Survival in neutropenic patients with severe sepsis or septic shock*

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Objective: **To determine whether the survival gains achieved in critically ill cancer patients in recent years exist in the subset with neutropenia and severe sepsis or septic shock.**

Design: **Retrospective 11-yr study (1998–2008).**

Setting: **Medical intensive care unit in a teaching hospital.**

Patients: **Four hundred twenty-eight intensive care unit patients with cancer, neutropenia, and severe sepsis or septic shock. The primary outcome was hospital mortality.**

Results: **The main underlying diseases were acute leukemia (35.7%), lymphoma (31.7%), and solid tumors (16.5%). Two hundred thirty-seven (55.5%) patients had microbiologically documented infections, 141 (32.9%) clinically documented infections, and 50 (11.9%) fever of unknown origin. Acute noninfectious conditions were diagnosed in 175 of 428 (41%) patients, including 26 of 50 (52%) patients with fever of unknown origin, 66 of 141 (47%) patients with clinically documented infections, and 83 of 237 (35%) patients with microbiologically documented infections. Early indwelling catheter removal was performed routinely in the 107 (25%) patients without clinical evidence of a septic focus at intensive care unit admission. Early beta-lactam plus aminoglycoside therapy was used in 391 (91.3%) patients. Hospital mortality was 49.8%. Hospital mortality decreased from 58.7% (108 of 184) in 1998–2003 to 43% in 2004–2008 (105 of 244, $p = .006$). Multivariate analysis identified nine independent predictors of hospital mortality, of which six were associated with higher mortality (older age; need for vasopressors; neurologic, respiratory, or hepatic dysfunction; and acute noninfectious condition) and three with lower mortality (intensive care unit admission after 2003, combination antibiotic therapy including an aminoglycoside, and early indwelling catheter removal).**

Conclusion: **In neutropenic patients with severe sepsis or septic shock, survival improved over time. Aminoglycoside use and early catheter removal in patients with undocumented sepsis may improve survival. Acute noninfectious conditions are associated with increased mortality, underlining the need for thorough and repeated clinical assessments. (Crit Care Med 2012; 40: 43–49)**

Key Words: diagnosis; management; neutropenia; outcomes; sepsis; shock

Until the last 15 yrs, critically ill cancer patients were considered poor candidates for intensive care unit (ICU) admission given their high short- and long-term mortality rates (1). Thus, 1-yr survival was only 10% in allogeneic bone marrow transplant recipients with critical illnesses (2) and in cancer patients with multiple organ dysfunctions. Furthermore, neutropenia in cancer patients was associated with higher mortality in several studies (3–5), a finding that has made intensivists reluctant to admit neutropenic patients. However, recent advances in the management of many malignancies have improved survival in cancer patients (6, 7). Increased survival has been reported (8, 9) in cancer patients selected for ICU admission based on performance status (9) or availability of lifespan-extending treatment (10). In ICU patients, improved understanding of organ dysfunction (7, 11, 12) and the development of early noninvasive diagnostic and therapeutic strategies (13, 14) have improved survival. However, whether these survival gains exist in the subset of critically ill cancer patients with neutropenia remains unknown.

Neutropenic patients are at risk for bacterial infection and subsequent severe sepsis or septic shock (15). However, very few studies evaluated outcomes of cancer patients with sepsis (16, 17), and none of them focused on neutropenic cancer patients with severe sepsis or septic shock.

We performed a large cohort study, including all neutropenic cancer patients with severe sepsis or septic shock admitted to our ICU over an 11-yr study period. Our primary objective was to determine whether hospital mortality in these patients diminished over time. We also looked for factors associated with hospital mortality, with the goal of identifying areas for improvement.

PATIENTS AND METHODS

All neutropenic cancer patients admitted to the medical ICU of the Saint Louis Teaching Hospital (Paris, France) between January 1998 and December 2008 and meeting criteria for severe sepsis or septic shock were included retrospectively. Some patients admitted between 1998 and 2000 were reported in previous studies (16, 34). The Saint Louis Teaching Hospital is a 650-bed university hospital with 330 hematology and oncology beds. Our Institutional Review Board approved the study. Informed consent was waived in accordance to French law regarding retrospective research.

Data Collection

Data reported in Tables 1 and 2 were abstracted from the medical charts. Performance

*See also p. 305.

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Table 1. Patient characteristics at intensive care unit admission

Patient Characteristics	Period 1998–2003 (n = 184)	Period 2004–2008 (n = 244)
Age (years)	52 [41–60]	51 [40–62]
Gender (male)	108 (59)	146 (60)
Performance status		
Ambulatory	2 (1.1)	3 (1.2)
Minor assistance	10 (5.4)	14 (5.7)
Major assistance	155 (84.2)	212 (86.8)
Bedridden	14 (7.6)	13 (5.3)
Comorbidities		
Chronic obstructive pulmonary disease	6 (3.3)	9 (3.7)
End-stage renal disease	5 (2.7)	4 (1.6)
Solid organ transplantation	5 (2.7)	2 (0.8)
Chronic heart failure	1 (0.5)	1 (0.4)
Immune system disease	7 (3.8)	11 (4.5)
Characteristics of the malignancy		
Acute leukemia	69 (37.5)	86 (35.2)
Acute myeloid leukemia	55 (29.9)	64 (26.2)
Acute lymphoid leukemia	14 (7.6)	22 (9.0)
Lymphoma	54 (29.3)	88 (36.0)
Solid tumor	29 (15.7)	41 (16.8)
Multiple myeloma	22 (11.9)	18 (7.4)
Idiopathic aplasia	4 (2.2)	5 (2.0)
Miscellaneous	6 (3.3)	7 (2.9)
Allogeneic stem cell transplantation	15 (8.1)	25 (10.2)
Autologous stem cell transplantation	22 (11.9)	23 (9.4)
Time from neutropenia to admission (days)	6 [2–10]	5 [2–10]
Duration of neutropenia (days)	9 [6–14]	13 [9–16]
Neutropenia recovery during intensive care unit stay	56 (30.4)	79 (32.4)
Severity scores		
Sequential Organ Failure Assessment score	10 [8–12]	9 [7–12]
Simplified Acute Physiology Score II	59 [47–84]	53 [42–70]

Neutropenia was defined as a neutrophil count of <500 cells/mm^3, or a count of <1000 cells/mm^3 within 24 hrs after intensive care unit admission. Results expressed in n (%) or median (25th–75th).

Table 2. Clinically and microbiologically documented sites of infections in 428 patients, including 237 patients with microbiologically documented infections, and 141 patients with clinically documented infections (%)

Site of Infection	141 Patients With Clinically Documented Infections, n (%)	237 Patients With Microbiologically Documented Infections, n (%)		
		Bacteria (198 Patients)	Fungi (47 Patients)	Virus (23 Patients)
Pneumonia	99 (70.2)	71 (29.9)	36 (15.2)	9 (3.8)
Abdomen	27 (19.1)	24 (10.1)	1 (0.4)	4 (1.7)
Skin and soft tissue infection	6 (4.3)	14 (5.9)	—	1 (0.4)
Catheter-related infection	4 (2.8)	31 (13.1)	—	—
Central nervous system	2 (1.4)	2 (0.8)	—	1 (0.4)
Pyelonephritis-prostatitis	2 (1.4)	13 (5.5)	—	—
Surgical site infection	1 (0.7)	—	—	—
Bloodstream infection	NA	43 (18.1)	11 (4.6)	8 (3.4)

NA, not applicable; —, no case.

status (18) was collected over the 3 months before ICU admission. Neutropenia was defined as a neutrophil count <500 cells/mm^3 or <1000 cells/mm^3 within 24 hrs after ICU admission (19). Cancer status at ICU admission was categorized as follows: complete remission, partial remission, stable, relapsing, or unknown. Reasons for ICU admission were categorized as acute respiratory failure, shock, coma, acute kidney injury, or other. Simplified Acute Physiology Score II and Sequential Organ Failure Assessment (SOFA) scores were computed on day 1 (20, 21). Organ failure was defined as a SOFA score of 3 or more for any system. Severe sepsis and septic shock were defined according to international criteria (22). Patients were included if they had suspected or proven infection.

Our admission policies preclude ICU admission for bedridden and severely disabled patients (7, 10). Life-sustaining treatments were used based on the clinical evaluation and recent recommendations (23). All patients underwent a comprehensive clinical assessment at ICU admission. Radiographs and microbiological tests were performed as indicated by the clinical presentation.

Antibiotics were administered as early as possible after ICU admission, according to international recommendations (19, 24). A beta-lactam was used routinely, and in patients with risk factors for *Pseudomonas aeruginosa*, a beta-lactam active on this organism was selected (19). An aminoglycoside was given in patients with hemodynamic instability or shock. Vancomycin was used according to international recommendations (19).

In our ICU, early removal of indwelling catheters is performed routinely in patients with severe sepsis or septic shock and either a clinical suspicion of catheter infection (local signs of infection and/or positive bloodstream culture with no obvious source), or no focus on infection detected within 4 hrs after ICU admission (25). Infections were classified in three groups as follows: microbiologically documented infection, defined as fever with positive microbiological tests from a focus on infection and/or blood culture (26); clinically documented infection, defined as fever with a focal infection (e.g., pneumonia or skin/soft tissue inflammation) that was not accessible to sampling or was sampled with negative microbiological results; and fever of unknown origin, defined as fever >38.3°C, or >38.0°C over at least 1 hr or twice within 12 hrs, with no detectable cause.

Patients were evaluated routinely at ICU admission and during the first 3 ICU days for acute noninfectious conditions that might be related to observed organ dysfunctions (Table 2). The investigations performed to identify acute noninfectious conditions were selected by the intensivists based on the clinical presentation.

Statistical Analysis

Quantitative parameters are reported as median and interquartile range (25th−75th percentile), and qualitative parameters as number and percentage. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann-Whitney *U* test. To investigate whether recent advances in management influenced outcomes, we divided the cohort into two groups according to year of admission, 1998–2003 (first period) and 2004–2008 (second period), with two near-sized groups over two near-long periods. This choice was furthermore driven by the trend of decrease mortality over years with a decrease of mortality rate after 2003.

Hospital mortality was our primary outcome; vital status at hospital discharge was known for all study patients. We also recorded 6-month and 12-month mortality rates.

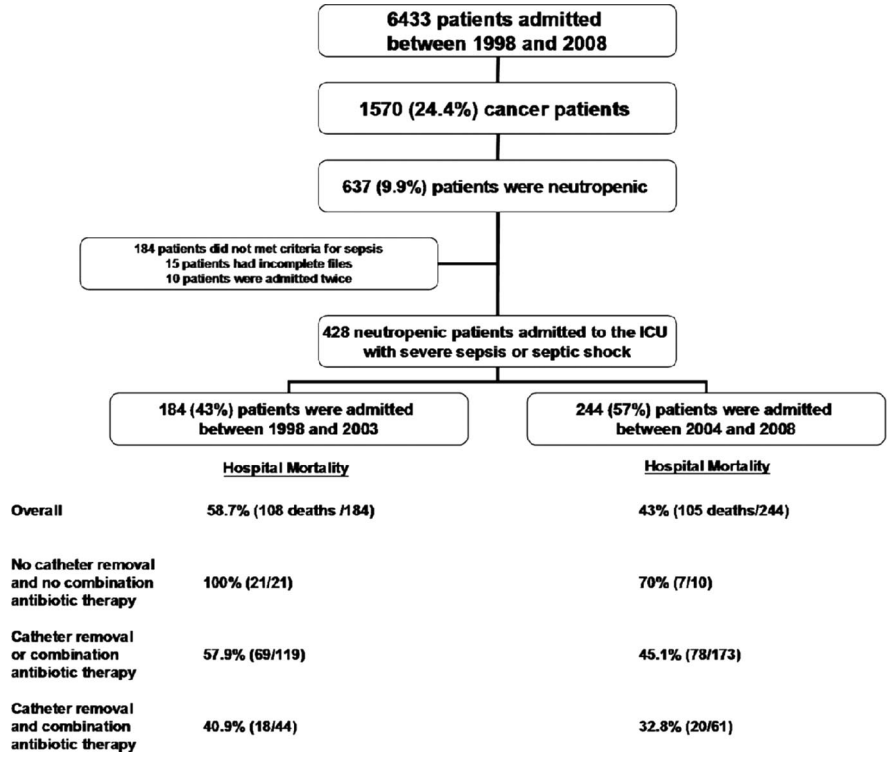

Figure 1. Flow chart of patients admitted to our medical intensive care unit (*ICU*) between 1998 and 2008.

To identify patient characteristics associated with hospital mortality, we used a logistic regression model. Multivariate analysis was performed using stepwise forward selection to introduce variables whose p values were smaller than .10 by univariate analysis. Then, the absence of a significant increase in the likelihood value after omission of each of the remaining variables was checked. Variables were tested for colinearity and interactions before inclusion in the multivariate model. Goodness of fit was evaluated by the Hosmer-Lemeshow statistic. Odds ratios and their 95% confidence intervals were computed. p values $<.05$ were considered statistically significant. Analyses were done using the SAS 9.1 software package (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

As reported in Figure 1, 6,433 patients were admitted to the ICU over the study period, including 1,458 cancer patients, of whom 637 (43.7%) were neutropenic. Among these 637 patients, 428 had severe sepsis or septic shock, which formed the basis for this study.

Table 1 reports the main patient characteristics at ICU admission. Of the 428 patients, 358 (83.6%) had hematologic malignancies and 70 (16.4%) solid tumors. The malignancy was progressive or relapsing in 109 (25.6%) patients. Patients were admitted to the ICU 6 days (2–10) after neutropenia onset. Among the 40 allogeneic bone marrow transplant recipients, 19 (47%) presented with graft-vs.-host disease, but none had a graft compromise or cancer recurrence. At ICU admission, 175 patients (41%) had severe sepsis and 253 (59%) septic shock. SOFA score was 10 (7–12) at admission. Organ failures, based on the SOFA score, were cardiovascular in 248 (58%) patients, respiratory in 104 (24%) patients, neurologic in 44 (10%) patients, renal in 30 (7%) patients, and hepatic in 27 (6%) patients. The most common sepsis-related reason for ICU admission was acute respiratory failure (n = 168, 39%). Over the first 48 hrs after ICU admission, vasopressors were needed in 292 (68.7%) patients, for a total of 3 days (2–5); mechanical ventilation in 232 (54%) patients, for a total duration of 5 (2–11) days; and renal replacement therapy in 76 (17.8%) patients. Overall, 271 (69.1%) patients received packed red blood cells. Only one patient received donor granulocyte transfusion. At ICU admission, 107 (25%) patients underwent indwelling catheter removal and 391 (91%) patients received early antibiotic therapy combining a beta-lactam and an aminoglycoside.

Of the 428 patients, 237 (55.5%) had microbiologically documented infections, 141 (32.9%) clinically documented infections, and 50 (11.9%) fever of unknown origin (Table 2). Bacteria were identified in 198 (83.5%) patients, fungi in 47 (19.8%), viruses in 23 (9.7%), and parasites in one (0.4%, Table 3). Bacterial, fungal, or viral polymicrobial infections were found in 33 (13.9%) patients.

Early acute noninfectious conditions were diagnosed in 175 (175 of 428, 41%) patients, including 25 (25 of 428, 5.8%) who had more than one acute noninfectious condition (Table 4). Acute noninfectious conditions were less common among patients with microbiologically documented infections (n = 83 of 237, 35%) than among patients with clinically documented infections (n = 66 of 141, 47%) or fever of unknown origin (n = 26 of 50, 52%).

Hospital mortality was 49.8% (n = 213). Neutropenia recovery occurred during the ICU stay in 105 (31.5%) patients, and median neutropenia duration was 11 days (8–16). ICU mortality was 40.1% (n = 175), 6-month mortality 59.5% (n = 254), and 12-month mortality 63.3% (n = 270). Duration of neutropenia did not affect outcomes.

Over the 11-yr study period, we found no significant changes in the number of neutropenic patients admitted to the ICU per year, or in the median SOFA score at ICU admission each year. Hospital mortality decreased significantly from the earlier to the later part of the study period, from 58.7% (n = 108 of 184) in the first period to 43% in the second period (n = 105 of 244, $p = .001$) (Fig. 2). Compared to the group admitted in the second period, the group admitted in the first period had higher proportions of patients with Gram-positive sepsis (27 of 184, 15% vs. 22 of 244, 9%, $p = .03$) and acute heart failure (15 of 184, 8% vs. 12 of 244, 5%, $p = .03$), and a smaller proportion of patients given combination antibiotic therapy (159 of 184, 86% vs. 232 of 244, 95%, $p = .004$). Smaller proportions of patients admitted in the second period received red blood cell packs (115 of 184, 62% vs. 156 of 244, 64%, $p = .03$) or a diagnosis of ICU-acquired infection (25 of 184, 14% vs. 17 of 244; 7%, $p = .02$). We found no significant differences between the two periods in the proportions of patients with indwelling catheter removal (45 of 184, 24% vs. 62 of 244, 25%) or early acute noninfectious conditions (66 of 184, 36% vs. 109 of 244, 44%). More patients needed vasopressor infusion on the day of admission during the first

Table 3. Microbiological documentation

Bacteria, n (%)	215 (100)
Gram-negative Bacteria, n (%)	158 (73)
Escherichia coli	65 (30)
Pseudomonas aeruginosa	53 (25)
Enterobacter cloacae	8 (4)
Klebsiella spp.	12 (6)
Stenotrophomonas maltophilia	8 (4)
Others	12 (6)
Gram-positive Bacteria, n (%)	54 (25)
Streptococcus spp.	11 (5)
Enterococcus spp.	9 (4)
Streptococcus pneumoniae	6 (3)
Staphylococcus aureus	16 (7)
Coagulase-negative Staphylococcus	7 (2)
Others	5 (2)
Mycobacterium tuberculosis	3 (1)
Fungi, n (%)	48 (100)
Aspergillus spp.	27 (56)
Candida spp.	11 (23)
Pneumocystis jiroveci	7 (15)
Cryptococcus neoformans	1 (2)
Fusarium	1 (2)
Zygomycete	1 (2)
Virus, n (%)	23 (100)
Cytomegalovirus	8 (35)
Herpes virus	7 (30)
Parainfluenzae	3 (13)
Respiratory syncitial virus	2 (9)
Influenzae	1 (4)
Metapneumovirus	1 (4)
Enterovirus	1 (4)

Sum of bacteria isolated exceeds 198 patients because of polymicrobial sepsis. One patient had concomitant aspergillosis and pneumocystis pneumonia holding 48 Fungi in 47 patients.

Table 4. Early acute noninfectious conditions associated with sepsis in 175 (41%) of the 428 neutropenic patients

Noninfectious Conditions	Number (%) of Patients (Out of 428)	N (%) Diagnosis Made at Admission	N (%) Diagnosis Made From Days 1 to 3
Cardiovascular disorders, n (%)	46 (10.7)	43 (93.5)	3 (6.5)
Acute pulmonary embolism	11	11	0
Acute heart failure	27	25	2
Anthracycline-related heart failure	20	20	0
Acute coronary syndrome	3	2	1
Deep venous thrombosis	5	5	0
Neurologic disorders, n (%)	17 (4)	7 (41)	10 (59)
Ischemic stroke	6	2	4
Hemorrhagic stroke	8	2	6
Subarachnoid hemorrhage	2	2	0
Cerebral edema	1	1	0
Hemorrhage, n (%)	53 (12.4)	38 (71.7)	15 (28.3)
Hemorrhagic shock	22	17	5
Gastrointestinal bleeding	19	14	5
Rupture of the spleen	1	1	0
Pancreatitis	1	1	0
Severe nosebleed	1	1	0
Diffuse alveolar hemorrhage	31	21	10
Tumor-related disorders, n (%)	39 (9.1)	25 (64.1)	14 (35.9)
Macrophage activation syndrome	31	18	13
Infiltration by the malignancy	8	7	1
Treatment-related disorders, n (%)	41 (9.6)	27 (65.8)	14 (34.1)
Severe graft-versus-host disease	14	7	7
Drug-related disorders	27 (13.4)	20 (74)	7 (36)
Anaphylaxis	4	4	0
Drug-related neurologic symptoms	5	5	0
Cytarabine (Ara-C) Syndrome	7	6	1
All-transretinoic acid syndrome	1	1	0
Bleomycin-induced pulmonary fibrosis	2	1	1
Toxic epidermal necrolysis	6	1	5
Chemotherapy overdose	2	2	0
Transfusion-related acute lung injury	2 (0.4)	2 (100)	0
Any noninfectious condition[a]	175 (41)	124 (70.8)	51 (29.2)

[a]In 25 (5.8%) patients there was more than one diagnosed acute noninfectious condition.

period (66% vs. 54%, $p = .001$), and patients had higher plasma creatinine at admission during the first period (124 μmol/L vs. 98 μmol/L, $p < .0001$). Patients developed less ICU-acquired infections during the second period (13.7% during the first period vs. 7.0% during the second period, $p = .005$). Characteristics of the underlying malignancy (i.e., type of malignancy, disease status, and bone marrow transplant status) were well balanced between the two study periods and were not predictors of hospital mortality.

Multivariate analysis (Table 5) identified nine independent predictors of hospital mortality. Six were associated with increased mortality: older age; need for vasopressors; neurologic, respiratory, or hepatic dysfunction; and at least one acute noninfectious condition. Three factors were associated with reduced mortality: ICU admission during the second period, aminoglycoside in the initial antibiotic combination, and early indwelling catheter removal. Granulocyte colony-stimulating factor administration was not associated with hospital mortality by multivariate analysis.

DISCUSSION

This is the first large cohort study of neutropenic cancer patients admitted to the ICU with severe sepsis or septic shock. Survival increased over the 1998–2008 study period. An unexpected finding was a high rate of early, life-threatening, acute, noninfectious conditions. Among nine factors independently associated with mortality in the multivariate analysis, two hold potential for improving survival, namely, giving an aminoglycoside in the initial antibiotic combination and routinely removing indwelling catheters early on in patients with no other detectable focus on infection.

ICU admission of cancer patients was considered futile in the 1990s, when studies showed very low survival rates in cancer patients requiring life-sustaining therapies (27). Since then, survival has increased in critically ill cancer patients overall (16, 18, 28), myeloma patients (29), cancer patients receiving mechanical ventilation after autologous bone marrow transplantation (11), and cancer patients with sepsis (16, 17). The impact of neutropenia on survival has been a matter of debate, since some studies found unacceptably high mortality rates (4, 30, 31), whereas others found no evidence that neutropenia independently affected mortality in cancer patients in the ICU (32–34). In the study reported here, mortality was 57% during the earlier period and 43% during the more recent period. This 43% mortality rate is not very different from mortality rates reported recently in non-neutropenic, noncancer patients with severe sepsis of similar severity (35). Several factors might explain this finding. First, management of various malignancies has improved over recent years. However, the higher survival observed early after ICU admission (i.e., over the first week) rather argues for improvement of care of acute illness. Second, we did not find any statistical differences in SOFA scores at admission across the study period,

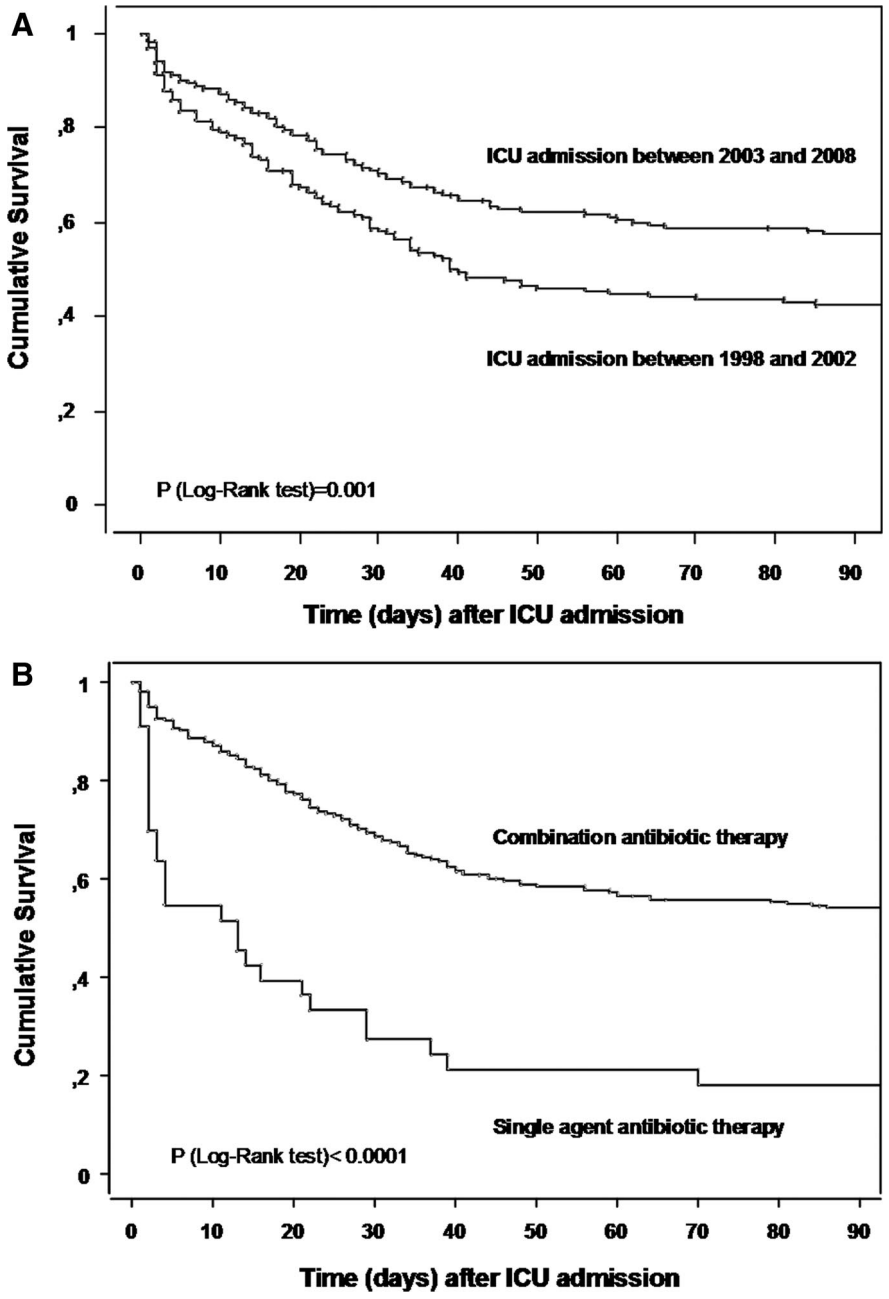

Figure 2. Kaplan-Meier estimates of in-hospital mortality in neutropenic cancer patients with severe sepsis or septic shock according to (*A*) the period of admission (1998–2003 or 2004–2008) and (*B*) combination antibiotics administration. *ICU*, intensive care unit.

arguing against differences in the severity of acute illness during the second period. Finally, neutropenic patients have probably benefited from recent advances in the management of septic shock over the last decade (i.e., early goal-directed therapy, hydrocortisone replacement therapy, and lung-protective ventilation) (23).

Cancer and neutropenia are associated with an increased risk not only of infections (36), but also of various acute, noninfectious conditions consisting in malignant or toxic organ involvement (37). Examples include infiltration by malignant cells (38), tumor lysis syndrome (39), and hemophagocytic lymphohistiocytosis (40). Cancer-associated endothelial damage and inflammation activation promote arterial and venous thrombosis, which in turn affect the prognosis (41). Diffuse alveolar hemorrhage (42) and stroke (43) are common in patients with thrombocytopenia. Thus, a four- to six-fold increase in the risk of pulmonary embolism has been reported in cancer patients, as well as a greater extent of the vascular occlusion at presentation. Finally, chemotherapeutic agents induce potentially life-threatening side effects. Anthracyclines may cause heart damage through oxidative injury, with heart failure ranging in severity from subclinical to severe. Our study provides the first data on the prognostic impact of early acute noninfectious conditions in neutropenic cancer patients with sepsis. Our finding that having one or more early acute noninfectious conditions was associated with increased mortality raises several issues. First, we cannot determine whether these patients had both sepsis and the associated noninfectious condition at ICU admission or whether the associated noninfectious condition mimicked sepsis. Second, the association between noninfectious conditions and mortality indicates that every effort must be made in neutropenic cancer patients with sepsis to diagnose and treat noninfectious conditions early on. Whether acute noninfectious conditions impact survival in non-ICU neutropenic cancer patients is of interest. Pulmonary embolism or drug-related toxicities are easily overlooked (44). Increased efforts to prevent, and to achieve the early diagnosis of, venous thromboembolism and pulmonary embolism may decrease in-hospital mortality (41). Other interventions that might decrease mortality include: more aggressive platelet transfusion to decrease the incidence of bleeding, including alveolar hemorrhage (45); strategies to minimize the toxicity of chemotherapy (46); and early appropriate management of hemophagocytic lymphohistiocytosis. In our study, the incidences of alveolar hemorrhage and acute heart failure declined over the study period, suggesting improvements in management.

Our findings emphasize the crucial impact of early appropriate antibiotic therapy on patient survival. Our policy in patients with severe sepsis or septic shock is to add an aminoglycoside, rather than a quinolone, to a beta-lactam (47). *In vitro* synergism has been demonstrated between aminoglycosides and beta-lactams, and the combination extends the antimicrobial spectrum. Although the results of recent meta-analyses have challenged the need for combination antibiotic therapy, the included trials focused neither on patients with severe sepsis or septic shock nor on immunocompromised patients (48). Furthermore, evidence is accumulating that inappropriate initial antibiotic therapy negatively affects survival in patients with severe sepsis or septic shock. Renal toxicity can be prevented via close therapeu-

Table 5. Multivariate analysis of factors associated with in-hospital mortality

Variable, N (%) or Median (25th–75th)	Alive (n = 215)	Dead (n = 213)	Odds Ratio (95% Confidence Interval)	p
Age, yrs	47 (35–57)	54 (43–65)	1.036 (1.02–1.05)	<.0001
Intensive care unit admission during the second period (between 2004 and 2008)	139 (64.6)	105 (49.3)	0.56 (0.36–0.89)	.01
Shock	123 (57.2)	181 (85.0)	2.69 (1.65–4.38)	<.0001
Acute respiratory failure	61 (28.4)	171 (80.3)	1.98 (1.14–3.44)	.015
Neurologic failure	7 (3.2)	37 (17.4)	4.03 (1.03–15.8)	.04
Hepatic failure	7 (3.2)	20 (9.4)	1.49 (1.16–1.91)	.002
Early acute noninfectious conditions	77 (35.8)	98 (46.0)	1.69 (1.06–2.68)	.02
Initial combination antibiotic therapy	210 (97.7)	181 (85.0)	0.164 (0.05–0.51)	.002
Indwelling catheter removal	68 (31.6)	39 (18.3)	0.50 (0.30–0.85)	.01

Goodness of fit (Hosmer-Lemeshow) chi-square p value = .64. Area under the receiver operating characteristic curve = .74.

tic drug monitoring (49). Finally, Kumar et al (50) recently reported improved outcome in septic shock patients receiving a combination antibiotic therapy. Furthermore, in the present study, patients who received aminoglycosides did not present with increased serum creatinine, need for renal replacement therapy, or duration of dialysis compared to patients not receiving aminoglycosides. A potential benefit of quinolone-based antibiotic combinations could not be addressed in our study but warrants evaluation in critically ill neutropenic patients (51).

Early indwelling catheter removal was another factor associated with survival in our study. Recent international guidelines recommend catheter removal in patients with catheter-related bloodstream infection associated with severe sepsis (25). However, waiting for bloodstream infection documentation before removing the catheter may delay the treatment of the cause of sepsis, with potentially negative effects on survival, most notably in immunocompromised patients. Therefore, we routinely remove indwelling catheters in neutropenic patients with proven catheter-related bloodstream infection, local focus on infection, or severe sepsis or septic shock without any detectable focus on infection. The nonrandomized design of this study does not allow us to draw any definite conclusion regarding the role of indwelling catheter removal in neutropenic patients with sepsis. However, it is likely that in cancer patients with severe sepsis or septic shock but no obvious source of infection, early catheter removal is associated with increased survival. A strategy that recommends delaying catheter removal only when infection is documented (either on blood or catheter culture) seems to delay optimal sepsis management, with potentially negative effects on survival in cancer patients with neutropenia. This statement may, however, not hold true in all scenarios, i.e., in non-neutropenic patients or no sign of severe sepsis (52).

Our study has several limitations. We used a retrospective design over 11 yrs. This design was suitable for our primary objective, which was to look for secular trends in the outcome of cancer patients with neutropenia and severe sepsis or septic shock. Second, catheter removal and combination antibiotic therapy were neither controlled nor randomized. Therefore, no definite conclusions can be drawn from our data about the impact of these interventions on survival. Third, our ICU has considerable experience with critically ill cancer patients. However, we identified targets for improvements that are relevant to all ICUs. Fourth, acute noninfectious conditions were more frequently documented in patients with unexplained fever, raising concerns on the reality of infection in these patients. However, Heffner et al (53) recently reported that 18% of the patients treated with severe sepsis had a noninfectious diagnosis that mimicked sepsis, and the clinical characteristics of these patients were similar to those of patients with culture-positive sepsis. Future studies using sensitive tools to diagnose bacterial infections should appraise the prevalence of unexplained fever during neutropenia, pointing out the reality of infection in this subset of patients. Last, the diagnosis of early acute noninfectious conditions may have been biased by the initial clinical presentation and natural history of the underlying disease. Furthermore, whether early diagnosis and treatment of these associated conditions improves survival remains to be determined.

In summary, in a large cohort of neutropenic cancer patients with severe sepsis and septic shock, survival increased over time. Combination antibiotic therapy with an aminoglycoside and early catheter removal may improve survival in this population. Acute noninfectious conditions are associated with increased mortality, indicating a need for a comprehensive clinical assessment to identify and treat these conditions.

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