Bloodstream infections in febrile neutropenic patients at a tertiary care center in Lebanon: a view of the past decade

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Neutropenic fever; Bacteremia; Gram-negative infection; Lebanon

Summary
Objectives: Previous studies from Lebanon have shown Gram-negative organisms to be the predominant agents in febrile neutropenic patients. The objective of this study was to evaluate the most current epidemiological trends among patients with neutropenic fever.
Methods: This prospective observational cohort study, the largest to date in the country, was conducted at the American University of Beirut Medical Center between January 2001 and December 2003, with the objective of describing the characteristics of patients with neutropenic fever and to assess temporal trends.
Results: We included 177 episodes of neutropenic fever. The most common underlying malignancy was lymphoma (42.4%). Gastrointestinal and abdominal infections were predominant (31.6%) and 23.7% of cases represented fever of unknown origin. Gram-negative organisms were responsible for 78.8% (26/33) of bloodstream infections compared to 33.3% (11/33) with Gram-positive organisms. The in-hospital mortality rate in this study (12.1%) was considerably lower than in previous years.
Conclusions: Gram-negative organisms are persistently predominant in our center. In a developing country like Lebanon with limited resources, lower mortality rates commensurate with worldwide reports were successfully achieved in this high-risk patient population. Protocols and guidelines should be adapted to the characteristics of individual institutions to ensure delivery of appropriate care to febrile neutropenic patients.

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Introduction

Infectious processes continue to pose a problem of considerable magnitude that impacts the quality of life and survival of cancer patients presenting with neutropenic fever. Over the past decade, advances in the field have been counterbalanced by a rising number of immunosuppressed patients with a multitude of new risk factors for infection and an ongoing emergence of antimicrobial resistance.

In recent years, a shift in the epidemiology of infections in febrile neutropenic patients in several parts of the world has been observed towards predominance of Gram-positive infections. This trend has not been corroborated in prior studies from Lebanon where Gram-negative organisms still occupied the biggest share of infecting agents, and where mortality rates were significant. In this observational cohort study, we describe the characteristics of patients presenting with febrile neutropenic episodes during the first three years of the 21st century, and compare the results to two studies published previously from the same institution to assess temporal trends over the past decade.

Materials and methods

Study location and patients

The study was conducted between January 2001 and December 2003 at the American University of Beirut Medical Center (AUBMC), a 400-bed teaching hospital in Lebanon. Eligible patients were individuals at least 13 years of age with neutropenic fever following chemotherapy. Patients were included more than once if they developed a second episode of neutropenic fever during the study period. The definitions of fever and neutropenia were based on the latest published guidelines of the Infectious Diseases Society of America (IDSA) on neutropenic fever. A focal infection was considered present if the patient had symptoms, radiographic evidence, or a positive culture suggestive of infection at a particular site. Patients were followed daily throughout their hospital stay and information was collected in a prospective fashion.

Table 1

<table>
<thead>
<tr>
<th>Organism</th>
<th>1995–98 (N = 104)</th>
<th>1999 (N = 50)</th>
<th>2001–04 (N = 177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative organisms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>9 (8.7)</td>
<td>4 (8.0)</td>
<td>17 (9.6)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>5 (4.8)</td>
<td>3 (6.0)</td>
<td>4 (2.3)</td>
</tr>
<tr>
<td><em>Klebsiella spp</em></td>
<td>2 (1.9)</td>
<td>0</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td><em>Enterobacter spp</em></td>
<td>0</td>
<td>1 (2.0)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td><em>Acinetobacter spp</em></td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Salmonella enteritidis</em></td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Bacteroides spp</em></td>
<td>0</td>
<td>1 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Gram-positive organisms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoNS</td>
<td>6 (5.8)</td>
<td>1 (2.0)</td>
<td>8 (4.5)</td>
</tr>
<tr>
<td>MSSA</td>
<td>2 (1.9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MRSA</td>
<td>2 (1.9)</td>
<td>3 (6.0)</td>
<td>0</td>
</tr>
<tr>
<td>Viridans streptococcus</td>
<td>1 (1.0)</td>
<td>1 (2.0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Group D streptococcus</td>
<td>0</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td><em>Enterococcus spp</em></td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Bacillus spp</em></td>
<td>0</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>0</td>
<td>1 (2.0)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>0</td>
<td>0</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>No growth</td>
<td>74 (71.2)</td>
<td>35 (70.0)</td>
<td>144 (81.4)</td>
</tr>
</tbody>
</table>

CoNS, coagulase-negative staphylococci; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Statistical analysis

Data were entered into a database using SPSS 11.0 for Windows (SPSS Inc, Chicago, IL, USA). Bivariate analysis was performed using the Chi-square test for categorical variables and the independent samples t-test for continuous variables. Variables that were significant on bivariate analysis were entered into a multivariate logistic regression model using Stata 7.0 (Stata Corporation, College Station, TX, USA).

Ethical considerations

The study was approved by the Institutional Review Board at AUBMC. Since this was an observational study, informed consent was waived.

Results

Patient characteristics

During the study period, we identified 177 episodes of neutropenic fever in 116 patients. Patient age ranged from 15 to 86 years, with a mean of 47.8 years. The most common underlying malignancy was lymphoma (42.4%), followed by leukemia (34.5%), and solid tumors (16.4%). Prophylactic antibiotics had been given in 32 cases (18.1%).
Description of neutropenic fever episodes

The mean duration of neutropenia in our patient population was 7.2 days. The majority of patients (62.2%) had severe neutropenia, as defined by an absolute neutrophil count less than 100 cells/mm³. Neutropenic episodes were labeled as clinically documented infections (46.9%), microbiologically documented infections (29.4%), or fever of unknown origin (23.7%). The most common source of infection was the abdominal and gastrointestinal tract (31.6%), followed by the respiratory system (20.9%).

Bloodstream infections

Positive blood cultures were documented in 33 episodes of neutropenic fever (18.6%) (Table 1). This represents a lower rate compared to previous years (30% in 1999 and 28.8% in 1995–98). Gram-negative organisms were responsible for 26 of 33 documented bloodstream infections compared to 11 of 33 infections with Gram-positive organisms. The rate of Gram-negative bloodstream infections exceeded that of Gram-positive bloodstream infections (14.7% vs. 6.2%), similar to the trend seen in the earlier studies, although to a different degree. Whereas in the period from 1995 to 1998 the ratio of Gram-positive to Gram-negative infections was 1.5:1, this ratio became 1.8:1 in 1999, and in the current study it was 2.4:1. Among the Gram-negative organisms, Escherichia coli has been consistently the most commonly isolated organism, followed by Pseudomonas aeruginosa. Similarly in the Gram-positive bacteremia group, coagulase-negative staphylococci continue to represent the majority of isolates. On the other hand, there were five episodes of polymicrobial bloodstream infections in the latest patient sample, which is a new and unique feature compared to the earlier cohorts.

Treatment

Cefepime was the antimicrobial agent most commonly used as first-line therapy in the studied episodes of neutropenic fever (50.3%), followed by ceftazidime (36.7%) and piperacillin/tazobactam (10.2%). Glycopeptides were used as additional first-line empiric treatment in 37 cases (20.9%). Antifungal agents were used in 101 cases (57.1%), fluconazole being used the most.

Outcome

Fourteen episodes of neutropenic fever (7.9%) led to a fatal outcome, giving an in-hospital mortality rate of 12.1%. On multivariate analysis, the only two variables associated with increased in-hospital mortality were treatment modification for clinical deterioration (OR = 21.26; 95% CI 4.14–109.25) and duration of neutropenia (OR = 1.14; 95% CI 1.03–1.26).

Discussion

Until recently, the epidemiology of neutropenic fever in Lebanon has been poorly described. Between 1995 and 1998, a prospective analysis of 104 episodes of neutropenic fever was reported, and in 1999, a follow-up study was done describing 50 consecutive episodes. The current study was carried out with the intention of testing the persistence of the previously observed findings and to describe in more detail the characteristics and outcome of patients with neutropenic fever.

The etiology of bacteremia in febrile neutropenic patients has witnessed momentous changes in the past few decades. Whereas in the 1950sconstituted the principal players throughout the 1990s, spearheaded by coagulase-negative staphylococci. Yet infections in the setting of neutropenic fever are proving to be quite dynamic, as a new trend is now starting to come into view, where Gram-negative organisms seem to be resurfacing. Several factors have been implicated in this ever-changing epidemiology, namely the increased placement of indwelling catheters, the administration of antimicrobial prophylaxis, the nature of chemotherapeutic regimens currently in use, as well as several environmental conditions that are still poorly elucidated.

In Lebanon, the pattern of infecting organisms in febrile neutropenic patients has been rather static in direction but not in magnitude. Data from this country extending over the past decade have consistently found a higher prevalence of Gram-negative infections. Not only did we show that Gram-negative organisms caused 26 of 33 bloodstream infections in the current study, we also noted that the gap is widening between Gram-positive and Gram-negative infections over time.

This trend does not seem to be shared by other countries in the region, where all studies have confirmed the predominance of Gram-negative infections. However, one report from Pakistan has recently shown a slight preponderance of infections with Gram-negative organisms (53%) compared to Gram-positive organisms.

A possible explanation of the observed high incidence of Gram-negative infections in Lebanon is the relatively low proportion of patients with indwelling catheters, although increased prevalence of Gram-positive infections has also been reported from other centers where long-term catheters are not commonly used. Another probable contributing factor is the low proportion of patients receiving antimicrobial prophylaxis compared to other studies. Prophylactic regimens containing old generation quinolones lack effective coverage against Gram-positive organisms and thus predispose to breakthrough Gram-negative infections. However, such regimens also promote the emergence of resistance among Gram-negative pathogens. At a time when there is a dire need to contain the rising antimicrobial resistance in Gram-negative organisms in Lebanon, and in the absence of a clear and consistent survival benefit, the decision to administer antimicrobial prophylaxis in febrile neutropenic patients should take into consideration the risks and benefits of this practice.

We found an in-hospital mortality of 12.1% in the present analysis compared to 20% in the two previous studies at AUBMC. These results are still slightly higher but more comparable to recent published data documenting mortality rates ranging between 4 and 7%. The decrease in the proportion of high-risk patients with leukemia in favor of...
patients with lymphoma and solid tumors, usually classified in the intermediate or low-risk group, could partially account for the observed decrease in in-hospital mortality. Nonetheless, in a developing country like Lebanon with limited resources, a lower in-hospital mortality rate commensurate with worldwide reports was achieved in this high-risk population.

Conclusions

In this third study from AUBMC describing the characteristics of patients with neutropenic fever, a continually increasing prevalence of Gram-negative infections was observed. This divergence from the worldwide reported data that denotes a predominance of Gram-positive infections underscores the importance of tailoring and revising international protocols and guidelines to correspond to the unique composition of our patient population. The considerable reduction in in-hospital mortality that has been achieved over the years attests to the success of this strategy.

Conflict of interest: No conflict of interest to declare.

References


