the episodes associated with a single positive blood sample.

Table 5. Offending pathogens isolated during bacteremic episodes reviewed in the present study. P, Clinical significance was probable; D, clinical significance was doubtful (one positive blood culture only)

Pathogen	Total	CDC groups						
		1 P	1 D	2 P	3 P	3 D	4 P	4 D
E. coli	123	91	32					
%[a]	11.7	22.9	14.7					
Klebsiella-Enterobacter-Serratia	71	55	16					
%[a]	6.8	13.8	7.3					
Other Enterobacteriaceae	25	13	12					
%[a]	2.4	3.3	5.5					
P. aeruginosa	55	34	21					
%[a]	5.2	8.5	9.6					
Other non-fermenters	54	35	19					
%[a]	5.1	8.8	8.7					
Coagulase-negative staphylococci	468	28	14	47	96	84	30	169
%[a]	44.5	7.0	6.4	100.0	102.1	96.6	100.0	95.5
S. aureus	114	82	32					
%[a]	10.8	20.6	14.7					
Streptococci	62	37	25					
%[a]	5.9	9.3	11.5					
Enterococci	25	20	5					
%[a]	2.4	5.0	2.3					
Strict anaerobes[b]	39	27	12					
%[a]	3.7	6.8	5.5					
Yeasts[b]	41	32	9					
%[a]	3.9	8.0	4.1					
Others	70	18	35	1	3	3	0	10
%[a]	6.7	4.5	16.1	2.1	3.2	3.4	0.0	5.6
No. of episodes with >1 organism	86	64	17	1	3	0	0	1
%[a]	8.2	16.1	7.8	2.1	3.2	0.0	0.0	0.6
Total bacteria	1147	472	232	48	99	87	30	179
Total episodes	1051	398	218	47	94	87	30	177
	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

[a] Percentage of episodes

[b] See Table 3

Growth of the offending pathogen was significantly more rapid in the probably significant episodes than in those of doubtful clinical significance (Kaplan–Meier; $P<0.001$).

Analysis of episodes classified as CDC group 4

According to the CDC criteria, these episodes are considered to be of no clinical significance.

These 207 episodes were subclassified into 177 episodes of doubtful clinical significance (85.5%) and 30 episodes of probable clinical significance (24.5%) according to the number of positive blood samples (Table 8). By definition, all episodes with at least two positive blood culture samples showed no signs of infection. In none of these cases was a new empiric therapy initiated. Other characteristics were similar in the two subgroups of patients, except for the presence of an implantable catheter, which was more frequent in the subgroup with several positive blood cultures. Growth was earlier in the latter subgroup. These patients either (mainly) had catheter-related infections under specific treatment and continued to have positive blood cultures in the follow-up to treatment (clinically significant positive culture), or were monitored systematically for surveillance of total parenteral nutrition and had several samples that grew a contaminating *S. epidermidis* (non-clinically significant positive cultures). The second category, of 177 episodes, is more difficult to interpret. Of these episodes, 97 correspond to a single blood culture obtained in the presence of fever and other signs of infection in patients. Most were receiving antibiotic treatment and no modification was made. Others were not receiving antibiotic treatment and went on without because fever was considered to have a non-bacterial cause. The remaining 80 episodes with a single positive blood culture despite collection of several samples were not treated, and their fever was considered to be of non-infectious origin.

Comparison between episodes occurring in neutropenic and in non-neutropenic patients (CDC groups 1–3)

Table 9 shows the characteristics of the 195 bacteremic episodes in neutropenic patients (<500/μl) compared with 628 episodes in non-neutropenic patients. Hypoten-

Table 6. Comparison of probably clinically significant (≥2 positive sets) and doubtful significant (one positive set only) bacteremic episodes within CDC group 1. Information missing for some episodes

Characteristic	Total	Significant bacteremia		*P*	Odds ratio
		Probable	Doubtful		
No. of episodes	616	398	218		
Fever >38° C	527	358	169	0.26	
Chills	263	190	73	0.02	1.4
Hypotension <90 mm	64	44	20		
Shock	63	48	15		
≥1 clinical sign	548	372	176		
Empiric antibiotics initiated	411	284	127		
Breakthrough bacteremia	229	144	85		
Neutropenia	140	96	44		
Central venous catheter	274	188	86		
Peripheral venous catheter	143	84	59		
Implantable catheter	183	113	70		
Hospital-acquired	476	306	170		
No. with >1 organism	81	64	17	0.01	2.1
Delay of positivity (h)					
<10	47	32	15		
10–24	318	237	81		
25–48	124	81	43		
49–72	56	23	33		
>72	71	25	46		

sion and shock were more likely to occur in neutropenic patients. More non-neutropenic patients had a peripheral catheter. Bacteremia occurred in 40.5% of neutropenic and 32% of non-neutropenic patients while they were receiving absorbable and/or systemic antimicrobial agents. The detection rate was identical in the two groups. Overall, 10.5% of the episodes were polymicrobial. The type of causative microorganisms did not differ significantly in the two groups, except that there was much more frequent isolation of *P. aeruginosa* in the neutropenic group of patients. Although *S. aureus* seemed to be more frequently isolated from non-neutropenic patients and streptococci from neutropenic patients, these differences were not statistically significant.

Polymicrobial episodes

Most polymicrobial episodes (Table 10) were associated with solid tumors (72% excluding lymphomas; 80% including lymphomas). Strict anaerobes accounted for 12 of 86 (13.9%) of the polymicrobial episodes. No significant differences were observed on comparison of the group of patients with several positive samples and those with a single isolate for symptoms, antibiotic administration, risk factors and growth detection rate.

Episodes associated with coagulase-negative staphylococci

Among the 1051 episodes, coagulase-negative staphylococci accounted for 468 (44.5%), 422 (40.1%) of which did not occur in the CDC group 1 (Table 11). There were 252 (59.7%) that were isolated only once and considered of doubtful clinical significance. The vast majority of the episodes associated with CNS were monomicrobial. As expected from the definitions of the CDC groups, symptoms were concentrated in groups 2 and 3, and the administration of empiric antibiotic therapy was the rule in group 3. In group 2, despite the presence of clinical signs of infection, only 12.7% of the episodes were treated with antibiotics. The episodes in group 4 were not associated with empiric antibiotics despite a 62.7% rate of clinical signs in the episodes associated with a single isolate.

Breakthrough bacteremia was more likely in group 4 than in groups 2 and 3.

Antibiotic susceptibility

Results of in vitro susceptibility tests were available for 459 (40.0%) isolates. Bacteremic strains of *S. aureus* (77 strains) were resistant to penicillin (91%), oxacillin (34%), perfloxacin (33%), ciprofloxacin (27%), fusidic acid (11%), erythromycin (40%), and gentamicin

Table 7. Comparison of probably clinically significant (≥2 positive sets) and doubtfully significant (1 positive set only) bacteremic episodes within CDC group 3

Characteristic	Total	Significant bacteremia		*P*	Odds ratio
		Probable	Doubtful		
No. of episodes	181	94	87		
Fever >38° C	150	79	71		
Chills	53	30	23		
Hypotension <90 mm	13	6	7		
Shock	8	7	1	0.06	6.5
≥1 Clinical sign	181	94	87		
Breakthrough bacteremia	42	19	23		
Neutropenia	49	24	25		
Central venous catheter	121	62	59		
Peripheral venous catheter	38	21	17		
Implantable catheter	53	31	22		
Hospital-acquired	131	72	59		
Number with >1 organism	3	3	0		
Delay of positivity (h)					
<10	8	7	1		
10–24	66	49	17		
25–48	61	27	34		
49–72	24	10	14		
>72	22	1	21		

Table 8. Comparison of probably clinically significant (≥2 positive sets) and doubtfully significant (1 positive set only) bacteremic episodes within CDC group 4. NA, Not applicable (by definition)

Characteristic	Total	Significant bacteremia		*P*	Odds ratio
		Probable	Doubtful		
No. of episodes	207	30	177		
Fever >38° C	111	0	111	NA	
Chills	33	0	33	NA	
Hypotension <90 mm	5	0	5	NA	
Shock	3	0	3	NA	
≥1 Clinical sign	115	0	115	NA	
Empiric antibiotics initiated	9	0	9	NA	
Breakthrough bacteremia	83	10	73		
Neutropenia	38	5	33		
Central venous catheter	112	19	93		
Peripheral venous catheter	33	2	31		
Implantable catheter	59	15	44	0.05	2.0
Hospital-acquired	167	25	142		
Number with >1 organism	1	0	1		
Delay of positivity (h)					
<10	3	0	3		
10–24	56	17	39		
25–48	44	7	37		
49–72	38	2	36		
>72	66	4	62		

(29%). Coagulase negative staphylococci (212 strains) were resistant to penicillin (86%), oxacillin (58%), perfloxacin (44%), fusidic acid (18%), erythromycin (38%), gentamicin (52%).

E. coli (85 strains) were resistant to ampicillin (40%), amoxycillin-clavulanic acid (33%), piperacillin (27%), ticarcillin-clavulanic acid (17%), cefazolin (41%), perfloxacin (3%), gentamicin (5%), netilmicin and amikacin (7%); all strains were susceptible to cefotaxime, ceftazidime, aztreonam, imipenem and ciprofloxacin. *Klebsiella* (28 strains) were resistant to piperacillin (15%), amoxycillin-clavulanic acid (21%), ticarcillin-clavulanic acid (12%), cefazolin (28%), cefotaxime (9%), ceftazidime (5%), pefloxacin (5%), ciprofloxacin (6%), gentamicin (5%), amikacin (5%); all strains were susceptible to aztreonam, imipenem and netilmicin. *Enterobacter* (22 strains) were resistant to ampicillin (94%), amoxycillin-clavulanic acid (93%), piperacillin (32%), ticarcillin-clavulanic acid (25%), cefazolin (67%), cefotaxime and ceftazidime (13%), imipenem (7%), gentamicin (13%), netilmicin (6%); all strains were susceptible to amikacin, pefloxacin and ciprofloxacin. *Pseudomonas* (45) were resistant to piperacillin (26%), aztreonam (35%), ceftazidime (26%), imipenem (16%), amikacin (31%), pefloxacin (60%), ciprofloxacin (22%).

Discussion

As far as probably significant episodes are concerned, the incidence of bacteremia reported in the present study (15.6/1000 admissions) was similar to that reported by Weinstein et al. [26, 27] with 16.5/1000 admissions and Roberts et al. [21] with 14.6/1000 admissions. Using the CDC criteria [11], our incidence was 23.1/1000 admissions. With criteria close to those of the CDC, Rotstein et al. [22] reported a rate of nosocomial bacteremia of 32.8/1000 admissions.

The range of incidence of bacteremia was large among the participating centers (8.6–72.6/1000 admissions). Several factors may explain this, including (1) patients' recruitment by type of cancer and extension, specificities of the cancer center, (2) sampling intensity, including systematic culturing of blood from patients with total parenteral nutrition, (3) activity of the infection prevention and hospital hygiene teams, (4) occurrence of epidemics, including possible epidemics of pseudo-bacteremia, (5) missed episodes. The importance of (1) has been well documented in the study by Rotstein et al. [22], who report a nosocomial infection rate of 6.27 episodes/1000 patients days, 20.6% of which were bloodborne infections. The lowest rate was observed in thyroid cancer (2.02 episodes/1000 patient-days) and the highest, in acute myelogenous leukemia (30.49 episodes/1000 patient-days). A similar study from one of the participating centers [5] reported a range of nosocomial infection from 3.11 in thyroid cancer to 21.04 in non-Hodgkin's lymphoma [5].

The fact that all patients are not systematically sampled at least twice and sets of blood cultures started may affect the rate of probably significant episodes as defined in the present study (at least two isolates of the same species from different sets). Single sampling may result in an incidence as high as 52% of suspected bacteremias in an emergency department and 11.7% in hospitalized patients [15].

The present study substantiates the very large proportion of Gram-positive bacteria associated with bacteremia in cancer patients. A similar observation has been reported during the last decade in most reviews of bacteremia in neutropenic cancer patients [8, 9, 17, 24] and in one review on both neutropenic and non-neutropenic cancer patients [30]. In the later study reporting on 431 episodes occurring in 1982 in 356 patients at a single center (Memorial Sloan Kettering Cancer Center), definitions were vague and neither the number of non-significant episodes nor the incidence of bacteremia was given. Coagulase-negative staphylococci represented 4% of the episodes. Several factors may contribute to the increasing role of Gram-positive bacteria: the large proportion of patients with indwelling intravascular catheters, some of which were in place for long periods of time (>1 year), the better control of Gram-negative bacillary infections by gastrointestinal decontamination (cotrimoxazole or quinolones), the more aggressive anticancer treatments associated with more severe skin reactions and mucositis, and the frequent reactivation of herpes simplex mucositis (mainly associated with an in-

Table 9. Comparison of bacteremic episodes associated with neutropenia and non-neutropenia within groups 1–3

Characteristic	Total	Blood neutrophils				*P*	Odds ratio
		<500/μl		≥500/μl			
		n	%	*n*	%		
No. of episodes	844	195		628[a]			
Fever >38° C		165	84.6	547	87.1		
Chills		71	36.4	266	42.3		
Hypotension <90 mm		27	13.8	53	8.4	0.05	1.6
Shock		25	12.8	49	7.8	0.06	1.6
≥1 Clinical sign		168	86.1	568	90.4		
Empiric antibiotics initiated		155	79.5	432	68.8		
Breakthrough bacteremia		79	40.5	201	32.0		
Central venous catheter		103	52.8	314	50.0		
Peripheral venous catheter		33	16.9	160	25.5	0.05	0.7
Implantable catheter		66	33.8	178	28.3		
Hospital-acquired		133	38.2	501	79.8		
Number with >1 organism		22	11.3	63	10.0		
Delay of positivity (h)							
<10		11		21			
10–24		99		337			
25–48		47		143			
49–72		14		67			
>72		24		69			
Offending pathogens							
E. coli		22	11.3	99	15.8		
Klebsiella-Enterobacter-Serratia		12	6.1	58	9.2		
Other Enterobacteriaceae		3	1.5	22	3.5		
P. aeruginosa		26	13.3	29	4.6	<0.001	2.9
Other non-fermenters		14	7.1	40	6.3		
Coagulase-negative staphylococci		62	31.8	203	32.3		
S. aureus		21	10.8	91	14.5		
Streptococci		18	9.2	43	6.8		
Enterococci		7	3.6	18	2.8		
Strict anaerobes[b]		8	4.1	30	4.8		
Yeasts[b]		8	4.1	32	5.1		
Others		17	8.7	42	6.7		
Total micro-organisms		218		707[c]			

[a] Not reported in 12 episodes
[b] See Table 4
[c] 13 microorganisms were associated with episodes for which the neutrophil count was not provided

crease in streptococcal bacteremia in bone marrow transplant patients) [2].

Coagulase-negative staphylococci bacteremia most usually arises from infected indwelling intravascular catheters [19]. In addition, neutropenic patients are usually receiving oral antibiotics, which may not be active against staphylococci, and it has been shown that the respiratory tract and the digestive tract can be sources of CNS bacteremia [25]. In neutropenic patients receiving fluoroquinolones, the fecal samples are almost always heavily colonized with quinolone-resistant strains of CNS [24].

A similar predominant role of CNS has been reported for nosocomial bloodborne infections [12]. CNS now ranks first with 25.5%, followed by *S. aureus* (15%) and enterococci (7.9%) before the most frequent Enterobacteriaceae (*E. coli* 6.8%). It is interesting that in the NNIS report, *Candida* species now account for 7.8% of nosocomial bloodborne infections. In the present study, *Candida* spp. accounted for 3.6% overall.

Bacteremia due to CNS has been associated with septic shock in 17% of cases and in 8% with disseminated intravascular coagulation, as outlined in a review of 171 cases of nosocomial bacteremia involving 47 patients with underlying neoplastic disease [19]. Interestingly, in this study, the authors reported an increasing rate of CNS bacteremia from 5.2 (1980) to 42.0/10000 admissions (1987).

Despite strong evidence that CNS are pathogenic, the dramatic increase in the incidence of CNS bacteremia may be due in part to underreporting earlier and to probable overreporting now. Overreporting may result from systematic blood cultures in high-risk patients, as seen in our CDC category 4 (Table 8).

The emergence of enterococci has been attributed to the increasing use of third-generation cephalosporins,

Table 10. Clinical data of polymicrobial bacteremic episodes in CDC group 1

Characteristic	Total	Significance of bacteremia				*P*
		Probable		Doubtful		
		n	%	*n*	%	
No. of episodes	81	64		17		
Fever >38° C		58	90.6	14	82.3	
Chills		26	40.6	4	23.5	NSS
Hypotension <90 mm		7	7.8	3	17.6	
Shock		5	7.8	1	5.9	
≥1 Clinical sign		60	93.7	14	82.3	
Empiric antibiotics initiated		49	76.6	9	52.9	0.1
Breakthrough bacteremia		16	25.0	8	47.0	0.14
Neutropenia		19	29.7	2	11.7	NSS
Central venous catheter		31	48.4	5	29.4	
Peripheral venous catheter		9	14.1	3	17.6	
Implantable catheter		19	29.7	8	47.1	
Duration of bacteremic episode (days)						
1		46		17		
2		13				
3		1				
4 or more		4				
Delay of positivity (h)						
<10		3		1		
10–24		35		6		
25–48		14		6		
49–72		4		4		
>72		8		0		

which are inactive against them. Because enterococci and other Gram-positive rods (such as *Corynebacterium* JK) are always susceptible to vancomycin, this antibiotic is used increasingly in the empiric treatment of infection in cancer patients once a Gram-positive infection is suspected [13]. However, it has been recently shown that the empiric addition of vancomycin early in the management of febrile neutropenic patients does not affect mortality and nor does the use of additional antimicrobial or antifungal drugs [9]. Early addition was associated with increased toxicity when any of these were used in combination with an aminoglycoside [9].

Our study is in marked contrast to a similar study published in 1987 from the Memorial Sloan-Kettering Cancer Center in New York [30]. This study dealt with 431 episodes, including 273 episodes in non-neutropenic patients and 158 episodes in neutropenic patients. All episodes had occurred in 1982. In non-neutropenic patients, the following pathogens were isolated: *E. coli* (20%), *S. aureus* (13%), polymicrobial (12%), *Pseudomonas* spp. (8%), *Klebsiella* spp. (7%), *Candida* spp. (7%), *Bacteroides* spp. (6%), *Enterobacter* spp. (4%), *Clostridium* spp. (4%). In neutropenic patients, the following pathogens were isolated: polymicrobial (21%), *E. coli* (16%), *Klebsiella* spp. (15%), *Pseudomonas* spp. (8%), *Candida* spp. (6%), *S. aureus* (6%), *E. faecalis* (5%), CNS (4%), and *Corynebacterium jekeium* (3%). Rotstein et al. [22] reported that a significant proportion of nosocomial bacteremia in cancer patients was due to coagulase-negative staphylococci (23.3% of 165 episodes). In total, Gram-positive bacteria caused 43% of all bacteremia.

Polymicrobial bacteremia has been reviewed recently in cancer [7] and non-cancer patients [28]. Half the 507 episodes reviewed occurred in patients with solid tumors, and 80% were nosocomially acquired. These episodes were frequently found to be associated with shock and pneumonia. Gram-negative bacilli were present in 76%, Gram-negative bacteria in 50%, and strict anaerobes in 21%. Only 7% of episodes were associated with yeasts.

Twenty-three percent of our episodes were acquired in the community, although, as stated by Bodey [3], the differentiation between nosocomial and community-acquired infection is less important in cancer patients than in other populations. The main reason is that most of these patients will be repeatedly readmitted to the hospital and thus will have an higher chance of colonization by more resistant or unusual bacteria. This might explain the lack of striking difference in the spectrum of pathogens isolated within the 48 h of admission versus those isolated later on. Furthermore, owing to their immunosuppression, less virulent pathogens are able to produce infection.

The present study shows the limitations of the actual CDC definition of clinically significant bacteremia [11]. This definition has a high sensitivity and a low specificity, as shown here.

As far as bacteremia with *Staph. epidermidis* is considered, our own definition of clinically significant epi-

Table 11. Clinical and microbiological data of bacteremic episodes attributable to coagulase-negative staphylococci. P, Episode of probable clinical significance; D, episode of doubtful clinical significance

Characteristic	Total	Group[a]				
		2	3P	3D	4P	4D
No. of isolates	426	47	96	84	30	169
No. of episodes	422	46	94	84	30	168
Fever >38° C		45	79	68	0	102
Chills		22	30	22	0	28
Hypotension <90 mm		4	6	7	0	4
Shock		3	6	1	0	2
≥1 Clinical sign		46	94	84	0	106
Empiric antibiotics initiated		6	94	84	0	9
Breakthrough bacteremia		9	19	20	10	71
Neutropenia		6	24	24	5	31
Central venous catheter		27	62	56	19	87
Peripheral venous catheter		13	21	17	2	29
Implantable catheter		8	30	22	15	41
No. with >1 organism		1	3	0	0	1

[a] According to CDC criteria

sodes (at least 2 positive samples), a classical definition used in the literature [21], missed highly symptomatic patients who had only a single positive sample. MacGregor et al. [18] have reported that in only 69% of significant episodes were multiple positive blood cultures found. On the other hand, 11% of non-significant episodes (contaminated cases) had more than one positive blood culture.

In a review of 1972 positive blood cultures Roberts et al. [21] reported that 63% of the episodes were clinically significant (signs and symptoms of infection with one or more positive blood sample), 26% represented contamination, 7% represented transient bacteremia (transient signs and symptoms, no specific treatment) and 3% were considered of indeterminate significance due to the lack of relevant clinical information. In our study, the rate of non-significant episodes was 19.7% according to CDC definitions [11].

Unfortunately, in the study of Roberts et al. [21], underlying diseases were not reported. Among their clinically significant episodes, Gram-positive cocci accounted for 42.8%, including CNS in 12.9%, *S. aureus* in 14.4%, streptococci in 11.7% and enterococci in 6.7%. Gram-negative bacilli represented 45%, including *E. coli* in 17.3%, *Pseudomonas* spp. in 9.2%, *Klebsiella* in 9.2%. Strict anaerobes were recovered in 5.2% of the episodes and yeasts in 5.6%. Polymicrobial episodes accounted for 16.2% (in our study: 8.1% overall, 10.1% from significant episodes according to CDC definitions, or 16.8% in CDC group 1 with multiple positive blood samples).

The low prevalence of strict anaerobes (3.4%) in our study questions the systematic use of a specific bottle. In recent reviews of anaerobic bacteremias in cancer patients [10, 14] (Noriega et al. manuscript submitted), most episodes were associated with cancer of the gastrointestinal and female reproductive tracts and of the head and neck. This was also confirmed in the present study. Furthermore, most anaerobes grow well in the usual rich media used for aerobic bottles (*Bacteroides* group "*fragilis*" and *Clostridium* spp.). This finding may have important practical consequences in saving costs for the laboratory procedures. In the absence of clinical indications for anaerobic infection (mainly patients with gynecological or digestive tract cancers who have been recently operated on or iradiated) a single bottle is probably enough and most cost-effective. Anaerobic culture therefore need only be done on targeted suspicion of strict anaerobic bacteremia.

As far as the duration of observation of the blood cultures is concerned, all episodes were detected within 5 days, supporting adoption of this period as the limit unless *Histoplasma* is suspected [20]. Most media used in the centers taking part seemed to have similar performances, although in Roche Septicheck initial growth was delayed by 1 day. In addition, the Signal (Oxoid) system performed well, despite disappointment expressed in several reports from the literature [6, 29]. It must be stressed, however, that comparisons were made between different institutions using different systems and not within a single institution comparing several media inoculated with aliquots of the same samples of blood.

Episodes with several positive samples were associated with more rapid detection than those with only one positive sample. Rapid detection was usually associated with more symptoms, with the notable exception of CDC group 4. In this group (mostly coagulase-negative staphylococci), fever was most often observed in patients with a single isolate, although the doctor did not alter the treatment specifically. In contrast, most patients with several isolates were not treated because these blood cultures were drawn as part of the systematic surveillance of patients with Hickman lines, implantable catheters, and/or total parenteral nutrition. The cost-effectiveness of such a systematic blood culturing procedure has not been supported by the literature and should probably not be performed.

As far as antimicrobial susceptibility testing is considered, the following comments can be made. The rate of methicillin resistance is fairly high compared with the mean rate in Belgium (25%, Institut d'Hygiène et d'Epidémiologie, National Survey 1991; unpublished results). As expected, almost all methicillin-resistant *S. aureus* were also resistant to the new fluoroquinolones, macrolides and gentamicin. More than half of the CNS were resistant to oxacillin, with a high degree of cross-resistance to fluoroquinolones and gentamicin.

Among Gram-negative bacilli, the rate of resistance was much lower than bacteria isolated from intensive care units in the same years as our study both in France (Jarlier 1992, unpublished results) and Belgium [23], with excellent susceptibility to ceftazidime, aztreonam, ciprofloxacin, aminoglycosides and imipenem. Among *Pseudomonas*, almost one-third of the strains were resistant to piperacillin, aztreonam, ceftazidime and amikacin. The most active antibiotics remaining were imipenem and ciprofloxacin.

In conclusion, we have shown that the CDC definition of significant bacteremia is highly sensitive but has a low specificity. There is a need for more specific criteria of clinically significant bacteremia. Our survey confirms the high prevalence of Gram-positive bacteria both in neutropenic and in non-neutropenic cancer patients. The incidence of bacteremia was variable from center to center, depending on the types and stages of cancer in the patients admitted and on the local blood culture sampling routines. Episodes due to strict anaerobes were less frequent than previously reported, which supports the selective use of anaerobic bottle in patients with high-risk tumors: cancers of the digestive tract, female reproductive tract and head and neck. Systematic collection of blood cultures in the absence of signs of infection should probably not be performed, as it increases costs and enlarges the category of clinically non-significant bacteremia.

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