Nosocomial Sepsis Associated with Interleukin-2

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Study Objective: To determine the incidence, clinical magnitude, and risk factors for nosocomial bacteremia in patients given interleukin-2 with or without (±) lymphokine activated killer (LAK) cells for cancer immunotherapy.

Design: Cohort study.

Setting: Clinical study unit of tertiary medical center.

Patients: All patients entering the interleukin-2 ± LAK cancer immunotherapy protocol during a 28-month period. Control groups were patients in a surgical intensive care unit, patients receiving total parenteral nutrition, and patients with solid tumors.

Measurements and Main Results: Twenty of 107 (19%) interleukin-2-treated patients developed sepsis; in 12 of these patients, sepsis was intravenous catheter-associated. The bacteremia rate among patients receiving total parenteral nutrition, in the surgical intensive care unit, or having solid tumors was 2.8%, 4.1%, and 1.9%, respectively. *Staphylococcus aureus* was the pathogen in 13 courses; *Staphylococcus epidermidis,* in 5; and *Escherichia coli,* in 2. Two patients died; three developed suppurative thrombophlebitis; one developed septic arthritis; one, septic arterial aneurysm; and one, peritonitis with probable meningitis. Colonization with *S. aureus* increased the risk of *S. aureus* bacteremia 6.3-fold (95% CI, 2.8 to 14.5; $P < 0.001$); skin desquamation at the catheter site increased the relative risk 2.0-fold (95% CI, 1.3 to 3.1; $P = 0.031$). Both colonization with *S. aureus* and skin desquamation increased the relative risk of *S. aureus* bacteremia 14.5-fold (95% CI, 4.1 to 50.9; $P < 0.0001$).

Conclusions: Staphylococcal bacteremia is more frequent in patients receiving interleukin-2 therapy and is associated with substantial morbidity and toxic skin reactions.

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Clinical trials (1, 2) using recombinant human interleukin-2 with or without autologous lymphokine activated killer (LAK) cells have been promising, especially in patients with melanoma or renal cell carcinoma. Several well-recognized acute toxicities are associated with interleukin therapy, including diffuse erythroderma, hyperbilirubinemia, myocardial infarction, anemia, hypothyroidism, thrombocytopenia, and a capillary leak syndrome that results in hypotension, edema, and renal insufficiency (3-9). Although bacteremia and infectious complications have been seen, the frequency and risk factors for these complications have not been generally appreciated.

Bacteremia has been reported in approximately 10% of patients in two series from Rosenberg's group (1, 10). An increased risk of bacterial infection was noted in patients with the acquired immune deficiency syndrome who received interleukin-2 therapy, when these patients were compared with similar patients receiving recombinant interferon treatment (11). However, these patients were treated with peripherally administered interleukin-2, and their underlying disease may not make them directly comparable to solid tumor patients. These studies showed that granulocytopenia was not associated with the development of bacterial infection.

In our institution, the bacteremia rate among interleukin-2-treated patients in the protocol sponsored by the National Cancer Institute is fivefold higher than the rate in our patients in intensive care or in our patients receiving total parenteral nutrition (12, 13). Furthermore, the morbidity associated with nosocomial bacteremia in the interleukin-2-treated patients was significant and led to major septic complications, including two deaths from sepsis.

We have done an epidemiologic study of risk factors for nosocomial bacteremia in patients with solid tumors receiving high-dose interleukin-2 therapy. We tried to assess factors associated with interleukin-2-associated sepsis and to provide a way to control this serious complication.

Patients and Methods

Patients with various advanced malignancies were treated at the New England Medical Center with high-dose interleukin-2 with or without LAK cells as part of the Extramural Interleukin-2/LAK Working Group studies sponsored by the National Cancer Institute. All treatment protocols were designed by the National Cancer Institute and approved by the Food and Drug Administration and the Human Investigation Review Committee at the New England Medical Center. Written, informed consent was obtained from each pa-

tient. All patients were hospitalized in the clinical study unit of the New England Medical Center.

Patients were treated with interleukin-2 according to six schedules. All protocols included an initial or priming phase of interleukin-2 administration that lasted from 3 to 5 days, followed by a hiatus of 6 to 10 days, during which the majority of patients were able to be discharged from the hospital. Finally, a second phase of interleukin-2 administration lasted 5 to 7 days. Patients on LAK-cell-containing regimens had four or five leukapheresis procedures during the hiatus period and received autologous LAK cell infusions during the second phase of interleukin-2 administration.

Thirty-one patients (34 treatment courses) were treated according to one of two schedules that involved bolus intravenous interleukin-2 and autologous LAK cell administration in a manner essentially identical to that described by Rosenberg and colleagues (1, 2, 10). Twenty-one patients (24 treatment courses) were treated according to one of two regimens that differed only in the length of the hiatus period. These regimens involved bolus intravenous injections of interleukin-2 alone (without LAK cells) in a manner otherwise essentially identical to that in the aforementioned protocols. Twenty patients (24 treatment courses) were treated according to a modified regimen that involved 3 days (instead of 5) of interleukin-2 administration before leukapheresis and a continuous infusion of interleukin-2 (1 μg/kg body weight per hour) for 7 days during the period of LAK cell administration. Twenty-one patients (25 treatment courses) were treated according to a second modified regimen that involved continuous infusion interleukin-2 administration (1 to 1.5 mg/m · d) before leukapheresis (days 1 to 5) and during the period of LAK cell administration.

Patients were followed for putative risk factors for infection, including age, sex, underlying tumor, dose of interleukin-2, use of leukapheresis, duration of therapy, type and duration of intravenous catheters or intraarterial catheters, use of antibiotics, evidence of erythroderma or skin desquamation, medications, and reasons for discontinuation from the protocol.

Culture Methods

When lines and dressings were changed, a culture sample from the skin cannula vascular interface site was taken using a premoistened Stuart culturette (Marion Laboratories, Kansas City, Missouri) according to our previously published protocol (12). When intravenous catheters were removed, all proximal vascular segments from intravenous catheters were cultured using the semiquantitative technique that Maki developed and that we and others (12-16) confirmed. Blood samples for culture were generally drawn by peripheral venipuncture. Occasionally, blood for culture was drawn through the indwelling catheter.

All culture samples were incubated aerobically at 35 °C for 72 hours. Bacteria were identified by the use of standard techniques: Coagulase-negative staphylococci were identified as *Staphylococcus epidermidis* by the automicrobic system (Vitek Systems, Hazelwood, Missouri). A subset of patients had isolates of *Staphylococcus aureus* phage typed in the Kundsen Laboratory to determine if there was strain relatedness. A subset of patients was also followed prospectively by culturing axilla, groin, and nares weekly for the presence of *S. aureus*.

Definitions

A patient was defined as having primary bacteremia related to interleukin-2 therapy if clinical, microbiologic, or necropsy data showed no other source for the bacteremia. A patient was defined as having secondary bacteremia related to the cannula if the cannula culture grew 15 or more bacterial colonies (12-14) of an isolate identical to the blood isolate. Bacteremia was defined as one or more positive blood culture(s) from specimens obtained by peripheral venipuncture. For possible skin contaminants, such as *S. epidermidis*, two or more positive blood cultures were required. The increase in hospitalization among bacteremic patients was determined by calculating the additional time necessary for treatment of infection.

Skin toxicity was defined using protocol definitions of the National Cancer Institute Extramural Interleukin-2/LAK Working Group (7). Briefly, the definitions were as follows: grade 1, erythema; grade 2, dry desquamation, vesiculation, pruritus; grade 3, moist desquamation, ulceration; grade 4, exfoliative dermatitis, necrosis requiring surgical intervention. Patients with skin desquamation as noted below were represented in grades 2 through 4.

Catheter Maintenance

Double lumen Arrow catheters (Arrow International, Inc., Reading, Pennsylvania) were used for intravenous access in all patients. Catheters were inserted by surgical residents into the patients' subclavian vein immediately before interleukin-2 treatment. Mask and sterile gloves were used for all dressing changes, and dressings were changed every other day by specially trained nursing personnel. Povidone iodine ointment was applied to the insertion site at the time of each dressing change. Tegaderm (3M, St. Paul, Minnesota) was placed over sterile gauze on all dressings to cover the insertion site. Skin assessments were made at each nursing shift.

In September 1987, the policy of leaving the central line in place for the duration of interleukin-2 therapy was modified; thereafter, central line catheters were generally removed after the first phase of interleukin-2 treatment, and a new catheter was inserted, often on the opposite side, just before the second phase of treatment. Occasionally, a vascular catheter was inserted over a guidewire at the same site for use during the leukapheresis period before removal.

Infection Control Measures

In September 1987, infection control measures were implemented, in addition to those already in place for intravenous catheter care at our institution. Routine intravenous catheter changes were made after 1 week of interleukin-2 therapy. In addition, blood taken for any protocol studies had to be drawn from peripheral intravenous sites during the third week of the interleukin-2 protocol. (Because of difficult venous access, the intravenous catheters had been frequently violated to obtain blood for studies.) Only four nurses were allowed to change dressings. The attack rate for either documented catheter-associated or primary bacteremia before September 1987 was 11 of 58 courses (19%). This rate was similar to that from September 1987 to August 1988 (7 of 49, 14%); therefore, for purposes of analysis, all patients were combined.

Statistical Analysis

Data analysis was done using EPISTAT software (Epistat Services, Richardson, Texas). Categorical variables were analyzed using the Fisher exact test or the chi-square test where appropriate. All P values are expressed as two tail. For continuous variables, the Student t-test was employed. Attack rates for interleukin-2-associated bacteremia were calculated by treatment schedule, use of continuous or bolus infusion therapy, use of leukapheresis and LAK cells, and by surgeon inserting intravenous catheters. Ninety-five percent confidence intervals (CI) were used.

Results

From 4 April 1986 to 1 August 1988, there were 20 cases of bacteremia among 107 (19%) courses of interleukin-2 therapy in 93 patients. *Staphylococcus au-*

Table 1. *Correlation of Organism Causing Bacteremia, Catheter Cultures, and Skin Site Colonization in Interleukin-2-Treated Patients with Bacteremia*

Patient Number	Blood Isolate	Quantitative Catheter Culture*		Skin Culture
		Organism	CFU	
1	*Escherichia coli*	*E. coli*	500-1000	NG
2	*Staphylococcus epidermidis*	*S. epidermidis*	100-500	*S. epidermidis*
3	*S. epidermidis*	*S. epidermidis*	ND	*S. epidermidis*
4	*Staphylococcus aureus*	*S. aureus*	> 1000	*S. epidermidis*
5	*S. aureus*	*S. aureus*	> 1000	*S. epidermidis*
6	*S. aureus*	*S. aureus*	> 1000	*S. aureus*
7	*S. aureus*†	*S. aureus*	> 1000	*S. epidermidis*
8	*S. aureus*	*S. aureus*	> 1000	*S. aureus*
9	*S. aureus*	*S. aureus*	15	*S. epidermidis*
10	*S. aureus*	ND	NA	NG
11	*S. epidermidis*	NG	NA	NG
12	*S. aureus*	*S. aureus*	> 1000	*S. aureus*
13	*S. aureus*	NG	NA	*S. aureus*
14	*S. aureus*‡	ND	NA	*S. aureus*
15	*S. aureus*	*S. aureus*	> 1000	*S. aureus*
16	*S. epidermidis*	ND	NA	*S. epidermidis*
17	*S. aureus*§	*S. aureus*	> 1000	*S. aureus*
18	*S. aureus*	*S. aureus*	> 1000	*S. aureus*
19	*S. epidermidis*	NG	NA	NG
20	*E. coli*‖	NG	NA	NG

* CFU = colony forming units, NG = no growth, ND = not done, NA = not applicable.
† Patient 7 had concomitant group B streptococcus isolated from blood.
‡ Patient 14 had preceding *S. aureus* pneumonia.
§ Patient 17 had eight blood cultures with *S. aureus*, one of which also included group G streptococcus.
‖ Patient 20 had *E. coli* peritonitis and bacteremia from colonic perforation.

reus was the commonest pathogen; it was isolated from 13 (65%) of the patients with bacteremia (Table 1). *Staphylococcus epidermidis* bacteremia occurred five times, and *E. coli* bacteremia occurred twice; two of the infections with *S. aureus* were polymicrobial, with streptococci found as additional isolates. Two control groups were followed concurrently to provide an institutional assessment of risk for bacteremia during long-term intravascular therapy (patients receiving total parenteral nutrition) and during severe illness (patients in the surgical intensive care unit). The patients on total parenteral nutrition received therapy for a mean of 15 days. The nosocomial bacteremia rates in these two sets of patients were 2.8% and 4.1%, respectively. An additional retrospective control group consisted of patients with solid tumors who were matched for age (within 5 years) and sex. Two nosocomial bacteremias occurred in 107 (1.9%) patient courses.

Catheter and Skin Pathogen Correlation

Twelve (55%) of the 20 episodes of bacteremia were documented as catheter related using quantitative catheter cultures. Two cases of bacteremia clearly were not catheter related; one of these was associated with preceding pneumonia, and the other, with intestinal perforation. The other six cases of primary bacteremia were not documented as catheter related, although two of the cases had isolates of the same organism from the skin-catheter interface before bacteremia (Table 1).

Timing of Cases

The relation of entrance into the protocol and onset of bacteremia is illustrated in Figure 1. The mean day of onset of bacteremia was 12.7 days after entrance into the protocol, and 65% of the cases occurred during the second phase of interleukin-2 administration. Further analysis of cases by duration of the intravenous catheter placement showed that there were two apparent clusters, one at day 7 and one at day 16. However, the separation of these two groups may be artificial, because many cases clustered at day 7 of catheter duration were associated with the use of the "prophylactic" catheter change after the first course of interleukin-2. Only 3 of the 20 nosocomial bacteremias occurred in patients who had a catheter threaded over a guidewire.

Risk Factor Analysis

Comparison of bacteremic and nonbacteremic patients for risk factors showed no difference between the two groups in age, type of underlying tumor, total interleukin-2 dosage, duration of intravenous catheter, leukapheresis and use of LAK cells, type of interleukin-2 infusion, and the mean number of days in the protocol (Table 2). In addition, there was no significant difference between the two groups in attack rate by individual protocol or the surgeon inserting catheter (data not shown).

However, patients with *S. aureus* colonization at the skin-vascular interface were more likely to have nosocomial bacteremia (relative risk = 3.8; 95% CI, 1.6 to

9.3; $P = 0.007$) (Table 3). Patients with bacteremia were more likely to have significant catheter colonization than those who did not develop bacteremia ($P < 0.001$, Table 3). *Staphylococcus aureus* was not isolated from any catheter not associated with bacteremia, whereas *S. epidermidis* was the only pathogen isolated in significant numbers from catheters of patients without bacteremia. An association of skin desquamation (skin toxicity grade 2 or higher) and the development of bacteremia (relative risk = 1.7; 95% CI, 1.1 to 2.8; $P = 0.044$) was also evident.

Analysis of *Staphylococcus aureus* Bacteremia

If the *S. aureus* bacteremia episodes are analyzed separately, the association of *S. aureus* bacteremia with colonization of the skin by *S. aureus* or the development of skin desquamation becomes more pronounced (Table 4). In patients with *S. aureus* skin colonization, the relative risk of *S. aureus* bacteremia was 6.3 (95% CI, 2.8 to 14.5; $P = 0.0003$). Patients with skin desquamation had a twofold increase in the risk of developing *S. aureus* bacteremia (95% CI, 1.3 to 3.1; $P = 0.031$). In patients with *S. aureus* colonization and skin desquamation, the relative risk of *S. aureus* bacteremia was increased almost 15-fold (95% CI, 4.1 to 50.9; $P < 0.0001$). In patients with *S. aureus* bacteremia in whom colonization of the skin-vascular interface with *S. aureus* preceded the onset, the median time of colonization to onset of bacteremia was 2 days (range, 1 to 4 days).

Outcome

The *S. aureus* and *E. coli* bacteremias tended to have very serious consequences. Of the patients with these bacteremias, two patients died from sepsis; three developed septic thrombophlebitis; one developed probable septic arthritis; one, septic arterial aneurysm at an arterial line site; and one, staphylococcal peritonitis with probable meningitis (or a parameningeal focus). The *S. aureus* bacteremias were "high grade." Among the 13 patients with *S. aureus* bacteremia, an average of 4 blood cultures (range, 1 to 8 cultures) were positive; the mean duration of bacteremia was 2.5 days (range, 1 to 6 days) in these patients. The average increase in the length of hospitalization was 12.3 days (range, 0 to 37 days). Furthermore, patients who survived the episode of bacteremia required a mean of 17.9 days of intravenous antibiotic therapy for cure.

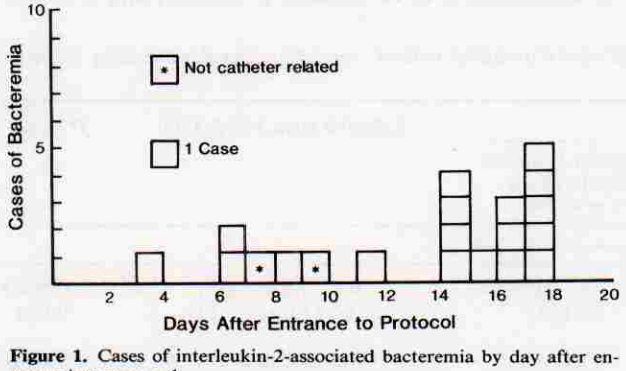

Figure 1. Cases of interleukin-2-associated bacteremia by day after entrance into protocol.

Table 2. *Comparison of Bacteremic and Nonbacteremic Courses of Interleukin-2 Therapy for Potential Risk Factors*

Risk Factors	Courses	
	Bacteremic, $n = 20$	Nonbacteremic, $n = 87$
Age, *mean years ± 1 SD*	46.6 ± 12.1	47.1 ± 12.2
Male, female	16, 4	51, 36
Underlying tumor, *n(%)*		
Melanoma	11 (55)	51 (59)
Renal cell carcinoma	5 (25)	25 (29)
Lymphoma	3 (15)	3 (3)
Solid tumor	1 (5)	8 (9)
Total interleukin-2 dose, *mean mg ± 1 SD*	43.1 ± 18.3	37.9 ± 20.2
Duration of intravenous catheter, *mean days ± 1 SD*	10.1 ± 5.1	10.5 ± 4.5
LAK therapy, *n(%)*	13 (65)	63 (73)
Type of interleukin-2 infusions, *n(%)*		
Bolus	11 (55)	46 (53)
Continuous	4 (20)	23 (27)
Both	5 (25)	18 (21)
Days in protocol, *mean days ± 1 SD*	12.7 ± 4.5	15.5 ± 3.2

Prospective Cultures

In November 1987, prospective weekly surveillance cultures of nares, axilla, and groin were done in addition to routine skin culture surveillance. Only 6 of 29 patients (21%) had *S. aureus* colonization of the nose; one patient developed *S. aureus* bacteremia. Phage typing of *S. aureus* isolates showed no strain common to any of the patients.

Discussion

Although infection has been reported as a complication of interleukin-2 therapy, the incidence, clinical magnitude, source of the bacteremia, and risk factors are not well documented (1, 2, 10). The bacteremia has been thought to be catheter associated, but catheter cultures, quantitative or otherwise, have rarely been done and are generally inconclusive.

In our prospective evaluation, we have shown that nosocomial bacteremia is a common complication of interleukin-2 therapy. In our institution, patients treated with interleukin-2 have a bacteremia rate of almost 20%. This rate is fivefold higher than the nosocomial bacteremia rate in patients in our surgical intensive care unit or in our prospectively followed patients who are receiving total parenteral nutrition (12, 13). Rates of nosocomial bacteremia in the other Extramural Interleukin-2/LAK Working Group hospitals have ranged from 20% to 38% (Klempner MS, Atkins, MA. Personal communication).

The clinical outcome of patients with interleukin-2-associated bacteremia was severe. Two patients died from sepsis, and 6 of the remaining 12 patients with

Table 3. *Association of Skin Colonization, Catheter Colonization, and Skin Desquamation with Bacteremia in Interleukin-2-Treated Patients*

Risk Factor	Patients		Relative Risk (95% CI)	*P* Value
	Bacteremic, $n = 20$	Non-bacteremic, $n = 87$		
	← *n (%)* →			
Skin colonization with *Staphylococcus aureus*	7 (35)	8 (9)	3.8 (1.6 to 9.3)	0.007
Catheter colonization ($\geq$ 15 CFU)*	13 (65)	20 (23)	2.8 (1.7 to 4.7)	< 0.001
S. aureus	10 (77)	0 (0)		
Staphylococcus epidermidis	2 (15)	20 (100)		
Escherichia coli	1 (8)	0 (0)		
Skin desquamation (toxicity $\geq$ grade 2)	12 (60)	30 (34)	1.7 (1.1 to 2.8)	0.044

* CFU = colony forming units.

S. aureus bacteremia had significant infections, such as septic thrombophlebitis or a distant focal infection. All 6 of these patients required prolonged hospitalization or treatment with intravenous antibiotic therapy, or both. The only bacteremias that had few complications were those due to *S. epidermidis.*

We have shown a very strong association of *S. aureus* bacteremia with preceding *S. aureus* skin colonization at the catheter site along with the development of interleukin-2-associated skin toxicity (desquamation of the skin) around the catheter insertion site. The timing of the onset of bacteremia is notable, because most patients developed bacteremia in the third week of therapy, when skin toxicity related to interleukin-2 therapy is maximal. The skin toxicity of interleukin-2 therapy and associated bacteremias might be analogous to skin toxicity in burn patients. Although there are differences in infecting flora among burn patients, namely gram negatives and candida, some differences between burn patients and interleukin-2-treated patients might be accounted for by the topical antimicrobials used in burn patients (17).

We found no association between bacteremia and the age of the patient, type of tumor, dosage or type of infusion therapy, or use of LAK cells. In most patients, sepsis occurred toward the end of interleukin-2 therapy; *S. aureus* was the pathogen most commonly associated with nosocomial bacteremia. A sampling of patients showed a *S. aureus* carrier rate of 21%. Although no concurrent hospitalized control group was surveyed for *S. aureus* carriage, the rate documented in interleukin-2-treated patients is not greater than that in other hospital-based studies (18).

The line care of these patients included the use of a transparent dressing that has been associated with increased rates of cutaneous bacterial colonization at the insertion site (19). In our institution, we use gauze under transparent dressings on all central lines, including lines for total parenteral nutrition. Using both gauze and a transparent dressing, we have not seen an increased rate of skin colonization in the interleukin-2-treated patients when compared with our patients receiving parenteral nutrition.

Other contributing factors may account for the frequency and severity of nosocomial bacteremia, especially *S. aureus* bacteremia, seen in these patients. Klempner and colleagues (20) have shown a markedly depressed neutrophil chemotactic response during interleukin-2 and interleukin-2 plus LAK therapy. This defect was evident during interleukin-2 therapy and persisted for several weeks after treatment. Other measures of polymorphonuclear leukocyte function, such as superoxide production, lysozyme secretion, and random migration, were minimally or not affected (20). These observations may account for the apparent severity of infection and, to some extent, clustering at the end of interleukin-2 treatment courses in these patients.

Despite very meticulous attention to line maintenance, including prophylactic line changes and restrictions of line use for blood drawing, patients continue to develop nosocomial sepsis. Skin toxicity may be a key element in the pathogenesis of catheter-associated sepsis in these patients. Other measures for prevention are clearly warranted. Prophylactic antibiotics, specialized catheters that may reduce nosocomial bacteremia (21), measures that may decrease the skin toxicity associated with interleukin-2 therapy, and frequent

Table 4. *Risk of Bacteremia with Staphylococcus aureus for Patients Colonized with S. aureus or Developing Skin Desquamation*

Risk Factor	Patients		Relative Risk (95% CI)	*P* Value
	With *S. aureus* Bacteremia, $n = 13$	Without *S. aureus* Bacteremia, $n = 94$		
	← *n (%)* →			
Colonization with *S. aureus*	7 (54)	8 (9)	6.3 (2.8 to 14.5)	0.0003
Skin desquamation	9 (69)	33 (35)	2.0 (1.3 to 3.1)	0.031
Both colonization with *S. aureus* and desquamation	6 (46)	3 (3)	14.5 (4.1 to 50.9)	<0.0001

catheter changes of central lines may need to be evaluated as preventive measures.

The findings in these patients may be generalizable to new therapies using biologic response modifying therapy, because skin toxicity is thought to be due to cytokines released by interleukin-2. Nosocomial staphylococcal bacteremia may be a significant limiting factor for such new approaches.

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