

Bloodstream Infections in Patients With Solid Tumors Epidemiology, Antibiotic Therapy, and Outcomes in 528 Episodes in a Single Cancer Center

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Abstract: Current information regarding bloodstream infection (BSI) in patients with solid tumors is scarce. We assessed the epidemiology, antibiotic therapy, and outcomes of BSI in these patients. We also compared patients who died with those who survived to identify risk factors associated with mortality. From January 2006 to July 2012 all episodes of BSI in patients with solid tumors at a cancer center were prospectively recorded and analyzed. A total of 528 episodes of BSI were documented in 489 patients. The most frequent neoplasms were hepatobiliary tumors (19%), followed by lung cancer (18%) and lower gastrointestinal malignancies (16%). Many patients had received corticosteroid therapy (41%), and 15% had neutropenia (<500 neutrophils/ μ L) at the time of BSI. The most common source of BSI was cholangitis (21%), followed by other abdominal (19.5%) and urinary tract infections (17%). Gram-negative BSI occurred in 55% of cases, mainly due to *Escherichia coli* (55%), *Pseudomonas aeruginosa* (18%), and *Klebsiella pneumoniae* (16%). Among gram-positive BSI (35%), viridans group streptococci were the most frequent causative organisms (22%), followed by *Staphylococcus aureus* (21%) and *Enterococcus* species (18%). We identified 61 multidrug-resistant (MDR) organisms (13%), mainly extended-spectrum β -lactamase-producing Enterobacteriaceae (n = 20) and AmpC-producing Enterobacteriaceae (n = 13). The majority of patients with BSI caused by MDR organisms had received antibiotics (70%), and they had been previously hospitalized (61.4%) more frequently than patients with BSI caused by susceptible strains. Inadequate empirical antibiotic therapy was given to 23% of patients, with a higher proportion in those with BSI due to a MDR strain (69%). Early (<48 h) and overall (30 d) case-fatality rates were 7% and 32%, respectively. The overall case-fatality rate was higher among cases caused by MDR organisms (39.3%). The only independent risk factors for the early case-fatality rate were the endogenous source of BSI (odds ratio [OR], 3.57; 95% confidence interval [CI], 1.06–12.02), shock at presentation (OR, 3.63; 95% CI, 1.63–8.09), and corticosteroid therapy (OR, 3.245; 95% CI, 1.43–7.32). The independent risk factors for overall case-fatality rate were the presence of a chronic advanced cancer (OR, 35.39; 95% CI, 2.48–504.91), shock at presentation (OR, 25.84; 95% CI, 3.73–179.0), and corticosteroid therapy (OR, 6.98; 95% CI, 1.61–30.21).

BSI in patients with solid tumors occurred mainly among those with hepatobiliary cancer, and cholangitis was the most frequent source;

gram-negative bacilli were the most frequent causative agents. MDR organisms were relatively common, particularly in patients who had previously received antibiotics and had been hospitalized; these patients were frequently treated with inadequate empirical antibiotic therapy and had a poorer outcome. The case-fatality rate of patients with solid tumors and BSI was high and was associated with chronic advanced cancer, corticosteroid therapy, and shock at presentation.

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Abbreviations: BSI = bloodstream infection, CI = confidence interval (CI), CLSI = Clinical and Laboratory Standards Institute, ESBL = extended-spectrum β -lactamase, MASCC = Multinational Association for Supportive Care in Cancer, MDR = multidrug-resistant, MRSA = methicillin-resistant *Staphylococcus aureus*, OR = odds ratio.

INTRODUCTION

Bloodstream infection (BSI) is a common complication in patients with cancer leading to delayed and reduced dosage of chemotherapeutics and longer hospitalization. Therefore, it contributes to suboptimal treatment, with higher morbidity and mortality rates.^{7,16,20} The available epidemiologic data for BSI in cancer patients are mainly derived from neutropenic patients with hematologic malignancies and stem-cell transplant recipients.^{17,31}

Although in the 1990s gram-positive bacteria were the leading causative agents, a trend is now emerging with a shift from gram-positive to gram-negative bacilli mostly caused by changes in the use of the antibiotic prophylaxis.¹² The development of infections caused by multidrug-resistant (MDR) organisms has become a major health problem worldwide, and is of particular concern in cancer patients, who are at particular risk for severe sepsis and poor outcome.¹³

Patients with solid tumors are a unique cohort; they frequently have implantable devices and are relatively immunocompromised, even without overt neutropenia. Surprisingly, only limited data have been reported on BSI in patients with solid tumors, in terms of the current epidemiology, etiology, impact of MDR organisms, and outcomes.^{1,26}

We conducted the present prospective study to assess the current epidemiology, antibiotic therapy, and outcomes in a large cohort of patients with solid tumors and BSI. We also compared patients who died with those who survived, to identify risk factors associated with mortality.

METHODS

Setting, Patients, and Study Design

We conducted a prospective observational study in a 200-bed university cancer center for adults in Barcelona, Spain, which

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has approximately 6500 admissions per year. From January 2006 to July 2012 all hospitalized cancer patients with solid tumors with at least 1 episode of BSI were included in the study. Information on baseline characteristics, etiology, clinical features, empirical antibiotic therapy, and outcome was recorded in a specific database. We also compared the characteristics of patients who died with those patients who survived, to determine the factors influencing mortality.

All episodes of BSI in our hospital are reported and followed up by an infectious disease physician. Changes in antimicrobial treatment and general management were recommended when necessary. During the study period, no universal antibacterial prophylaxis to prevent bacterial infections was administered to patients with neutropenia. This study was approved by the ethics committee of our institution.

Definitions

Chronic advanced cancer was considered in patients with confirmed metastatic disease (stage IV) and some tumors in stage III (lung, pancreas, gastric, esophagus, and urothelial) not suitable for treatment or in progressive outbreak during treatment. Breast and prostate cancer affected with bone metastasis, colorectal cancer with resectable hepatic and lung metastasis and metastatic germinal tumors were excluded.¹⁰

Neutropenia was defined as an absolute neutrophil count ≤ 500 neutrophils/ μL . BSI was considered to be nosocomially acquired, health care related, or community acquired, applying criteria described previously.⁸ Prior antibiotic therapy was defined as the receipt of any systemic antibiotic for 48 hours in the previous month. Severe mucositis was defined as the presence of multiple ulcerations covering more than 25% of the oral mucosa. A BSI caused by coagulase-negative staphylococci and other potential skin contaminants was considered to be significant when they grew in at least 2 blood cultures or in 1 blood culture and in 1 other clinical sample.

An endogenous source of BSI was considered in patients with typhlitis, neutropenic enterocolitis, spontaneous bacterial peritonitis, or those who were neutropenic and did not have any other evident source of infection. An unknown source was considered when no clear source of BSI was found.

Corticosteroid therapy was recorded when a patient was receiving corticosteroids at the time of the episode of BSI or in the previous month. Hypotension was considered when systolic blood pressure was less than 90 mm Hg or diastolic less than 60 mm Hg. Shock was defined as a systolic pressure < 90 mm Hg that was unresponsive to fluid treatment and/or required vasoactive drug therapy.²¹ We used the Multinational Association for Supportive Care in Cancer (MASCC) score that identifies patients at low risk for complications and was calculated as described elsewhere.¹⁸

Empirical antibiotic therapy was considered inadequate if the treatment regimen did not include at least 1 antibiotic active in vitro against the infecting microorganism. In patients with extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae BSI, treatment with an oxymino- β -lactam (with or without an aminoglycoside) was considered inadequate, regardless of the MIC. The following gram-negative bacilli were considered to be MDR: 1) ESBL-producing Enterobacteriaceae, 2) AmpC cephalosporinase hyperproducing Enterobacteriaceae, 3) microorganisms with intrinsic resistance mechanisms such as *Stenotrophomonas maltophilia*, 4) MDR strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. MDR strains were defined as those resistant to at least 3 classes of antibiotics: carbapenems, ureidopenicillins, cephalosporins (ceftazidime and

cefepime), monobactams, aminoglycosides, and fluoroquinolones.⁶ MDR gram-positive organisms included methicillin-resistant *Staphylococcus aureus* (MRSA) and ampicillin-resistant *Enterococcus faecium*.

Time to adequate antibiotic therapy was considered as time from the blood culture collection to the first adequate antibiotic dose administration and was recorded in days, considering the closest day to the hour that the antibiotic was administered. The early case-fatality rate was defined as death within 48 hours of the onset of BSI. The overall case-fatality rate was defined as death by any cause within the first 30 days of onset.

Microbiologic Studies

Two sets of 2 blood samples (BACTEC Plus Aerobic and Anaerobic, BD), taken 30 minutes apart, and containing 8–10 mL of blood each, were drawn from patients who had fever of 38°C or when BSI was suspected based on any clinical sign or symptom. Microbial identification was performed using commercially available panels (MicroScan [Siemens] or Vitek [Bio erieux]) or by standard biochemical and/or enzymatic test.

Antibiotic susceptibility was tested using the microdilution method following the Clinical Laboratory Standard Institute (CLSI) guidelines. The screening of MDR-phenotypes including MRSA, ampicillin- and vancomycin-resistant enterococci, ESBL production, and carbapenemase production was conducted according to CLSI recommendations.^{2,3}

Statistical Analysis

Continuous variables were compared using the Mann-Whitney U test and the Student t test. Qualitative variables were compared using the chi-square test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A p value of < 0.05 was considered statistically significant. The analysis was performed with the stepwise logistic-regression model of the SPSS software package v. 15.0 (SPSS Inc., Chicago, IL).¹⁴

RESULTS

Study Population and Patient Characteristics

During the study period 528 episodes of BSI in 489 adult patients with solid tumors were identified. Thirty-nine episodes of BSI were excluded from the analysis because they occurred within less than 4 weeks after a first episode of BSI. The epidemiologic and clinical characteristics of the patients are outlined in Table 1. BSI occurred mainly in hepatobiliary tumors (19%), followed by lung tumors (18%) and lower gastrointestinal tract malignancies (16%).

Almost half of the patients had comorbidities. Most of the BSIs (84%) were health care related or nosocomially acquired, whereas only 16% of them were community acquired. Thirty-seven percent of the patients had received previous antibiotic therapy, mainly β -lactams + β -lactamase inhibitors (73%) followed by quinolones (30%) and oxymino- β -lactams (16%). Chemotherapy had been given to 63% of the patients within the last month and 41% had received corticosteroid therapy. Fourteen percent of the patients had a biliary prosthesis, 10% a urinary catheter, 10% a port-a-cath, and 5% a central venous catheter. Eighty episodes (15%) occurred in neutropenic patients and 52% of them had a MASCC risk score < 21 . The most common sources of BSI were cholangitis (21%), followed by other abdominal (19.5%) and urinary tract infections (17%).

TABLE 1. Epidemiologic and Clinical Characteristics of 528 Episodes of BSI in Patients With Solid Tumors

Characteristic	No.	Percentage (%)
Male sex	343	65
Underlying tumor		
Hepatobiliary tumor	99	19
Lung tumor	95	18
Lower GI tumor	85	16
Genitourinary tumor	65	12
Breast tumor	39	7
Gynecologic tumor	37	7
Upper GI tumor	36	7
Head and neck tumor	30	6
Sarcoma	14	3
Other tumor*	27	5
Chronic advanced cancer	419	80.6
Comorbidities†	242	46
Diabetes mellitus	115	22
Chronic obstructive pulmonary disease	66	12.5
Chronic heart disease	66	12.5
Chronic hepatopathy	28	5
Chronic renal insufficiency	8	1.5
Neutropenia (<500 neutrophils/ μ L)	80	15
MASCC risk score <21	43	52
Previous chemotherapy (1 mo)	335	63
Previous radiotherapy (1 mo)	72	14
Previous hospital admission (3 mo)	234	44.5
Corticosteroid therapy (1 mo)	213	41
Peripheral catheter	132	25
Biliary prosthesis	74	14
Port-a-cath	54	10
Urinary catheter	54	10
Central venous catheter	27	5
Previous antibiotic therapy (1 mo)	193	37
Site of acquisition		
Health care	300	57
Nosocomial	145	27.5
Community acquired	83	16
Source of BSI		
Cholangitis	111	21
Other abdominal site	103	19.5
Urinary tract	90	17
Respiratory tract	57	11
Catheter related‡	53	10
Unknown	44	8
Endogenous source	29	5.5
Soft tissue	17	3
Mucositis	11	2
Other source§	13	2.5

Abbreviation: GI = gastrointestinal.
 *Other tumor: central nervous system tumor (n=12), melanoma (n=6), unknown origin (n=4), other (n=5).
 †Some patients had more than 1 comorbidity.
 ‡Catheter related: includes central and peripheral catheters.
 §Other source: endocarditis (n=4), surgical wound (n=3), otorhinolaryngologic infection (n=2), perianal infection (n=1), nervous system infection (n=1), other (n=2).

Etiology and Antibiotic Resistance

Table 2 details the causative organisms of all episodes of BSI. Gram-negative organisms accounted for 55% of cases. The most frequent gram-negative bacilli were *Escherichia coli* (55%), followed by *P. aeruginosa* (18%), and *Klebsiella pneumoniae* (16%). Among gram-positive organisms (35%), viridans group streptococci were the most frequently isolated (22%), followed by *S. aureus* (21%) and *Enterococcus* species (18%).

We identified 61 (13%) MDR organisms, mostly ESBL-producing Enterobacteriaceae (n = 20), AMP-C-producing Enterobacteriaceae (n = 13), MRSA (n = 7), MDR *P. aeruginosa* (n = 5), *S. maltophilia* (n = 1), and *A. baumannii* (n = 1). No vancomycin-resistant *Enterococcus faecalis* or *Enterococcus faecium* organisms were found. No carbapenemase-producing bacteria were found. We did not identify and special temporal trend in resistance. On analyzing these BSI caused by MDR organisms, we found that they also occurred mainly in hepatobiliary and lower gastrointestinal tumors, but in a higher proportion compared with BSI caused by susceptible strains (31% and 24%, respectively). The episodes of nosocomial or health care-acquired BSI were clearly predominant (93%), and previous antibiotic therapy had been administered to 70% of the patients. Twenty-eight percent of the patients had a urinary catheter and 24% of them had a biliary prosthesis. A large proportion of the patients had been previously hospitalized (within the last 3 months) (61.4%) and the most frequent sources of BSI were cholangitis (34.5%) and urinary tract infection (26%), whereas respiratory tract infections were rare (<2%).

Clinical Manifestations, Antibiotic Therapy, and Outcomes

Table 3 shows the outcomes of all episodes of BSI. Fever was documented in 77% of cases, systolic hypotension in 30%, and shock in 13%. Ninety-four percent of the patients received empirical antibiotics, the most prevalent being the β -lactam + β -lactamase inhibitor combination (56%), followed by oxymino- β -lactams (23%), cephalosporin + aminoglycoside (14%), carbapenem (13%), and quinolones (12%). Inadequate empirical antibiotic therapy was given to 23% of patients, with a higher proportion in those with BSI due to a MDR strain (69%). The early and overall case-fatality rate was 7% and 32%, respectively, whereas in episodes caused by MDR organisms the rates were 7% and 39.3%, respectively.

Prognostic Factors

We compared patients who died with those who survived in order to identify risk factors associated with mortality. Tables 4 and 5 summarize the risk factors associated with the early and overall case-fatality rate, respectively.

According to the univariate analysis, lower gastrointestinal tumors, hepatobiliary tumors, and tumors of unknown origin; a MASCC index score <21; shock at presentation; corticosteroid therapy; and respiratory, endogenous, and unknown sources were significantly more frequent in patients with an early case-fatality rate. Multivariate analysis using a logistic regression model showed that the only significant independent risk factors for early case-fatality rate were an endogenous source, septic shock at presentation, and corticosteroid therapy.

The results of the univariate analysis of the overall case-fatality rate showed that older age, chronic advanced neoplasm, corticosteroid therapy, MASCC index <21, shock at presentation, unknown source of BSI, and BSI from abdominal sites other than cholangitis were significantly more frequent in

TABLE 2. Causative Organisms of All Episodes of BSI in Patients With Solid Tumors

Causative Organisms	No.	Percentage (%)
Gram-negative bacteria	291	55
<i>Escherichia coli</i>	161	55
<i>Pseudomonas aeruginosa</i>	52	18
<i>Klebsiella pneumoniae</i>	47	16
<i>Klebsiella oxytoca</i>	9	3
<i>Enterobacter cloacae</i>	20	7
<i>Enterobacter aerogenes</i>	7	2
<i>Proteus mirabilis</i>	10	3
<i>Salmonella enteritidis</i>	8	3
<i>Aeromonas hydrophila</i>	4	1
<i>Acinetobacter baumannii</i>	2	1
Gram-positive bacteria	184	35
Viridans group streptococci	40	22
<i>Staphylococcus aureus</i>	38	21
Methicillin-resistant <i>S. aureus</i>	7	34*
<i>Enterococcus</i> spp	33	18
<i>E. faecalis</i>	16	48.5†
<i>E. faecium</i>	12	36†
<i>E. avium</i>	2	6†
Coagulase-negative staphylococci	30	16
<i>Corynebacterium</i> spp	2	1
<i>Streptococcus pneumoniae</i>	28	15
<i>Streptococcus bovis</i>	9	5
<i>Listeria monocytogenes</i>	16	9
Anaerobes	25	4.5
<i>Bacteroides</i> spp	14	56
<i>Clostridium</i> spp	13	52
<i>Peptostreptococcus</i>	3	12
<i>Fusobacterium</i> spp	2	8
Polymicrobial BSI‡	24	4.5
MDR gram-negative bacilli§	43	15
MDR gram-positive and gram-negative bacilli¶	61	13

*Percentage of methicillin-resistant *S. aureus* among all *S. aureus* isolates.

†Percentage of different *Enterococcus* spp among all enterococcal isolates.

‡Polymicrobial BSI was defined as a BSI caused by at least 2 different microorganisms.

§MDR (multidrug-resistant) gram-negative bacilli: extended-spectrum- β -lactamase-producing Enterobacteriaceae (n=20), AmpC-producing Enterobacteriaceae (n=13), MDR *Pseudomonas aeruginosa* (n=5), *Acinetobacter baumannii* (n=1), *Stenotrophomonas maltophilia* (n=1), OXA-1 β -lactamase-producing *E. coli* (n=2), chromosomal β -lactamase hyperproducing *klebsiella oxytoca* (n=1).

¶MDR gram-positive and gram-negative bacilli: MDR gram-negative plus methicillin resistant *S. aureus* and ampicillin-resistant *Enterococcus*.

patients who ultimately died. Multivariate analysis found that the only significant independent risk factors for overall case-fatality rate were the presence of a chronic advanced neoplasm, septic shock at presentation, and corticosteroid therapy.

Neither inadequate empirical antibiotic therapy nor time >48 hours to adequate antibiotic therapy were significant prognostic factors for mortality. A subanalysis excluding the

TABLE 3. Outcomes of 528 Episodes of BSI

Outcome	No.	Percentage (%)
Inadequate initial empirical antibiotic therapy	123	23
Time to adequate antibiotic therapy		
>48 h	43	9
>24 h	90	18
Intensive care unit admission	9	2
Invasive mechanical ventilation	6	1
Early case-fatality rate (2 d)	36	7
Overall case-fatality rate (30 d)	163	32

episodes caused by coagulase-negative staphylococci was performed, but the outcome was the same.

DISCUSSION

To date, most information on BSI in patients with solid tumors has been extrapolated from studies of hematologic malignancies or studies that included both hematologic malignancies and solid tumors as a unique group.^{12,32} The current prospective study involving a large number of hospitalized adults with BSI and solid tumors offers a comprehensive evaluation of epidemiology, etiology, and outcomes exclusively in patients with BSI and solid tumors.

We found that BSI occurred mainly in patients with hepatobiliary tumors which were the main cause of cholangitis in these patients, followed by lung cancer and lower gastrointestinal tract malignancies. A retrospective study with a smaller sample size (157 episodes of BSI) conducted by Anatoliotaki et al¹ in 2004 found breast (22%) and lung (18%) tumors as the most frequent underlying malignancies, whereas hepatobiliary tumors accounted for only for 8% of cases.

Almost half of our patients had comorbidities and most of them were receiving active chemotherapy at the time of infection, which mostly occurred in the health care setting. Of note, a large proportion of them had previously received antibiotic and corticosteroid therapy, and most of them had implantable devices (biliary prosthesis, urinary catheter, port-a-cath, and venous catheters). These figures were even higher in those with episodes caused by a MDR organism according to the literature.¹⁴

We identified 98 episodes of cholangitis, which represented the most common source of BSI, followed by other abdominal and urinary tract infections, whereas Anatoliotaki et al¹ found urinary tract infections to be the most frequent source of BSI (34%). In the current study, catheter-related infection causing BSI accounted for only 10% of the total, in contrast with other studies that included hematologic malignancies, in which catheter-related bacteremia was more prevalent.^{12,26,32} In a prospective study involving a small number of cancer patients, catheter-related infections were found to be the major source of BSI in patients with solid tumors and hematologic malignancies.²⁴

It is noteworthy that only 15% of the episodes of BSI in patients with solid tumors occurred during periods of neutropenia. This finding contrasts with those of studies involving patients with hematologic malignancies, in which the majority of the episodes occurred during periods of neutropenia.^{4,11,32}

Analysis of the causative pathogens of BSI revealed that gram-negative bacilli were the most frequent microorganisms

TABLE 4. Risk Factors for Early Case-Fatality Rate According to Univariate and Multivariate Analysis

Risk Factor	Survived (N=488) No. (%)	Died (N=36) No. (%)	P	Adjusted OR (95% CI)	P
Age, yr; median (range)	63 (14–85)	66.5 (31–85)	0.078	0.06 (0.99–1.07)	0.68
Male sex	312 (64%)	27 (75%)	0.209	0.76 (0.32–1.80)	0.537
Chronic advanced neoplasm	382 (80%)	33 (92%)	0.84		
Lower gastrointestinal tumor	82 (17%)	1 (3%)	0.030	4.65 (0.59–36.40)	0.143
Hepatobiliary tumor	96 (20%)	2 (6%)	0.043	0.36 (0.08–1.63)	0.185
Unknown origin tumor	2 (0.4%)	2 (3%)	0.025	8.01 (0.91–70.31)	0.060
Corticosteroid therapy	185 (38%)	26 (72%)	<0.001	3.24 (1.43–7.32)	0.005
MASCC <21	38 (47%)	8 (100%)	0.06		
Shock at presentation	55 (11%)	15 (42%)	<0.001	3.63 (1.63–8.09)	0.002
MDR gram-positive and gram-negative bacilli	52 (11%)	4 (11%)	0.664		
MDR gram-negative bacilli	36 (7.4%)	3 (8.6%)	0.738		
Respiratory source	49 (10%)	8 (22%)	0.045	2.05 (0.74–5.63)	0.163
Endogenous source	24 (5%)	5 (14%)	0.041	3.57 (1.06–12.02)	0.040
Unknown source	36 (7.4%)	7 (20%)	0.021	1.87 (0.64–5.42)	0.249
Inadequate empirical antibiotic therapy	109 (22%)	11 (31%)	0.303		
Time to adequate antibiotic therapy >48 h	41 (9%)	0 (0%)	0.251		
Time to adequate empirical antibiotic, d; median (range)	0 (0–6)	0 (0–2)	0.159		

isolated in patients with solid tumors, mainly *E. coli*, *P. aeruginosa* and *K. pneumoniae*. Among gram-positive BSI, viridans group streptococci were the most frequent causative organisms, followed by *S. aureus* and *Enterococcus* species, which is well

known to be increasing in prevalence worldwide.²⁰ Coagulase-negative staphylococci accounted for only 16% of all gram-positive bacilli, which represents an important decrease compared with hematologic series.^{12,32}

TABLE 5. Risk Factors for Overall Case-Fatality Rate According to Univariate and Multivariate Analysis

Risk Factor	Survived (N=340) No. (%)	Died (N=163) No. (%)	P	Adjusted OR (95% CI)	P
Male sex	218 (64)	108 (66)	0.690	4.81 (0.77–29.79)	0.091
Age, yr; median (range)	62 (14–85)	66 (31–85)	0.004	1.02 (0.96–1.09)	0.385
Chronic advanced neoplasm	247 (74)	149 (91)	<0.001	35.39 (2.48–504.91)	0.009
Lung tumor	53 (16)	37 (23)	0.051		
Breast tumor	31 (9)	7 (4)	0.055		
Comorbidities*	146 (43)	84 (51.5)	0.070		
Corticosteroid therapy	99 (29)	100 (61)	<0.001	6.98 (1.61–30.21)	0.009
MASCC <21	26 (42)	18 (72)	0.017	0.65 (0.14–3.09)	0.597
Neutropenia†	50 (15)	28 (17)	0.511		
Shock at presentation‡	28 (8)	41 (25)	<0.001	25.84 (3.73–179.0)	0.001
MDR gram-positive and gram-negative bacilli	33 (10)	22 (14)	0.221		
MDR gram-negative bacilli	23 (7)	15 (9)	0.366		
Respiratory tract source	36 (11)	20 (12)	0.650		
Cholangitis source	77 (23)	31 (19)	0.417		
Other abdominal source	50 (15)	46 (28)	<0.001	1.75 (0.14–20.86)	0.658
Unknown source	19 (6)	23 (14)	0.002	8.04 (0.52–122.63)	0.134
Inadequate empirical antibiotic therapy	74 (22)	40 (24.5)	0.497		
Time to adequate empirical antibiotic, d; median (range)	0.0 (0–10)	0.0(0–5)	0.696		
Time to adequate antibiotic therapy >48 h	32 (9%)	7 (5%)	0.102		

*Comorbidities: diabetes mellitus (n=115), chronic obstructive pulmonary disease (n=66), chronic heart disease (n=66), chronic hepatopathy (n=28), chronic renal insufficiency (n=8), ischemic stroke (n=8), and other: 3 human immunodeficiency virus (HIV) infection, 2 chronic myeloid leukemia, 1 liver transplantation. Some patients had more than 1 comorbidity.

†Neutropenia: ≤500 neutrophils/μL.

‡Shock: systolic pressure <90 mm Hg that was unresponsive to fluid treatment and/or required vasoactive drug therapy.

A large longitudinal study performed in the United Kingdom²⁶ comparing the etiology of BSI in hematologic and oncology patients found a predominance of gram-positive organisms, with coagulase-negative staphylococci being the most frequent bacteria causing BSI in both patient groups. These discrepancies could be explained by the scarce use of antibiotic prophylaxis in patients with solid tumors in our hospital and the reduction of indwelling catheters, as highlighted in a recent systematic review of the changes in BSI epidemiology over the last 5 years.²⁰ In fact, current guidelines recommend primary antibiotic prophylaxis with quinolones in patients with expected durations of prolonged and profound neutropenia (absolute neutrophil count <100 cells/mm³ for >7 d), who are mainly patients with hematologic malignancies.⁷

Of note, we identified 61 MDR organisms, mostly ESBL-producing Enterobacteriaceae and AmpC-producing Enterobacteriaceae. This finding is consistent with those of recent studies that reported an increase in antibiotic resistance among gram-negative bacilli worldwide.^{13,19,22,25,28}

The majority of patients received empirical antibiotic, the most prevalent being the β -lactam + β -lactamase inhibitor, followed by oxymino- β -lactams. It should be noted that inadequate empirical antibiotic therapy was given to 23% of patients, with a higher proportion in those with BSI due to a MDR strain. In line with these findings, we observed that patients with MDR organisms received inadequate empirical antibiotic therapy more frequently than patients with BSI caused by susceptible strains and had a poorer outcome.

To our knowledge, only 1 study¹ has analyzed clinical outcomes and prognostic factors of BSI in patients with solid tumors to date. The investigators found that the administration of inappropriate initial empirical antibiotic therapy and the occurrence of shock were the only risk factors associated with mortality. In the present study, we found high early and overall case-fatality rates of 7% and 32%, respectively. The only independent risk factors associated with the early case-fatality rate were an endogenous source, shock at presentation, and corticosteroid therapy, while the presence of a chronic advanced neoplasm, corticosteroids, and shock were significantly associated with the overall case-fatality rate. It should thus be noted that shock at presentation and corticosteroid therapy were associated with both early and overall case-fatality rate.

Corticosteroids play a decisive role in the immune function of macrophages and granulocytes, as well as in systemic cytokine expression. Additionally, chronic corticosteroid treatment suppresses the production of corticotrophin-releasing hormone and corticotrophin, and can induce adrenal atrophy. Consequently, the adrenal responses to infection may be insufficient to control the inflammatory situation.⁵

Moreover, severe sepsis and septic shock remain major health problems in which the speed and appropriateness of therapy administered in the initial hours are likely to influence outcome. It is now widely thought that the intrinsic relationship between the host and the microorganism is critical in the pathogenesis of septic shock, and many host factors influence the ability to develop an optimal immune response against infection. New strategies against septic shock are being assessed.³⁰ Importantly, there remains a great dilemma whether patients with chronic advanced neoplasms should be admitted to the intensive care unit and receive mechanical ventilation.

A relationship between infection with resistant bacteria and poor outcome has been reported in several settings.^{9,15,23,27,29} Nevertheless, in the present study, we found no significant statistical association of poor outcome with inappropriate empirical antibiotic therapy, nor with time to adequate antibiotic

therapy. This was confirmed even after excluding those episodes caused by coagulase-negative staphylococci that are known to be less virulent organisms. Moreover, we observed that inadequate empirical antibiotic therapy was given to a higher proportion of patients with BSI due to a MDR strain, but this was not statistically associated with a higher case-fatality-rate. These findings could be attributed to the fact that patients who received inadequate antibiotic therapy or adequate antibiotic therapy later than 24 hours or even 48 hours after the diagnosis frequently had infections not classically considered severe (urinary tract infections, cholangitis, or soft tissue infections). Despite this, our results suggest that patients who present risk factors for BSI caused by MDR organisms, such as previous hospitalization, presence of devices, or previous antibiotics, might benefit from early broad-spectrum empirical antibiotic therapy.

Despite a number of strengths, the present prospective study of a large cohort of patients with BSI has some limitations that should be acknowledged. First, it was performed in a single institution, which may not reflect the epidemiology of different centers and/or different geographic areas. Second, we analyzed a heterogeneous group of patients with solid tumors, who may have different epidemiologic and clinical characteristics and behaviors than other patients. Finally, molecular typing of MDR isolates was not performed.

In conclusion, we found that patients with solid tumors and BSI have particular characteristics: hepatobiliary and lung tumors are the most frequently involved neoplasms, and cholangitis is the most recurrent source of BSI, mainly caused by gram-negative bacilli. MDR organisms are relatively common among patients with solid tumors and BSI, particularly when patients have previously received antibiotic therapy or have been hospitalized, and patients frequently received inadequate empirical antibiotic therapy. The case-fatality rate in patients with solid tumors and BSI is high, especially among those with chronic advanced neoplasms, corticosteroid therapy, and shock at presentation. Appropriate use of corticosteroids and better strategies for managing shock in these patients should be considered to reduce mortality.

REFERENCES

- Anatoliotaki M, Valatas V, Mantadakis E, Apostolou H, Mavroudis D, Georgoulas V, Rolston KV, Kontoyiannis DP, Galanakis E, Samonis G. Bloodstream infections in patients with solid tumors: associated factors, microbial spectrum and outcome. *Infection*. 2004;32:65–71.
- Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, Eighth Edition: Approved Standard M07-A8*. Wayne, PA: CLSI; 2009.
- Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: Twentieth Informational Supplement. CLSI document M100-S22*. Wayne, PA: CLSI; 2012.
- Cometta A, Zinner S, de Bock R, Calandra T, Gaya H, Klastersky J, Langenaeken J, Paesmans M, Viscoli C, Glauser MP. The International Antimicrobial Therapy Cooperative Group of the EORTC. Piperacillin-tazobactam plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. *Antimicrob Agents Chemother*. 1995;39:445–452.
- Cooper M, Stewart P. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med*. 2003;348:727–734.
- Falagas ME, Koletsi PK, Bliziotis IA. The diversity of definitions of multidrug-resistant (MDR) and pandrug-resistant (PDR) *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *J Med Microbiol*. 2006;55:1619–1629.

7. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR. Infectious Diseases Society of America (2011) clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:427–431.
8. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, Lamm W, Clark C, MacFarquhar J, Walton AL, Reller LB, Sexton DJ. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med*. 2002;137:791–797.
9. Giske CG, Monnet DL, Cars O, Carmeli Y. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. *Antimicrob Agents Chemother*. 2008;52:813–821.
10. Gomez-Batiste X, Martinez-Munoz M, Blay C, Amblas J, Vila L, Costa X. Identification of people with chronic advanced diseases and need of palliative care in sociosanitary services: elaboration of the NECPAL CCOMS-ICO tool. *Med Clin (Barc)*. 2013;140:241–245.
11. Gonzalez-Barca E, Fernandez-Sevilla A, Carratala J, Salar A, Peris J, Granena A, Gudiol F. Prognostic factors influencing mortality in cancer patients with neutropenia and bacteremia. *Eur J Clin Microbiol Infect Dis*. 1999;18:539–544.
12. Gudiol C, Bodro M, Simonetti A, Tubau F, Gonzalez-Barca E, Cisman M, Domingo-Domenech E, Jimenez L, Carratala J. Changing aetiology, clinical features, antimicrobial resistance, and outcomes of bloodstream infection in neutropenic cancer patients. *Clin Microbiol Infect*. 2013;474–479. Epub 2012 Apr 24.
13. Gudiol C, Tubau F, Calatayud L, Garcia-Vidal C, Cisman M, Sanchez-Ortega I, Duarte R, Calvo M, Carratala J. Bacteremia due to multidrug-resistant gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes. *J Antimicrob Chemother*. 2011;66:657–663.
14. Hosmer DW, Lemeshow S. Logistic regression: variable selection. In: Hosmer DW, Lemeshow S, eds. *Applied Logistic Regression*. 2nd ed. New York: John Wiley & Sons; 2000.
15. Kang CI, Kim SH, Park WB, Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, Oh MD, Choe KW. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. *Antimicrob Agents Chemother*. 2005;49:760–766.
16. Klastersky J. Management of fever in neutropenic patients with different risks of complications. *Clin Infect Dis*. 2004;39:S327.
17. Klastersky J, Ameye L, Maertens J, Georgala A, Muanza F, Aoun M, Ferrant A, Rapoport B, Rolston K, Paesmans M. Bacteremia in febrile neutropenia cancer patients. *Int J Antimicrob Agents*. 2007;30(Suppl 1):S51–S59.
18. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, Gallagher J, Herrstedt J, Rapoport B, Rolston K, Talcott J. The Multinational Association for Supportive Care in Cancer Risk Index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol*. 2000;18:3038–3051.
19. Linares L, Cervera C, Cofan F, Lizaso D, Marco F, Ricart MJ, Esforzado N, Oppenheimer F, Campistol JM, Moreno A. Risk factors for infection with extended-spectrum and AmpC beta-lactamase-producing gram-negative rods in renal transplantation. *Am J Transplant*. 2008;8:1000–1005.
20. Montassier E, Batard E, Gastinne T, Potel G, de la Cochetiere MF. Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. *Eur J Clin Microbiol Infect Dis*. 2013;32:841–850.
21. Munford RS. Severe sepsis and septic shock. In: Kasper DL, Braunwald E, Hanser SL, et al., eds. *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw-Hill; 2005: 1607–1612.
22. Oliveira AL, Souza M, Carvalho-Dias VM, Ruiz MA, Silla L, Tanaka PY, Simoes BP, Trabasso P, Seber A, Lotfi CJ, Zanichelli MA, Araujo VR, Godoy C, Maiolino A, Urakawa P, Cunha CA, de Souza CA, Pasquini R, Nucci M. Epidemiology of bacteremia and factors associated with multi-drug-resistant gram-negative bacteremia in hematopoietic stem cell transplant recipients. *Bone Marrow Transplant*. 2007;39:775–781.
23. Pena C, Gudiol C, Calatayud L, Tubau F, Dominguez MA, Pujol M, Ariza J, Gudiol F. Infections due to *Escherichia coli* producing extended-spectrum beta-lactamase among hospitalized patients: factors influencing mortality. *J Hosp Infect*. 2008;68:116–122.
24. Raad I, Hachem R, Bahna P, Chatzizakoulou I, Fang X, Jiang Y, Chemaly RF, Rolston K. Sources and outcome of bloodstream infections in cancer patients: the role of central venous catheters. *Eur J Clin Microbiol Infect Dis*. 2007;26:549–556.
25. Rodriguez-Bano J, Picon E, Gijon P, Hernandez JR, Ruiz M, Pena C, Almela M, Almirante B, Grill F, Colomina J, Gimenez M, Oliver A, Horcajada JP, Navarro G, Coloma A, Pascual A. Community-onset bacteremia due to ESBL-EC: risk factors and prognosis. *Clin Infect Dis*. 2010;50:40–48.
26. Schelenz S, Nwaka D, Hunter PR. Longitudinal surveillance of bacteremia in haematology and oncology patients at a UK cancer centre and the impact of ciprofloxacin use on antimicrobial resistance. *J Antimicrob Chemother*. 2013;68:1431–1438.
27. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteremia: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2007;60:913–920.
28. Spanik S, Krupova I, Trupl J, Kunova A, Novotny J, Mateicka F, Pichnova E, Sulcova M, Sabo A, Jurga L, Kremer VV Jr. Bacteremia due to multiresistant gram-negative bacilli in neutropenic cancer patients: a case-controlled study. *J Infect Chemother*. 1999;5:180–184.
29. Trecarichi EM, Tumbarello M, Spanu T, Caira M, Fianchi L, Chiusolo P, Fadda G, Leone G, Cauda R, Pagano L. Incidence and clinical impact of extended-spectrum-beta-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by *Escherichia coli* in patients with haematological malignancies. *J Infect*. 2009;58:299–307.
30. Van Der Poll T, Opal S. Host-pathogen interactions in sepsis. *Lancet Infect Dis*. 2008;8:32–43.
31. Velasco E, Byington R, Martins CA, Schirmer M, Dias LM, Goncalves VM. Comparative study of clinical characteristics of neutropenia and non-neutropenia adult cancer patients with bloodstream infections. *Eur J Clin Microbiol Infect Dis*. 2006;25:1–7.
32. 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;36:1103–1110.