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RISK FACTORS FOR *STENOTROPHOMONAS MALTOPHILIA* BACTEREMIA IN ONCOLOGY PATIENTS: A CASE–CONTROL STUDY

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ABSTRACT

OBJECTIVE: To characterize risk factors for *Stenotrophomonas maltophilia* bloodstream infection in oncology patients.

DESIGN: A 3:1 case–control study.

SETTING: Stem Cell Transplant and Leukemic Center at Barnes–Jewish Hospital (St. Louis), a 1,442-bed, tertiary-care teaching hospital with a 26-bed transplantation ward.

METHOD: From June 1999 to April 2001, 13 patients with *S. maltophilia* bacteremia were compared with 39 control-patients who were on the transplantation unit on the same day as the case-patients' positive blood cultures. Information collected included patient demographics, medical history, history of transplantation, transplantation type, graft versus host disease, neutropenia, antibiotic use, chemotherapy, mucositis, diarrhea, the presence of central venous catheter(s), cultures, and concomitant infections.

RESULTS: Significant risk factors for *S. maltophilia* bacteremia included severe mucositis (7 [53.8%] of 13 vs 8 [20.5%] of 39; $P = .034$), diarrhea (7 [53.8%] of 13 vs 8 [20%] of 39; $P = .034$), and the use of metronidazole (9 [69.2%] of 13 vs 8 [20.5%] of 39; $P = .002$). In addition, the number of antibiotics used (median, 9 vs 5; $P < .001$), duration of mucositis (median, 29 vs 15 days; $P = .032$), and length of hospital stay (median, 34 vs 22 days; $P = .017$) were significantly different between case- and control-patients. Nine *S. maltophilia* isolates tested by pulsed-field gel electrophoresis were found to be distinctly different.

CONCLUSION: Interventions to ameliorate the severity of mucositis, reduce antibiotic pressure, prevent diarrhea, and promote meticulous central venous catheter care may help prevent *S. maltophilia* bloodstream infection in oncology patients. The role of gastrointestinal tract colonization as a potential source of *S. maltophilia* bacteremia in oncology patients deserves further investigation (*Infect Control Hosp Epidemiol* 2003;24:269-274).

Stenotrophomonas maltophilia, formerly known as *Pseudomonas maltophilia*, is a nonfermentative, gram-negative bacillus that has been isolated from human feces, animals, intravenous solution, and environmental sources including water, soil, sewage, and raw milk.[1-4] Although it is usually considered a colonizer and is rarely responsible for community-acquired infections,[5] its role as a pathogen has been increasingly recognized among immunocompromised patients, especially patients with malignancies.[2,6-8]

S. maltophilia accounted for 0.6% to 0.9% of all bloodstream infections reported from the United States, Canada, and Latin America from 1997 through 1999.[9,10] Septicemia due to this organism occurs rarely, although several nosocomial outbreaks have been reported.[3,8,11-16] Recognized risk factors associated with *Stenotrophomonas* bacteremia include antibiotic pressure, presence of a central venous catheter, prolonged hospital stay, length of intensive care unit stay, mechanical ventilation, and aggressive chemotherapy treatment for malignancies.[2,3,6-8,11,13,17-21] In addition, severe neutropenia (neutrophil count < 50/mm^3) and mucositis were shown to be significant risk factors for *S. maltophilia* bacteremia in a recent outbreak study of patients receiving allogeneic bone marrow transplants.[8]

From June 1999 through April 2001, 13 patients on the transplantation unit acquired *S. maltophilia* bacteremia compared with 1 patient between July 1997 and May 1999. During this period, the incidence rate of *S. maltophilia* bacteremia on the oncology service was 94 per 10,000 admissions versus 7 per 10,000 admissions during the prior 23 months ($P = .001$) (Fig. 1). Incidence rates of other waterborne, gram-negative bacteremia did not change during this period. In an effort to characterize risk factors for *S. maltophilia* bacteremia among oncology patients, a case–control study was conducted.

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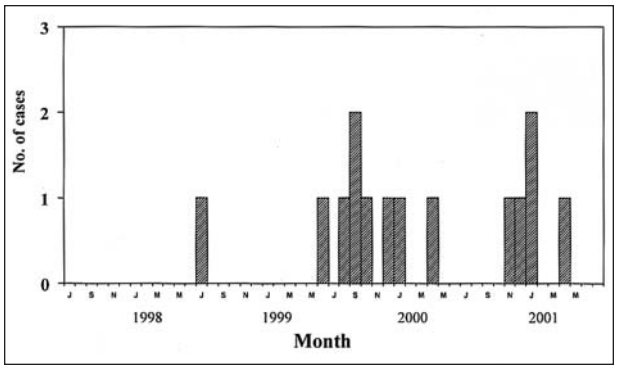

FIGURE 1. Distribution of cases in which *Stenotrophomonas maltophilia* was isolated in recent years in the Stem Cell Transplant and Leukemic Center.

METHODS

Setting

Barnes–Jewish Hospital is a 1,442-bed, tertiary-care teaching hospital with a 26-bed transplantation ward. In the year 2000, the Stem Cell Transplant and Leukemic Center program performed a total of 225 transplants (123 [55%] autologous and 102 [45%] allogeneic transplants) with a total of 10,260 patient-days and 600 admissions. The Stem Cell Transplant and Leukemic Center program also treats patients with leukemia with aggressive or recurrent disease that fails to respond to chemotherapy. All patients who underwent autologous transplants received peripheral blood stem cell transplants, whereas 45% and 55% of patients receiving allogeneic transplants underwent bone marrow and peripheral blood stem cell transplants, respectively.

Case Stratification and Ascertainment

A case-patient was defined as any oncology patient hospitalized at the Stem Cell Transplant and Leukemic Center at Barnes–Jewish Hospital from June 1, 1999, through April 30, 2001, for whom *S. maltophilia* was isolated from one or more blood cultures. Patient identification was based on review of microbiology laboratory data. Medical records were reviewed to ascertain that these patients developed *S. maltophilia* bacteremia and were associated with clinical infection. Control-patients were randomly selected from patients who did not develop bacteremia and were on the same unit on the day of the case-patient's first positive blood culture for *S. maltophilia*. Room numbers were drawn randomly to select the control-patients. Centers for Disease Control and Prevention definitions for bloodstream and other nosocomial infections were applied for all case- and control-patients.[22] For organisms likely to be due to skin contamination, such as coagulase-negative *Staphylococcus* species and *Corynebacterium* species, bacteremia was defined by a temperature of 38°C or greater with two positive blood cultures within 24 hours.

Case–Control Study

To determine risk factors for *S. maltophilia* bacteremia among oncology patients, 13 case-patients were compared with 39 control-patients (3 control-patients per case-patient). Information collected on case- and control-patients included demographics, medical history, history of transplantation, transplantation type, graft versus host disease, neutropenia, prophylactic and therapeutic antimicrobial use, chemotherapy, the presence of central venous catheters, mucositis, severe mucositis (defined by ulcers with plaques involving more than 25% or hemorrhagic ulcers of the oral mucosa), diarrhea, and other concurrent infections. Therapeutic antibiotics analyzed included penicillin, extended-spectrum penicillins, first-, second-, third-, and fourth-generation cephalosporins, quinolones, aminoglycosides, glycopeptides, macrolides, metronidazole, clindamycin, cotrimoxazole, chloramphenicol, streptogramins, oxazolidinones, and carbapenems. In addition, prophylactic antibiotic (cotrimoxazole), antiviral (acyclovir, famcyclovir, and gancyclovir), and antifungal (polyenes and azoles) medications were included in the analysis. With the exception of diarrhea, all risk factors were evaluated from the time of admission until the occurrence of *S. maltophilia* bacteremia for case-patients and during the entire hospital stay for control-patients. Diarrhea was defined as 3 or more loose or watery stools in 24 hours within 72 hours before the onset of bacteremia for case-patients and any time during the entire hospital stay for control-patients.

The population of the Stem Cell Transplant and Leukemic Center included patients with leukemia who did not receive transplants and patients who underwent allogeneic and autologous transplants. To determine risk factors for *S. maltophilia* bacteremia in patients undergoing transplants, we compared 6 case-patients who had received their transplants within 6 months prior to the hospitalization during which *S. maltophilia* bacteremia was detected with 20 patients (control-patients) who received a transplant during the same time period. To further determine risk factors for *S. maltophilia* bacteremia in allogeneic transplantation, we restricted the analysis to 5 case-patients who had received an allogeneic transplant within 6 months of the hospitalization during which *S. maltophilia* bacteremia was detected. These 5 case-patients were compared with 11 patients receiving allogeneic transplants (control-patients) who were hospitalized during the same time period. These patients were compared regarding all of the characteristics described above.

Nursing Care, Infection Control Practices, and Supportive Anti-Infectious Therapy

During the study period, there was no change in standard nursing care practices (eg, mucosal care for patients with severe mucositis). Standard precautions were applied to all patients. Contact precautions were used when patients were identified as having multidrug-resistant organisms or epidemiologically significant organisms such as *S. maltophilia*. For *Pneumocystis carinii* pneumonia prophylaxis, patients received oral cotrimoxazole, starting on the day of engraftment. To prevent endogenous reactivation of herpes simplex virus and human cytomegalovirus, patients received prophylactic intravenous or oral treat-

TABLE 1
CHARACTERISTICS OF CASES VERSUS CONTROLS IN HOSPITALIZED HEMATOLOGY–ONCOLOGY PATIENTS

Characteristic	Cases (N = 13) No.	(%)	Controls (N = 39) No.	(%)	*P*
Gender					
Male	10	(77)	25	(64)	.50
Female	3	(23)	14	(36)	.73
Diabetes mellitus	2	(15)	6	(15)	1.00
Hematologic malignancy					
Acute leukemia	9	(69)	21	(54)	.51
Lymphoma	1	(7.7)	11	(28)	.25
Other	1	(7.7)	12	(31)	.14
Solid tumors	4	(30.7)	4	(10.2)	.09
Bone marrow transplantation					
Allogeneic	5	(38)	11	(28)	.50
Autologous	1	(7.7)	9	(23)	.42
Chemotherapy	10	(77)	30	(77)	1.00
Antibacterial prophylaxis					
Quinolone	3	(23)	5	(13)	.66
Trimethoprim–sulfamethoxazole	1	(7.7)	5	(13)	1.00
Therapeutic antimicrobials					
Extended-spectrum penicillin	4	(30.7)	4	(10.2)	.09
Fourth-generation cephalosporin	11	(85)	26	(67)	.30
Imipenem	7	(53.8)	11	(28)	.10
Central venous catheter	8	(61.5)	24	(61.5)	1.00
Neutropenia	11	(85)	29	(74.3)	.70
Mortality	4	(30.7)	5	(13)	.20

ment with acyclovir at a dosage of 30 mg/kg starting 2 days before to 30 days after transplantation. Recombinant human granulocyte colony-stimulating factor was given to all patients after transplantation to accelerate the kinetics of neutrophil recovery. In our Stem Cell Transplant and Leukemic Center, a fourth-generation cephalosporin was used for empirical treatment of febrile neutropenia, and antifungal therapy (azoles and polyenes) was employed in the presence of clinical evidence of fungal infection or fever persisting after 5 days of antibiotic therapy. In addition, metronidazole was started empirically for most patients who developed diarrhea.

Microbiological Characterization

All clinical isolates were identified to the species level using VITEK-GNI Cards (bioMérieux VITEK, Hazelwood, MO). If the probability of *S. maltophilia* was less than 85% by VITEK-GNI Cards, the organism was confirmed by the API 20 NE system (bioMérieux VITEK). *S. maltophilia* recovered from case-patients were genotyped by pulsed-field gel electrophoresis with the use of DNA digested with *Spe*I and *Xba*I and separated by means of a CHEF Mapper XA apparatus (Biorad, Hercules, CA). Because all organisms tested by pulsed-field gel electrophoresis were found to be distinctly different and all case-patients were admitted to different rooms, no environmental samples were taken.

TABLE 2
UNIVARIATE ANALYSIS OF RISK FACTORS FOR *STENOTROPHOMONAS MALTOPHILIA* BLOODSTREAM INFECTION IN HOSPITALIZED HEMATOLOGY–ONCOLOGY PATIENTS

Dichotomous Variable	OR	CI_{95}	*P**
Severe mucositis	4.52	1.18 to 17.2	.03
Diarrhea†	4.52	1.18 to 17.2	.03
Metronidazole use	8.71	2.16 to 35.75	.002
Graft versus host disease	1	0.09 to 10.54	1.00
Mucositis	0.64	0.05 to 7.80	1.00
Neutropenia	1.89	0.35 to 10.06	.70

OR = odds ratio; CI_{95} = 95% confidence interval.
*Analyzed by chi-square test.
†Diarrhea within 72 hours prior to bacteremia.

Statistical Methods

Data were collected by an infectious disease fellow and an infection control specialist. SPSS software (version 10.0; SPSS, Inc., Chicago, IL) was used to analyze the data. Proportions were compared using the chi-square or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann–Whitney test. All *P* values were two-tailed; a *P* value of .05 or less was considered statistically significant.

RESULTS

Descriptive Epidemiology

From June 1, 1999, to April 30, 2001, 13 hematology–oncology patients with *S. maltophilia* bacteremia met the case-patient definition. During this period, the incidence of *S. maltophilia* bacteremia on the transplantation unit was 94 per 10,000 admissions or 76 per 1,000 hospital-days compared with 7 per 10,000 admissions or 6 per 1,000 hospital-days during the previous 23 months ($P = .001$) (Fig. 1). Diarrhea developed in 8 case-patients within 72 hours prior to the development of bacteremia (5 [71%] in primary bloodstream infection, 2 [29%] in secondary bloodstream infection). The demographic and medical characteristics of case-patients and control-patients are detailed in Table 1. For case-patients, the median duration from central venous catheter insertion to the development of bacteremia was 60 days (range, 11 to 325 days). The median

TABLE 3
UNIVARIATE ANALYSIS OF RISK FACTORS FOR *STENOTROPHOMONAS MALTOPHILIA* BLOODSTREAM INFECTION IN HOSPITALIZED HEMATOLOGY–ONCOLOGY PATIENTS

Continuous Variable	Median Case-Patient (Interquartile Range)		Median Control-Patient (Interquartile Range)		*P**
Length of hospital stay, d	34	(19.0 to 55.5)	22	(14.5 to 34.7)	.01
Duration of mucositis, d	29	(15.7 to 49.7)	15	(10.5 to 21.0)	.03
No. of antibiotics used	9	(6.0 to 10.5)	5	(4.0 to 7.0)	< .001
Duration of neutropenia, d	20	(8.0 to 36.0)	12	(7.0 to 15.5)	.09
Duration of antibiotics, d	17	(13.5 to 38.5)	22	(13.0 to 32.0)	.97

*Analyzed by Mann–Whitney test.

duration from admission to the development of mucositis was 2 days (range, 0 to 31 days) and the median duration from admission to the development of *S. maltophilia* bacteremia was 14 days (range, 1 to 50 days). Nine patients died (4 of 13 case-patients vs 5 of 39 control-patients). The crude mortality rate was 30.7% for case-patients and 12.8% for control-patients ($P = .20$; 95% confidence interval [CI_{95}], 0.52 to 17.31).

Univariate Analysis (Tables 2 and 3)

There were no statistically significant differences between case- and control-patients regarding demographic characteristics and underlying diseases (Table 1). When compared with control-patients concurrently hospitalized on the transplantation unit, case-patients were significantly more likely to have severe mucositis (7 [53.8%] of 13 vs 8 [20.5%] of 39; odds ratio [OR], 4.52; $P = .034$; CI_{95}, 1.18 to 17.24), to have diarrhea (7 [53.8%] of 13 vs 8 [20%] of 39; OR, 4.52; $P = .034$; CI_{95}, 1.18 to 17.24), and to have been given metronidazole (9 [69.2%] of 13 vs 8 [20.5%] of 39; OR, 8.719; $P = .002$; CI_{95}, 2.16 to 35.75). We evaluated the correlation between diarrhea and *S. maltophilia* bacteremia in subgroups of case-patients (primary vs secondary bloodstream infection). Between these two subgroups, a significant correlation between diarrhea and *S. maltophilia* was observed only in patients with primary bloodstream infection (5 [71.4%] of 7 vs 8 [20.5%] of 39; OR, 9.68; $P = .014$; CI_{95}, 1.57 to 59.47).

We evaluated metronidazole use with neutropenia, mucositis, severe mucositis, diarrhea, *Clostridium difficile*–associated diarrhea, and vancomycin-resistant *Enterococcus* (VRE) colonization. Of all risk factors evaluated, the use of metronidazole was significantly associated with diarrhea (diarrhea with metronidazole use vs diarrhea without metronidazole use: 10 [58.8%] of 17 vs 4 [11.4%] of 35; OR, 11.07; $P = .001$; CI_{95}, 2.67 to 45.81) and *Clostridium difficile*–associated diarrhea (with metronidazole use vs without metronidazole use: 6 [35.2%] of 17 vs 2 [5.7%] of 35; OR, 9.00; $P = .011$; CI_{95}, 1.58 to 51.26). There were no differences among case- and control-patients regarding other anti-anaerobic medications (clindamycin, extended-spectrum penicillin, and imipenem).

Case-patients were also more likely to have a prolonged hospital stay (median, 34 vs 22 days; $P = .017$) and duration of mucositis (median, 29 vs 15 days; $P = .032$), and to have been treated with a greater number of antibiotics (median, 9 vs 5; $P < .001$) (Mann–Whitney test). There were no significant differences between case- and control-patients regarding the other characteristics and risk factors examined, including previous (from 6 months prior) and recent history and type of transplantation, chemotherapeutic regimen, graft versus host disease, neutropenia, human leukocyte antigen matching, receipt of prophylactic or therapeutic antimicrobials, catheter insertion, duration of catheter insertion, and mucositis. There were no significant differences between case- and control-patients in subgroups of patients who underwent transplantation (allogeneic and autologous) regarding demographic characteristics and risk factors examined. The actual cause of the increase in *S. maltophilia* bacteremia was not discovered.

Microbiology

For all case-patients, *S. maltophilia* was initially isolated from blood cultures (range, one to five sets of positive blood cultures per case-patient) and was associated with clinical infection. Six (46%) of 13 case-patients had *S. maltophilia* presenting as secondary infection (3 [23%] respiratory tract and 3 [23%] wound). Seven case-patients (54%) developed primary *S. maltophilia* bacteremia after receiving cytotoxic chemotherapy and were neutropenic on the day of the positive culture. The patient who had only one positive blood culture developed *S. maltophilia* bacteremia secondary to *S. maltophilia* pneumonia.

Polymicrobial bacteremia was identified in 3 of 13 case-patients. The source of *S. maltophilia* bacteremia in these patients was pneumonia (1 patient; 33.3%), wound (1 patient; 33.3%), or primary bloodstream infection (1 patient; 33.3%). Most of these organisms were enteric microorganisms. Organisms isolated from case-patients with polymicrobial bacteremias were *Escherichia coli* (1), *Klebsiella pneumoniae* (1), *Lactobacillus* species (1), *Alcaligenes xylosoxidans* (1), *Enterococcus faecalis* (1), and coagulase-negative *Staphylococcus* species (1).

All patients were treated with intravenous antibiotics;

5 (71%) of 7 case-patients with primary bloodstream infection also had their catheters removed at the discretion of attending physicians to prevent possible complications. There was no recurrent infection in any of the 7 patients. Pulsed-field gel electrophoresis was performed on 9 case isolates from blood and all were distinctly different (Fig. 2). No case-patients had been admitted to a room that had been occupied by another case-patient, and as a result, no environmental cultures were performed.

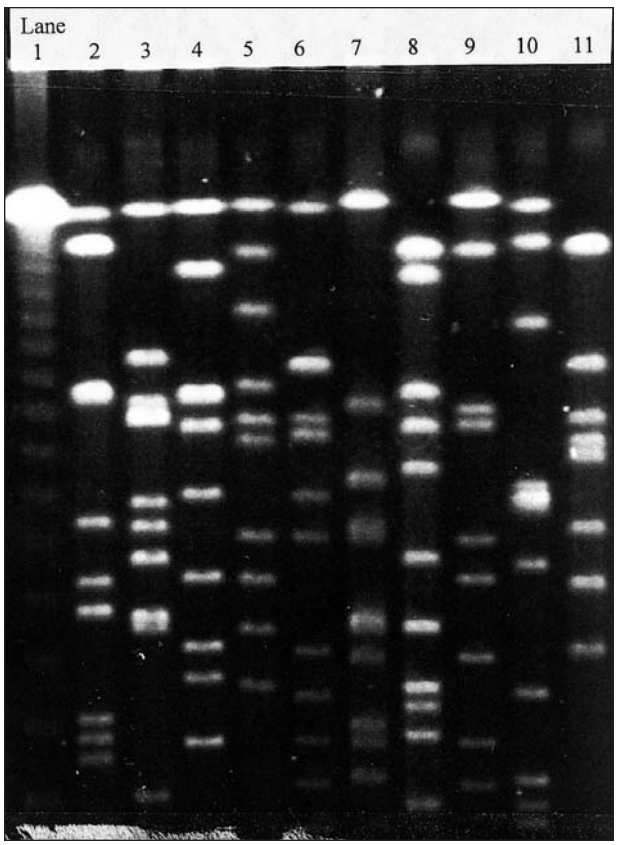

FIGURE 2. Pulsed-field gel electrophoresis banding patterns of DNA segments (digested with *Spe*I) from *Stenotrophomonas maltophilia* isolates that were recovered from our hematology–oncology patients on the stem cell transplant unit at Barnes–Jewish Hospital (St. Louis). All nine case isolates were distinctly different. Lane 1 = molecular standard; lane 2 = *S. maltophilia* quality control strain; and lanes 3 to 11 = the *S. maltophilia* isolate from patients 1 to 9.

DISCUSSION

In our investigation, severe mucositis, diarrhea, and the use of metronidazole were significant risk factors for *S. maltophilia* bacteremia. Subgroup analysis of case-patients revealed a significant correlation between diarrhea and *S. maltophilia* bacteremia only in patients with primary bloodstream infection (5 [71.4%] of 7 vs 8 [20.5%] of 39; $P = .014$). In addition, case-patients were more likely to have prolonged duration of mucositis and hospitalization, and to have received more antibiotics. Recognized risk factors for *S. maltophilia* bacteremia in oncology patients have included severe and prolonged neutropenia, intravascular devices, prolonged hospital stay, aggressive chemotherapy treatment, and increased antibiotic pressure.[2,6-8,23,24] Severe mucositis was recently identified as a significant risk factor for *S. maltophilia* bacteremia in the investigation of an outbreak among patients receiving bone marrow transplants.[8] Our study confirmed the association of severe mucositis with *S. maltophilia* bacteremia in oncology patients. Because all risk factors were evaluated from the time of admission until the occurrence of *S. maltophilia* bacteremia for case-patients and during the entire hospital stay for control-patients, any potential bias that occurred would strengthen our findings.

Sources of *S. maltophilia* bacteremia have included central venous or arterial catheters, wounds, skin and soft tissue, and respiratory, urinary, and gastrointestinal tracts.[1,6] Central venous catheters are the most frequently implicated as the source of *S. maltophilia* bloodstream infection.[19] It has also been suggested that *S. maltophilia* can be found colonizing the gastrointestinal tract in oncology patients.[23] In our study, the significance of severe mucositis, prolonged duration of mucositis, and diarrhea (within a 72-hour period prior to bacteremia) suggested that severe and prolonged gastrointestinal mucosal breakdown may aid in the development of *S. maltophilia* bacteremia in oncology patients, if they are previously colonized.[8,23]

The use of metronidazole and the increased number of antibiotics used were significant factors associated with *Stenotrophomonas* bloodstream infection in our investigation. Although not statistically significant, case-patients were more likely to have received imipenem (7 [53.8%] of 13 vs 11 [28.2%] of 39; $P = .10$) and extended-spectrum penicillins (4 [31%] of 13 vs 4 [10.3%] of 39; $P = .09$). The antibiotic preferences of different faculty and prolonged length of hospital stay in case-patients increase the possibility of receiving more antibiotics. Because metronidazole was used empirically for most patients who developed diarrhea, the correlation between metronidazole use and *Clostridium difficile*–associated diarrhea or other diarrhea was not surprising.

Outbreaks of *S. maltophilia* have been identified with nosocomial cross-transmission from patient to patient and from the hospital environment and equipment, including aerosol nebulizers, tracheal suction catheters, faucet aerators, and respirator circuits.[6,15,21,25-27] In our study, the heterogeneity of the *S. maltophilia* strain types documented by pulsed-field gel electrophoresis of nine isolates suggested that the organisms came from multiple sources.

Our study has several limitations. *S. maltophilia* is not a common occurrence and the small sample size of our study limits our capability of performing multivariate analysis. In addition, the large confidence intervals of the odds ratios prevent true quantification of the degree of risk posed by diarrhea in subgroups of patients who developed primary bloodstream infection. The lack of prospective stool cultures and pulsed-field gel electrophoresis to assess the source of *Stenotrophomonas* bacteremia in primary infection make it difficult to ascertain the true relationship

between gastrointestinal colonization and the development of *S. maltophilia* bacteremia. Although diarrhea, severe mucositis, and metronidazole use were associated with *S. maltophilia* bacteremia in our study, we were not able to identify the actual cause of the *S. maltophilia* bacteremia.

Our investigation confirmed the relevance of severe mucositis, antibiotic pressure, and prolonged hospital stay as risk factors for *S. maltophilia* bacteremia. Given the significance of diarrhea in our study, gastrointestinal tract colonization should be evaluated as a potential source of *S. maltophilia* bacteremia. Interventions to ameliorate the severity of mucositis and attempts to decrease antibiotic pressure, prevent diarrhea, and promote meticulous central venous catheter care may help prevent *Stenotrophomonas* bloodstream infection in oncology patients. Further studies to determine the prevalence of gastrointestinal carriage, environmental reservoirs, and the correlation between gastrointestinal carriage and *Stenotrophomonas* bloodstream infection are warranted to help devise infection control strategies for high-risk patients.

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