

Epidemiology and Outcomes of Bloodstream Infections in Patients With Solid Tumors in a Central American Population at Mexico Hospital, San Jose, Costa Rica

abstract

Purpose Bloodstream infections (BSIs) are an important cause of mortality in patients with solid tumors. We conducted a retrospective study to evaluate the epidemiologic profile and mortality of patients with solid tumors who have BSIs and were admitted to Mexico Hospital. This is the first study in Costa Rica and Central America describing the current epidemiologic situation.

Methods We analyzed the infectious disease database for BSIs in patients with solid tumors admitted to Mexico Hospital from January 2012 to December 2014. Epidemiology and mortality were obtained according to microorganism, antibiotic sensitivity, tumor type, and presence of central venous catheter (CVC). Descriptive statistics were used.

Results A total of 164 BSIs were recorded, the median age was 58 years, 103 patients (63%) were males, and 128 cases of infection (78%) were the result of gram-negative bacilli (GNB). *Klebsiella pneumoniae* (21%), *Escherichia coli* (21%), and *Pseudomonas aeruginosa* (15%) were the most common microorganisms isolated. Gram-positive cocci (GPC) were found in 36 patients, with the most frequent microorganisms being *Staphylococcus aureus* (10%) and *Staphylococcus epidermidis* (6%). With respect to tumor type, BSIs were more frequent in the GI tract (57%) followed by head and neck (9%) and genitourinary tract (8%). Regarding antibiotic susceptibility, only 17% (GNB) expressed extended-spectrum beta-lactamase and 12% (GPC) had methicillin resistance. Patients with CVCs (n = 59) were colonized mainly by GNB (78%). Overall the mortality rate at 30 days was about 30%.

Conclusion GNB are the most frequent cause of BSIs in solid tumors and in patients with CVCs. GI cancers had more BSIs than other sites. Mortality and antibiotic sensitivity remained stable and acceptable during this observational period in this Latin American population.

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INTRODUCTION

According to the World Health Organization, cancer is a leading cause of death worldwide, with approximately 14 million new cases annually.¹ Patients with cancer often experience several types of complications during their treatments, including bloodstream infections (BSIs), which are a common cause of morbidity and mortality.² Most of the published data on BSIs in patients with cancer are from patients with hematologic malignancies³; information is scarce on BSIs in solid tumors worldwide and even less is available for patients in Latin America.⁴ We conducted a

retrospective study to evaluate the epidemiologic profile and mortality of patients with solid tumors who had BSIs and had been admitted to Mexico Hospital. To the best of our knowledge, this is the first study that describes the current epidemiologic situation in Costa Rica and Central America.

METHODS

This is a retrospective study conducted at Mexico Hospital in San Jose, Costa Rica. We included all hospitalized patients with solid tumors who had BSIs who were entered into our infectious

Table 1. BSIs in Patients with Malignant Solid Tumors Admitted to Mexico Hospital, San Jose, Costa Rica

Year	No. of Hospitalized Patients	No. of BSIs	Episodes of BSIs in Patients With Febrile Neutropenia		Yearly BSIs (%)
			No.	%	
2012	371	47	8	17	12
2013	353	56	14	25	16
2014	486	61	11	17	13
Total	1,210	164	33	20	14

Abbreviation: BSI, bloodstream infection.

disease database from January 1, 2012, to December 31, 2014. Patients with hematologic malignancies were excluded. We analyzed the episodes of BSIs according to demographic characteristics, microorganism, antimicrobial sensitivity, tumor type, and the presence of a central venous catheter (CVC). This study was approved by the local ethics committee.

Centers for Disease Control and Prevention criteria for defining infections were used,^{5,6} as well as the Third International Consensus definitions for sepsis and septic shock (Sepsis-3).⁷

BSI was defined as the presence of a microorganism in the blood, isolated by at least one positive blood culture that must have occurred close to or concomitant with a clinically or laboratory-proven site of infection. For a definitive diagnosis of intravascular catheter-related BSIs, the same microorganism was required to be isolated from at least one percutaneous blood culture of the intravascular catheter according to the updated Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of intravascular catheter-related infections.⁸

Blood samples were inoculated into BacT/ALERT FA (bioMérieux, Durham, NC) culture bottles and

incubated in a BacT/ALERT 3D automated continuous monitoring system until microbial growth became evident or for 6 days. Bacteria were identified and antibiotic susceptibility was obtained by using the automated Vitek 2 System (bioMérieux). Clinical and Laboratory Standards Institute breakpoints and rules were used to determine antimicrobial susceptibility.⁹ The antibiotics used for antimicrobial susceptibility testing for gram-negative bacilli (GNB) were amikacin, nalidixic acid, ampicillin/sulbactam, cefalotin, cefotaxime, ceftazidime, ciprofloxacin, gentamicin, piperacillin/tazobactam, nitrofurantoin, and trimethoprim/sulfamethoxazole. Those used for gram-positive bacilli were ampicillin, ciprofloxacin, levofloxacin, linezolid, minocycline, nitrofurantoin, teicoplanin, tetracycline, trimethoprim/sulfamethoxazole, and vancomycin.

Statistical Analysis

Because of the retrospective nature of this study, all patients with solid tumors who had BSIs were included; during the observational time period, neither prespecified sample sizes nor pre-established hypotheses were available for evaluation. Categorical variables are presented as percentages and were compared by the χ^2 test when appropriate. Continuous variables are presented as the mean \pm standard deviation. Mortality rate was defined as the number of all causes of death within 30 days after the date of documented BSI divided by the total number of BSIs in the same period. Data were analyzed by using SPSS for Mac version 20.0 (SPSS, Chicago, IL).

RESULTS

We used our biostatistical database to review 1,210 patients who were admitted to the Mexico Hospital and were diagnosed with malignant solid tumors from January 1 to December 31, 2012. One hundred sixty-four episodes of BSIs were adequately documented, and 14% of hospitalized patients with solid tumors experienced at least one episode of BSI. The annual distribution is summarized in Table 1. The median age was 57.9 years (range, 15 to 88 years). One hundred four cases (63%) of BSIs occurred in males, and 33 patients (20%) had febrile neutropenia.

Table 2 shows the distribution by year of BSIs according to microorganism. A statistically significant

Table 2. Distribution of Causative Organisms of All Episodes of BSIs by Year

Year	Microorganism				Total
	Gram-Negative Bacilli		Gram-Positive Cocci		
	No. of Episodes	%	No. of Episodes	%	
2012	32	68	15	32	47
2013	50	89	6	11	56
2014	46	75	15	25	61
Total	128	78	36	22	164

NOTE. χ^2 , 7.09.

Abbreviation: BSI, bloodstream infection.

Table 3. Bacterial Pathogens Isolated in BSIs

Microorganism	Isolates		No. of BSIs in Patients With Febrile Neutropenia
	No.	%	
<i>Escherichia coli</i>	35	21.3	6
<i>Klebsiella pneumoniae</i>	35	21.3	8
<i>Pseudomonas aeruginosa</i>	25	15.2	7
<i>Staphylococcus aureus</i>	16	9.8	4
<i>Staphylococcus epidermidis</i>	9	5.5	2
<i>Enterobacter cloacae</i>	7	4.3	1
<i>Serratia marcescens</i>	7	4.3	1
<i>Enterobacter aerogenes</i>	5	3.0	0
<i>Proteus mirabilis</i>	4	2.4	2
<i>Enterococcus faecalis</i>	3	1.8	1
<i>Acinetobacter baumannii</i>	2	1.2	1
<i>Citrobacter freundii</i>	2	1.2	0
<i>Stenotrophomonas maltophilia</i>	2	1.2	0
<i>Streptococcus gallolyticus</i>	2	1.2	0
<i>Citrobacter koseri</i>	1	0.6	0
<i>Aeromonas hydrophila</i>	1	0.6	0
<i>Enterococcus gallinarum</i>	1	0.6	0
<i>Moraxela group</i>	1	0.6	0
<i>Staphylococcus haemolyticus</i>	1	0.6	0
<i>Streptococcus gordonii</i>	1	0.6	0
<i>Streptococcus group c</i>	1	0.6	0
<i>Streptococcus pyogenes</i>	1	0.6	0
Unknown	2	1.2	0
Total	164	100	33

Abbreviation: BSI, bloodstream infection.

predominance of GNB over gram-positive cocci (GPC) was found (78% v 22%; $\chi^2 P = .029$). Overall, the most frequent GNB were *Escherichia coli* (21.3%), *Klebsiella pneumoniae* (21.3%), and *Pseudomonas aeruginosa* (15.2%). The most frequent gram-positive organisms were *Staphylococcus aureus* (9.8%), *Staphylococcus epidermidis* (5.5%), and all *Streptococci* species together (3%). Among neutropenic patients, GNB were more common than GPC (81% v 19%, respectively; Table 3). Table 4 describes antibiotic susceptibility.

Most of the patients (n = 105 [64%]) had peripheral venous catheters, 45 (27%) had short-term CVCs, and 14 (9%) had implantable ports. There was no statistical difference in terms of the BSIs detected and the type of venous catheter inserted or the site of insertion ($\chi^2 P = .27$);

however, in patients with CVCs, GNB are the prevalent microorganisms.

We found that BSIs occurred more frequently in patients with GI tumors; 93 patients (57%) had gastric cancer, colorectal cancer, or no colorectal carcinomas, and 15 (9%) had head and neck carcinomas (Table 5). Mortality rate at 30 days remained stable during the observational period, being on average 30%.

DISCUSSION

Little information has been reported about BSIs in hospitalized patients with solid tumors worldwide. As far as we know, there are no published data for either Costa Rica or Central America, and even less is known regarding the epidemiology and mortality of BSIs in our region. Most of the data on BSIs have been extrapolated from studies on hematologic malignancies in Europe and the United States.¹⁰⁻¹²

One interesting finding is that 14% of hospitalized patients with solid tumors in Mexico Hospital developed a BSI, ranging from 1.2 to 1.6 cases per 1,000 admissions of patients with solid malignancies per year. In the United States, the incidence of sepsis in patients with cancer in this setting is about 16.4 (including hematology patients); in the United Kingdom, 3.6 per 1,000 admissions per year;¹³⁻¹⁵ thus, the number of epidemiologic events in our population is similar to that in Spain.

GNB were by far the most frequent causative agents isolated in BSIs in our patients (78% of the episodes). This was statistically significant when compared with GPC ($P = .029$). In the last two decades, GPC were the leading cause

Table 4. Antibiotic susceptibility

Antibiotic susceptibility profile	No.	%
Extended-spectrum beta-lactamase among all GNB	27	21
Methicillin-resistant <i>Staphylococcus aureus</i> among GPB	19	50
Metallo beta-lactamase producers	2	1.5
Vancomycin-resistant, linezolid-susceptible	1	2.0
Not performed	2	1.2

Abbreviations: GNB, gram-negative bacilli; GPB, gram-positive bacilli.

Table 5. Frequency of BSIs According to Solid Malignancy

Solid Tumor Histology	No.	%
Gastric adenocarcinomas	43	26.21
Noncolorectal GI	27	16.46
Colorectal adenocarcinomas	23	14.02
Head and neck carcinomas	15	9.15
Genitourinary cancer	14	8.54
Sarcomas (osteosarcomas and soft tissue sarcomas)	14	8.54
Breast cancer	8	4.88
Non-small-cell lung cancer	7	4.30
Gynecologic malignancies	6	3.60
Other solid malignancies	7	4.30
Total	164	100.00

Abbreviation: BSI, bloodstream infection.

of BSIs in patients with cancer (including those with hematologic malignancies), but several institutions have recently reported that up to 65% of BSIs are the result of GNB.³ We have observed the same epidemiologic trend, with *K. pneumoniae*, *E. coli*, and *P. aeruginosa* being the main microorganisms involved in BSIs, and the same microorganisms that are responsible for bacteremia in other series reported in Europe.^{4,12,16} This high incidence of GNB can be attributed to the fact that most of the bacteremias occur after surgery in the GI tract.¹⁷ In our series, we found that about 20% of the BSIs occurred in neutropenic patients, with gram-negative rods being the most commonly isolated, in concordance with other reports mainly from developing countries.¹⁸ In terms of susceptibility profile, 68% of the bacteria were susceptible to the majority of antibiotics tested, and 21% expressed extended-spectrum beta-lactamase; *E. coli* and *K. pneumoniae* isolates that produced extended-spectrum beta-lactamase ranged from 12% to 75% (mean, 35%) in patients with cancer (including those with and without febrile neutropenia).¹⁹

Of the 59 patients with bacteremia and CVCs, 43 (73%) experienced BSIs associated with GNB, which is concerning because gram-positive microorganisms are more frequently described as the causative agents in catheter-related bacteremia.²⁰ This increased prevalence of gram-negative bacteria could be attributed to inadequate handling of CVCs by health care personnel. There was no statistical difference between type of catheter and the site of insertion, which means

that regardless of the type of CVC (long-term or short-term), the incidence of catheter-related BSIs was the same and was mainly due to GNB. This information is particularly useful for prescribing empirical antibiotics. In our case, we should start antibiotics with an anti-GNB spectrum as first-line therapy, either including or omitting anti-GPC treatment.

With respect to tumor site, 57% of BSI episodes occurred in GI cancers, followed by head and neck cancers (9.2%) and genitourinary cancers (8.5%). This distribution may explain the high incidence of BSIs caused by GNB, because this population underwent surgery, and bacteria may have translocated from the GI tract. In other studies, gram-negative BSIs were reported in about 62% of the patients in this setting.¹⁷

Our mortality rate at 30 days was about 30%, and the mortality rate ranged from 16% to 30% in the United States, Brazil, and Spain.^{3,11} On the basis of those data, we had an acceptable and stable mortality rate during the observation time period.

Our study has some limitations. First, it was based on a retrospective database, and we cannot exclude any selection bias. In addition, we cannot rule out any misclassification bias resulting from the retrospective collection of the data. Furthermore, our findings are based on a single institution experience, and the external validity of our research could be limited. Despite these caveats, we think our findings increase the knowledge about this important topic in our area.

In conclusion, limited data are available in Latin America regarding BSIs in patients with solid malignancies. With this study, we were able to determine that GNB are by far the most frequent cause of BSIs in our population. Neutropenic patients with solid tumors are infected mainly by GNB. BSIs are more frequent in patients with GI tumors. In our environment, infected CVCs are due to GNB. Mortality and antibiotic susceptibility remain stable and acceptable in this Latin American population. Understanding the epidemiology in our area can improve and optimize first-line antimicrobial therapies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Stewart BW, Wild CP (eds). World Cancer Report. Geneva, Switzerland, World Health Organization, 2014
2. Velasco E, Byington R, Martins CA, et al: Comparative study of clinical characteristics of neutropenic and non-neutropenic adult cancer patients with bloodstream infections. *Eur J Clin Microbiol Infect Dis* 25:1-7, 2006
3. Gudiol C, Aguado JM, Carratalà J: Bloodstream infections in patients with solid tumors. *Virulence* 7:298-308, 2016
4. Anatiotiaki M, Valatas V, Mantadakis E, et al: Bloodstream infections in patients with solid tumors: Associated factors, microbial spectrum and outcome. *Infection* 32:65-71, 2004
5. Centers for Disease Control and Prevention: Bloodstream Infection Event (central line-associated bloodstream infection and non-central line-associated bloodstream Infection). January 2017. https://www.cdc.gov/nhsn/pdfs/psc-manual/4psc_clabscurrent.pdf
6. Garner JS, Jarvis WR, Emori TG, et al: CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 16:128-140, 1988
7. Singer M, Deutschman CS, Seymour CW, et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 315:801-810, 2016 .
8. Mermel LA, Allon M, Bouza E, et al: Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 49:1-45, 2009
9. Clinical and Laboratory Standard Institute: Performance Standards for Antimicrobial Susceptibility Testing (ed 27). CLSI Supplement M100. January 2017. Wayne, PA. <http://em100.edaptivedocs.info/dashboard.aspx>
10. Gudiol C, Bodro M, Simonetti A, et al: Changing aetiology, clinical features, antimicrobial resistance, and outcomes of bloodstream infection in neutropenic cancer patients. *Clin Microbiol Infect* 19:474-479, 2013
11. Wisplinghoff H, Seifert H, Wenzel RP, et al: 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* 36:1103-1110, 2003
12. Marín M, Gudiol C, Garcia-Vidal C, et al: Bloodstream infections in patients with solid tumors: Epidemiology, antibiotic therapy, and outcomes in 528 episodes in a single cancer center. *Medicine (Baltimore)* 93:143-149, 2014
13. Williams MD, Braun LA, Cooper LM, et al: Hospitalized cancer patients with severe sepsis: Analysis of incidence, mortality, and associated costs of care. *Crit Care* 8:R291-R298, 2004

14. Schelenz S, Nwaka D, Hunter PR: Longitudinal surveillance of bacteraemia in haematology and oncology patients at a UK cancer centre and the impact of ciprofloxacin use on antimicrobial resistance. *J Antimicrob Chemother* 68:1431-1438, 2013
15. Marin M, Gudiol C, Ardanuy C, et al: Bloodstream infections in neutropenic patients with cancer: Differences between patients with haematological malignancies and solid tumours. *J Infect* 69:417-423, 2014
16. Montassier E, Batard E, Gastinne T, et al: Recent changes in bacteremia in patients with cancer: A systematic review of epidemiology and antibiotic resistance. *Eur J Clin Microbiol Infect Dis* 32:841-850, 2013
17. Velasco E, Soares M, Byington R, et al: Prospective evaluation of the epidemiology, microbiology, and outcome of bloodstream infections in adult surgical cancer patients. *Eur J Clin Microbiol Infect Dis* 23:596-602, 2004
18. Kanafani ZA, Dakdouki GK, El-Chammas KI, et al: Bloodstream infections in febrile neutropenic patients at a tertiary care center in Lebanon: A view of the past decade. *Int J Infect Dis* 11:450-453, 2007
19. Trecarichi EM, Tumbarello M: Antimicrobial-resistant Gram-negative bacteria in febrile neutropenic patients with cancer: Current epidemiology and clinical impact. *Curr Opin Infect Dis* 27:200-210, 2014
20. Mollee P, Jones M, Stackelroth J, et al: Catheter-associated bloodstream infection incidence and risk factors in adults with cancer: A prospective cohort study. *J Hosp Infect* 78:26-30, 2011