The Epidemiology of Bacteremia with Febrile Neutropenia: Experience from a Single Center, 1988–2004

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Abstract

Background: The epidemiology of bacteremic febrile neutropenia differs between locations and constitutes the basis for selection of empiric antibiotic therapy for febrile neutropenia.

Objectives: To describe the epidemiology of bacteremia among patients with neutropenia in a single center in Israel.

Methods: We conducted a prospective data collection on all patients with neutropenia (< 500/mm^3) and clinically significant bacteremia or fungemia during the period 1988–2004.

Results: Among adults (462 episodes) the most common bloodstream isolate was *Esherichia coli.* Gram-negative bacteria predominated throughout the study period and the ratio between Gram-negative and Gram-positive bacteremia increased from 1.7 to 2.3. Among children (752 episodes), the ratio between Gram-negative and Gram-positive bacteremia reversed from 1.2 to 0.7, due to increasing prevalence of coagulase-negative staphylcoccal bacteremia. Both among adults and children, the length of hospital stay prior to bacteremia had a major impact on the pathogens causing bacteremia and their antibiotic susceptibilities. The prevalence of *E. coli* decreased with time in hospital, while the rates of *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter* spp., *Acinetobacter* spp., *Enterococcus* spp. and *Candida* spp. increased. Resistance to broad-spectrum empiric monotherapy in our center was observed in > 40% of Gram-negative bacteria when bacteremia was acquired after 14 days in hospital.

Conclusions: Improved infection-control measures for neutropenic cancer patients in our center are needed. Empiric antibiotic treatment should be tailored to patients' risk for multidrug-resistant organisms. Individual hospitals should monitor infection epidemiology among cancer patients to guide empiric antibiotic treatment.

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Febrile neutropenia comprises a spectrum of clinical syndromes ranging from non-infectious fever to severe life-threatening infections. Patients with febrile neutropenia and bacteremia form a small subgroup within this spectrum, including severely infected patients. This is our window into the epidemiology of bacterial infections among patients with febrile neutropenia.

The epidemiology of bacteremic febrile neutropenia constitutes the basis for selection of empiric antibiotic therapy for febrile neutropenia. A shift from the predominance of Gram-negative bacteria to predominance of Gram-positive bacteria has been observed in many centers during the last two decades [1-4]. In a series of randomized controlled trials conducted by the EORTC (European Organization for Research and Treatment of Cancer), the frequency of single-agent Gram-positive bacteremia increased from 29% in the trial conducted between 1973 and 1976, to 41% between 1983 and 1986, 64% between 1986 and 1988, 67% between 1991 and 1992, and 69% between 1993 and 1994, while the rate of single-agent Gram-negative bacteremia dropped from 71% to 31% [1]. However, more recently, a reverse of this trend has been seen in several centers reporting on the re-emergence of Gram-negative bacteria in febrile neutropenic patients [5-7]. The significant variability between locations calls for the study of local trends to guide more appropriate antibiotic treatment.

We describe the epidemiology of bacteremia among patients with febrile neutropenia over a 16 year period in a university hospital in central Israel. We analyze the secular trends as well as the trends related to the duration of hospital stay.

Patients and Methods

The study was conducted at the Rabin Medical Center (Beilinson campus), a 900-bed primary and tertiary care university hospital treating the largest number of adult cancer patients in Israel. Patients with fever and neutropenia were hospitalized mainly in six departments of internal medicine (234 beds). During the study period no bone marrow transplantations were performed

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and no antibiotic prophylaxis was used. Empiric therapy for febrile neutropenia included ceftazidime with an aminoglycoside in the first half of the study period, and as monotherapy since 1996.

The pediatric and pediatric hemato-oncologic departments were separated from this hospital in 1992 and 1993, respectively, and relocated to a new building – called the Schneider Children's Medical Center – on the same campus. Schneider Children's Medical Center is a 350-bed primary and tertiary university-affiliated pediatric hospital. Children with febrile neutropenia are treated mainly in a 20-bed pediatric hemato-oncology ward performing bone marrow transplantations since 1993. Antibacterial prophylaxis was not used. The recommended empiric antibiotic treatment for febrile neutropenia included ceftazidime with aminoglycoside for most of the study period, and was switched to piperacillin-tazobactam + amikacin in 2001.

Data collection and definitions

Data were derived from a surveillance program for bloodstream infections that was conducted in both hospitals by the same research microbiologist and using the same definitions throughout the study period. Data were collected prospectively from the day of bacteremia and recorded in the Beilinson bacteremia database [8-10]. All consecutive patients hospitalized with bacteremia or fungemia (thereafter referred to as bacteremia) and neutropenia (absolute neutrophil count < 500/mm^3) occurring between the years 1988 and 2004 were included. Isolation of coagulase-negative staphylococci or Gram-positive bacilli in a single bottle were considered as contaminants and excluded from this analysis. Patients were included more than once in the analysis for separate episodes of bacteremia. Mortality was defined as all-cause in-hospital mortality up to 30 days after the bacteremia date. Bacteremia developing after 48 hours in hospital was defined as hospital-acquired.

The same microbiology laboratory serves both hospitals. The Bactec 460 was used between 1988 and 1992 and the Bactec 9240 microbial system (Becton Dickinson, Franklin Lakes, NJ, USA) after 1992. Susceptibility to antibiotics was tested by the disk diffusion method on Mueller-Hinton agar, according to Clinical and Laboratory Standards Institute (formerly NCCLS) procedures.

Analysis

To assess trends throughout the study period, we divided it into four periods: 1988–1991, 1992–1995, 1996–2000 and 2001–2004. To assess trends throughout the hospital stay we compared patients whose bacteremia occurred on day 0–1 after hospital admission, 2–7, 8–14 and > 14 days after admission. Comparisons were performed using the chi-square test for dichotomous and non-parametric tests for continuous variables. Trends were assessed using chi-square for linear associations. Analyses for mortality were conducted per patient; other analyses were conducted per bacteremia episode. Odds ratios are expressed with 95% confidence intervals. Analyses were conducted using SPSS version 11.5.

Results

Beilinson Hospital – adult population

Throughout the study period 414 adult patients with neutropenia developed 462 separate episodes of bacteremia. Mean age was 63 ± 16 years and 55% were female. No source of infection was identified in 68.4% of all episodes (316/462). The patients were hospitalized mainly in internal medicine (69%) or oncology (17%) wards. The median time for development of hospital-acquired bacteremia was 10 days (range 3–88). Polymicrobial bacteremia was detected in 80 episodes (17.3%).

- *Pathogen distribution and antibiotic susceptibilities*

Gram-negative bacteria were more common than Gram-positives throughout the study period. The ratio of Gram-negative to Gram-positive bacteria among single-organism bacteremias (382 episodes) increased from 1.7 to 2.3 throughout the study period (P = 0.01 for trend of Gram-negative bacteremia out of all bacteremias) [Figure 1]. A similar trend was observed for all 557 isolates, including the polymicrobial bacteremias (Gram-negative to Gram-positive ratio 1.6 to 2.5). Pathogen distribution among all isolates is shown in Table 1. *Escherichia coli* was the most common bloodstream isolate overall (18.9%), followed by *Pseudomonas aeruginosa* (16.7%). Throughout the study period the rate of coagulase-negative staphylococci and *Candida* decreased (P for

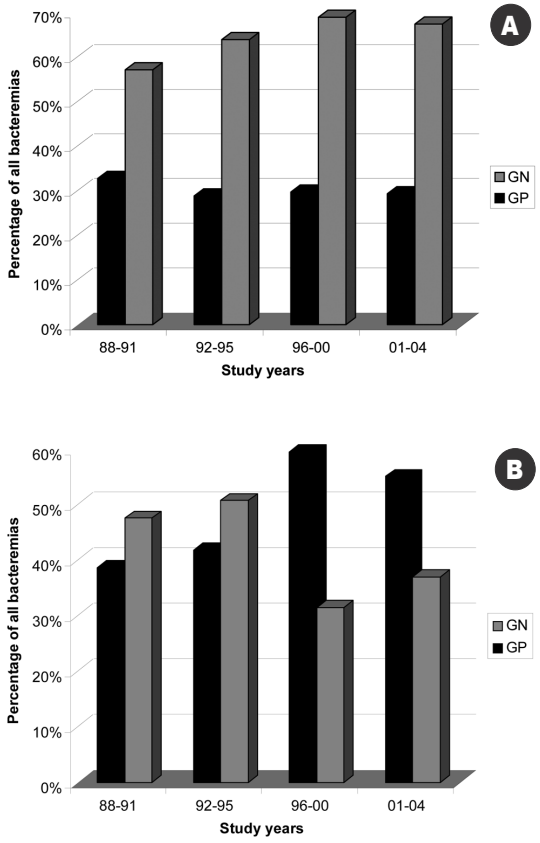

Figure 1. Single organism bacteremia: Gram-positive (GP) to Gram-negative (GN) ratio trends during the study period. **[A]** Adults. **[B]** Children

Table I. Pathogens associated with bacteremia in febrile neutropenic adult patients, 1988–2004

Pathogen	< 48 hr in hospital	> 48 hr in hospital	Total
Gram-negative			
Escherichia coli	80 (23.5)	25 (11.6)	105 (18.9)
Pseudomonas aeruginosa	54 (15.8)	39 (18.1)	93 (16.7)
Klebsiella pneumoniae	30 (8.8)	31 (14.4)	61 (11.0)
Acinetobacter spp.	9 (2.6)	21 (9.7)	30 (5.4)
Enterobacter spp.	9 (2.6)	13 (6.0)	22 (3.9)
Proteus spp.	7 (2.1)	7 (3.2)	14 (2.5)
Other Gram-negatives	23 (6.7)	5 (2.3)	28 (5.0)
Total	212 (62.2)	141 (65.3)	353 (63.4)
Gram-positive			
Staphylococcus aureus	28 (8.2)	24 (11.1)	52 (9.3)
Staphylococcus coagulase negative	17 (5.0)	10 (4.6)	27 (4.8)
Enterococcus spp.	11 (3.2)	14 (6.5)	25 (4.5)
Streptococcus viridans	21 (6.2)	3 (1.4)	24 (4.3)
Streptococcus pneumoniae	16 (4.7)	2 (0.9)	18 (3.2)
Other streptococci	15 (4.4)	8 (3.7)	23 (4.1)
Other Gram-positives	6 (1.8)	2 (0.9)	8 (1.4)
Total	114 (33.4)	63 (29.2)	177 (31.8)
Anaerobes	7 (2.1)	1 (0.5)	8 (1.4)
Candida spp.	6 (1.8)	8 (3.7)	14 (2.5)
Other fungi	0	1 (0.5)	1 (0.2)
Unknown/others	2 (0.6)	2 (1.0)	4 (0.8)
Total	341 (100)	216 (10)	557 (100)

trend 0.03 for coagulase-negative staphylococci and 0.02 for *Candida*), while *Klebsiella* spp. increased from 8.6% to 16.2% of all bacteremias (P for trend 0.05). No significant trends were seen for the other pathogens.

Pathogen distribution changed with the length of hospital stay before bacteremia. The prevalence of E. *coli* decreased significantly from 23.9% within 48 hours of admission to 7.6% after 14 days in hospital ($P < 0.001$ for trend), while the prevalence of other Gram-negative bacteria, mainly *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, increased throughout the hospital stay. The prevalence of Gram-positive bacteria remained stable, while *Candida* became more common as hospital duration increased (from 1.6% to 6.3%, $P = 0.02$ for trend).

Resistance of Gram-negative bacteria to broad-spectrum beta-lactams, commonly used for empiric treatment of febrile neutropenia, increased with the length of time in hospital prior to bacteremia acquisition [Figure 2]. Thus, resistance to ceftazidime increased from 8% when acquired before hospitalization to 48% when acquired after 14 days in hospital. *Staphylococcus aureus* was resistant to methicillin in 24% of patients (12/50), increasing from 16% during the first week of hospital stay to 80% after 14 days in hospital.

- *Mortality*

In-hospital 30 day mortality among all patients was 38.3% (158/412). Mortality increased with age and decreased throughout the study period, from 45.2% during the first study period to 31.3% during the last ($P = 0.03$ for trend). The median time from bacteremia to death was 8 days (range 0–30) and did not change significantly during the study period. Catheter-related infections were associated with lower mortality (1/26, 3.8%) compared to patients with bacteremia of unknown source (100/243, 41.2%; $P < 0.001$). Unadjusted mortality was similar with bacteremia caused by Gram-negative (39.9%, 97/247) and Gram-positive bacteria other than coagulase-negative staphylococci (36.7%, 44/120). Bacteremia due to coagulase-negative staphylococci was associated with lower mortality (13.6%, 3/22; $P = 0.02$ for coagulase-negative staphylococci vs. others). The mortality with candidemia was 80% (8/10).

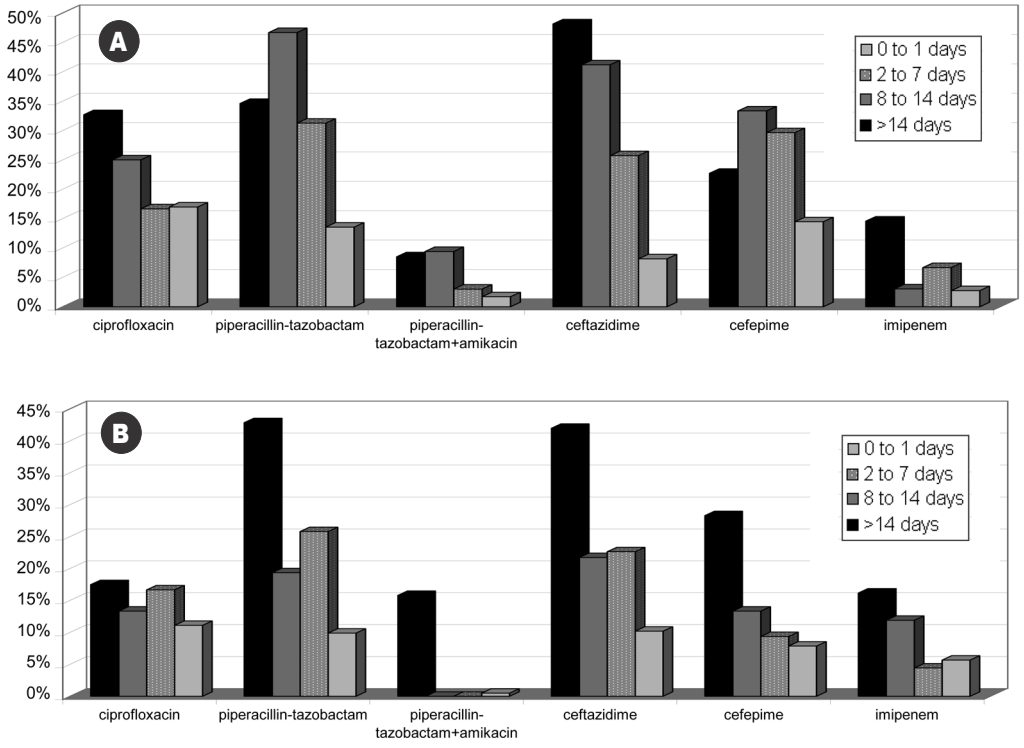

Figure 2. Resistance among Gram-negative bacteria as a function of length of hospital stay prior to bacteremia: % resistant per hospital day. **[A]** Adults. **[B]** Children.

Table 2. Pathogens associated with bacteremia in febrile neutropenic pediatric patients, 1988–1995 and 1996–2004

	1988–1995			1996–2004		
Pathogen	< 48 hr in hospital	> 48 hr in hospital	Total	< 48 hr in hospital	> 48 hr in hospital	Total
Gram-negative						
Escherichia coli	32 (17.3)	11 (8.4)	43 (13.6)	31 (12.7)	26 (7.6)	57 (9.7)
Pseudomonas aeruginosa	23 (12.4)	16 (12.2)	39 (12.3)	26 (10.6)	31 (9.1)	57 (9.7)
Klebsiella pneumoniae	18 (9.7)	9 (6.9)	27 (8.5)	17 (6.9)	20 (5.8)	37 (6.3)
Enterobacter spp.	9 (4.9)	8 (6.1)	17 (5.4)	4 (1.6)	15 (4.4)	19 (3.2)
Acinetobacter spp.	2 (1.1)	7 (5.3)	9 (2.8)	9 (3.7)	15 (4.4)	24 (4.1)
Proteus spp.	2 (1.1)	5 (3.8)	7 (2.2)	1 (0.4)	1 (0.3)	2 (0.3)
Other Gram-negatives	9 (4.9)	3 (2.3)	12 (3.8)	12 (4.9)	22 (6.4)	34 (5.9)
Total	95 (51.3)	59 (45.0)	154 (48.7)	100 (40.8)	130 (38.0)	230 (39.2)
Gram-positive						
Staph. coagulase negative	26 (14.0)	18 (13.7)	44 (13.9)	73 (30.0)	83 (24.3)	156 (26.6)
Strept. viridans	33 (17.8)	10 (7.6)	43 (13.6)	35 (14.3)	41 (12.0)	76 (12.9)
Enterococcus spp.	2 (1.1)	11 (8.4)	13 (4.1)	7 (2.9)	39 (11.4)	46 (7.9)
Staph. aureus	8 (4.3)	9 (6.9)	17 (5.4)	7 (2.9)	2 (0.6)	9 (1.5)
Strept. pneumoniae	5 (2.7)	1 (0.8)	6 (1.9)	8 (3.3)	3 (0.9)	11 (1.9)
Other streptococci	1 (0.5)	3 (2.3)	4 (1.3)	2 (0.8)	0	2 (0.3)
Other Gram-positives	4 (2.2)	1 (0.8)	5 (1.6)	5 (2.0)	10 (2.9)	15 (2.5)
Total	79 (42.7)	53 (40.4)	132 (41.8)	137 (55.9)	178 (52.0)	315 (53.7)
Anaerobes	3 (1.6)	1 (0.8)	4 (1.3)	1 (0.4)	3 (0.9)	4 (0.7)
Candida spp.	5 (2.7)	17 (13.0)	22 (7.0)	5 (2.0)	20 (6.9)	25 (4.2)
Other fungi	0	0	0	0	4 (1.2)	4 (0.7)
Unknown/others	3 (1.3)	1 (0.8)	4 (1.3)	2 (0.8)	7 (2.0)	9 (1.6)
Total	185 (100)	131 (100)	316 (100)	245 (100)	342 (100)	587 (100)

Schneider Children's Medical Center – pediatric population

Throughout the same study period 478 children developed 752 separate episodes of bacteremia during neutropenia. The mean age was 9 ± 6 years and 40% were female. The source of bacteremia was unknown in 64% of the episodes (481/752). Most children were hospitalized in the pediatric oncology department (93%). The median time to development of hospital-acquired bacteremia was 13 days (range 3–373 days). Polymicrobial bacteremia was present in 110 episodes (14.6%) and 34% of the children (162/476) had more than one episode of bacteremia

- *Pathogen distribution and antibiotic susceptibilities*

Among 642 single-organism bacteremia episodes, Gram-negative bacteria were more common than Gram-positives before 1995 and less common thereafter. Gram-negative to Gram-positive ratio was 1.2 in the first period and 0.7 in the last [Figure 1]. Among all the isolates (903) the ratio changed from 1.2 during the first half of the study to 0.7 during the second half. Pathogen distribution among all isolates is shown in Table 2. Throughout the study period the prevalence of coagulase-negative staphylococci increased significantly from 11.5% to 28.1% ($P < 0.001$ for trend). The prevalence of *Staphylococcus aureus* and *Candida* decreased (6.5% to 1.3%, $P = 0.001$, and 7.9% to 3.9%, $P = 0.05$ for trend, respectively), while no significant trends were seen for the other pathogens. The prevalence of all Gram-negatives combined decreased significantly throughout the study period ($P = 0.02$ for trend).

The prevalence of E. *coli* decreased with increasing length of hospital stay prior to development of bacteremia (14.7% within 48 hours of admission to 5.4% after 14 days, $P < 0.001$ for trend), while the prevalence of *Enterococcus* and *Candida* spp. increased (1.8% to 14.7%, $P < 0.001$, and 2.5% to 8.1%, $P = 0.003$ for trend, respectively). The prevalence of other Gram-negative bacteria and staphylococci did not change as a function of time in hospital.

Similar to the trends observed among adults, the resistance of Gram-negative bacteria to broad-spectrum beta-lactams increased with longer hospital stay before onset of bacteremia [Figure 2]. Overall, 37% of the streptococci (52/140) and 30% of the enterococci (17/56) were susceptible to penicillin. *Staph. aureus* remained susceptible to methicillin in 87% of the episodes (20/23).

- *Mortality*

All-cause 30 day in-hospital mortality was 8.8% (42/476), which decreased significantly during the study period. Among children under the age of 18 years mortality was 19.4% (18/93) between 1998 and 1991, 8.7% (9/104) between 1992 and 1995, 6.2% (8/129) between 1996 and 2000, and 4.7% (7/150) between 2001 and 2004 ($P < 0.001$ for trend). The median interval from bacteremia to death increased from 10 days (range 1–26) before 1996 to 21 days (range 3–28) afterwards ($P = 0.002$). Catheter-related infections were associated with lower mortality (2/122, 1.6%) than bacteremia of unknown origin (30/287, 10.5%, $P < 0.001$). There was no significant difference between mortality with bacteremia caused by Gram-negative (9.8%, 19/194) vs. Gram-positive bacteria other than coagulase-negative staphylococci (8.4%, 11/131). Again, bacteremia due to coagulase-negative staphylococci was associated with significantly lower mortality (1.9%, 2/104, $P = 0.01$).

Discussion

We present data on febrile neutropenia and bacteremia among adults and children in a single center in Israel over nearly two decades. The adult population consisted mainly of cancer patients with solid tumor since bone marrow transplantations were not performed in our center during this period. Among adults, Gram-negative bacteria predominated and their prevalence increased throughout the study period, in contrast to the shift towards Gram-positive infections described in other centers during this period [1-4]. E. *coli* and *P. aeruginosa* were the most common bloodstream isolates and their prevalence did not change significantly during the study period.

The pediatric population consisted primarily of hematological cancer patients and bone marrow transplant recipients treated at our center. An increase in Gram-positive bacteria was observed

due to the increasing prevalence of coagulase-negative staphylococci bacteremia. Greenberg et al. [11] recently described a similar increase in Gram-positive organisms among pediatric febrile oncology patients. The major stated risk factors for Gram-positive bacteremia among neutropenic cancer patients include long-term indwelling catheters, high dose chemotherapy-induced mucositis, and antibiotic prophylaxis [2,4]. Antibiotic prophylaxis was not used routinely at our center, while long-term catheters have become routine in recent years, bone marrow transplantations were introduced, and the intensity of chemotherapy regimens has increased. A significant decrease in mortality rates following bacteremia was observed throughout the study period.

Both among adults and children the spectrum of pathogens changed with time in hospital. The prevalence of E. *coli* decreased while rates of P*seudomonas aeruginosa*, K*lebsiella pneumonia*e, E*nterobacter* spp., A*cinetobacter* spp., E*nterococcus* spp. and C*andida* spp. increased. Resistance to antibiotics commonly used for the treatment of febrile neutropenia increased with longer duration of hospital stay prior to bacteremia acquisition. After 14 days in hospital, 15% of bloodstream isolates were resistant to imipenem and 40% were resistant to ceftazidime and piperacillin-tazobactam.

Beta-lactam–aminoglycoside combination therapy afforded a broader spectrum of coverage *in vitro* than beta-lactam monotherapy. The data are shown for piperacillin-tazobactam and amikacin. Amikacin covered > 70% of Gram-negative bacteria resistant to piperacillin-tazobactam. This trend is likely to be observed in other centers with increasing prevalence of extended-spectrum β-lactamases among Gram-negative bacteria in the hospital. However, broadening the spectrum of coverage using aminoglycosides, effectively leaving a large percentage of bacteria covered by single aminoglycoside treatment, may not translate to clinical benefit. Single aminoglycoside treatment is minimally effective in the setting of severe neutropenia (< 100/mm^3) [12]. In a systematic review and meta-analysis of randomized trials we showed that broad-spectrum monotherapy is superior to a narrower spectrum beta-lactam combined with an aminolycoside [13]. Mortality is non-significantly higher, while treatment failure and adverse events are significantly more frequent with combination therapy. Subgroup analyses of patients with microbiologically documented infections, documented Gram-negative and P*seudomonas aeruginosa* infections showed no advantage to combination therapy. Thus, appropriate beta-lactam monotherapy, selected according to local antibiotic resistance patterns, should be used both empirically and for documented Gram-negative infections. Treatment with a carbapenem is warranted for patients who develop severe sepsis following prolonged hospitalization in settings with an epidemiology similar to ours.

The distribution of pathogens as a function of hospital stay among neutropenic patients was similar to that observed among non-neutropenic patients at our center and in U.S. hospitals [3,14]. The similarity of pathogens causing bacteremia and their susceptibility patterns suggest cross-infection in the hospital among neutropenic patients, similar to that occurring among non-neutropenic patients.

We did not collect data on previous antibiotic exposure, antibiotic treatment, underlying malignancy, and culture-negative patients with febrile neutropenia. These variables are mandatory to correctly interpret the epidemiology of infections among cancer patients. Given the limitations of our data set, we drew the following conclusions. Firstly, cancer centers must monitor the epidemiology of infections among neutropenic cancer patients to guide empiric antibiotic treatment and decisions regarding antibiotic prophylaxis. The incidence of Gram-positive infections is highly variable between centers. Both the spectrum of infecting bacteria and antibiotic resistance patterns change throughout hospital stay, dictating different treatment regimens. When local data are lacking, we recommend that data from centers with similar epidemiology be used. Although data on children in Israel had been previously reported [11], we did not find a recent description on adult cancer patients in Israel.

Secondly, our data point to the need for improved infection control measures among patients with neutropenia in hospitals to prevent cross-infection with multiresistant bacteria [15,16]. Minimizing the length of hospital stay following chemotherapy and outpatient treatment of cancer patients should be considered [17,18]. To the best of our knowledge, there are no uniform recommendations of contact precautions for hospitalized patients with neutropenia, other than in the setting of bone marrow transplantation [19]. Such guidelines are necessary.

Finally, we suggest that the management of febrile neutropenia shift towards a more individualized approach. Antibiotic prophylaxis for afebrile neutropenic cancer patients should be considered following evidence showing a significant reduction in all-cause mortality with prophylaxis [20]. Given current trends in antibiotic resistance we cannot afford broad-spectrum therapy for all patients. Conversely, the mortality from bacteremia remains unacceptably high. Thus, patients should be stratified according to risk for a severe bacterial infection and antibiotic resistance. The effect of a previous antibiotic exposure should be investigated and the duration of hospital stay prior to infection should be considered a risk factor for antibiotic resistance. Infections constitute the most common preventable cause of death among cancer patients. Improving prevention, monitoring and treatment are essential for improved patient care.

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