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REVIEW

Bloodstream infections in patients with solid tumors

Carlota Gudiol[a,b,c], José María Aguado[b,d], and Jordi Carratalà[a,b]

[a]Department of Infectious Diseases, Hospital Universitari de Bellvitge, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), University of Barcelona, Barcelona, Spain; [b]REIPI (Spanish Network for Research in Infectious Disease), Instituto de Salud Carlos III, Madrid, Spain; [c]Institut Català d'Oncologia, Barcelona, Spain; [d]Unit of Infectious Diseases, Instituto de Investigación Hospital, Complutense University, Madrid, Spain

ABSTRACT

Little information is currently available regarding bloodstream infection (BSI) in patients with solid tumors who, for a variety of reasons, are particularly predisposed to develop this condition. In this review we focus on the incidence, epidemiology, clinical features, etiology, antimicrobial resistance, and outcomes of BSI of adult cancer patients with solid tumors. Most episodes of BSI occur in non-neutropenic patients, in whom the site of primary or metastatic tumor often serves as the portal of entry. The urinary tract and the abdomen are the most frequent sources of infection, and cholangitis is the most common recurrent source of BSI. Gram-negative bacilli are becoming the leading cause of BSI in patients with solid tumors, and the rate of multidrug resistance is increasingly being recognized. The case-fatality rate in patients with solid tumors and BSI is high, especially among those with comorbidities, advanced neoplasms, corticosteroid therapy, and shock at presentation.

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Introduction

Bloodstream infection (BSI) represents a major complication in cancer patients. In fact, cancer is the most common comorbid condition in patients with sepsis, reported to be present in approximately 17% of cases.[1] BSI in cancer patients may delay initiation of chemotherapy and reduce the dosage that can be administered; also, it prolongs hospitalization, increases costs and raises morbidity and mortality.[2] In a study performed in a large community hospital in The Netherlands, Bos et al. found that 90-day mortality in patients with BSI and cancer (mainly solid tumors) was significantly higher than in patients without cancer.[3]

Most of the information available on BSI in patients with cancer involves patients with hematologic malignancies and HSCT recipients, who are considered the group of cancer patients with the highest risk for bacterial infections due to the frequently prolonged (>7 days) and profound (<100 neutrophils/mm3) neutropenia.[4-6] Other studies have analyzed hematologic and solid tumor patients together, thus creating groups that are too heterogeneous to be analyzed properly.[4,7-11] In this review we focus on the recent literature regarding the incidence, epidemiology, clinical features, etiology, antimicrobial resistance, and outcomes of BSI of adult cancer patients with solid tumors. To this end, we conducted a comprehensive literature search in the PubMed/MEDLINE database, using the following search terms: bloodstream infection, bacteremia, cancer, solid tumor, solid neoplasm, solid malignancy, adults, neutropenia, epidemiology, etiology, causative agents, antimicrobial resistance, outcome, mortality, and case-fatality.

Risk factors for infection in patients with solid tumors

Patients with solid tumors should be considered as a distinctive population as they are predisposed to developing infections, specially BSI, due to a variety different of mechanisms: an often progressive catabolic state, malnutrition, ulcerating lesions in the skin and mucosal surfaces, obstructive processes, invasive procedures and indwelling devices, and immune suppression due to chemotherapy, radiation and/or the malignancy itself.[12] New treatment modalities such as the use of colony-stimulating factors and new outpatient management systems may also have modified the epidemiological profile of BSI in patients with solid tumors. Additionally, the recent introduction of new immune-modulatory therapies such as monoclonal antibodies and related small molecules and their impact on infections in cancer patients needs to be evaluated further.[13,14]

CONTACT José María Aguado jaguadog1@gmail.com Hospital 12 de Octubre, Av Andalucía Km 5,4. 28041 Madrid, Spain.

Another important risk factor for infection and BSI in patients with solid tumors is the performance of surgery. Patients who undergo extensive tumor resections, in particular involving the respiratory and gastrointestinal tracts, are at an even greater risk of developing postoperative nosocomial infections. In this regard, a study from Texas of 3.522 respiratory and gastrointestinal tumor resections identified BSI as the third-leading cause of nosocomial infection following surgery in 16% of cases, after pneumonia (43%) and wound infection (28%), and the risk of serious postoperative infections varied by resection site: esophagus (25%), stomach (19 %), pancreas (17 %), lung (10 %), rectum (8 %), and colon (7%).[15] Some of the more relevant risk factors for presenting postoperative nosocomial infections were increased age, male sex, comorbidities, distant metastasis, and receiving surgery in rural or low-volume hospitals. In another prospective cohort study evaluating the epidemiology and microbiology of nosocomial BSI in adult surgical cancer patients, Velasco *et al.* identified 112 episoses in 112 patients during a 26-month period.[16]

Incidence of bloodstream infection in patients with solid tumors

In the United States it has been estimated that the incidence of sepsis is as high as 16.4 cases/1000 cancer patients/year.[17] In a longitudinal surveillance study of BSI in cancer patients (neutropenic and non-neutropenic) in the UK over a 14 y period, the authors found a fluctuating incidence of BSI with an overall incidence of 5.5/1000 admissions.[18] Not surprisingly, the individual incidence for hematology patients was three times higher than in oncology patients (10.9/1000 admissions versus 3.6/1000 admissions respectively). Hematology patients presented a significant downward trend in BSI episodes during the study period, but this finding was not observed in patients with solid tumors.

In another large prospective study of 579 episodes of BSI involving only neutropenic patients in Barcelona, Spain, Marín *et al.* observed an even higher difference in the incidence of BSI in neutropenic cancer patients depending on the underlying disease; the incidence in hematologic patients was eight times higher than in patients with solid tumors (7.48/1000 admissions vs. 0.95/1000 admissions respectively).[19] This finding was probably due to that fact that hematologic patients have higher levels of immunosuppression, with more profound and prolonged neutropenia, and also more frequent chemotherapy-induced mucositis, which favors invasive bacterial infections such as BSI.

The changing epidemiology of bloodstream infection in patients with cancer

Throughout the 1960s and 1970s, Gram-negative organisms were the most frequent causative agents of BSI in neutropenic cancer patients.[20] During the next two decades, the etiology of BSI shifted dramatically from Gram-negative bacilli (GNB) to Gram-positive cocci, especially viridans group streptococci and coagulase-negative staphylococci.[10] Some of the reasons for this change were the frequent use of chemotherapy which resulted in significant oral mucositis, the almost universal use of central venous catheters, and the use of antibacterial prophylaxis directed primarily against enteric GNB.[21] In recent years, however, several institutions have reported a resurgence in the frequency of GNB as the leading cause of BSI, which can reach up to 65% of the episodes in some series.[6,9,22,23]

In this regard, the emergence of resistance to antimicrobial agents commonly used to treat of bacterial infections has become a significant problem worldwide, including onco-hematological patients.[24,25] Prompt administration of appropriate empirical antibiotic therapy in neutropenic febrile cancer patients is the standard of care. However, choosing the right empirical antibiotic therapy in this era of growing antimicrobial resistance is a clinical challenge.

Of special concern is the widespread dissemination of extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, which often leads to an increased use of carbapenems and thus facilitates the selection of multidrug-resistant (MDR) microorganisms, including bacteria resistant to carbapenems, and *Clostridium difficile*-associated diarrhea.

The emergence of carbapenem-resistant GNB is even more disturbing, since treatment options against these organisms are very limited. Physicians are often forced to use less attractive antibiotics such as tigecycline and other older antibiotics, namely colistin/polymyxin B and fosfomycin, which have recently been reintroduced but present efficacy, resistance and/or toxicity issues. Moreover, at present, very little has been published on the use of these antibiotics in cancer patients.

The emerging resistance in Gram-positive organisms, especially vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus*, is also a matter of concern. However, more new antimicrobial agents which are active against these organisms, such as daptomycin and linezolid, are becoming available.

Clinical characteristics of patients with solid tumors and bloodstream infection

Table 1 shows the main clinical characteristics of BSI in patients with solid tumors reported in two series, and details the differences between the episodes of BSI of neutropenic patients with solid tumors compared with neutropenic patients with hematologic malignancies. In a large prospective series of 528 episodes of BSI in 489 patients with solid tumors in Barcelona, Spain, Marin *et al*. reported that hepatobiliary tumor was the most frequent tumor type in 19% of patients, followed by lung cancer (18%) and lower gastrointestinal malignancy (16%).[26] Almost half of the patients had comorbidities and 81% had chronic advanced cancer. Chemotherapy had been given to 63% of the patients within the last month and 41% had received corticosteroid therapy. Eighty episodes (15%) occurred in neutropenic patients, 52% of whom had a MASCC risk score <21 . The majority of episodes (57%) were considered to be health care-related. Fourteen per cent of the patients had a biliary prosthesis and 10% had a urinary catheter in place. The most common source of BSI was cholangitis (21%), followed by other abdominal sites (19.5%) and the urinary tract (17%).

Table 1. Clinical characteristics of bloodstream infections in patients with solid tumors. Differences between neutropenic patients with hematologic malignancies and solid tumors.

	Marin *et al.* 2014 [26]	Anatoliotaki *et al.* 2004 [27]	Marin *et al.* 2014 [19]		
Population studied	Patients with solid tumors (neutropenic and non-neutropenic) N = 528 (%)	Patients with solid tumors (neutropenic and non-neutropenic) N = 157 (%)	Neutropenic patients with hematological malignancies N = 493 (%)	Neutropenic patients with solid tumors N = 86 (%)	*p*
Age (years, median, range)	—	64 (18-83)	57 (19-89)	61 (14-79)	<0.001
Male sex	343 (65)	68 (47)	306 (62.1)	51 (59.3)	0.63
Underlying disease					
Hepatobiliary tumor	99 (19)	9 (6.6)			
Lung tumor	95 (18)	25 (18)			
Lower gastrointestinal tumor	85 (16)	15 (11)			
Genitourinary tumor	65 (12)	11 (8)			
Breast tumor	39 (7)	30 (22)			
Gynecologic tumor	37 (7)	21 (15)			
Upper gastrointestinal tumor	36 (7)	3 (2.2)			
Head and neck tumor	30 (6)	2 (1.5)			
Sarcoma	14 (3)	5 (3.6)			
Comorbidities	242 (46)		132 (26.8)	32 (37.2)	0.052
COPD	66 (12.5)		26 (5.3)	16 (18.8)	<0.001
Neutropenia (<500)	80 (15)	29 (18)	493 (100)	86 (100)	NS
MASCC risc score <21	43 (52)		145 (31.5)	40 (50.6)	0.001
Severe mucositis (grade III.IV)	—	23 (15)	61 (12.4)	10 (11.6)	1.00
Previous chemotherapy	335 (63)	43 (27)	440 (89.4)	84 (97.7)	0.014
Previous radiotherapy	72 (14)	22 (14)			
Corticosteroid therapy (1 month)	213 (41)		129 (26.2)	37 (43)	0.003
Central venous catheter	81 (15.3)	31 (20)			
Intravenous vascular catheter	213 (40.3)	—	427 (86.6)	25 (29.1)	<0.001
Biliary prosthesis	74 (14)				
Urinary catheter	54 (10)	—	27 (5.5)	25 (29.1)	<0.001
Previous antibiotic therapy (1 month)	193 (37)	22 (14)	283 (57.4)	24 (27.9)	<0.001
Previous invasive procedure	—	93 (59)			
Axillary temperature ≥ 38°C	406 (77)	142 (90.5)			
Site of acquisition					
Heath care	300 (57)	80 (51)	74 (15)	59 (68.6)	<0.001
Nosocomial	145 (27.5)	55 (35)	408 (82.9)	14 (16.3)	<0.001
Community acquired	83 (16)	22 (14)	10 (2)	13 (15.1)	<0.001
Source of BSI					
Cholangitis	111 (21)	—	2 (0.4)	3 (3.5)	0.025
Other abdominal sites	103 (21)	—	6 (1.2)	9 (10.5)	<0.001
Urinary tract	90 (17)	35 (22.3)	12 (2.4)	9 (10.5)	0.002
Respiratory tract	57 (11)	24 (15.2)	20 (4.1)	22 (25.6)	<0.001
Catheter related	53 (10)	16 (10.1)	125 (25.4)	6 (7)	<0.001
Unknown	44 (8)	53 (34)	25 (5.1)	4 (4.7)	1.00
Endogenous source	29 (5.5)	—	253 (51.3)	23 (26.7)	<0.001
Skin and soft tissue	17 (3)	—	5 (1)	4 (4.7)	0.032
Mucositis	11 (2)	—	27 (5.5)	4 (4.7)	1.00

Note. COPD= Chronic obstructive pulmonary disease.

Anatoliotaki et al. published a retrospective series of 157 episodes of BSI in 137 patients with solid tumors, in whom breast cancer was the most frequent type of malignancy (22%), followed by lung cancer (18%), and genital cancer (15%).[27] As in the Spanish study, the majority of episodes (82%) occurred in non-neutropenic patients, fever was frequently documented (90.5%) and most episodes were health care-associated (51%). However, in Anatoliotaki *et al.*'s study, the urinary tract was the most common source of infection (34%), followed by the respiratory tract (23%) and the abdomen (22%). Interestingly, the portal of entry in 37% of the episodes with a known source was the site of the primary or metastatic tumor. When interpreting the results of both studies, it has to be taken into account that the first study was carried out ten y after the second, which may explain, at least partially, some of the differences found between the studies.

In order to identify the different characteristics and etiology of BSI occurring in patients with solid tumors and hematologic malignancies and to assess their impact on empirical antibiotic therapy and outcomes, Marín *et al.* performed a prospective study of a large cohort of BSI in neutropenic cancer patients and compared the differences between them according to the underlying disease.[19] (Table 1). Regarding the clinical characteristics, patients with hematological malignances were significantly younger, were more likely to have a vascular catheter in place, and had received previous antibiotic therapy more frequently. Patients with solid tumors were more likely to have comorbidities and had received corticosteroid therapy more frequently. Endogenous source of BSI and catheter-related infection were more common in patients with hematological malignancies, whereas pneumonia and urinary tract source were more frequent in the solid tumor group.

Etiology of bloodstream infection in patients with solid tumors

The most important causative agents of BSI documented in the two available studies involving only patients with solid tumors are detailed in Table 2. In both series GNB predominated over Gram-positive pathogens, *Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneumoniae* being the most frequent isolates. However, whereas in the Greek study the rate of antimicrobial resistance among GNB was low, in the Spanish study it was found to be 15%, mainly due to ESBL-producing *Enterobacteriaceae*, Amp-C-producing *Enterobacteriaceae* and MDR *P. aeruginosa*.[26,27] Patients infected by MDR organisms had close contact with the hospital, with frequent previous admissions, previous antibiotic administration and invasive procedures such as urinary catheterization or biliary prosthesis. The difference in the resistance rate between the two studies may be attributed to the differences in the definitions of multi-drug resistance used in the studies, and because the Greek study dates from the late 1990s, when antimicrobial resistance was not as disseminated as it is in the current era. Among Gram-positive pathogens, viridians group streptococci, coagulase-negative staphylococci, *Staphylococcus aureus* and *Enterococcus spp*. were the most frequent isolates, with rates varying depending on the study.

Table 2. Causative agents of bloodstream infection in patients with solid tumors.

Causative Agent	Marin *et al.* 2014 [26] N = 528 (%)	Anatoliotaki *et al.* 2004 [27] N = 157 (%)
Gram-negative bacteria	291 (55)	73 (47)
Escherichia coli	161 (55)	39 (25)
Pseudomonas aeruginosa	52 (18)	11 (7)
Klebsiella spp.	56 (10.6)	3 (2)
Enterobacter spp	27 (5.1)	5 (1)
Proteus spp.	10 (3)	2 (1)
Salmonella spp	8 (3)	7 (4.5)
Aeromonas hydrophila	4 (1)	—
Acinetobacter baumannii	2 (1)	1 (1)
Other Gram-negative bacteria	—	5 (1)
Gram-positive bacteria	184 (35)	54 (34)
Viridans group streptococci	40 (22)	6 (4)
Staphylococcus aureus including MRSA	38 (21)	11 (7)
Enterococcus spp.	33 (18)	4 (2.5)
Coagulase-negative staphylococci	30 (16)	24 (15)
Streptococcus pneumoniae	28 (15)	3 (2)
Listeria monocytogenes	16 (9)	—
Streptococcus bovis	9 (5)	—
Corynebacterium spp	2 (1)	5 (3)
Other Gram-positive bacteria	—	1 (0.5)
Anaerobes	25 (4.5)	5 (3)
Polymicrobial	24 (4.5)	22 (14)
MDR Gram-negative bacilli	43 (15)	—
MDR Gram-positive and Gram-negative bacteria	61 (13)	—

Notes. MDR: multidrug resistant
MRSA: methicillin.resistant *Staphylococcus aureus*.

Table 3 shows the causative agents of BSI comparing patients with solid tumors with those with hematologic malignancies. In the study with only neutropenic patients, GNB were the leading cause of BSI in both groups, but they were significantly more frequent in patients with solid tumors, mainly due to *P. aeruginosa*.[19] Gram-positive BSI tended to be more frequent in patients with hematologic malignancies than in those with solid tumors, with coagulase-negative staphylococci and *Enterococcus spp* being significantly more frequent in this group. MDR GNB were more frequently isolated in the hematological group, mainly due to ESBL-producing *Enterobacteriaceae* and *Stenotrophomonas maltophilia.* Hematological patients had more frequently received previous antibiotic therapy than patients with

solid tumors, which is a well-known risk factor for development of resistance.[28]

In the longitudinal surveillance study by Schelenz *et al.* of neutropenic and non-neutropenic patients, Gram-positive BSI was more frequent than Gram-negative, with coagulase-negative staphylococci being the most frequent causative agents.[18] The authors did not specify the rate of multidrug resistance among GNB, but the rate of ciprofloxacin resistance was higher in hematological patients than in those with solid tumors.

In the specific subgroup of patients with solid tumors undergoing surgery, Gram-negative BSI was also predominant in 62% of cases, *Enterobacter spp., Klebsiella spp, Acinetobacter spp.* and *P. aeruginosa* being the most frequent isolates. The high incidence of Gram-negatives other than *E. coli* may be explained by the fact that BSI occurred in the postoperative setting, and that concomitantly infected sites, such as surgical-site infection and pneumonia occurred frequently.[16] Interestingly, non-fermentative isolates were significantly more common in patients with central venous catheters. Martino *et al.* also showed a high frequency of catheter-related non-fermentative BSI in cancer patients, which they attributed to contaminated fluids, instruments, and material used for patient care.[29]

The *Acinetobacter baumannii* is emerging as a cause of BSI in patients with solid tumors, mainly in non-neutropenic patients who have undergone invasive procedures and/or who have been admitted in the ICU.[9,30,31]

Empirical antibiotic therapy and outcomes of bloodstream infection in patients with solid tumors

Immunosuppressed patients with cancer are at risk of severe sepsis due to bacterial infections such as BSI, especially when they present during profound neutropenia. In-hospital mortality due to BSI in cancer patients remains high, in spite of the updated guidelines for the management of febrile neutropenia and the improvement of shock management.[5,32,33] The role played in reducing mortality by the rapid initiation of empirical antibiotic therapy for febrile neutropenia is now undisputed. In addition, some studies have reported that inappropriate empirical antibiotic treatment is associated with worse outcome and has a significant impact on survival.[34]

Table 3. Causative agents of bloodstream infection in patients with solid tumors compared with patients with hematologic malignancies.

Population studied	Marin *et al.* 2014 [19] Only neutropenic patients were inlcuded			Schelenz *et al.* 2013 [18] Neutropenic and non-neutropenic patients		
Causative agents	Hematological malignancy N = 493 (%)	Solid tumor N = 86 (%)	*p*	Hematological malignancy N = 473 (%)	Solid tumor N = 441 (%)	*p*
Gram-positive bacteria	206 (41.8)	27 (31.4)	0.075	302 (62)	258 (56)	0.03
Coagulase-negative staphylococci	94 (45.6)	6 (22.2)	0.005	168 (35.5)	125 (28.3)	—
Staphylococcus aureus including MRSA	31 (6.3)	6 (7)	0.80	37 (7.8)	44 (10)	—
Viridans group streptococci	39 (18.9)	6 (22.2)	1.0	54 (11.4)	19 (4.3)	—
Enterococcus spp.	44 (21.3)	2 (7.4)	0.032	20 (4.2)	20 (4.5)	—
Streptococcus pneumoniae	12 (5.8)	3 (11.1)	0.47	7 (1.5)	12 (2.7)	—
β.hemolytic streptococci	—	—	—	7 (1.5)	13 (2.9)	—
Bacillus spp	—	—	—	5 (1.1)	8 (1.8)	—
Other Gram-positive bacteria	—	—	—	3 (0.9)	5 (1.6)	—
Gram-negative bacteria	234 (47.5)	52 (60.5)	0.027	163 (33)	189 (41)	0.03
Escherichia coli	121 (51.7)	19 (36.5)	0.68	40 (8.5)	61 (13.8)	—
Pseudomonas aeruginosa	52 (22.2)	22 (42.3)	<0.001	33 (7.0)	23 (5.2)	—
Klebsiella spp.	54 (23)	12 (23)	0.46	16 (3.4)	27 (6.1)	—
Enterobacter spp	20 (8.5)	1 (1.92)	0.34	22 (4.7)	14 (3.2)	—
Serratia spp.	—	—	—	2 (0.4)	4 (0.9)	—
Proteus spp	—	—	—	3 (0.6)	4 (0.9)	—
MDR Gram-negative bacilli[a]	36 (15.4)	2 (3.84)	0.1	—	—	—
ESBL-producing Enterobacteriaceae	21 (58.3)	2 (2.4)	0.55	—	—	—
Stenotrophomonas maltophilia	9 (25)	0 (0)	0.36	21 (4.4)	32 (7.3)	—
AmpC-producing Enterobacteriaceae	3 (8.3)	0 (0)	1.00	—	—	—
MDR *Pseudomonas aeruginosa*	2 (3.33)	0 (0)	1.00	—	—	—
Acinetobacter baumannii	1 (2.7)	0 (0)	1.00	7 (1.5)	7 (1.6)	—
Other Gram-negative bacteria	—	—	—	5 (3)	3 (1.5)	—
Ciprofloxacin-resistant GNB	—	—	—	(22)	(5)	0.058
Anaerobes	11 (2.2)	3 (3.5)	0.44	6 (1.3)	8 (1.8)	—
Polymicrobial	51 (10.3)	8 (9.3)	1.00	—	—	—
Fungi	11 (2.2)	0 (0)	0.36	5	13	—

Notes. MDR: Multidrug resistant
ESBL.Extended.spectrum β-lactamase

Patients with solid tumors and febrile neutropenia often present low-risk MASCC index scores compared with patients with hematological malignancies, due to the less profound and less prolonged neutropenia. Therefore, they are often administered oral and/or outpatient antibiotic therapy. In an attempt to assess the risk for complications in patients with febrile neutropenia, Carmona-Bayonas *et al.* recently developed a new model to more accurately classify patients with cancer with seemingly stable febrile neutropenia episodes.[35]

In spite of the apparently better outcomes for patients with solid tumors and febrile neutropenia, which allow management on an outpatient basis in many cases, the presence of a solid neoplasm as the underlying disease was found to be an independent risk factor associated with mortality in two studies involving cancer patients with BSI caused by MDR Gram-negative bacilli.[36,37]

The information available regarding the initial empirical antibiotic therapy and outcomes of patients with solid tumors and BSI is detailed in Table 4. In the study dealing with neutropenic and non-neutropenic patients with solid tumors, the most frequent empirical antibiotic regimen administered was β-lactam + β-lactamase inhibitor combination, followed by oxymino-β-lactams. In the study which compared neutropenic hematological patients with those with solid tumors, the cephalosporin + aminoglycoside combination was the most frequent regimen used in both groups. In neutropenic patients with solid tumors, the combinations β-lactam + β-lactamase inhibitor and amoxicillin-clavulanate + ciprofloxacin were used significantly more often than in neutropenic patients with hematological malignancies, in whom, on the other hand, the use of a glycopeptide was significantly more common.[19,26]

The Spanish and Greek studies found a similar percentage of patients with solid tumors and BSI receiving inadequate initial empirical antibiotic therapy (23% and 29.2% respectively).[26,27] In contrast, neutropenic hematological patients were more likely to receive inadequate initial empirical antibiotic therapy than neutropenic solid tumor patients.[19] This finding is probably due to the higher rates of BSI due to MDR microorganisms and coagulase-negative staphylococci in the hematological patients.

Septic shock was present in 13%–19% of patients with solid tumors.[26,27] Interestingly, even though more neutropenic patients with solid tumors presented with shock, more patients in the hematological group were admitted to the intensive care unit and underwent invasive mechanical ventilation.[19] Hematological patients were younger and had a better global prognosis; however, whether or not patients with advanced solid tumors should be admitted to intensive care remains a matter of debate.

Overall case-fatality rates were high in patients with solid tumors and BSI (32% and 20% in the Spanish and Greek studies respectively), and it were significantly higher in the group of neutropenic patients with solid tumors than in those with hematological malignancies. This difference remained significant when analyzing

Table 4. Empirical antibiotic therapy and outcomes of patients with solid tumors and bloodstream infection. Empirical antibiotic therapy and outcomes of neutropenic patients with solid tumors compared with patients with hematologic malignancies.

Characteristic	Marín *et al.* 2014 [26]	Anatoliotaki *et al.* 2004 [27]	Marín *et al.* 2014 [19]		
Population studied	Neutropenic and non-neutropenic patients with solid tumors N = 528 (%)	Neutropenic and non-neutropenic patients with solid tumors N = 157 (%)	Neutropenic patients with hematological malignancies N = 493 (%)	Neutropenic patients with solid tumors N = 86 (%)	*p*
Empirical antibiotic therapy	497 (94)	—	478 (97)	86 (100)	0.144
Monotherapy					
Carbapenem	69 (13)	—	43 (8.7)	4 (4.7)	0.209
Glycopeptide	—	—	34 (7.1)	1 (1.2)	0.029
Oxymino.β.lactam	122 (23)	—	26 (5.4)	1 (1.2)	0.062
β.lactam + β.lactamase inhibitor	296 (56)	—	20 (4.2)	14 (16.3)	<0.001
Quinolone	64 (12)				
Combination therapy					
Cephalosporin + aminoglycoside	74 (14)	—	220 (46)	46 (53.5)	0.2
Amoxicillin clavulanate + ciprofloxacin			0 (0)	5 (5.8)	<0.001
Other	—	—	135 (28.2)	15 (17.4)	0.766
Inadequate initial empirical antibiotic therapy	123 (23)	46 (29.2)	120 (24.4)	11 (12.8)	0.017
Growing factors	—	—	129 (26.7)	32 (38.1)	0.036
Shock at presentation	69 (13)	30 (19)	49 (10)	25 (29)	<0.001
Intensive care unit admission	9 (2)	—	55 (11.2)	2 (2.3)	0.009
Invasive mechanical ventilation	6 (1)	—	29 (52.7)	0 (0)	0.014
Overall case-fatality rate (30 days)	163 (32)	32 (20)	59 (12.1)	32 (37.6)	<0.001
Early case-fatality rate (48 hours)	36 (7)	—	19 (3.9)	11 (12.8)	0.02

early case-fatality rates.[19,26,27] Interestingly, case-fatality rates were higher among patients with solid tumors in spite of having a more frequently low-risk MASCC index score and receiving more often adequate empirical antibiotic therapy than those with hematological malignancies. However, solid tumor patients were older, with more comorbidities, and more frequent advanced neoplasm and concomitant corticosteroid therapy, which may had influenced in the final outcome. Also, it should be noted that most bacteraemic episodes in hematologic patients receiving inadequate therapy were caused by coagulase-negative staphylococci, which has been classically associated with a good prognosis. In fact, coagulase-negative staphylococci BSI was found to be a predictor of lower mortality in patients with haematological malignancies. These organisms are frequently resistant to the empiric antibiotics commonly used in neutropenic patients with febrile neutropenia, but they rarely cause death.

Factors influencing mortality in patients with solid tumors and bloodstream infection

Neutropenia has historically been identified as one of the most important risk factors for severe sepsis and fatal outcome in patients with cancer. However, other specific host-related factors may also influence the final outcome of patients with cancer and BSI, such as the underlying disease, the age, the presence of other comorbidities, illness severity and the source of the infection. Other related factors are the promptness of the initiation of the empirical antibiotic therapy and the susceptibility pattern of the infecting microorganism.

In the study by Marín *et al.* the presence of shock at presentation and the receipt of previous corticosteroids were found to be independent risk factors associated with early and overall case-fatalities. An endogenous source of BSI was also an independent risk factor for early case-fatality, whereas advanced neoplasm was an independent risk factor for overall case-fatality.[26] Interestingly, the study by Anatoliotaki et al. is the only one that has identified inadequate empirical antibiotic therapy as an independent risk factor associated with mortality, together with the presence of septic shock.[27]

When analyzing the cohort of neutropenic patients with BSI, the variables found to be associated with overall case-fatality in patients with solid tumors were the same as those identified for the global cohort of neutropenic and non-neutropenic patients (septic shock, corticosteroids and advanced neoplasm).[19,26] In contrast, in neutropenic hematological patients, risk factors for overall case-fatality were intensive care unit admission, advanced neoplasm, corticosteroid therapy, high-risk MASCC risk score, and MDR Gram-negative bacilli BSI. Patients with coagulase-negative staphylococci BSI and those treated with combination empiric antibiotic therapy were more likely to survive.[19]

Velasco et al. analyzed the risk factors for mortality in the specific cohort of patients with solid tumors undergoing surgery. In this setting, risk factors associated with mortality were the presence of ≥ 4 comorbid conditions, advanced neoplasm, catheter retention, thoracic surgery and pulmonary infiltrates.[16]

Other investigators have addressed this issue in the setting of specific microorganisms causing BSI. In a case-control study performed to identify risk factors for *P. aeruginosa* BSI among Gram-negative bacterial infections in non-neutropenic patients with solid tumors, risk factors for 30-day mortality were gastric cancer, increased Charlson's weighted index of comorbidity, septic shock, complicated intra-abdominal infection and pneumonia.[38] Finally, in 2 more studies of BSI due to *A. baumannii* spp in patients with solid tumors, infection with *A. baumannii* and a high APACHE II score in one study, and a high Pitt BSI score and previous chemotherapy in the other, were found to be independent risk factors associated with mortality.[30,31]

Prevention of bloodstream infection in patients with solid tumors

Prevention of catheter-related bloodstream infection

Patients with solid tumors often carry some type of short-term or long-term central venous catheter (CVC) in order to receive the medication they need during treatment cycles (chemotherapy, blood products, antibiotics, parenteral nutrition, and so on). Currently, there is insufficient evidence to recommend the use of any specific type of central venous catheter, including tunneled catheters, totally implantable venous ports (port-a-cath), or peripherally-inserted venous catheters (PICC), since all of them may become infected.[39,40]

Until recently, Gram-positive bacteria were the most frequently isolated pathogens causing catheter-related BSI in cancer patients, and preventive strategies were established mainly for patients with BSI in the intensive care.[41] However, recent studies suggest a resurgence of GNB as the major pathogens of BSI in cancer patients, including episodes of catheter-related BSI, which may account for more than 50% of the episodes in patients with permanently implantable venous ports.[39,22]

The most important measures in preventing CVC infections are: (i) education and training of health professionals; (ii) strict hand hygiene care; and (iii) the use

of aseptic techniques during dressing placement and replacement.[41] In this regard, a recent study by Kao *et al.* showed that topical skin disinfection with chlorhexidine was associated with a significant improvement in time to first port-a-cath associated BSI in patients with solid tumors compared with disinfection with povidone-iodine.[42]

Routine replacement of CVCs and the application of topical antimicrobials in the insertion point are not recommended because they can favor fungal infections and the development of resistance. The use of CVC coated or impregnated with antimicrobials/antiseptics such as chlorhexidine and silver sulfadiazine or minocycline/rifampin may reduce the risk of infections, although its benefit is relative and its cost is high.[43]

Another strategy that has proved useful in preventing catheter-related BSI (mainly due to Gram-positive bacteria) in cancer patients is flushing or locking the CVCs with a combination of an antibiotic and heparin.[44,45] Finally, the suggestion that the use of prophylactic antibiotics before placing a CVC reduces the incidence of infections has not been desmonstrated.[46]

Antibacterial prophylaxis

Patients with solid tumors who receive conventional chemotherapy are considered to have a low risk of infectious complications.[33] In these patients, the use of fluoroquinolones has shown to provide a protective effect but has no impact on mortality.[47,48] Given the high number of patients requiring treatment to prevent one death (34 according to the study of Gafter-Gvili *et al*), and the economic costs, adverse effects, occurrence of superinfections and the risk of antimicrobial resistance selection, antibacterial prophylaxis in low-risk patients receiving conventional chemotherapy with or without biological agents is not indicated.[48-50] In some specific situations, the administration of antibacterial prophylaxis may be considered on an individual basis.

Granulocyte colony-stimulating factors

In cancer patients undergoing chemotherapy, the use of granulocyte colony-stimulating factors (G-CSF) decreases the incidence, duration and severity of neutropenia and prevents the associated infections.[51] The prophylactic use of G-CSF is recommended in patients with an estimated risk of febrile neutropenia >20%.[33,52] If the estimated risk is <20 %, an individualized risk assessment for each patient needs to be performed.

Treatment with G-CSF in the setting of febrile neutropenia shortens hospital stay and time to neutrophil recovery, but is not associated with a survival benefit.[53] Therefore, G-CSF should be administered in cases that are associated with a high risk of complications, such as severe (neutrophil <100 /mm3) or anticipated long-term (>10 days) neutropenia. They should also be considered for use in patients >65 years, in cases of sepsis, pneumonia, or previous episodes of febrile neutropenia.[54]

Streptococcus pneumoniae vaccination

S. pneumoniae represents an important cause of BSI among patients with cancer. In fact, in a prospective study of bacteremias in cancer patients, García-Vidal *et al.* found that 6.5% of all episodes of BSI were caused by *S. pneumoniae*, and importantly, that only 23% of the patients had received the 23-valent polysaccharide pneumococcal vaccine.[55]

Patients with cancer should receive pneumococcal vaccination before starting chemotherapy and/or other immunosuppressive therapies, preferably before their initiation. The effect of pneumococcal vaccine in cancer patients may be low as a result of the reduced immunogenicity, especially that of the 23-valent polysaccharide vaccine. However, conjugate vaccines are associated with a stronger, longer-lasting response because they contain a range of serotypes conjugated to a protein that allows for a T cell-dependent response, thereby facilitating the formation of memory B cells.[56] Currently, the 13-valent conjugate vaccine is the antipneumococcal vaccine routinely recommended for inmunocompromised patients with cancer.

Conclusions

Little information is available regarding BSI in patients with solid tumors who are particularly predisposed to developing bacterial infections due a range of factors. The incidence of BSI in patients with solid tumors is notable, but is lower than that observed in hematological patients. Most episodes of BSI in patients with solid tumors occur in non-neutropenic patients, in whom the site of the primary or metastatic tumor often serves as the portal of entry of the BSI. The urinary tract and the abdomen are the most frequent sources of infection, and cholangitis is the most frequent source of recurrent BSI.

GNB are becoming an important cause of BSI in patients with solid tumors in some institutions, and the growth of multidrug resistance is increasingly being recognized. Patients with BSI due to MDR organisms often receive inadequate initial empirical antibiotic therapy, and present poor outcomes.

There are significant differences in the etiology, antibiotic resistance and clinical outcomes of BSI occurring in neutropenic patients with solid tumors and in those

with hematologic malignancies. Further information on these aspects may help physicians when selecting an empirical antibiotic therapy in febrile neutropenic patients.

The case-fatality rate in patients with solid tumors and BSI is high, especially among those with comorbidities, chronic advanced neoplasms, corticosteroid therapy, and shock at presentation. Appropriate use of corticosteroids and better strategies for managing shock in these patients are key factors in reducing mortality.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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