Clinical Infections and Bloodstream Isolates Associated with Fever in Patients Undergoing Chemotherapy for Acute Myeloid Leukemia

T.A. Madani

Summary

Background: Patients with acute myeloid leukemia (AML) are at high risk for infections.The aim of this study was to identify the sources of fever and the type of pathogens that cause bloodstream infection in patients with AML undergoing cytotoxic chemotherapy and antibiotic prophylaxis.

Patients and Methods: The source of fever and the type of pathogens causing bloodstream infection were identified for 129 febrile episodes experienced by 42 patients with AML receiving cytotoxic chemotherapy and antibiotic prophylaxis.

Results: A source of fever was identified in 81% of all febrile episodes. Mucositis (21.7%), pneumonia (13.2%), central venous catheter infection (12.4%), neutropenic enterocolitis (9.3%) and invasive fungal disease (9.3%) were the most common sources of fever. Of 16 central venous catheter infections, seven (43.8%) were not associated with local signs. 49 febrile episodes (37.9%) were associated with bloodstream infections, of which 14 (28.6%) were polymicrobic and seven (14.3%) had an undefined source of infection. Bloodstream infection was commonly associated with cellulitis (60%), mucositis (57.1%), central venous catheter infection (55.6%), neutropenic enterocolitis (41.7%) and invasive fungal disease (41.7%). Gram-positive microorganisms were the most common blood isolates (75.8%). Gram-negative bacteremic infections occurred in eight episodes (12.1%) experienced by patients who were not receiving ciprofloxacin prophylaxes at the time of bacteremia. Noninfectious sources of fever accounted for 23 (17.8%) of the 129 febrile episodes.

Conclusion: Although the spectrum of pathogens that cause infection in this group of patients has shifted from gram-negative to gram-positive bacteria, the most common sources of infection remain the same as previously described and they mainly involve integumental surfaces.

Key Words

Fever · Infections · Bacteremia · Neutropenia · Leukemia

Infection 2000; 28: 367-373

Introduction

Patients with acute myeloid leukemia (AML), particularly those undergoing chemotherapy, are at high risk for infections. The source of fever in this population of patients is often not clinically evident . Therefore, antimicrobial therapy directed mainly against gram-negative bacilli is usually started empirically. Prophylactic oral antibiotics for gut decontamination to prevent infections have also been used extensively in most cancer centers. Despite early and aggressive empiric antimicrobial therapy and use of prophylactic antibiotics, infections remain a major cause of morbidity and mortality in this group of patients. Furthermore, the spectrum of pathogens that cause infections in neutropenic patients has changed dramatically over the past decade. Gram-positive microorganisms have become the most common pathogens, whereas gram-negative bacilli are less frequently isolated [1–9]. However, information about the sources of fever in this population of patients after this recent change in the spectrum of bacterial pathogens is limited. The objective of this retrospective study was to identify the sources of fever and the type of pathogens that cause bloodstream infection in patients with AML receiving cytotoxic chemotherapy and antibiotic prophylaxis.

Patients and Methods

42 consecutive patients underwent induction, consolidation, salvage or pre-bone marrow transplant conditioning chemotherapy for AML at the Health Sciences Center, Winnipeg, Canada, between January 1992 and December 1994. Mitoxantrone and etoposide or idarubicin, etoposide, and carboplatinum were used as induction chemotherapy regimens. High-dose cytosine arabinoside was used for consolidation chemotherapy. Busulfan, cyclophosphamide and intrathecal cytosine arabinoside were used for pre-bone marrow transplant conditioning chemotherapy.

Fever was defined as an oral temperature of more than 38 °C on at least three occasions during a 12-h period or a single raised temperature of more than 39 °C with chills. The 42 patients expe-

T.A. Madani
Dept. of Medicine, King Abdulaziz University Hospital, P.O. Box: 80215, Jeddah 21589, Saudi Arabia; Phone: (+966/2) 640-1000, Fax: -3975, e-mail: tmadani@saudidoctors.org.sa

Received: December 5, 1999 • Revision accepted: August 8, 2000

rienced 129 febrile episodes during which blood and other appropriate specimens for culture were obtained. A blood culture set consisted of 20 ml of blood obtained by peripheral venipuncture inoculated as two 10 ml aliquots into one Isolator tube (Isostat®; Wampole Laboratories, Cranbury, New Jersey, USA) and one anaerobic BacT/Alert bottle (Organon Teknika Inc., Scarborough, Ontario, Canada) as well as 10 ml blood samples obtained from each lumen of the double or triple lumen central venous catheter inoculated into aerobic BacT/Alert bottles. Thus, one blood culture set would consist of 40–50 ml of blood. After collection, all samples were transported to the microbiology laboratory. Samples received between 8:00 and 23:00 h were immediately processed, whereas those received after 23:00 h were incubated at 35 °C and then processed at 8:00 h the next morning. The Isolator tubes were processed as directed by the manufacturer. Briefly, the Isolator tube was centrifuged and the supernatant was discarded. The sediment from the Isolator tube was inoculated onto five agar plates: chocolate blood agar incubated at 35 °C in 5% carbon dioxide for 5 days with daily inspection, blood agar with vitamin K incubated anaerobically at 35 °C for 5 days with inspection every other day, and three fungal media (inhibitory mold agar, brain heart infusion blood agar and Sabhi medium) incubated at 30 °C for 6 weeks with inspection daily for the first 2 weeks and then twice weekly for the remaining 4 weeks.

The vented aerobic and the unvented anaerobic BacT/Alert bottles were incubated in the BacT/Alert cabinet for 5 days. A positive result was signaled immediately upon detection by the instrument. Aliquots obtained from the positive bottles were Gram stained and subcultured onto sheep blood agar incubated at 35 °C, chocolate blood agar incubated at 35 °C in 5% carbon dioxide, and blood agar with vitamin K incubated anaerobically at 35 °C. Aliquots from the negative bottles of the same set were also Gram stained and subcultured onto similar media if the Gram stain showed microorganisms, otherwise the bottles were reincubated for the remainder of the 5 days and then discarded.

Data pertaining to all negative and positive BacT/Alert and Isolator blood culture sets were retrieved from the BacT/Alert computer data base and from patients' charts. A chart review of all patients was performed with standardized data collection. Information collected included patients' demographics, number of febrile episodes, neutrophil count, source of fever and clinical significance of blood isolates.

The source of fever was determined on the basis of findings on history and physical examination, recovery of a microorganism from a locally infected site, and, when applicable, radiographic imaging features and/or histopathology and culture results of biopsies obtained from suspected sites of infection. Additionally, the opinions of the infectious diseases consultants and the hematology/oncology attending physicians who were following the patients were taken into account for determining the source of fever. Central venous catheter infection without local signs was diagnosed based on isolation of the same microorganism from blood culture specimens obtained from the catheter lumens and from a peripheral venipuncture in the absence of any infected site, confirmed by recovery of the organism from culture of the tip of the removed central venous catheter.

Bloodstream infection was defined as isolation from blood of one (monomicrobial) or more (polymicrobial) clinically significant organisms during a febrile episode. A number of parameters were used in the assessment of clinical significance of isolated microorganisms. These included the presence of fever, chills or shock; the presence or absence of a likely source of infection; the number of positive bottles per blood culture set; the number of sites or blood culture sets from which the same microorganism was isolated during the same febrile episode; the type and number of isolates; the time to detection of microorganisms; the number of colonies on the solid media planted from Isolator tubes; the response to therapy, and the opinions of the infectious diseases consultants and the hematology/oncology attending physicians who were following the patient. Criteria used to designate a microorganism as a pathogen regardless of its type included detection of the same microorganism from two or more BacT/Alert bottles, detection of the same microorganism from the Isolator tube and one or more BacT/Alert bottles, or detection of the same microorganism from two or more blood culture sets obtained during the same febrile episode. The clinical significance of isolates recovered from single BacT/Alert bottles or Isolator tubes was based on the genus and species of a microorganism and its potential pathogenicity [1–3, 10]. Three categories of microorganisms were thus defined. Definite pathogens [10] included *Staphylococcus aureus*, *Enterococcus* spp., *Streptococcus pneumoniae*, *Streptococcus agalactiae*, gram-negative bacteria, and *Candida* spp.. These microorganisms were considered pathogens unless the patient's clinical status was completely stable, the patient had no potential source for the microorganism, and there was no more than one colony of the isolate on no more than one of the five solid media inoculated from the Isolator tube or the time to detection of non-fastidious bacteria from the Isolator tube was more than 5 days. Potential pathogens [1, 3, 10] included coagulase-negative staphylococci and viridans streptococci. These microorganisms were considered pathogens if they were associated with a clinically infected site as the potential source. For example, an association between an inflamed central venous catheter site and the isolation of a coagulase-negative *Staphylococcus* or a severe oropaharyngeal mucositis and the isolation of a viridans group *Streptococcus*. Contaminants included *Micrococcus* spp., diphtheroids, *Propionebacterium* spp., *Bacillus* spp., *Streptomyces* spp., *Penicillium* spp., *Aspergillus* spp. and *Cladosporium* spp.. A microorganism from this group was considered a pathogen only if it was isolated from at least two BacT/Alert bottles, from the Isolator tube and one or more BacT/Alert bottles, or from two separate sets obtained during the same febrile episode.

All patients except one received oral ciprofloxacin for prophylaxis against gram-negative infection starting on the 1st day of chemotherapy and stopping after the recovery of absolute neutrophil count (ANC) to more than 500 cells/μl. One patient did not receive prophylactic antibiotics due to ciprofloxacin and cotrimoxazole hypersensitivity. All patients with positive IgG serology for herpes simplex virus received acyclovir prophylaxis for 6 weeks from the beginning of chemotherapy.

Results

42 consecutive patients diagnosed with AML between January 1992 and December 1994 were included in the study. The patients' mean age was 55 years, and 47.6% were male. The French-American-British (FAB) subtypes of AML were as follows: M0 (two patients), M1 (seven patients), M2 (13 patients), M3 (four patients), M4 (five patients), M5a (one patient), M5b (one patient), M6 (three patients) and M7 (one patient). In five patients, the FAB subtype was not applicable (secondary AML). All patients received induction chemotherapy with mitoxantrone and etoposide (21 patients) or idarubicin, etoposide, and carboplatinum (21 patients) followed by consolidation chemotherapy with

Table 1
Identified sources of fever, frequency of bloodstream infection and organisms isolated from blood in 129 febrile episodes.

Possible sources of fever	No. of febrile episodes in which the source was encountered (%)[a]	Frequency of bloodstream infection (%)[b]	Organisms isolated from blood [c] (frequency of isolation)
No focus	24 (18.6)	7 (29.2)	*Streptococcus viridans* (2), *Staphylococcus epidermidis* (1), CNS[d] not epidermidis (3), *Clostridium perfringens* (1), *Pseudomonas aeruginosa* (1), *Klebsiella pneumoniae* (1).
Mucositis	28 (21.7)	16 (57.1)	*Candida albicans* (1), *Candida krusei* (1), *Cryptococcus laurentii* (1), *Streptococcus viridans* (8), *Staphylococcus epidermidis* (1), CNS not epidermidis (7), *Micrococcus* (1).
Pneumonia	17 (13.2)[e]	5 (29.4)	*Candida albicans* (2), *Candida lusitaniae* (1), *Cryptococcus laurentii* (1), *Staphylococcus epidermidis* (1).
Neutropenic enterocolitis	12 (9.3)	5 (41.7)	*Staphylococcus epidermidis* (3), CNS not epidermidis (2), *Streptococcus viridans* (2), *Micrococcus* (1), *Staphylococcus aureus* (2), *Enterococcus faecalis* (1).
Invasive fungal disease	12 (9.3)	5 (41.7)	*Candida albicans* (3), *Candida lusitaniae* (1), *Cryptococcus laurentii* (1).
Central venous catheter local signs	9 (7.0)	5 (55.6)	CNS not epidermidis (4), *Streptococcus viridans* (1), *Staphylococcus aureus* (1), *Klebsiella oxytoca* (1), *Candida krusei* (1)
Central venous catheter without local signs	7 (5.4)	7 (100)[f]	*Staphylococcus epidermidis* (4), CNS not epidermidis (1), *Streptococcus viridans* (1), *Micrococcus* (1), *Enterobacter cloacae* (1), *Stenotrophomonas maltophilia* (1).
Periodontitis	6 (4.7)	2 (33.3)	*Streptococcus viridans* (2)
Cellulitis	5 (3.9)	3 (60)	*Staphylococcus aureus* (1), *Streptococcus pneumoniae* (1), *Klebsiella oxytoca* (1), *Citrobacter freundii* (1), *Escherichia coli* (1), *Klebsiella pneumoniae* (1)
Urinary tract infection	3	1 (33.3)	*Streptococcus agalactiae*
Sinusitis	3	0	
Perirectal infection	2	0	
Paronychia with olecranon bursitis	1	1	*Staphylococcus aureus*
Pyogenic liver abscesses	1	1	*Staphylococcus epidermidis*
Lymphadenitis	1	1	*Staphylococcus aureus*
Leukemia	16	0	
Graft versus host disease	3[g]	0	
Others[h]	8	0	

[a] some patients had two sources of fever during a single febrile episode; [b] positive blood cultures due to contaminants are excluded; [c] some infections were associated with polymicrobial bacteremia, hence the number of organisms isolated from blood may be higher than the frequency of blood culture total positivity; [d] coagulase-negative staphylococci; [e] including three patients whose pneumonia infections were part of disseminated fungal disease; [f] positive blood culture was a prerequisite to diagnose central venous catheter infection without local signs; [g] experienced during three separate febrile episodes in the two patients who received allogeneic bone marrow transplants; [h] one case each of otitis media, *Candida* esophagitis, endometritis post dilatation and curettage procedure, meningitis, thrombotic thrombocytopenic purpura, antibiotic fever, central venous catheter leakage, subdural hemorrhage

high-dose cytosine arabinoside. Eight patients required re-induction chemotherapy. Four and two patients received autologous and allogeneic bone marrow transplantation, respectively.

The study patients experienced 129 febrile episodes. 75% of febrile episodes occurred during severe neutropenia (ANC < 500 cells/μl). Table 1 lists the identified sources of fever, the frequency of bloodstream infection and the types of organisms isolated from blood. At least one source of fever was identified in 105 (81.4%) febrile episodes. A single source of fever was identified in 79 (61.3%) febrile episodes, two sources in 23 (17.8%) episodes, and three sources in three (2.3%) episodes. In the remaining 24 febrile episodes, no source of fever could be identified despite thorough clinical, radiological and microbiological evaluation.

Mucositis (13 of 26 episodes; 50%), followed by central venous catheter infection (ten of 26 episodes; 38.5%) were the most common sources of fever in episodes with multiple sources. Pneumonia was diagnosed in 17 (13.2%) febrile episodes based on radiographic presence of new or progressive pulmonary infiltrates not explained by other diseases such as pulmonary edema or thromboembolism. Sputum culture was positive for a possible pathogen for pneumonia in only two (11.8%) cases (*Pseudomonas aeruginosa* in both instances), and in one case *Legionella maceachernii* was isolated from a lung biopsy. *Mycobacterium gordonae* was isolated from sputum of another patient with pneumonia but the clinical significance of this organism was uncertain since this organism is rarely pathogenic. The patient failed therapy directed against this organism and he was subsequently proven to have invasive fungal disease. Five episodes (29.4%) of pneumonia were associated with bloodstream infection. Three of such episodes were associated with invasive fungal disease and thus were believed to be due to pulmonary involvement by the offending fungus. *Candida albicans*, *Candida lusitaniae* and *Cryptococcus laurentii* were isolated from blood of these cases. *C. albicans* was also isolated from blood of a fourth patient who had pneumonia and cellulitis. A fifth patient with patchy nodular pneumonia believed to be secondary to septic emboli from an infected central venous catheter had *Staphylococcus epidermidis* isolated from all BacT/Alert bottles and the Isolator tube. Echocardiogram showed no evidence of right side endocarditis.

Neutropenic enterocolitis was diagnosed in 12 (9.3%) febrile episodes based on the presence of fever, right lower quadrant abdominal pain and tenderness, and radiological evidence on computed tomography scan such as thickening of the wall of the cecum, pneumatosis coli, dilatation of the cecum, pericecal inflammation, and/or intramural or pericecal collection. Five (41.7%) cases were associated with polymicrobial bloodstream infection; all due to gram-positive bacteria.

Invasive fungal disease was diagnosed in 12 (9.3%) febrile episodes. All patients with clinically diagnosed invasive fungal disease had fever that failed to respond to broad-spectrum antibiotic therapy, right hypochondrial pain, elevated liver enzymes, and computed tomography scan disclosing many hypodense lesions in the liver. Eight of these patients had liver biopsies that showed multiple granulomatous abscesses consistent with invasive fungal disease but in only four patients (50%), the offending fungi were actually seen in the tissue, and in only one case the fungus was isolated from tissue culture. Two more patients had postmortem autopsies that confirmed the diagnosis; one had disseminated aspergillosis, and the other had disseminated candidiasis. All patients empirically received amphotericin B for at least 3 days before undergoing liver biopsies or postmortem autopsies. Three of the 12 (25%) cases were associated with pneumonia that was likely due to pulmonary involvement by the offending fungus.

Urinary tract infection was diagnosed in three febrile episodes based on the presence of fever, dysuria, urinary frequency, loin pain and tenderness, and isolation from urine of more than 10^8 cfu/l. *Enterobacter cloacae* and *Escherichia coli* were isolated from urine culture of two patients who were not receiving ciprofloxacin prophylaxis as their ANC was more than 500 cells/μl. *S. agalactiae* was isolated from both urine and blood cultures of the third patient who was receiving ciprofloxacin prophylaxis. One patient had multiple pyogenic liver abscesses that were surgically drained. Cultures of drained pus recovered pure growth of *S. epidermidis*.

49 febrile episodes (37.9%) were associated with bloodstream infection, of which 14 episodes (28.6%) were polymicrobial. At least one source of infection was identified in 42 (85.7%) of these episodes, whereas in the remaining seven (14.3%) episodes, no source was identified.

A total of 333 blood culture sets were obtained during these febrile episodes. The number of blood culture sets obtained during each febrile episode ranged from one to ten sets (mean 3 ± 2 sets per febrile episode). All blood culture sets were obtained according to the defined protocol described above. Microorganisms were isolated from 103 (30.9%) blood culture sets. Of these 103 positive sets, 70 (68%, that is 21% of total cultures) were considered clinically significant and 33 sets (32%, that is 9.9% of total cultures) were considered contaminants. Isolates classified as significant are shown in table 2.

Gram-negative bacilli accounted for only 12.1% (8/66) of all clinically significant microorganisms. The eight isolates were recovered during six febrile episodes experienced by six patients who were not receiving ciprofloxacin prophylaxis at the time of bacteremia (ANC > 500/μl). Central venous catheter infection (three episodes), and cellulitis (one episode associated with three gram-negative organisms isolated from blood) caused six of the eight gram-negative bacteremias. In the remaining two gram-negative bacteremias, no focus of infection was identified.

Among 64 isolates that contaminated 33 blood culture sets, gram-positive cocci were the most common (41/64; 64.1%), followed by gram-positive bacilli (12/64; 18.8%), fungi (6/64; 9.4%) and gram-negative bacilli (5/64; 7.8%). Contaminant gram-positive cocci included *S. epidermidis* (15 isolates), other coagulase-negative staphylococci (13 isolates), *Micrococcus* spp. (six isolates), *Streptococcus viridans* (five isolates), *Enterococcus faecalis* (one isolate) and non-hemolytic *Streptococcus* spp. not group D (one isolate). Contaminant gram-positive bacilli included diphtheroids (seven isolates), *Bacillus* spp. (two isolates), *Streptomyces* spp. (two isolates), and *Propionebacterium* spp. (one isolate). Contaminant fungi included *Penicillium* spp. (two isolates), and one isolate each of *Aspergillus niger*, *Aspergillus* spp., *Candida paraspilosis* and *Cladosporium* spp. Contaminant gram-negative organisms included *Acinetobacter lwoffi* (two isolates), *Neisseria spp.* (other than *N. gonorrhoeae* and *N. meningitidis*, two isolates), and *Enterobacter agglomerans* (one isolate).

Discussion

Infection is a common cause of morbidity and mortality in patients with AML. Two thirds of such patients develop infection after induction therapy and one third after consolidation cytotoxic therapy. [11, 12]. Mortality in this group of patients is attributable to infection in about two thirds of cases [13]. Fever is the most common manifestation of infection. However, fever can also be a manifestation of many noninfectious causes such as the underlying leukemia, transfusion reactions, thromboembolism, drugs, allergic reactions, hematomas and radiation injury.

Bacteria account for 85–90% of pathogens associated with febrile neutropenic episodes in patients with hematological malignancies [14, 15]. Over the past decade, the spectrum of such bacterial pathogens has changed dramatically. Gram-positive microorganisms have become the most common pathogens, whereas gram-negative bacilli are less frequently isolated [1–9]. Several reasons have been postulated to explain this phenomenon, including the use of high-dose cytosine arabinoside to treat acute leukemia [3], better prophylactic oral antibiotics especially fluoroquinolones [16, 17], increased incidence of severe oropharyngeal mucositis and bowel damage with the use of more intense chemotherapy, and increased use of central venous catheters for the administration of more intensive chemotherapy [18].

In this study, at least one source of fever was identified in 81.4% of all febrile episodes. One source of fever was identified in 75.2% of febrile episodes that had defined sources of fever, and in the remaining episodes (24.8%) two or three sources were identified. Multiplicity of sources of fever in this host group adds to the difficulties that clinicians may face in their attempts to identify the exact source of bloodstream infection.

Mucositis (21.7%), pneumonia (13.2%), central venous catheter infections (12.4%), neutropenic enterocolitis (9.3%) and invasive fungal disease (9.3%) were the most common sources of fever (Table 1). Central venous catheter infection was not associated with local signs in 43.8% of cases. Noninfectious sources of fever accounted for 17.8% of all febrile episodes. The underlying disease (leukemia, 12.4%) and graft versus host disease (2.3%) occurring in the two patients who received allogeneic bone marrow transplant were the most common noninfectious causes.

Culture of specimens from the respiratory tract of patients with radiological evidence of pneumonia was unrevealing in the majority of cases. In difficult cases that fail to respond to antibacterial and antifungal therapy, transbronchial or open lung biopsy is usually indicated to obtain tissues for microbiological cultures and histopathological examination. One such patient with pneumonia had *Legionella maceachernii* isolated from a lung biopsy even though repeated sputum cultures for respiratory pathogens including *Legionella* spp. were negative.

Invasive fungal disease accounted for 9.3% of all febrile episodes. The offending fungus was isolated from blood in 41.7% of cases and included *Candida* spp. in four episodes and *Cryptococcus laurentii* in one. Fever refractory to antibiotic therapy, right hypochondrial pain, elevated liver enzymes, and computed tomography scan disclosing multiple hypodense lesions in the liver were the

Table 2
Clinically significant organisms isolated from blood.

Organism	Frequency of isolation (%)
Gram-positive cocci	49 (74.2)
Coagulase-negative staphylococci	23 (34.8)
Streptococcus viridans	15 (22.7)
Staphyococcus aureus	5 (7.6)
Micrococcus spp.	3 (4.5)
Streptococcus agalactiae	1 (1.5)
Streptococcus pneumoniae	1 (1.5)
Enterococcus faecalis	1 (1.5)
Clostridium perfringens	1 (1.5)
Gram-negative bacilli	8 (12.1)
Klebsiella pneumoniae	2 (3)
Enterobacter cloacae	1 (1.5)
Klebsiella oxytoca	1 (1.5)
Pseudomonas aeruginosa	1 (1.5)
Stenotrophomonas maltophilia	1 (1.5)
Citrobacter freundii	1 (1.5)
Escherichia coli	1 (1.5)
Candida spp.	7 (10.6)
Candida albicans	5 (7.6)
Candida krusei	1 (1.5)
Candida lusitaniae	1 (1.5)
Cryptococcus laurentii	1 (1.5)
Total	**66**

presenting features in all cases. Histopathological changes consistent with invasive fungal disease were seen in all patients who had liver biopsies (eight patients) or autopsies (two patients) but fungi in liver tissues were seen in only half of the cases, and culture of liver tissue was positive in one case only. The low sensitivity of liver tissue stain and culture for fungi was likely due to the fact that all patients received amphotericin B for at least 3 days prior to undergoing liver biopsies or postmortem autopsies. Three of the 12 (25%) cases were associated with pneumonia that was likely due to pulmonary involvement by the offending fungus.

Bloodstream infection was commonly associated with cellulitis (60%), mucositis (57.1%), central venous catheter infection (55.6%), neutropenic enterocolitis (41.7%) and invasive fungal disease (41.7%). At least one site of infection was identified in most cases (85.7%) of bloodstream infection. In only 14.3% of cases the source of bloodstream infection was not identified despite thorough clinical, laboratory and radiographic evaluation. Gram-positive microorganisms were the most common blood isolates (75.8%), a finding consistent with the observations of others [1–9]. Coagulase-negative staphylococci and viridans streptococci accounted for more than half (57.6%) of all blood isolates. Inadequate activity of ciprofloxacin against these microorganisms has likely contributed to their increased pathogenicity. The few gram-negative bacteremias occurred only in patients who were not receiving ciprofloxacin prophylaxis at the time of bacteremia, confirming the important role antibiotic prophylaxis plays in preventing gram-negative septicemia and in changing the spectrum of microorganisms that cause bloodstream infection in this group of patients, as previously described [19–23].

In conclusion, infections remain important causes of fever in leukemic patients receiving cytotoxic therapy despite the use of prophylactic antibiotics. Although the spectrum of pathogens that cause infection in this group of patients has shifted from gram-negative to gram-positive bacteria, the most common sources of infection remain the same as previously described with integumental surfaces (skin and mucous membranes of gastrointestinal, respiratory and urinary tracts) being involved in the majority of cases. It is hoped that this information will assist in the future development and improvement of measures to prevent and treat infections in leukemic patients.

Acknowledgments

I wish to thank to Dr. Eric J. Bow and Mrs. Ruth Loewen for providing the list of patients included in this study, and Dr. Amin Kabani and Mrs. Joan Koss for providing information related to the relevant culture techniques used in the Microbiology Laboratory at Health Sciences Center, Winnipeg, Manitoba.

References

1. Winston DJ, Dudnick, DV, Chapin M, Winston G, Gale RP, Martin WJ: Coagulase negative staphylococcal bacteremia in patients receiving immunosuppressive therapy. Arch Intern Med 1983; 143: 32–36.
2. Viscoli C, van der Auwera P, Meunier F: Gram-positive infections in granulocytopenic patients: an important issue. J Antimicrob Chemother 1988; 21 (suppl C):1988; 149–156.
3. Kern W, Jurrie E, Schmeiser T: Streptococcal bacteremia in adult patients with leukemia undergoing aggressive chemotherapy. A review of 55 cases. Infection 1990; 18: 138–145.
4. Klastersky J, Zinner SH, Calandra T, Gaya H, Glauser MP, Meunier F, Rossi M, Schimpff SC, Tattersall M, Viscoli C, and the EORTC Antimicrobial Therapy Cooperative Group: Empiric antimicrobial therapy for febrile granulocytopenic cancer patients: Lessons from four EORTC trials. Eur J Cancer Clin Oncol 1988; 24: 35–45.
5. Karp JE, Dick JD, Angelopulos C, Charache P, Green L, Burke PJ, Saral R: Empiric use of vancomycin during prolonged treatment-induced granulocytopenia. Am J Med 1986; 81: 237–242.
6. Whimbey E, Kiehn TE, Brannon P, Blevins A, Armstrong D: Bacteremia and fungemia in patients with neoplastic disease. Am J Med 1987; 82: 723–729.
7. EORTC International Antimicrobial Therapy Cooperative Group: Gram-positive bacteremia in granulocytopenic cancer patients. Eur J Cancer Clin Oncol 1990; 26: 569–574.
8. EORTC International Antimicrobial Therapy Cooperative Group: Efficacy and toxicity of single daily doses of amikacin and ceftriaxone versus multiple daily doses of amikacin and ceftazidime for infection in patients with cancer and granulocytopenia. Ann Intern Med 1993; 119: 584–593.
9. Bochud P, Calandra T, Francioli P: Bacteremia due to viridans streptococci in neutropenic patients: a review. Am J Med 1994; 97: 256–264.
10. Weinstein MP, Reller LB, Murphy JR, Lichtenstein KA: The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. I. Laboratory and epidemiologic observations. Rev Infect Dis 1983; 5: 35–53.
11. Bishop JF, Matthews JP, Young GA, Szer J, Gillett A, Joshua D, Bradstock K, Enno A, Wolf MM, Fox R, Cobcroft R, Herrmann R, Van Der Weyden M, Lowenthal RM, Page F, Garson OM, Juneja S: A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. Blood 1996; 87: 1710–1717.
12. Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P, Omura GA, Moore JO, McIntyre OR, Frei III E for the Cancer and Leukemia Group B: Intensive post remission chemotherapy in adults with acute myeloid leukemia. N Engl J Med 1994; 331: 896–903.
13. Young LS: Management of infections in leukemia and lymphoma. In: Rubin RH, Young LS (eds): Clinical approach to infection in the compromised host, 3rd ed Plenum, New York 1994; pp. 551–579.
14. Pizzo PA, Robichaud KJ, Wesley R, Commers JR: Fever in the pediatric and young adult patients with cancer: a prospective study of 1001 episodes. Medicine (Baltimore) 1982; 61: 153–165.
15. Schimpff SC: Overview of empiric antibiotic therapy for the febrile neutropenic patient. Rev Infect Dis 1985; 7 (suppl 4): 5734–5740.
16. Awada A, van der Auwera P, Meunier F, Daneau D, Klastersky J: Streptococcal and enterococcal bacteremia in patients with cancer. Clin Infect Dis 1992; 15: 33–48.

17. Richard V, Meunier F, van der Auwera P, Dejace P, Daneau D, Klastersky J: Pneumococcal bacteremia in cancer patients. Eur J Epidemiol 1988; 4: 242–245.
18. Elting LS, Bodey GP, Keefe BH: Septicemia and shock due to viridans streptococci: a case control study of predisposing factors. Clin Infect Dis 1992; 14: 1201–1207.
19. Karp JE, Merz WG, Hendricksen C, Laughon B, Redden T, Bamberger BJ, Bartlett JG, Saral R, Burke PJ: Oral norfloxacin for prevention of gram-negative bacterial infections in patients with acute leukemia and granulocytopenia. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1987; 106: 1–7.
20. Dekker AW, Rozenberg-Arska M, Verhoef J: Infection prophylaxis in acute leukemia: a comparison of ciprofloxacin with trimethoprim-sulfamethoxazole and colistin. Ann Intern Med 1987; 106: 7–11.
21. Donnelly JP, Maschmeyer G, Daenen S: Selective oral antimicrobial prophylaxis for the prevention of infection in acute leukemia-ciprofloxacin versus co-trimoxazole plus colistin. The EORTC-Gnotobiotic Project Group. Eur J Cancer 1992; 28A: 873–878.
22. Bow EJ, Rayner E, Louie TJ: Comparison of norfloxacin with cotrimoxazole for infection prophylaxis in acute leukemia. The trade-off for reduced gram-negative sepsis. Am J Med 1988; 84: 847–854.
23. Bow EJ, Loewen R, Vaughan D: Reduced requirement for gram-negative antibiotic therapy in febrile, neutropenic patients with cancer who are receiving antibacterial chemoprophylaxis with oral quinolones. Clin Infect Dis 1996; 20: 907–912.