BLOODSTREAM INFECTIONS IN PATIENTS WITH OR WITHOUT CANCER IN A LARGE COMMUNITY HOSPITAL

CHAPTER 6

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Abstract

Purpose: Cancer is associated with an increased risk to acquire bloodstream infection (BSIs). Most knowledge on pathogens and outcome of are derived from specialized cancer centres. We here sought to compare causative microorganisms in BSIs in patients with or without cancer in a 600-bed teaching community hospital.
Methods: We analysed all positive blood cultures from adult patients between January 2005 and January 2011.
Results: 4,918 episodes of BSI occurred in 2,891 patients, of whom 13.4% had a diagnosis of cancer (85.5% with a solid tumour). In both patient groups Gram-positive isolates were more prevalent (58.7 and 61.4% in patients with and without cancer respectively) than Gram-negative isolates (31.8 and 32.3% respectively). Amongst Gram-positive organisms, coagulase negative staphylococci, *Staphylococcus (S.) aureus* and enterococci were most frequently isolated in both patient groups; in cancer patients twice as many BSIs were caused by *Enterococcus (E.) faecalis* and *E. faecium*. Amongst Gram-negative organisms, *Escherichia (E.) coli* was the most common isolate; in cancer patients twice as many BSIs were caused by *Pseudomonas aeruginosa* and *Enterobacter cloacae*. Yeasts were grown from 3.0% of blood cultures from cancer patients versus 1.5% of cultures from non-cancer patients. Cancer patients had a 90-day mortality of 35.8% following BSI versus 23.5% in patients without cancer.
Conclusion: These data demonstrate distinct BSI pathogens and impaired outcomes in patients with cancer in the setting of a large community teaching hospital.

Introduction

Bloodstream infections (BSIs) represent a major cause of morbidity and mortality in cancer patients [1-3]. Cancer is associated with a strongly increased risk to acquire BSI [4-6]. In accordance, cancer is the most common comorbid condition in patients with sepsis, reported to be present in approximately 17% of cases [7, 8]. Cancer patients are more vulnerable to develop invasive infection due to various reasons, including an often progressive catabolic state, ulcerating lesions in mucosal surfaces and immune suppression secondary to chemotherapy, radiation, immune modulating therapeutics and/or the malignancy itself [9]. Patients with neutropenia are particularly prone to develop BSI, with the highest risk for patients who have undergone bone marrow transplantation [3, 10-12]. BSIs not only cause considerable mortality, but also prolong hospital stay and increase patient care costs [13].

Until the 80s, Gram-negative bacteria were the most common cause of BSIs in the western world. Since then, Gram-positive organisms have become increasingly frequent as causative agents of BSIs [5, 8, 14]. In addition, the proportion of *Candida* species among BSI isolates has increased in recent decades [5, 8]. In a large survey involving 2,340 cancer patients studied between 1995 and 2001 Gram-positive organisms accounted for 62% of all nosocomial BSIs in 1995 and for 76% in 2000, whereas Gram-negative organisms accounted for 22% and 14% of all BSIs for these years, respectively; the predominant pathogens were coagulase-negative staphylococci [12]. Other investigations have examined the causative agents implicated in BSIs in cancer patients in specialized cancer centres and/or specific cancer populations, such as patients with haematological malignancies, neutropenia and/or after bone marrow transplantation [3, 15-18]. In the Netherlands most cancer patients are treated in community hospitals. The primary objective of the current study was to obtain insight into the distribution of pathogens causing BSI in cancer patients (as compared with patient without malignancy) in the setting of a community teaching hospital. For this we analysed all positive blood culture results obtained in our institution from adult patients between January 2005 and January 2011. We report blood culture isolates, resistance patterns, demographics , referring specialties, type of cancer, cancer treatments and outcome.

Materials and Methods

Patient and design

This study is a single centre retrospective analysis of all positive blood culture results obtained from adult patients (> 16 years of age) between January 2005 and January 2011 registered in a 600-bed community teaching hospital in the Netherlands (Reinier de Graaf Hospital, Delft). For this study, BSIs were diagnosed solely on the basis of at least one positive blood culture irrespective of the causative microorganism. Multiple positive blood cultures with the same microorganism in the same patient within a 24-hour time frame were considered as a single positive blood culture. Positive blood cultures were identified in the hospital microbiology information system (General Laboratory Information Management System, GLIMS®, MIPS Diagnostics Intelligence, Gent, Belgium). Identification numbers of patients with a positive blood culture were linked with (a) the hospital patient registration system containing encoded "diagnosis and treatment combinations" (a nationwide coding and registration system for all patients entering a hospital, either as outpatient or inpatient, providing information about the

diagnosis and treatment specified by the attending physician), and (b) the hospital laboratory information system (GLIMS), containing data on routine laboratory tests. Laboratory test results were included in the analysis if obtained in the period from 24 hours before to 48 hours after the blood culture was taken. Information about all-cause mortality, also after hospital discharge, was collected from the hospital information system.

Blood cultures

Blood was routinely inoculated into two separate bottles for aerobic and anaerobic culture respectively (Becton-Dickinson, Breda, the Netherlands; 10 mL each). All cultures were processed in a Bactec 9000-seriescontinuous monitoring system (Becton-Dickinson) and incubated until microbial growth was detected or for four days; incubation periods were longer in case of suspected endocarditis or infection with *Legionella* or yeasts. Isolates from positive bottles were mostly identified by standard methods using the Phoenix 100 system(Becton-Dickinson) or API-methodology (bioMérieux, Lyon, France). Antimicrobial susceptibility testing was done with a Phoenix Automated Microbiology System (BD Diagnostics, USA) or disk diffusion with breakpoint criteria according to Clinical and Laboratory Standards Institute (CLSI) guidelines.

Statistical analysis

Data are shown as medians with interquartile ranges unless indicated otherwise. Differences between groups were analysed by Mann-Whitney U tests. Survival data were analysed by log-rank (Mantel Cox) and Chi-square tests. A p value < 0.05 was considered statistically significant. The analyses were performed using Statistical Package for the Social Sciences version 20 (SPSS, Chicago, IL).

Results

Patients

In the six-year study period, 4,918 microorganisms were cultured from a total of 4,196 positive blood cultures in 2,891 patients (Table 1). Of these 386 patients (13.4%) had a diagnosis of cancer. The vast majority of cancer patients had a solid tumour (330 or 85.5%, versus 56 or 14.5% with a hematologic malignancy, Table 2). When compared with patients without a malignancy, cancer patients were more frequently male (61.4% versus 51.8%); the age distribution was similar between groups. The hospital locations where positive blood cultures were obtained differed considerably between cancer and non-cancer patients, although in both patient groups most cultures were acquired in non-surgical departments (31.1% and 43.1% in cancer and non-cancer patients respectively, Table 1). The proportion of (positive) blood cultures taken in the emergency room or non-surgical departments was higher in patients without cancer, whereas the fraction of blood cultures drawn in the intensive care unit and surgical departments was higher in patients with cancer.

Pathogens

Table 3 shows blood culture isolates in patients with and without cancer. In both patient groups Gram-positive isolates were more prevalent (58.7 and 61.4% in patients with and without cancer respectively) than Gram-negative isolates (31.8 and 32.3% respectively). Amongst Gram-positive organisms, coagulase negative staphylococci *Staphylococcus (S.) aureus* and en-

Table 1: Demographic characteristics of all patients with blood stream infections

		Cancer			Non-cancer		*p*
Number of patients (%)		386	(13.4)		2,505	(86.4)	-
Number of positive cultures		765			4,153		-
Mean age in years (IQR[1])		69	(61-76)		70	(52-80)	*ns*
Male (%)		237	(61.4)		1,299	(51.8)	*<0.01*
Number of CVC[2] with positive cultures (%)		119	(30.8)		382	(15.2)	*<0.01*
Location cultures were drawn (%)							
Emergency Room		121	(15.8)		1,047	(25.2)	*<0.01*
Intensive Care Unit		100	(13.1)		257	(6.2)	*<0.01*
Surgical departments[3]		168	(22.0)		500	(12.0)	*<0.01*
Non-surgical departments[4]		238	(31.1)		1,789	(43.1)	*<0.01*
Other		138	(18.0)		560	(13.5)	*<0.01*
Laboratory results †, *data are given as median (IQR[1])*							
Data are given as median (IQR[1])	#			#			
Hemoglobin (mmol per liter)	286	6.2	(5.5-7.1)	1,579	7.0	(5.9-8.1)	*<0.01*
White blood count (x 10^9 per liter)	278	11.4	(5.8-16.2)	1,575	12.2	(8.7-17.2)	*0.02*
Neutrophils (x 10^9 per liter)	205	10.0	(6.8-14.2)	1,357	9.9	(6.7-14.4)	*0.90*
Absolute neutrophil count < 1x10^9 per liter	196	9	(4.6%)	1,357	26	(1.9%)	*0.03**
Thrombocytes (x 10^9 per liter)	270	200	(99-326)	1,520	209	(144-280)	*0.40*
Creatinin (micromole per liter)	273	85	(65-112)	1,487	100	(76-158)	*<0.01*
Prothrombin Time (seconds)	126	16.0	(15.2-17.1)	614	16.3	(14.9-18.4)	*0.40*
C-Reactive Protein (milligram per liter)	238	143	(76-219)	1,379	128	(61-208)	*0.20*
Albumin (gram/liter)	212	22	(17-30)	1,180	27	(21-34)	*<0.01*
Glucose (mmol/liter)	105	7.4	(6.1-8.6)	774	7.1	(6.0-8.9)	*0.20*

[1] *Interquartile range*

[2] *Central Venous Catheter*

[3] *Including department of surgery, gynecology, urology, ENT, and orthopedics*

[4] Including department of medicine, gastro-enterology, pulmonology, neurology, cardiology

 # Number of samples tested

** By Chi-square*

† Laboratory results drawn minus 24 hours or plus 48 hours after blood culture was taken

terococci were most frequently isolated in both patient groups. However, within the group of Gram-positive isolates differences existed between patients with and without malignancy: in cancer patients with positive blood cultures, *Enterococcus (E.) faecalis* and *E. faecium* were twice as common when compared with non-cancer patients, while patients without malignancy had almost five times as many positive cultures for haemolytic streptococci. Amongst Gram-negative organisms, *Escherichia (E.) coli* was the most common isolate in both patient groups. Notably, P*seudomonas (P.) aeruginosa* and *Enterobacter (E.) cloacae were twice as common in patients with cancer* whereas *E. coli* was cultured more frequently from patients without cancer. Yeasts were grown from 3.0% of positive blood cultures from cancer patients

Table 2: Type of malignancy and treatment in cancer patients with positive blood cultures

Type of cancer	patients (%) n=386
Lung cancer	28 (7.3)
Colorectal cancer	74 (19.2)
Pancreaticobilliary cancer	63 (16.3)
Esophageal/Gastric cancer	35 (9.1)
Prostate cancer	23 (6.0)
Other urinary tract cancer	53 (13.7)
Breast cancer	31 (8.0)
Gyneacological cancer	11 (2.8)
Melanoma	3 (0.8)
Head and Neck cancer	3 (0.8)
CNS malignancy	3 (0.8)
Other	3 (0.8)
Leukemia[1]	24 (6.2)
Malignant lymphoma	32 (8.3)
Type of treatment	
Surgery	56 (14.5)
Radiation therapy	9 (2.3)
Chemotherapy	99 (25.6)
Hormonal Therapy[2]	10 (2.6)
Endoscopic procedures[3]	120 (31.1)
Other /no treatment	92 (23.8)

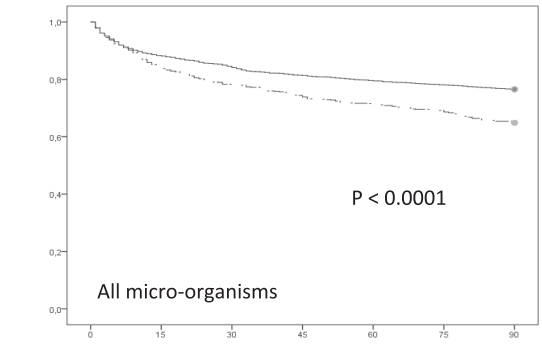
[1] *Includes acute and chronic leukemia*
[2] *Includes tamoxifen, aromatase-inhibitors, LH-RH and anti-androgenic therapy*
[3] *includes cystoscopy, hysteroscopy, colonoscopy, gastroscopy, and bronchoscopy.*

versus 1.5% of cultures from non-cancer patients; this difference was caused by a higher incidence of *Candida non-albicans* species in cancer patients. In 502 patients who had a central venous catheter (119 patients with cancer and 382 non-cancer patients), 919 pathogens were cultured (Table 4); in patients with cancer, positive blood cultures more often yielded Gram-negative bacteria, in particular *P.aeruginosa*, while coagulase negative staphylococci were more common in non-cancer patients. In Table 5 susceptibility patterns for the most relevant micro-organisms are enlisted. Only meropenem resistance of *P.aeruginosa* was higher in cancer patients. All other antimicrobial resistance patterns did not significantly differ between cancer and non-cancer patients.

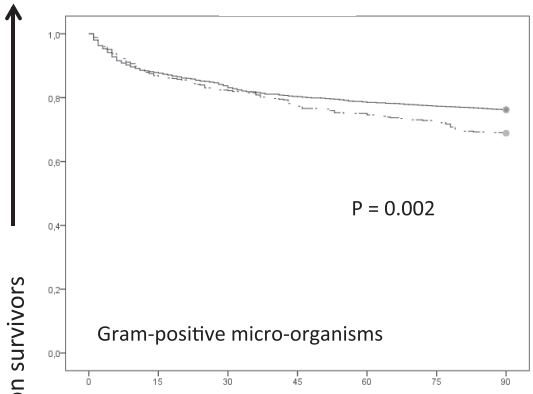
Laboratory results

Laboratory results at the time of blood cultures are shown in Table 1. Cancer patients had lower haemoglobin levels and white blood cell counts; Cancer patients also had lower plasma creatinin and albumin concentrations. C-reactive protein levels did not differ between groups. Blood culture isolates in neutropenic patients are shown in Table 6.

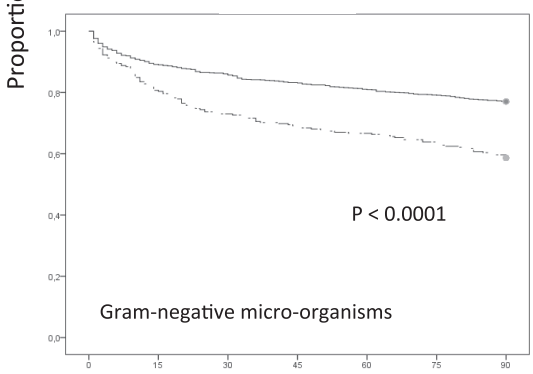
Figure 1: Survival for cancer and non-cancer patients



All types of micro-organisms	cancer	non-cancer
7 days	0.91	0.91
30 days	0.78	0.84
60 days	0.71	0.80
90 days	0.65	0.77



Gram-positive micro-organisms	cancer	non-cancer
7 day	0.92	0.91
30 day	0.82	0.83
60 days	0.75	0.79
90 days	0.69	0.76



Gram-negative micro-organisms	cancer	non-cancer
7 days	0.89	0.92
30 days	0.73	0.86
60 days	0.67	0.81
90 days	0.59	0.77

Kaplan-Meier curves and proportion survivors of patients with or without cancer with bloodstream infection caused by any pathogen (upper panels), a Gram-positive micro-organism (middle panels) or a Gram-negative micro-organism (lower panels). Dotted lines represent patients with cancer, solid lines represent patients without cancer.

Table 3: Blood culture isolates

	Cancer		Non-cancer		
	n=765	(%)	n=4,153	(%)	*p*
Gram-positive	**449**	**(58.7)**	**2,551**	**(61.4)**	***0.17***
Staphylococcus aureus	45	(5.9)	345	(8.3)	*0.03*
Coagulase negative Staphylococci[1]	212	(27.7)	1,217	(29.3)	*0.30*
Streptococcus pneumoniae	25	(3.3)	200	(4.8)	*0.07*
Hemolytic Streptococci (A,B,C,F,G)	5	(0.7)	135	(3.3)	*<0.01*
Other *Streptococcus* species[2]	20	(2.6)	169	(4.1)	*0.07*
Enterococcus faecalis	59	(7.7)	196	(4.7)	*<0.01*
Enterococcus faecium	33	(4.3)	82	(2.0)	*<0.01*
Other Enterococcus species[3]	5	(0.7)	28	(0.7)	*0.80*
Other gram-positive organism[4]	45	(5.9)	179	(4.3)	*0.07*
Gram-negative	**243**	**(31.8)**	**1,342**	**(32.3)**	***0.65***
Escherichia coli	100	(13.1)	758	(18.3)	*<0.01*
Pseudomonas aeruginosa	36	(4.7)	91	(2.2)	*<0.01*
Haemophilus (para-)influenzae	1	(0.1)	17	(0.4)	*0.40*
Klebsiella pneumoniae	25	(3.3)	108	(2.6)	*0.40*
Other *Klebsiella* species[5]	15	(2.0)	50	(1.2)	*0.10*
Proteus[6]	7	(0.9)	89	(2.1)	*0.03*
Serratia[7]	11	(1.4)	34	(0.8)	*0.10*
Enterobacter cloacae	19	(2.5)	42	(1.0)	*<0.01*
Other *Enterobacter* species[8]	3	(0.4)	15	(0.4)	*0.80*
Citrobacter[9]	9	(1.2)	26	(0.6)	*0.20*
Fermentative gram-negative rods[10]	10	(1.3)	21	(0.5)	*0.02*
Non- fermentative Gram-negative rods[11]	3	(0.4)	45	(1.1)	*0.10*
Other gram-negative organisms[12]	4	(0.5)	46	(1.1)	*0.20*
Anaerobes[13]	**39**	**(5.1)**	**132**	**(3.2)**	***0.02***
Enteropathogens	**3**	**(0.4)**	**28**	**(0.6)**	***0.60***
Salmonella species[14]	3	(0.4)	26	(0.6)	*0.60*
Other enteropathogens[15]			2	(0)	
Yeast	**23**	**(3.0)**	**63**	**(1.5)**	***0.03***
Candida albicans	10	(1.3)	32	(0.8)	*0.20*
Other *Candida* and yeast species[16]	13	(1.7)	31	(0.7)	*0.02*
Other micro-organism	**5**	**(0.7)**	**11**	**(0.3)**	***0.20***
Missing	**3**	**(0.4)**	**26**	**(0.6)**	***0.60***

[1] *Includes Staphylococcus epidermidis, haemolyticus, hominis, hyicus, lentus, lugdunensis, pasteuri, saprophyticus, schleiferi, simulans, warneri, xylosus, carnosus, cohnii, urealyticum, capitis. Dermacoccus nishinomlyaensis, Micrococcus luteus, Stomatococcus mucilaginosus.*

[2] *Includes Streptococcus mitis, bovis (1&2), sanguis, salivarius, mutans, oralis, parasanguinis, sobrinus, vestibularis, acidominimus, anginosusm, constellatusm, cristatus, dysgalactiae, equisimillis, equinus, gallolyticus.*

[3] *Includes Enterococcus casseliflavus, gallinarum, durans.*

[4] *Includes Difteroid rods, Bacillus cereus, circulans, Corynebacterium accolens, amycolatum, minitissimum, stri-*

atum, jeikeium, propinquum, Leuconostoc species, Propionibacterium acnes, Rothia mucilaginosa, Aerococcus, Lactococcus and unspecified Gram-positive bacteria.

[5] *Includes Klebsiella oxytoca, ozaenae.*

[6] *Includes Proteus mirabilis, vulgaris.*

[7] *Includes Serratia marcescens,liquefaciens, odorifera, plymuthica.*

[8] *Includes Enterobacter aerogenes, sakazakii, hermannii.*

[9] *Includes Citrobacter freundii, koseri, werkmanii, amalonaticus, braakii, farmer.*

[10] *Includes Morganella morganii, Aeromonas caviae, hydrophila, sobria, Eubacterium aerofaciens, Hafnia alvei, Providencia rettgeri,stuartii, Raoultella terrigena.*

[11] *Includes Acinetobacter baumannii, calcoaceticus-baumannii complex, lwoffii, haemolyticus. Alcaligenes faecalis, Chryseobacterium indologenes, meningosepticum, Metylobacterium mesophilicum, Rhizobium radiobacter, Stenotrophomonas maltophilia, Achromobacter xylosoxidans.*

[12] *Includes Neisseria species, Moraxella catarrhalis, Listeria monocytogenes.*

[13] *Includes Bacteroides fragilis,Clostridium paraputrificium, perfringens (welchii), septicum, tertium, Fusobacterium necrophorum, nucleatum, Pasteurella multocida, Bifidobacterium species, Gemella morbillorum, -Peptostreptococcus saccharolyticus, Prevotella loescheii, oralis.*

[14] *Includes Salmonella group B, C, D, paratyphi A, typhi. Typhimurium*

[15] *Shigella sonnei, Campylobacter jejuni.*

[16] *Includes Candida glabrata, intermedia, krusei, parapsilosis, tropicalis, and other types of yeast.*

Table 4: Blood culture isolates in patients with a central venous catheter

	Cancer		Non-cancer		
	n=219	(%)	n=700	(%)	*p*
Gram-positive	**156**	**(71.2)**	**564**	**(80.6)**	***<0.01***
Staphylococcus aureus	8	(3.7)	27	(3.9)	*0.90*
Coagulase negative Staphylococci	91	(41.6)	346	(49.4)	*0.05*
Streptococci	1	(0.5)	7	(1.0)	*0.70*
Enterococci	26	(11.9)	99	(14.1)	*0.50*
Other Gram-positive organisms	30	(13.7)	85	(12.1)	*0.60*
Gram-negative	**48**	**(21.9)**	**98**	**(14.0)**	***<0.01***
Escherichia coli	3	(1.4)	8	(1.1)	*0.90*
Pseudomonas aeruginosa	16	(7.3)	22	(3.1)	*0.01*
Klebsiella	8	(3.7)	12	(1.7)	*0.10*
Proteus	2	(0.9)	7	(1.0)	*0.80*
Serratia	6	(2.7)	8	(1.1)	*0.07*
Enterobacter	3	(1.4)	11	(1.6)	*0.90*
Citrobacter	2	(0.9)	4	(0.6)	*0.90*
Other Gram-negative organisms	8	(3.7)	26	(3.7)	*0.80*
Yeast	**10**	**(4.6)**	**28**	**(4.0)**	***0.90***
Candida albicans	5	(2.3)	17	(2.4)	*0.90*
Other yeast species	5	(2.3)	11	(1.6)	*0.70*
Other micro-organisms	**5**	**(2.3)**	**10**	**(1.4)**	***0.60***

Table 5: Antimicrobial resistance in cultured isolates in patients with cancer and non-cancer patients

	Cancer patients			Non-cancer patients			
	#	Resistant (%)		#	Resistant (%)		*p*
Staphylococcus aureus							
oxacillin	45	0	(0)	345	5	(1.4)	*0.90*
erytromycin	33	3	(9.1)	233	34	(14.6)	*0.60*
vancomycin	37	0	(0)	315	1	(0.03)	*0.20*
Streptococcus pneumoniae							
penicillin	24	0	(0)	190	4	(2.1)	*0.90*
erytromycin	24	2	(8.3)	184	22	(12.0)	*0.90*
Enterococcus faecalis							
ampicillin	55	0	(0)	159	0	(0)	-
vancomycin	55	1	(1.8)	177	4	(2.3)	*0.70*
Enterococcus faecium							
ampicillin	27	19	(70.4)	76	59	(77.6)	*0.60*
vancomycin	27	0	(0)	79	7	(8.9)	*0.20*
Escherichia coli							
ampicillin	95	46		703	302		*0.40*
ciprofloxacin	93	5	(5.4)	707	74	(10.5)	*0.20*
cefuroxim	94	8	(8.5)	692	44	(6.4)	*0.60*
ceftazidime	92	4	(4.3)	699	23	(3.3)	*0.80*
meropenem	63	0	(0)	557	0	(0)	-
Klebsiella pneumoniae							
ampicillin	23	22	(95.7)	103	101	(98.1)	*0.90*
ciprofloxacin	23	1	(4.3)	100	7	(7.0)	*0.90*
cefuroxim	23	2	(8.7)	99	8	(8.1)	*0.70*
ceftazidime	23	2	(8.7)	103	7	(6.8)	*0.90*
meropenem	15	0	(0)	98	0	(0)	-
Pseudomonas aeruginosa							
ciprofloxacin	30	6	(20)	81	5	(6.2)	*0.07*
ceftazidime	25	1	(4)	75	3	(4)	*0.60*
meropenem	24	5	(20.8)	70	0	(0)	*<0.01*

 # Number of samples tested

Survival

To obtain insight into the impact of documented BSI on outcome we determined 30-, 60 and 90-day all-cause mortality following blood culture positivity in both patient groups (Figure 1). Cancer patients with BSI had a significantly increased crude mortality when compared to patients without cancer. Differences between cancer and non-cancer patients were present in both Gram-positive and Gram-negative BSI, albeit to a larger extent in the latter group.

Table 6: Bloodstream infections in neutropenic patients (absolute neutrophil count <1x10^9 per liter)

	Cancer (%) n=9		Non-cancer (%) n=26	
Gram-positive	**4**	**(44.4)**	**16**	**(61.5)**
Staphylococcus aureus			2	(7.7)
Coagulase negative Staphylococci	2	(22.2)	6	(23.1)
Streptococcus pneumoniae			5	(19.2)
Other Streptococci	1	(11.1)	3	(11.4)
Other Gram-positive organism	1	(11.1)		
Gram-negative	**5**	**(55.5)**	**10**	**(38.5)**
Escherichia coli	3	(33.3)	5	(19.2)
Pseudomonas aeruginosa	1	(11.1)	1	(3.8)
Haemophilus (para-) influenzae			2	(7.7)
Proteus mirabilis			1	(3.8)
Other micro-organisms	**1**	**(11.1)**	**1**	**(3.8)**

Discussion

Current knowledge of causative organisms in BSI in patients with cancer is predominantly derived from investigations performed in specialized cancer treatment centres. The primary objective of the current study was to obtain insight into the distribution of pathogens causing BSI in cancer patients (as compared with patient without malignancy) in the setting of a community teaching hospital. For this we analysed all positive blood culture results obtained in our institution from adult patients between January 2005 and January 2011. We found a predominance of Gram-positive isolates in both patients with and patients without cancer. Positive blood cultures in cancer patients were caused more often by enterococci, *P. aeruginosa*, *E. cloacae* and yeasts when compared with non-cancer patients, while patients without malignancy had more positive blood cultures for haemolytic streptococci and *E. coli.* Mortality rates were much higher in patients with cancer. With the exception of meropenem resistance by *P. aeruginosa* no difference in antimicrobial resistance patterns were found between bacteria cultured in cancer and non-cancer patients. The difference in meropenem resistance might be related to local transmission of a *Pseudomonas* strain in the oncology unit as has been described in nosocomial outbreaks [19].

The current cohort of cancer patients with BSI predominantly consisted of patients with solid tumours (85.5%). As such, our result predominantly apply to this group of cancer patients. Previous studies have documented differences in causative BSI pathogens in patients with solid tumours and haematological malignancies, with a higher incidence of *E. coli* and *Klebsiella* spp. in the latter group [20].

Our study comprised all BSI irrespective of place of acquisition or hospital location. We found a marked predominance of Gram-positive organisms in both patients with and without cancer (58.7 and 61.4% respectively). Similarly, in a cohort of 2,340 cancer patients with nos-

ocomial BSI 61% of all episodes were caused by Gram-positive organisms [12]. The most frequently isolated pathogens in our investigation were coagulase negative staphylococci, *E. coli*, *S. aureus* and enterococci, which resembles the data obtained from nosocomial blood cultured isolates in cancer patients in the United States [12]. Similarly, coagulase negative staphylococci, *S. aureus* and *E. coli* were reported as most frequent BSI pathogens in various rank orders in patients with haematological malignancies or solid tumours [15, 21, 22]. The current results in addition show that among these common BSI pathogens, enterococci were more prevalent in cancer patients and *E. coli* in non-cancer patients. *E. faecalis* was more common than *E. faecium* in our study (7.7 and 4.3% of all isolates respectively), whereas in the United States nosocomial BSI were caused more often by *E. faecium* (5.2%) than *E. faecalis* (4.6%) [12]. Cancer has been implicated as a risk factor for BSI by a number of specific pathogens, including *S. aureus* [23], *E. coli* [24], *K. pneumoniae* [25] and *P. aeruginosa* [26]. However, we only found an increased incidence of *P. aeruginosa* in cancer patients, whereas *S. aureus* and *K. pneumoniae* were equally common in both patient groups and *E. coli* was more frequent in patients without cancer. Fungi accounted for 10% of BSI isolates in hospitalized cancer patients in the United States [12] versus only 3% in the current study, which at least partially can be explained by differences in the populations studied (i.e. restricted to nosocomial BSI in the earlier investigation) [12].

In the subgroup of patients in whom neutrophil counts were measured, cancer patients had absolute neutropenia in < 5% of cases versus < 2% of non-cancer patients; this group was too small to adequately investigate the impact of neutropenia on BSI pathogens. Of note, however, in the largest study performed to date neutropenia only modestly influenced the distribution of specific causative organisms of BSI in cancer patients, with a slightly altered incidence of viridans group streptococci (increased) and *E. faecium* (reduced) in neutropenic patients; the incidence of the most common BSI pathogens was not influenced by the presence or absence of neutropenia [12]. Another smaller study conducted in a tertiary oncology care center with a mixed solid tumor and hematological malignancy population reported higher incidences of BSI caused by *E. coli*, *Klebsiella* spp. and *P. aeruginosa* in neutropenic patients [20].

The impact of BSI on outcome was evaluated by determining 30-, 60- and 90-day mortality; we considered assessment of mortality beyond this time point of less relevance because late deaths are less likely to be related to the BSI and more likely to cancer. Nonetheless, the extent to which the cancer itself, more so than the BSI per se, contributed to short-term mortality cannot be deducted from our study. Cancer patients had a 90-day mortality of 35.8% following BSI caused by any pathogen versus 23.5% in patients without cancer. In the largest survey conducted to date, in hospital mortality following nosocomial BSI was 36% for neutropenic patients and 31% for patients without neutropenia [12]. Earlier investigations reported mortality rates of 20-25% of BSI in patients with solid tumours [1, 27, 28]. In accordance with the current results, in ICU patients with documented infection cancer was associated with a greater risk of hospital death [6]. Notably, in cancer patients we found a considerably higher 90-day mortality after Gram-negative BSI (41.4%) than after Gram-positive BSI (31.2%); this difference in 90-day mortality after Gram-negative and Gram-positive BSI was not present in patients without cancer (22.3 and 23.8% respectively).

We evaluated several laboratory results obtained in the period from 24 hours before to 48 hours after blood culture positivity. We specifically chose for this time window in order to obtain insight in the systemic response to BSI in both patient groups. Based on C-reactive pro-

tein levels (inflammatory response), platelet counts and prothrombin time (both indicative of coagulopathy) cancer patients did not differ from non-cancer patients. Patients with malignancy did show lower albumin concentrations, which could have been caused by either a stronger acute phase response (albumin is a negative acute phase protein) or a worse pre-existing nutritional status; the latter explanation may be more likely considering the similar C-reactive protein levels in both patient groups. Cancer patients did not show more evidence of renal insufficiency during BSI; on the contrary, plasma creatinin concentrations were even higher in patients without cancer.

There are some important limitations in this study. First, our survey represents a descriptive retrospective evaluation using laboratory and hospital information systems data; clinical data and bloodstream isolates were not prospectively collected. Second, no information is available regarding the source of infection in patients with bacteremia. We can not exclude that differences exist in the source of infection between cancer and non-cancer patients. Such differences could also influence the likelihood of survival in these patients. Furthermore, positive blood cultures not necessarily imply the presence of blood stream infections but could also result from skin contaminants. In this respect, it is important that coagulase negative staphylococci represented almost 30% of cultured isolates. The clinical significance of these isolates remain unknown. However, as the proportion of coagulase negative staphylococci among bacteria from positive blood cultures was similar we can conclude that the presence of cancer has no important influence on the likelihood of coagulase negative staphylococci as causative microorganism in BSIs. In this study, positive blood cultures with the same bacteria were considered as distinct cultures if taken more than 24 hours apart. Consequently, the number of positive cultures as reported here may be an overestimation of the true incidence. However, this limitation applies equally for both cancer and non-cancer patients. Therefore, we consider it unlikely, that this definition could have an important influence on the comparisons between cancer and non-cancer patients made in this study. Finally, a limitation of our retrospective study is that in only one third of patients peripheral blood neutrophil counts were determined within the time window of 24 hours before to 48 hours after the positive blood culture.

In conclusion, we here report that in a large community teaching hospital in the Netherlands Gram-positive organisms are the most common isolates from blood cultures in both cancer and non-cancer patients. Specific pathogens were more present in cancer patients, in particular enterococci, *P. aeruginosa*, *E. cloacae* and yeasts. Mortality rates after BSI were much higher in cancer patients than in patients without cancer with the greatest difference in BSI caused by Gram-negative bacteria.

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References

1. Singer C, Kaplan MH, Armstrong D: Bacteremia and fungemia complicating neoplastic disease. A study of 364 cases. Am J Med 1977, 62(5):731-742.
2. Whimbey E, Kiehn TE, Brannon P, Blevins A, Armstrong D: Bacteremia and fungemia in patients with neoplastic disease. Am J Med 1987, 82(4):723-730.
3. Collin BA, Leather HL, Wingard JR, Ramphal R: Evolution, incidence, and susceptibility of bacterial bloodstream isolates from 519 bone marrow transplant patients. Clin Infect Dis 2001, 33(7):947-953.
4. Laupland KB, Gregson DB, Zygun DA, Doig CJ, Mortis G, Church DL: Severe bloodstream infections: a population-based assessment. Crit Care Med 2004, 32(4):992-997.
5. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB: Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004, 39(3):309-317.
6. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y et al: International study of the prevalence and outcomes of infection in intensive care units. Jama 2009, 302(21):2323-2329.
7. Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, Sicignano A, Palazzo M, Moreno R, Boulme R et al: Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med 2002, 28(2):108-121.
8. Martin GS, Mannino DM, Eaton S, Moss M: The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003, 348(16):1546-1554.
9. Safdar A, Armstrong D: Infectious morbidity in critically ill patients with cancer. Crit Care Clin 2001, 17(3):531-570, vii-viii.
10. Pizzo PA: Fever in immunocompromised patients. N Engl J Med 1999, 341(12):893-900.
11. Gaytan-Martinez J, Mateos-Garcia E, Sanchez-Cortes E, Gonzalez-Llaven J, Casanova-Cardiel LJ, Fuentes-Allen JL: Microbiological findings in febrile neutropenia. Arch Med Res 2000, 31(4):388-392.
12. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB: Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. Clin Infect Dis 2003, 36(9):1103-1110.
13. Pittet D, Tarara D, Wenzel RP: Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. Jama 1994, 271(20):1598-1601.
14. Diekema DJ, Pfaller MA, Jones RN: Age-related trends in pathogen frequency and antimicrobial susceptibility of bloodstream isolates in North America: SENTRY Antimicrobial Surveillance Program, 1997-2000. Int J Antimicrob Agents 2002, 20(6):412-418.
15. Gonzalez-Barca E, Fernandez-Sevilla A, Carratala J, Granena A, Gudiol F: Prospective study of 288 episodes of bacteremia in neutropenic cancer patients in a single institution. Eur J Clin Microbiol Infect Dis 1996, 15(4):291-296.
16. Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia. The EORTC International Antimicrobial Therapy Cooperative Group. N Engl J Med 1987, 317(27):1692-1698.
17. Velasco E, Byington R, Martins CA, Schirmer M, Dias LM, Goncalves VM: Prospective evaluation of the epidemiology, microbiology, and outcome of bloodstream infections in hematologic patients in a single cancer center. Eur J Clin Microbiol Infect Dis 2003, 22(3):137-143.
18. Oliveira AL, de Souza M, Carvalho-Dias VM, Ruiz MA, Silla L, Tanaka PY, Simoes BP, Trabasso P, Seber A, Lotfi CJ et al: Epidemiology of bacteremia and factors associated with multi-drug-resistant gram-negative

bacteremia in hematopoietic stem cell transplant recipients. Bone Marrow Transplant 2007, 39(12):775-781.

19. Yakupogullari Y, Otlu B, Dogukan M, Gursoy C, Korkmaz E, Kizirgil A, Ozden M, Durmaz R: Investigation of a nosocomial outbreak by alginate-producing pan-antibiotic-resistant Pseudomonas aeruginosa. Am J Infect Control 2008, 36(10):e13-18.
20. Velasco E, Byington R, Martins CS, Schirmer M, Dias LC, Goncalves VM: Bloodstream infection surveillance in a cancer centre: a prospective look at clinical microbiology aspects. Clin Microbiol Infect 2004, 10(6):542-549.
21. Hann I, Viscoli C, Paesmans M, Gaya H, Glauser M: A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). Br J Haematol 1997, 99(3):580-588.
22. Spanik S, Kukuckova E, Pichna P, Grausova S, Krupova I, Rusnakova V, Kralovicova K, Krchnakova A, Mrazova M, Lacka J et al: Analysis of 553 episodes of monomicrobial bacteraemia in cancer patients: any association between risk factors and outcome to particular pathogen? Support Care Cancer 1997, 5(4):330-333.
23. Laupland KB, Ross T, Gregson DB: Staphylococcus aureus bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000-2006. J Infect Dis 2008, 198(3):336-343.
24. Laupland KB, Gregson DB, Church DL, Ross T, Pitout JD: Incidence, risk factors and outcomes of Escherichia coli bloodstream infections in a large Canadian region. Clin Microbiol Infect 2008, 14(11):1041-1047.
25. Meatherall BL, Gregson D, Ross T, Pitout JD, Laupland KB: Incidence, risk factors, and outcomes of Klebsiella pneumoniae bacteremia. Am J Med 2009, 122(9):866-873.
26. Parkins MD, Gregson DB, Pitout JD, Ross T, Laupland KB: Population-based study of the epidemiology and the risk factors for Pseudomonas aeruginosa bloodstream infection. Infection 2010, 38(1):25-32.
27. Spanik S, Sufliarsky J, Mardiak J, Sorkovska D, Trupl J, Kunova A, Kukuckova E, Rusnakova V, Demitrovicova A, Pichna P et al: Predictors of mortality in bacteremic cancer patients: retrospective analysis of 64 deaths occurring among 262 bacteremic episodes. Support Care Cancer 1998, 6(3):291-294.
28. Anatoliotaki M, Valatas V, Mantadakis E, Apostolakou H, Mavroudis D, Georgoulias V, Rolston KV, Kontoyiannis DP, Galanakis E, Samonis G: Bloodstream infections in patients with solid tumors: associated factors, microbial spectrum and outcome. Infection 2004, 32(2):65-71.