INFECTIONS IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES

Etiology, trends and management

HONAR CHERIF

Stockholm 2005
To my family
Whoever seeketh knowledge and findeth it, will get two rewards; one of them the reward for desiring it, and the other for attaining it; therefore, even if he do not attain it, for him is one reward.

The prophet Muhammad (570-632)
ABSTRACT

Infectious complications are an important cause of morbidity and mortality in patients with hematological diseases, especially during chemotherapy induced neutropenia. This study was undertaken with the ultimate goal to improve the clinical management of infections in patients with hematological diseases.

In a relatively large hematology centre where antibiotic prophylaxis was generally not used, the incidence of bacteremia and the spectrum of causative pathogens during the period 1988-2001, were determined. No tendency to a shift from gram-negative to gram-positive etiology was noted. Except for a significant increase in Enterococcus faecium bacteremia, the species distribution was essentially stable. The rates of antimicrobial resistance were low. The 7- and 30-day mortality rates were 6.3 and 15.6%, respectively.

Species distribution and triazole susceptibility of colonising yeasts in neutropenic patients treated for hematological malignancies were prospectively analysed. Previous exposure to fluconazole prophylaxis was not associated with a shift from Candida albicans to non-albicans Candida species. However, fluconazole MICs were significantly higher in yeast isolates from patients who had received prophylaxis, indicating that azole prophylaxis may contribute to the emergence of less susceptible yeast strains.

Cefepime monotherapy was, in a prospective randomised study, found to be as safe and as effective as imipenem-cilastatin in the management of febrile neutropenia in patients treated for hematological malignancies. In patients with neutropenia and fever of unknown origin (FUO), the early discontinuation of all antibiotic therapy 48 hours after fever defervescence was not associated with an increased rate of fever relapse or mortality. This therapeutic approach seems promising in patients with FUO. Prospective large randomised trials are warranted.

The Multinational Association of Supportive Care in Cancer (MASCC) risk-index score was validated in patients with hematological malignancies. The risk-index identified patients with febrile neutropenia who were at low risk for the development of serious medical complication with a specificity, sensitivity and positive predictive value of 87%, 58% and 84%, respectively. Accordingly, this risk-index was found to be a valuable tool for the identification of low-risk patients.

A substantial proportion (36%) of low-risk patients with febrile neutropenia were ineligible for oral antibiotic therapy; while the remaining 64% received oral antibiotic treatment following discharge from the hospital 24 hours after fever defervescence. Upon final evaluation 95% remained afebrile and there was no early mortality in this group. The strategy of early hospital discharge with oral antibiotic therapy of carefully selected low-risk patients offered a feasible, safe and cost-effective alternative to the conventional management of these patients.

Splenectomy is associated with increased risk to pneumococcal infections. Antibody response to vaccination with 23-valent pneumococcal polysaccharide vaccine in splenectomised patients with hematological disorders was determined. A substantial proportion (28%) of these patients had a poor antibody response to vaccination. During the long follow-up period (median observation time 7.5 years) all recorded episodes of pneumococcal infections were confined to poor responders. Patients who had a poor response to vaccination did not benefit from revaccination. With the possible exception of age, no other clinical characteristics could predict a poor antibody response. Poor responders should be offered other prophylactic measures.
LIST OF PUBLICATIONS

This thesis is based on the following papers, which are referred to in the text by their roman numerals:


V. Cherif H, Johansson E, Björkholm M, Kalin M. The feasibility of early hospital discharge with oral antimicrobial therapy in low risk patients with febrile neutropenia following chemotherapy for hematological malignancies. *Submitted for publication*
# TABLE OF CONTENTS

Background .................................................................................................................. 1
Definitions ...................................................................................................................... 2
Etiology ......................................................................................................................... 2
Bacterial infections ....................................................................................................... 2
  Antibacterial prophylaxis .......................................................................................... 5
Fungal infections ......................................................................................................... 6
  Diagnosis .................................................................................................................. 6
  Treatment ............................................................................................................... 7
  Antifungal prophylaxis ............................................................................................ 9
  *Pneumocystis jiroveci* infection ......................................................................... 10
Viral infections .......................................................................................................... 11
Catheter related infections ......................................................................................... 13
Infections in splenectomised patients ....................................................................... 14
Management of patients with febrile neutropenia ..................................................... 17
Clinical examination ................................................................................................. 17
Investigations .............................................................................................................. 17
Risk stratification ....................................................................................................... 18
Fever of unknown origin in neutropenic patients ....................................................... 19
Empirical antibiotic treatment ................................................................................. 20
Combination antibacterial therapy versus monotherapy .......................................... 20
Oral antibiotic therapy ............................................................................................... 21
  The role of glycopeptides ....................................................................................... 22
Empirical antifungal therapy ..................................................................................... 22
Modification of initial antibiotic treatment ............................................................... 23
Duration of antimicrobial therapy .......................................................................... 24
Granulocyte transfusions ......................................................................................... 25
Colony stimulating factors ....................................................................................... 25
Immunoglobulin prophylaxis ..................................................................................... 26
Purpose of the present investigation ....................................................................... 28
Epidemiological and antibiotic resistance trends ..................................................... 29
  Bacteremia in hospitalized patients with malignant blood disorders .......... 29
  Triazole susceptibility of colonizing yeasts in relation to fluconazole prophylaxis .. 32
Therapeutic studies .................................................................................................. 35
  Cefepime as monotherapy in the empirical treatment of febrile neutropenia ........ 35
  The safety and feasibility of early discontinuation of antibacterial therapy in neutropenic patients with FOU ................................................................. 37
  Early hospital discharge with oral antimicrobial therapy in low-risk patients with febrile neutropenia ............................................................... 38
  Pneumococcal vaccination in splenectomised patients ......................................... 43
Summary and conclusions .......................................................................................... 47
Acknowledgements .................................................................................................. 48
References ................................................................................................................... 50
LIST OF ABBREVIATIONS

AmB  Amphotericin B
ANC  Absolute neutrophil count
BDG  Beta-D-Glucan
CLL  Chronic lymphocytic leukemia
CMC  Cytomegalovirus
CNS  Coagulase negative staphylococci
CRI  Catheter related infection
CRP  C-reactive protein
CVC  Central venous catheter
FUO  Fever of unknown origin
G-CSF  Granulocyte colony-stimulating factor
GM-CSF  Granulocyte-macrophage colony-stimulating factor
HL  Hodgkin lymphoma
HRCT  High resolution computed tomography
HSCT  Hematopoietic stem cell transplantation
IATG-EORTC  International Antimicrobial Group of European Organisation of Research and Treatment in Cancer
IDSA  Infectious Disease Society of America
IFI  Invasive fungal infection
IL  Interleukin
MASCC  Multinational Association of Supportive Care in Cancer
MIC  Minimal inhibitory concentration
OPSI  Overwhelming postsplenectomy infection
OVS  Oral viridans streptococci
PS  Polysaccharide
PCP  Pneumocystis jiroveci pneumonia
PCR  Polymerase chain reaction
PCT  Procalcitonin
RSV  Respiratory syncytial virus
VRE  Vancomycin-resistant enterococci
CHAPTER 1

INTRODUCTION

BACKGROUND

Infectious complications are an important cause of morbidity and mortality in patients with hematological diseases, especially in those receiving chemotherapy. Infection, with or without bleeding, is the direct cause of death in about 50-80% of patients dying with acute leukemia and in about 50% of those dying with malignant lymphoma. There are often multiple factors that predispose these patients to infections such as neutropenia induced by therapy or bone marrow involvement, hypogammaglobulinemia, T-cell dysfunction, asplenia, and mucosal damage. Febrile neutropenia is still the most important factor limiting the planned intensity of antineoplastic chemotherapy. Compelling delays in treatment or reduced dosage with potential implications for the effectiveness of antineoplastic therapies. The incidence and severity of infections in this patient population are inversely related to the absolute neutrophil count (ANC) and to the duration of neutropenia, and is highest when granulocyte counts fall below 0.1x10^9/L. If empirical treatment is not promptly undertaken, mortality in severely neutropenic patients with Gram-negative bacteremia can approach 40%. This provides the rationale for early empirical administration of broad-spectrum antibiotics at the development of fever in neutropenic patients.

The changing pattern of the causative pathogens, the rapid development of bacterial resistance, and the emergence of new clinical problems related to new treatment modalities make the specific composition of infection management complicated and controversial. During the last 10 years clinical research has improved our knowledge regarding many of these issues: Many centres are reporting an increase in the incidence of gram-negative bacteremia; cefepime and piperacillin-tazobactam have been reported to be safe and effective as monotherapy of febrile neutropenia; the importance of congenital factors, intensity of chemotherapy, medical interventions such as antifungal prophylaxis, and vaccinations are recognised as of increasing importance in the determination of risk for infections; it is now possible to identify patients with good prognosis (low-risk) by means of validated scoring systems; the feasibility of oral therapy has been studied in low-risk patients with febrile neutropenia; the empirical addition of glycopeptides in persistently febrile neutropenic patients is discouraged; opportunistic infections related to newly developed anticancer agents such as purine analogs and monoclonal antibodies are better understood and prevented.

However, for the optimal treatment or, better still, prevention of infections in patients with hematological disorders there is still much to be done.
DEFINITIONS

**Fever.** A body temperature which is clearly greater than normal constitutes a febrile state. In practice, a single oral temperature measurement (or tympanic thermometry) of \( \geq 38.5 \, ^\circ C \) or a temperature \( \geq 38.0 \, ^\circ C \) for at least 4 hours in the absence of obvious environmental causes, is usually defined as fever.

**Neutropenia** is an absolute neutrophil count (ANC) of \( < 0.5 \times 10^9/L \), or a count \( < 1.0 \times 10^9/L \) with a predicted decrease to \( < 0.5 \times 10^9/L \). Increased susceptibility to infection is expected when ANC decreases to \( < 1.0 \times 10^9/L \), with a frequency and severity inversely proportional to neutrophil counts.\(^8\)

**Opportunistic infections** are defined as any infection that occurs with increased frequency and severity almost exclusively in immunocompromised patients.

**Breakthrough bacteremia** is the development of continuous or new onset of bacteremia whilst receiving appropriate antibiotics against the microorganism recovered in the cultures.

**Classification of febrile neutropenia episodes.** Unexplained fever or fever of unknown origin (FUO) is defined as a new fever not accompanied by clinical or microbiological evidence of infection. Clinically documented infection is defined as fever accompanied by an ambiguous, clinically localised evidence when pathogens can not be identified, e.g. pneumonia or cellulitis. A microbiologically documented infection is present if the infection has been localised and microbiologically plausible evidence has been found, or if an infectious agent can be demonstrated in a blood culture even if a localised infection can not be identified.

**Hematopoietic stem cell transplantation (HSCT)** is the infusion of hematopoietic stem cells from a donor into a patient who has received chemotherapy, which is myeloablative or suppressive (non-myeloablative). The source of stem cells may be bone marrow, peripheral blood or placenta/umbilical cord blood. The transplant type may be allogeneic or autologous.

ETIOLOGY

**BACTERIAL INFECTIONS**
Bacterial infections mostly develop due to translocation of gram-negative bacilli from the intestinal tract or of gram-positive cocci from skin or oral cavity into the blood stream (bacteremia). Apart from fever, bacteremia can occur without any striking symptoms and can rapidly evolve to septic shock. The crude mortality rate of bacteremia during neutropenia amounts to 10-15% overall.

Historically, gram-negative bacilli have been the most prominent pathogens in neutropenic hosts. During the 1960s and mid-1970s, *Escherichia coli, Klebsiella*
species and *Pseudomonas aeruginosa* accounted for the majority of microbiologically documented infections. However, the pattern of infective pathogens has changed significantly over time (Figure 1). Several studies have clearly documented that Gram-positive cocci, predominantly coagulase negative staphylococci (CNS), *Staphylococcus aureus*, enterococci and alpha hemolytic streptococci, which were prevalent in the 1950s and early 1960s, became again more prevalent in the mid-1980s.10, 11

These trends have been confirmed by the findings in the therapeutic trials that the International Antimicrobial Group of the European Organization for Research and Treatment in Cancer IATG-EORTC have performed.12-16 The selective pressure of antibiotics (Table 1); the more intensive treatment of cancer leading to more severe damage to mucosal barriers and increased risk for infection from the resident gastrointestinal flora; the increasing use of proton pump inhibitors; and the frequent use of indwelling vascular catheters constituted, most probably, the most important contributing factors.17, 18 Very recently, there were some indications that the etiological pattern of pathogens causing bacteremia is changing again. In the most recent trial performed by the IATG-EORTC, there was an increase in the rate of bacteremia among all febrile and neutropenic episodes (from 23% to 28%; p= 0.03). This was mainly due to an increase in the proportion of gram-negative bacteremia (from 6.5% to 12%; p < 0.01).19 A similar pattern with an again increasing incidence of gram-negative bacteremia is reported in other recent studies.20-24

The reason for this cyclic variation of infecting pathogens is probably multifactorial and it is today unclear to what extent the new increase in gram-negative infections is associated with a decreasing use of quinolone prophylaxis or with the increase in quinolone resistance. However, for the correct interpretation of results from epidemiological surveys, it is worth to mention that the majority of these surveys focus only on bacteremia. This may result in an incomplete or inaccurate picture, as only 15-30% of patients with neutropenia develop bacteremia. Moreover, bacteremia are predominantly caused by gram-positive microorganisms whereas infections at other sites are predominantly gram-negative or polymicrobial.25, 26 Another important information is that the proportion of polymicrobial infections, which may be as high as 23%27 is often ignored in epidemiological surveys.
Among the enterococci, *Enterococcus faecium* has overtaken *Enterococcus faecalis* as the most common organism and vancomycin-resistant Enterococci (VRE) have been reported from many centres. \(^2^8\) Resistance among viridans streptococci, especially *Streptococcus mitis* and *Sreptococcus salivarius*, has also become an issue. \(^2^9\) Drug resistance has become an important problem for gram-negative pathogens as well. The use of fluoroquinolones for prophylaxis has been associated with the emergence of resistance in *E. coli* and *P. aeruginosa*. \(^3^0, 3^1\) Anaerobic bacteremia occurs in less than 5% of patients with febrile neutropenia, a percentage that remained unchanged over the past 30 years. \(^2^6\)

Breakthrough bacteremias, i.e. positive blood cultures despite appropriate antibiotic therapy, are not uncommon in neutropenic patients treated for hematological malignancies. The pathogenesis of these breakthrough infections is not completely understood. Some have related anecdotal cases of breakthrough bacteremia to the use of unsuitable antibiotics (drug resistance or low therapeutic level of active drug). Others have related it to particular types of microorganisms. In a recent retrospective analysis of 6,324 episodes of bacteremia, by Lopez-Dupla and coworkers, \(^3^2\) breakthrough bacteremia was detected in 329 (6.1%) episodes. The most frequent source of infection in breakthrough bacteremia was central intravenous devices (70% of episodes). CNS, *S. aureus*, and *P. aeruginosa* were the most frequent microorganisms involved. The crude mortality rate was greater in patients with breakthrough bacteremia (16% vs. 12.3%). These findings indicate the importance of searching after endovascular focus of infection in patients with breakthrough bacteremia. Early adequate management with appropriate antibiotics together with withdrawing of venous catheters when no other apparent source of breakthrough bacteremia is found may be lifesaving.

The causative pathogen usually defines the clinical course of the febrile illness. For example, bacteremia due to CNS hardly ever leads to severe sepsis and is rarely fatal (even though treatment with initial empirical antibiotics is often not adequate), while bacteremia due to alpha hemolytic streptococci may be complicated by development of organ failure. On average bacteremia caused by *S. aureus* and streptococci takes longer to resolve than that by most other pathogens. \(^3^3\) Polymicrobial bacteremia, bacteremia due to *Pseudomonas* species and bacteremia leading to shock as well as bacteremia associated with pneumonia or extensive soft tissue infection usually take a less favourable course. \(^3^4\)

Some recently recognised congenital and acquired factors may also influence the clinical course of a bacterial infectious episode: Genetically determined serum deficiency of mannose-binding lectin, an important component of the innate immune system, seems to influence the duration of fever during the neutropenic episodes; \(^3^5\) antifungal prophylaxis with absorbable drugs was, in a multivariate analysis, associated with a slightly increased risk of bacteremia; \(^3^6\) furthermore, the substitution of piperacillin-tazobactam for third generation cephalosporins has, in retrospective studies, been reported to be associated with a reduced colonisation with vancomycin resistant enterococci (VRE). \(^3^7\) However, this has not been proven to be an effective control measure for VRE when used prospectively as an antimicrobial formulary
Recent studies suggest that non-myeloablative conditioning regimens during allogeneic hematopoietic stem cell transplantation (HSCT) may decrease the risk for bacterial infections. There are data supporting the view that infection morbidity and mortality may be improved in patients who receive non-myeloablative conditioning regimens. The treatment of bacterial infections is discussed later in this chapter.

**Table 1. Most commonly isolated pathogens causing bacteremia in patients with febrile neutropenia and the influence of antibacterial prophylaxis on organisms isolated.**

<table>
<thead>
<tr>
<th>Isolated pathogens (%)</th>
<th>Winston et al.⁴¹</th>
<th>Cherif et al.¹</th>
<th>Del Favero et al.⁴²</th>
<th>Cordonnier et al.⁴³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis administered</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gram-positive organisms</td>
<td>127 (44.4)</td>
<td>767 (54.7)</td>
<td>166 (66.1)</td>
<td>112 (67.1)</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>14 (4.9)</td>
<td>125 (8.9)</td>
<td>14 (5.6)</td>
<td>14 (8.4)</td>
</tr>
<tr>
<td>CNS</td>
<td>44 (15.4)</td>
<td>245 (17.5)</td>
<td>110 (43.8)</td>
<td>52 (31.1)</td>
</tr>
<tr>
<td><em>Streptococcus</em> species</td>
<td>41 (14.3)</td>
<td>178 (12.7)</td>
<td>31 (12.4)</td>
<td>34 (20.4)</td>
</tr>
<tr>
<td><em>Enterococcus</em> species</td>
<td>14 (4.9)</td>
<td>103 (7.3)</td>
<td>5 (2.0)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (4.9)</td>
<td>116 (8.1)</td>
<td>6 (2.4)</td>
<td>6 (3.6)</td>
</tr>
<tr>
<td>Gram-negative organisms</td>
<td>159 (55.6)</td>
<td>635 (45.3)</td>
<td>85 (33.9)</td>
<td>55 (32.9)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>63 (22.0)</td>
<td>228 (16.3)</td>
<td>41 (16.3)</td>
<td>30 (18.0)</td>
</tr>
<tr>
<td><em>Klebsiella</em> species</td>
<td>39 (13.6)</td>
<td>133 (9.5)</td>
<td>4 (1.6)</td>
<td>...</td>
</tr>
<tr>
<td><em>Pseudomonas</em> species</td>
<td>5 (1.7)</td>
<td>77 (5.5)</td>
<td>24 (9.6)</td>
<td>13 (7.8)</td>
</tr>
<tr>
<td>Other</td>
<td>52 (18.2)</td>
<td>197 (14)</td>
<td>16 (6.4)</td>
<td>12 (7.2)</td>
</tr>
<tr>
<td>Total</td>
<td>286</td>
<td>1402</td>
<td>251</td>
<td>167</td>
</tr>
</tbody>
</table>

CNS: coagulase negative staphylococci

**Antibacterial prophylaxis**

The benefits of oral antibacterial prophylaxis in neutropenic patients are debatable. Fluoroquinolones, especially ciprofloxacin, are still the most commonly used antibiotic for prophylaxis. Several studies have reported a decrease in the incidence infections, in particular of gram-negative infections, when using antibiotic prophylaxis.⁴⁴-⁴⁷ Meanwhile, the intensive use of fluoroquinolones for prophylaxis and treatment has led to an increased resistance to these agents,⁴⁸-⁵² which limits their clinical efficacy. Furthermore, the emergence of cross resistance between fluoroquinolones and other unrelated classes of antibiotics has been reported.³⁰, ⁵³ Another disadvantage of quinolone prophylaxis is the inadequate coverage of gram-positive bacteria. Consequently, the practice of administrating antimicrobial prophylaxis to patients with neutropenia has been questioned for many years. Two large meta-analyses were unable to provide evidence for a reduction of infection-related mortality among patients receiving antibacterial prophylaxis.¹⁸, ⁵⁴ Accordingly, the routine use of fluoroquinolones prophylaxis during neutropenia should be avoided.
**Fungal Infections**

Systemic/invasive fungal infections (IFI) represent one of the leading causes of morbidity and mortality in chemotherapy-treated patients with hematological malignancies.\(^{55}\) Up to 50% of these patients have evidence of IFI at autopsy\(^ {56}\) and according to a recent survey, the 1-year survival of allogeneic HSCT patients who were diagnosed to have IFI was only 20%.\(^ {57}\) Moreover, the incidence of fungal infections has increased substantially during the past 30 years, with *Candida* and *Aspergillus* being the most common fungi causing infections in this setting.

*Candida* species are a normal part of the microflora of the oropharynx and the gut. Invasive candidosis can present as acute or chronic disseminated disease and is generally preceded by colonisation of mucosal surfaces, which is an important risk factor for candidemia. Other major risk factors for systemic candidal infection in neutropenic patients include: the use of antibiotics, corticosteroids, bacterial infections, graft versus host disease and intravenous catheter devices.\(^ {58}\) Systemic aspergillosis is most commonly manifested as invasive pulmonary aspergillosis. It is usually caused by *Aspergillus fumigatus* although other species, such as *A. terreus* and *A. flavus* may also be found. In contrast to candidosis, aspergillosis is invariably acquired through the respiratory tract. Risk factors as graft-versus host disease, high doses of corticosteroids, and recurrent prolonged neutropenia may explain the increasing rate of pulmonary aspergillosis among recipients of HSCT.

**Diagnosis**

Progress has been made over the last years concerning diagnostic tests and procedures for IFI including the use of high resolution computer tomography (HRCT) and surrogate markers. A rapid diagnostic tool is direct microscopy. Morphological characteristics may help differentiating between yeasts, zygomycetes and other moulds. The detection of hyphal elements provides strong evidence of the presence of IFI. Cultures are especially helpful for the diagnosis of blood stream infection caused by yeast, but are of limited value in the diagnosis of aspergillosis. Fungal cultures of BAL fluid are positive in only 30-50% of cases and importantly, they become positive at a late stage of infection.

Detection of fungal DNA in biological samples by polymerase chain reaction (PCR) is a promising technique and has been intensively evaluated as a diagnostic tool.\(^ {59}\) Genomic fungal DNA can be detected in the blood of patients with IFI before diagnosis by conventional methods. Furthermore, quantitative PCR techniques can also be used for monitoring fungal burden and a patient’s response to treatment.\(^ {60}\) A major drawback is the low number of positive whole blood samples in which fungal DNA is detected when consecutive samples are obtained from infected patients.\(^ {61}\) Other problems are related to lack of a commercial product, cost, and risk of false positive results. Furthermore, the performance of PCR detection is affected by exposure of patients to prophylactic antifungal agents. The sensitivity of PCR in patients receiving antifungal agents may be as low as 40%.\(^ {62}\)
Galactomannan, a cell wall-associated molecule, which is released by all medically important *Aspergillus* species, can be detected in the blood by use of ELISA. Circulating galactomannan antigen can be detected at a median of 8 days (range, 1-27 days) before a diagnosis of IFI can be made by other means. Major drawbacks of this test is the variability in its performance (sensitivity 50% to 92%), low sensitivity in patients treated with antifungal agents and false positive ELISA reactivity in patients receiving certain beta-lactam antibiotics including piperacillin and amoxicillin-clavulanic acid. Beta-D-Glucan (BDG) is another cell wall component of most medically important fungi which can be detected by commercial methods. In a study testing serial serum samples obtained from 283 subjects with hematological malignancies, at least one serum sample was positive for BDG at a median of 10 days before clinical diagnosis in 100% of subjects with IFI. Again, a drawback of this test is false positive ELISA reactivity. Further studies are awaited to improve our experience with this assay.

Characteristic lesions caused by *Aspergillus* infection can be visualised by using HRCT scanning. Nodular lesions and the so called halo sign are seen early in the course of infection, while the air crescent sign is usually visible following recovery of neutropenia. Unfortunately, in many patients with pulmonary fungal infections the lesions may be atypical. The use of HRCT together with markers of fungal infections has improved our ability to identify patients that need antifungal therapy.

**Treatment**

Several antifungal agents are currently available including polyenes (Amphotericin B (AmB) deoxycholate and lipid formulations of Amphotericin B), triazoles (fluconazole, itraconazole, and voriconazole), flucytosine and echinocandins (caspofungin).

**Candida.** In a prospective randomised study, Anaissie and coworkers suggested an equal efficacy of fluconazole and AmB in the treatment of candidemia. Accordingly, candidemia without evidence of deep-site infection may be adequately treated with fluconazole alone if the patient had noazole prophylaxis. Treatment needs to be continued for at least two weeks after eradication of Candida from blood cultures and resolution of all clinical manifestations, but at any rate until neutrophil recovery. For patients with chronic disseminated candidiasis therapy has to be continued for up to 6 months until resolution of fungal manifestations.

Caspofungin, an echinocandin, is a relatively new antifungal agent with activity against Candida and Aspergillus; it targets the fungal cell wall and it retains activity against isolates with resistance to azoles or polyenes. Caspofungin was compared recently with conventional AmB in the treatment of invasive candidiasis and was found to be at least as effective, in patients with neutropenia. In candidemia, the response rates for caspofungin and AmB were 72% and 63% respectively. The mortality rate was similar in the two treatment groups, but proportion of patients
Infections in patients with hematological malignancies

with drug related adverse events was significantly higher in the AmB group.\textsuperscript{68} Cryptococci are known to be resistant to echinocandins.

\textbf{Aspergillus.} The duration of therapy and the recovery of neutropenia are important factors for the success of aspergillosis treatment. A number of studies have shown that liposomal AmB is less toxic and as effective as conventional AmB.\textsuperscript{71, 72} The response rates are between 30-60\%.\textsuperscript{72, 73} In a study by Leenders and coworkers\textsuperscript{74} a higher response rate on day 14 in proven and suspected systemic mycoses and a better outcome in patients with progressive underlying malignancy was reported with liposomal AmB as compared with AmB deoxycholate.

Voriconazole, a broad spectrum triazole that is active against both \textit{Candida} and \textit{Aspergillus} species, was compared with AmB in a randomized trial in patients with invasive aspergillosis.\textsuperscript{75} In this study which was the largest controlled trial ever mounted to assess the efficacy of an antifungal agent, initial treatment with voriconazole led to better response rates (53\% versus 31\%) and improved survival and resulted in fewer severe side effects than the standard approach of initial therapy with AmB (Figure 2). Voriconazole has established itself as a new standard for treatment of aspergillosis. Itraconazole is also active against \textit{Aspergillus} species, but its questionable bioavailability makes the drug less suited to use under critical circumstances.

One of the major limitations of azoles is their propensity to interact with co-administered drugs. All azoles inhibit CYP3A4, the primary oxidative drug metabolizing enzyme in humans. Caspofungin has proved useful for treating infection due to resistant fungi\textsuperscript{68} and is a potential drug for the treatment of invasive aspergillosis especially in patients with refractory aspergillosis and/or intolerance to voriconazole and AmB formulations.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Survival of the modified intention-to-treat population according to treatment group. Figure is reproduced after permission from the publisher.\textsuperscript{75}}
\end{figure}

Several in vitro and animal studies have shown antagonism between azoles and AmB for aspergillosis. Meanwhile, combination therapy with AmB and flucytosine is
considered to be the treatment of choice for cryptococcal infections. The combination of azoles and echinocandins may have additive activity against *Aspergillus* species. The effect of this combination was evaluated for salvage therapy in 16 patients and was found to be associated with an improved 3-month survival rate, compared with voriconazole alone. However, randomised trials are needed to determine whether this combination should be considered for primary therapy of aspergillosis.

Cytokines as G-CSF and GM-CSF have been shown to shorten the period of neutropenia and enhance neutrophil and macrophage activities. However, the addition of growth factors to systemic antifungal therapy has not improved survival. Finally, surgery may be lifesaving in some cases with severe localised fungal infections.

**Antifungal prophylaxis**

Given the difficulties in the diagnosis and successful treatment of fungal infections, antifungal prophylaxis may be appropriate in high-risk patients treated at institutions in which these infections are encountered frequently. Fluconazole prophylaxis has been used in patients treated with allogeneic HSCT and has been shown to reduce the frequency of IFI. A recent randomised, double blind trial of 274 adult neutropenic patients with cancer showed that fluconazole prophylaxis reduced the incidence of both superficial and invasive fungal infections and fungal related death. Antifungal prophylaxis with itraconazole was studied in two large randomised, double-blind trials showing its efficacy in reducing systemic fungal infections due to *Candida*. One of these trials showed a decrease in the *Candida* associated mortality rate. In a systemic meta-analytical review by Bow and coworkers, the efficacy of antifungal prophylaxis with azoles or AmB formulations among > 7000 randomised subjects was analyzed. A reduction in the use of empirical antifungal therapy, superficial fungal infection, invasive fungal infection, and the fungal-infection related mortality was observed. These effects were most pronounced in patients with malignant diseases who had prolonged neutropenia and HSCT recipient.

As *Aspergillus* prophylaxis, investigators have studied several options such as: systemic low dose AmB administered daily; lipid formulations of AmB given three times weekly; itraconazole capsules; itraconazole intravenous/oral solution; voriconazole; and echinocandins. However, there is still no consensus on the efficacy of antifungal prophylaxis in neutropenic patients after more than 50 trials. Glasmacher and coworkers have, in a recent review, evaluated the current evidences of the use of antifungal prophylaxis in neutropenic patients with hematological malignancies. The results of four systemic reviews with meta-analysis and one evidence based review without meta-analysis were reviewed. Itraconazole was found to be the only agent effective for prolonged prophylaxis after allogeneic HSCT. Direct comparison between fluconazole and itraconazole for this indication showed superiority of itraconazole being the only drug able to prevent invasive *Aspergillus* infections. Itraconazole prophylaxis, when given in appropriate doses, was associated with reduced IFI by 53% and reduced mortality from IFI by 47% (p < 0.05).
However, concerns about the problem of emerging drug-resistant Candida species due to extensive use of prophylaxis, plus the fact that such prophylaxis has not been shown to consistently reduce overall mortality rates leads to the conclusion that routine antifungal prophylaxis in all neutropenic patients should be avoided. Furthermore, studies conducted in a bone marrow transplant setting do not apply automatically to other categories of patients.

In conclusion, antifungal prophylaxis is presumably warranted in neutropenic patients with high risk for IFI (Table 2). Candida prophylaxis with fluconazole should be restricted to high-risk patients treated in institutions where the frequency of systemic infection due to C. albicans is high and the frequency of infection due to other Candida species and Aspergillus is low. Patients with a prior episode of Aspergillus infection and who are at risk for relapse when receiving additional immunosuppression should be given secondary anti-Aspergillus prophylaxis. Otherwise, antifungal prophylaxis should only be given as a part of a well designed trial.

Table 2. Possible indications for and duration of antifungal prophylaxis in neutropenic patients with hematological malignancies

<table>
<thead>
<tr>
<th>Indications</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with acute leukemia or myelodysplastic syndromes who undergo protracted myelosuppressive chemotherapy with expected duration of neutropenia of more than 7-10 days. Prophylaxis to be restricted to the duration of neutropenia.</td>
<td></td>
</tr>
<tr>
<td>Allogeneic HSCT recipients for the first 100 days (or longer if corticosteroids are administered).</td>
<td></td>
</tr>
<tr>
<td>Autologous HSCT recipients: only if recently received treatment with T-cell suppressive purine analogues. Prophylaxis duration determined individually.</td>
<td></td>
</tr>
</tbody>
</table>

Pneumocystis jiroveci infection

Pneumocystis infection was first described in human in 1942. It was first thought to be a protozoa parasite. Subsequent phylogenic analyses using rRNA sequences suggested the organism to be a fungus. Infection with Pneumocystis jiroveci (PCP) is seen in patients with a broad array of immune deficits, including those caused by organ transplantation, use of corticosteroids, radiation therapy, neutropenia, CD4+ lymphopenia, malnutrition, and malignancies (especially hematological). The infection causes variable presenting symptoms of pneumonia that may evolve over a few days with a severe clinical course, often with a severe hypoxemia. The chest radiograph may be completely normal. A computed tomogram scan often reveals diffuse parenchymal involvement. In most patients, the level of serum lactic dehydrogenase is elevated. However, these clinical or radiological findings are not specific for PCP and the diagnostic technique of choice is the use of immunofluorescent antibodies against surface epitopes from Pneumocystis cysts and trophozoites. PCR assays are also available and may have a higher sensitivity than the use of immunofluorescent antibodies, but are less specific.

Cotrimoxazole is the most effective agent against Pneumocystis and is recommended as the drug of choice for both treatment and prophylaxis. As the
replication of *Pneumocystis* is slow, the use of intermittent medication (usually three times weekly for cotrimoxazole) is usually sufficient to prevent infection (Table 3).

The purine analogs fludarabine, cladribine, and pentostatin are increasingly used in the treatment of indolent lymphomas. These chemotherapeutic agents are immunosuppressive and myelosuppressive. They induce marked lymphocytopenia that develops rapidly following administration of a purine analog, with CD4+ cells primarily affected. These cells decrease within 2-3 months of therapy to levels similar to that observed in AIDS, and remain depressed for several months to years. Patients receiving purine analogs are therefore at increased risk infection with a wide range of opportunistic organisms including *Pneumocystis*. This risk is increased further when purine analogs are given to elderly patients or to patients previously heavily treated with chemotherapy or when purine analogs are combined with corticosteroids or other cytostatics. These patients should receive anti-*Pneumocystis* prophylaxis routinely (Table 3).

**Table 3. Indications for the use of anti-*Pneumocystis* prophylaxis in patients with hematological malignancies**

1. Allogeneic HSCT recipients with high risk:
   - Previous PCP or frequent opportunistic infections
   - CMV disease or high risk for CMV disease
   - Intensive immunosuppression
   - Anti-T-cell therapies

2. Autologous HSCT
   - Intensive conditioning regimens or graft manipulation
   - After purine-analog therapy

3. Prolonged neutropenia, i.e. after chemotherapy for relapsing acute leukemia
4. Treatment with corticosteroid in high doses (>20 mg prednisone per day) for > 2-3 weeks
5. Treatment with purine analogs combined with corticosteroids/other chemotherapy, or high risk patient (elderly, low performance status, previously heavily treated, relapsing disease, neutropenic, or previously treated with purine analogs)
6. Treatment with anti-CD 52 monoclonal antibodies (alemtuzumab)

PCP, *Pneumocystis jiroveci* pneumonia; CMV, cytomegalovirus

**VIRAL INFECTIONS**

Beside increased risk for infection with encapsulated bacteria, patients treated with HSCT are at risk for viral infections including cytomegalovirus (CMV) infection, *Varicella zoster* virus (VZV) infection, and community acquired respiratory virus infection.

**CMV.** Reactivation of CMV may occur in patients treated for hematological malignancies. This is most common in CMV-seropositive allogeneic HSCT patients
and seronegative recipients with seropositive donor (risk patients). Asymptomatic CMV infection occurs in up to 80% of at-risk patients and approximately one-third of these patients subsequently develop symptomatic CMV disease (organ disease, disseminated disease, or pneumonitis). This disease is associated with significant morbidity, decreased patient survival, and considerable cost to health-care systems. CMV disease is difficult to treat. Intravenous ganciclovir, alone or in combination with intravenous immune globulin (IVIG) is often unsuccessful, and 30-70% of patients with pneumonitis succumb to their illness.

Two different strategies are used to prevent post-transplantation CMV disease: (1) prophylaxis; or (2) preemptive treatment. The first strategy involves administration of ganciclovir prophylaxis to all at risk HSCT patients from engraftment to day 100 post transplant. The second strategy involves screening HSCT patient routinely after engraftment for evidence of CMV antigenemia or virus excretion. Treatment is started if CMV screening tests become positive. Several diagnostic methods are used to determine the need for preemptive treatment: (1) detection of CMV pp65 antigen in leukocytes (antigenemia); (2) detection of CMV-DNA by use of PCR; (3) isolation of virus from saliva, blood, urine or bronchoalveolar washings by use of rapid shell-vial culture.

CMV reactivation occurs also during therapy with alemtuzumab with an estimated rate of reactivation of 15-25%. Alemtuzumab is a monoclonal antibody used in the treatment of chronic lymphocytic leukemia and other lymphoid malignancies. It binds to the CD52 antigen which is present on the surface of all lymphocytes. Therefore, it depletes both B- and T-lymphocytes and is associated with a pattern of infections similar to that seen after purine analogs. The window of CMV reactivation peaks between 3 and 6 weeks of therapy, soon after the nadir in T-cell counts. However, CMV disease develop relatively rarely and treatment with ganciclovir is usually followed by a prompt resolution of fever and clearance of CMV viremia. Considering the very low incidence of CMV disease in these patients, it remains questionable whether regular monitoring of virus reactivation is necessary and whether specific antiviral therapy should be given to all patients showing CMV antigenemia and/or PCR positivity.

**Herpes simplex virus.** Both primary and reactivated herpes virus infections are common among patients with hematological malignancies. Herpes simplex virus (HSV) usually causes oral lesions that exacerbate chemotherapy-induced mucositis. However, life threatening disseminated infections may occur in severely immunocompromised patients, necessitating early treatment with antiviral agents. Acyclovir given orally or intravenously is the drug of choice. Moreover, acyclovir prophylaxis reduces HSV-associated morbidity and mortality after HSCT. It should be offered to all HSV-seropositive HSCT recipients to prevent reactivation during the early posttransplantation period. Prophylaxis with acyclovir has also shown to reduce the risk for bacteremia in patients treated for acute leukemia. Patients who are HSV-seronegative should be advised for behaviours that will decrease the risk of HSV transmission.
**Varicella-zoster virus.** Post-transplant VZV infection occurs usually within one year after allogeneic HSCT and is more common among patients with GVHD and patients with acute leukemia as underlying disease. Primary VZV infection may be potentially life threatening, therefore post exposure prophylaxis should be given to all seronegative HSCT recipients. In addition, in order to prevent VZV infection in HSCT patients, susceptible family members, household contacts, and health care workers should be vaccinated against VZV.

**Respiratory viruses (RV).** Over the past several years, the epidemiology and management of other viral infections, especially due to respiratory viruses have received increased focus in patients with hematological malignancies. Ljungman et al. conducted a prospective study of HSCT recipients at 37 centres. Forty RV infections were confirmed in 819 allogeneic and 1154 autologous HSCTs, representing a 3.5% and 0.4% frequency of laboratory confirmed disease, respectively. Twenty patients were diagnosed with respiratory syncytial virus (RSV), 16 with influenza, and four with parainfluenza virus. In this study, the risk for lower respiratory tract disease (2.1% versus 0.2%) and mortality (1.1% versus 0%) was higher in allogeneic recipients than in autologous recipients.

**RSV virus** can be efficiently spread by respiratory droplets and direct contact with infectious material. It is therefore commonly nosocomially acquired and can be prevented by effective infection control methods. Modalities for RSV treatment include ribavirin (aerosolised or intravenous), intravenous antibody preparations (IVIG), and donor lymphocyte infusion (DLI).

**Adenoviruses.** This is a family of DNA viruses which is also found to infect HSCT recipients with an incidence ranging between 3 and 29%. The source of this infection is not documented, but evidence suggests that many of the infections are due to reactivation of latent infection. Diarrhoea and fever are the most common presenting symptoms, although severe infection with multi-organ damage may occur. Infection can sometimes be complicated by graft failure, delayed engraftment and fungal infections.

**CATHETER RELATED INFECTIONS**

*S. aureus* and CNS are the most common causes of catheter related infections (CRI) followed by *Candida* species. Various risk factors for CRI have been identified. Apart from the type and extent of the patient’s immunosuppression, long duration of catheterisation, high frequency of manipulations, and administration of parenteral nutrition are among the main risk factors for CRI. Totally implantable subcutaneous port systems (PORT) may be associated with fewer infections than central venous catheter (CVC). However, due to the risk for extensive local bleeding after placement of PORT in patients with acute leukemia, the use of CVC is still preferred.
Different methods may help in detecting bloodstream infections due to long dwelling catheters before removal of the device: blood samples drawn through the catheter showing a concentration of the same organisms five to ten times higher than that in a blood sample drawn concomitantly from a peripheral vein; a single quantitative culture of a sample drawn from a catheter giving a result of more than 100 colony forming units/ml, and a differential time to positivity of > 120 minutes between culture drawn through the catheter and from the peripheral vein. Vascular access devices may be left in place during antibiotic treatment for most patients, even if infection of local entry site or catheter related bacteremia are observed. Infection due to CNS is most likely to respond to antibiotic therapy alone. However, catheter removal combined with generous debridement of infected tissue may be necessary in many cases (Table 4).

The use of antibiotic-impregnated catheters, the use of all lumens for antibiotic delivery, and the use of antibiotic containing heparin lock solutions have been proposed by some investigators to reduce CRI. Such practices are controversial and not enough studied in patients with neutropenia.

Table 4. Indications for removal of central venous catheters (CVC) in patients with febrile neutropenia

<table>
<thead>
<tr>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVC infection caused by <em>S. aureus</em>, <em>Bacillus</em> spp, <em>Corynebacterium</em> spp, <em>Mycobacterium</em> spp, or fungi</td>
</tr>
<tr>
<td>Progressive exit site infection despite intravenous antibiotic therapy through catheter</td>
</tr>
<tr>
<td>Persistent bacteremia despite intravenous antibiotic therapy through catheter</td>
</tr>
<tr>
<td>Infected tunnel</td>
</tr>
<tr>
<td>Septic thrombosis of central vein or septic pulmonary embolism</td>
</tr>
<tr>
<td>Endocarditis</td>
</tr>
</tbody>
</table>

INFECTIONS IN SPLENECTOMISED PATIENTS WITH HEMATOLOGICAL DISEASES

Splenic macrophages have an important filtering and phagocytic role in removing bacteria and parasitised red blood cells from the circulation. Absence of the spleen allows microorganisms to multiply enormously and to spread rapidly throughout the body and predisposes individuals to risk of overwhelming postsplenectomy infection (OPSI). These infections are most often due to encapsulated bacteria especially *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *meningococci*. Fulminant, potentially life-threatening infections are most commonly caused by *S. pneumoniae*. Strategies to prevent OPSI include: (1) vaccination; (2) antibiotic prophylaxis; (3) patient and physician education. However, despite the introduction of these preventive strategies, OPSI still poses a clinical challenge reflected in a yet high annual mortality rate of 1.0-3.8%.
Vaccines including pneumococcal capsular polysaccharide (PS) antigens induce type-specific antibodies that enhance opsonization, phagocytosis, and killing of pneumococci by leukocytes and phagocytic cells. Recent systemic reviews of observational studies and randomised controlled trials have reported an estimated vaccine efficacy (in non-splenectomised high-risk individuals) against invasive pneumococcal disease of 53% and 38% respectively.\textsuperscript{138, 139}

Though splenectomy is no more used for staging of hematological malignancies such as Hodgkin lymphoma (HL), the procedure may still be indicated in the treatment of patients with hereditary spherocytosis, immune thrombocytopenic purpura, autoimmune hemolytic anemia, sickle cell anemia and thalassemia. In splenectomised patients with hematological malignancies, antibody response to pneumococcal vaccination is substantially lower than the response among immunocompetent individuals. Moreover, compared with healthy adults, a more rapid decline of antibody concentrations is found in these patients. In patients with HL, the antibody response to vaccination is greater if the vaccination is given before splenectomy, radiation or chemotherapy.\textsuperscript{140-143} Therefore, vaccination during chemotherapy and radiation therapy should be avoided. Reimmunisation of splenectomised patients is currently recommended every 5-10 years.\textsuperscript{144, 145} However, it may be necessary to revaccinate more frequently, particularly in splenectomised patients with hematological malignancies.\textsuperscript{142}

A drawback of polysaccharide vaccine is that it does not induce T-cell-dependent responses associated with immunological memory. Antibody levels usually increase after vaccination, but no anamnestic response occurs. The new polysaccharide-protein conjugated vaccines, including 7-11 serotypes have been found to be safe, immunogenic and effective for the prevention of invasive disease and severe pneumonia.\textsuperscript{146, 147} Included serotypes correspond to those often associated with penicillin resistance. This vaccine may be considered as an alternative/complement to pneumococcal PS vaccines. However, the limited number of included serotype and the need for repeated doses may limit its use. Priming with pneumococcal conjugate vaccine has shown encouraging results regarding the improvement of antibody response to PS pneumococcal vaccine in patients with HL.\textsuperscript{148} However, this strategy is not yet studied in splenectomised patients. Vaccines containing surface antigens common to all pneumococci-preliminary proteins are in different stages of testing.\textsuperscript{149} These vaccines, if effective, would protect against all pneumococci, regardless serotype.

Prophylaxis against pneumococcal infections using daily oral penicillin has been proven to be effective, especially in pediatric patients.\textsuperscript{150-152} However, compliance in taking daily antibiotics is a concern. Another significant environmental problem is the risk of selecting antibiotic-resistant strains.\textsuperscript{153, 154} Therefore, an alternative strategy may be standby antipneumococcal antibiotic treatment. The patient keeps a personal supply of penicillin to be taken at the first sign of respiratory illness, fever or rigor.
Splenectomised patients should be educated regarding the risk and the importance of prompt recognition and treatment of infection. These patients should carry a card with information about their lack of spleen and other clinical details. In an emergency this information may be lifesaving. Further studies are needed to better clarify: (1) the clinical efficacy of pneumococcal vaccine in patients with different hematological diagnosis; (2) the levels of antibodies that correlate with protection; (3) alternative prophylactic measures in patients not responding to vaccination; (4) the role of conjugated pneumococcal vaccine in splenectomised patients with hematological malignancies; (5) the optimal interval for revaccination in this patient category.
MANAGEMENT OF PATIENTS WITH FEBRILE NEUTROPENIA

Clinical examination
Given the inability of immunocompromised hosts to mount an adequate inflammatory response, the classic signs and symptoms of infection, other than fever, may be minimal or absent. Diminished inflammatory response leaves the patient with a pulmonary infection without a discernible infiltrate on radiograph, meningitis without pleocytosis in the CSF and a urinary tract infection without pyuria. Therefore, a meticulous physical examination and observation of every subtle sign or symptom of infection need to be undertaken. A focused physical examination should be repeated daily as long as symptoms persist and always should include the examination of skin, genitalia, sinuses, anal area, periodontium and oropharynx. Intravenous lines should be inspected carefully, and any exudates from catheter sites should be stained and cultured.

Investigations
The lack of an adequate inflammatory response renders some laboratory tests unreliable. Laboratory evaluations should include a complete blood cell count, measurement of serum creatinine, and liver enzymes. Initial laboratory evaluation should include a chest radiograph, especially in patients with respiratory symptoms. Concomitant blood cultures from a peripheral vein and central venous catheter should also be performed. Cultures of stool or urine samples and a lumbar puncture should be performed when there are clinical signs of infections involving these sites. Biopsy and culture of skin lesions may also be helpful in many cases.

The yield of bacterial and fungal isolates from blood is related to the culture systems used and to the volume of blood sample. The value of surveillance blood cultures in neutropenic patients was studied in a prospective pilot study by Penack et al. Interestingly, microbial growth prior to onset of infection symptoms was detected in 3 of 45 neutropenic episodes. These results suggest that further prospective studies are warranted to determine the clinical usefulness of surveillance with blood culture. High resolution chest computed tomography may reveal evidence of pneumonia in more than one-half of febrile neutropenic patients with normal findings on chest radiographs.

Reliable and readily available clinical variables to detect or to rule out infection before microbiological proof of an infection is obtained may be of great value. Several markers have been studied in this setting. The most commonly used is C-reactive protein (CRP), an acute phase reactant produced after proinflammatory cytokine release. The CRP concentration rises within 24 hours and is elevated in almost all cases of microbial infection, but its reliability as a marker is hampered by low specificity. Interleukin-6 (IL-6) a proinflammatory cytokine that quickly reaches high levels after stimulation with endotoxin, tumour necrosis factor alpha or IL-1 has recently been evaluated as a predictor of infection. It has a much shorter half-life than CRP and several studies support its value as a sensitive and specific indicator of bacteremia.
As a potentially specific marker of bacteremia, procalcitonin (PCT) has been investigated. This is a prohormone of calcitonin which is normally produced in the C-cells of the thyroid gland, but it is highly upregulated in monocytes and hepatocytes after stimulation with endotoxin and proinflammatory cytokines. Serum levels are highly elevated in septic conditions. Low levels of PCT have a high predictive value for the absence of bacteremia. Most recent trials confirm the value of using PCT measurement as marker of systemic infection in neutropenic patients. However, PCT has shown to be of little value in discriminating infections from other inflammatory complications in allogeneic HSCT recipients. A possible initial application of infection markers may be for tailoring the duration of antibiotic treatment. For example, if the level returns to normal after fever defervescence, antibiotic therapy may be shortened. However, further studies are needed before the establishment of the use of these markers in daily clinical practice.

Risk stratification
It has become evident that patients with febrile neutropenia do not constitute a homogenous group and do not run the same risk of the development of life-threatening complications or death. Accordingly, individual risk assessment of febrile neutropenic patients with cancer is gradually becoming an integral part of their initial evaluation. This allows better classification of patients to different therapeutic strategies, ranging from ambulatory antibiotic treatment to more intensive treatment with a combination of antibiotics together with early antifungal therapy. A number of different models based on the characteristics demonstrated by patients at onset of febrile neutropenia have been designed to enable clinicians to assign patients to high- or low-risk groups, attempting to identify those patients with the greatest chance to recover without serious medical complication. A potential shortcoming of these models may be that they are difficult to assess in clinical trials. Talcott et al. classified patients with febrile neutropenia into 4 groups, according to the status of their underlying disease and comorbidity on the first day of fever. Patients in 3 of the 4 groups were considered to be at high risk for major complications and to require hospitalisation and were defined as follows: (1) patients who were already hospitalised for cancer treatment; (2) outpatients who had underlying illness that either was in remission or was not progressing but who had significant comorbid symptoms, such as pain, nausea, and volume depletion; and (3) outpatients whose underlying illness was uncontrolled. The forth group (4) of patients had uncomplicated fever and neutropenia only and were expected to have few complications. This hypothesis was validated in a larger group of patients. However, in a third study performed by the same group of investigators, this approach could not discriminate satisfactorily between favourable and unfavourable outcomes. In that study low-risk patients were discharged from the hospital after two days from the time of onset of fever. Nine patients (30%) had to be readmitted to hospital because medical complications developed.

The prognostic factors included in the model developed by the Multinational Association of Supportive Care in Cancer (MASCC) are presented in Table 5.
Patients with a score of $\geq 21$ generally exhibit fewer serious medical complications (6%) and a low mortality rate of (1%). This risk-index score has been validated prospectively\textsuperscript{182, 183} and is now recommended for use as an aid in choosing therapeutic strategies for individual patients.\textsuperscript{176, 184, 185} One limitation of the MASCC study is that it included relatively few patients with active acute leukemia who typically display neutropenia of longer duration and generally demonstrate a higher risk for complication and a higher rate of mortality than do patients treated for solid tumours. The clinical application of this risk-index is to be validated in prospective studies.

**Table 5. The risk-index score designed by the Multinational Association of Supportive Care in Cancer (MASCC) for the identification of low-risk patients at onset of febrile neutropenia**

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of illness\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Mild symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>No hypotension</td>
<td>5</td>
</tr>
<tr>
<td>No chronic obstructive pulmonary disease</td>
<td>4</td>
</tr>
<tr>
<td>No previous fungal infection</td>
<td>4</td>
</tr>
<tr>
<td>No dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Out-patient at the time of fever onset</td>
<td>3</td>
</tr>
<tr>
<td>Age $&lt; 60$ years</td>
<td>2</td>
</tr>
</tbody>
</table>

* A risk-index score $\geq 21$ indicates that the patient is likely to be at low risk for complication and morbidity, \textsuperscript{a} choose one item only. This scoring system was adapted from that proposed by Klastersky et al.\textsuperscript{181}

**Fever of unknown origin in neutropenic patients**

Fever without clinical signs of localised infection is the commonest presentation of infection in neutropenic patients. In more than half of all patients with febrile neutropenia no infection can be clinically or microbiologically documented. Efforts have been made to find viral or fungal pathogens as possible causative pathogens, but results have not been encouraging.\textsuperscript{186, 187} Prospective studies have shown that outcome is significantly better in these patients than in patients with clinically/microbiologically documented infections.\textsuperscript{188, 189} At start of fever, broad spectrum antibiotic therapy has to be initiated in all patients. However, if, after a few days, the patient has become afebrile and the diagnosis is still FUO, early discontinuation of antibiotics may be considered. Lehrnbecher et al. found that discontinuation of antibiotics regardless of ANC or evidence of bone marrow recovery in pediatric cancer patients with FUO, was safe and effective when children had been afebrile for at least 24 hours and had been treated for a minimum of 72 hours.\textsuperscript{190} Similar results have been obtained in few other small studies.\textsuperscript{191, 192} This strategy for management of FUO has the advantage of providing better compliance, less antibiotic usage with decreased risk of side effects and emergence of antibiotic resistance, in addition to cutting hospital costs. However, it needs to be better investigated in adult patients with hematological malignancies.
Infections in patients with hematological malignancies

Furthermore, more clinical and laboratory studies are needed in order to improve our knowledge on FUO, especially regarding etiology and optimal clinical management.

**Empirical antibiotic treatment**

The increasing resistance of common pathogens to antibiotics indicates that there are no treatment guidelines that can be applied universally. The choice of the empirical antibiotic regimen should be tailored to local considerations and experience. The type of underlying disease and the antineoplastic regimen used being probably the most relevant factors predisposing to infection, since they influence the severity and type of damage to host immunity (neutropenia and mechanical damage). The type of intravenous device used, local bacterial ecology including the current pattern of infective pathogens, local pattern of antibiotic resistance, and antibiotic prophylaxis policies are also important factors that need to be considered.

**Combination therapy versus monotherapy**

Despite extensive clinical studies since the 1970s, no single empirical therapeutic regimen of initial treatment of febrile patients with neutropenia can be universally recommended. Several studies have shown that the combination of a penicillin or a cephalosporin with an aminoglycoside is the best therapeutic approach to the treatment of febrile neutropenia. The advantages of this type of regimen include a potential synergic effect against gram-negative bacilli, and a possible reduction of emergence of resistant strains. Drawbacks of these regimens include poor activity against staphylococci and streptococci, and aminoglycoside related toxicities such as nephrotoxicity and ototoxicity. To overcome the disadvantages of combination therapy, several strategies have been proposed including a single daily dose of aminoglycosides.

The effectiveness of both single agent and combination therapy has been suggested by many authors. Well designed studies have shown that monotherapy with ceftazidime, cefepime, meropenem, imipenem, or piperacillin-tazobactam are equally effective as conventional beta-lactam/aminoglycoside combinations. In the study by Del Favero et al., monotherapy with piperacillin-tazobactam was, in a prospective double blind trial, compared with the combination of the same agent and amikacin in the therapy of febrile neutropenia. The response rate was (49% for monotherapy versus 53% in combined therapy; p= 0.2). Recently, a meta-analyses by Paul and coworkers showed that monotherapy was associated with a trend (though non-significant) towards better survival, a significant advantage in preventing treatment failures, fewer side effects, and similar superinfection rates. At the present time, available evidence suggests that the addition of aminoglycosides is unnecessary.

Carbapenems have a better activity against viridans streptococci and pneumococci than ceftazidime. Some studies that compared carbapenems with ceftazidime demonstrated the superiority of imipenem or meropenem over ceftazidime.
monotherapy,\textsuperscript{203, 204} whereas other studies showed comparable efficacy and safety of cefepime and imipenem.\textsuperscript{133, 205} Cefepime or ceftazidime may be used in the presence of mild to moderate renal dysfunction without dose modification and in patients being treated with nephrotoxic drugs. Linezolid, which is an oxazolidinone, offers promise for treatment of drug-resistant gram-positive bacterial infections, including those due to VRE, though a drug-related myelosuppression may be problematic.\textsuperscript{206}

**Oral antibiotic therapy**

The routine therapeutic approach to febrile neutropenia, involving hospitalisation and administration of intravenous broad-spectrum antibiotics during the entire episode has been questioned for many years now. However, in order to use oral antibiotic treatment in patients with febrile neutropenia a reliable means of identifying low-risk patients is essential. The potential risk of complications makes the lowering of the intensity of care for these patients ethically, medically and legally difficult. With increasing accuracy, as discussed above, it is now possible to identify low-risk patients for whom less intensive and more convenient treatment may be appropriate.

Different therapeutic options have been tried in low-risk patients, among which outpatient treatment with oral antibiotics may be the most attractive, reducing hospital costs, avoiding catheter complications, improving the quality of the patient’s life and reducing the risk for infection by resistant nosocomial microorganisms. This approach has been tested in hospitalised patients with neutropenia of short duration in two prospective randomised studies,\textsuperscript{207, 282} the results of which showed an efficacy and safety comparable to intravenous antibiotic treatment.

Malik et al\textsuperscript{208} compared out-patient treatment with an oral antibiotic (ofloxacin) to in-patient oral treatment with this same antibiotic, in patients experiencing neutropenia of short duration. A considerable proportion (21\%) of their subjects receiving oral antibiotic treatment as out-patients required re-hospitalisation and this group had a 4\% mortality rate, raising concerns about the safety of this approach. A safer approach might involve early stabilisation of low-risk febrile neutropenic patients with intravenous antibiotic treatment in the hospital, followed by early discharge of carefully selected patients with subsequent oral antibiotic therapy. This treatment strategy provides time for the proper assessment of the patient’s clinical condition, thereby making it possible to exclude patients with infections that are not expected to respond to oral antibiotic treatment and to reduce the potential risk of life-threatening complications occurring outside hospital. At the same time, this approach allows individual tailoring of the oral therapy to the patient’s clinical signs and results of clinical investigations thereby minimizing the need for extensive monitoring of out-patients.

In a study by Klastersky et al. currently in progress, low-risk patients according to the MASCC score receive oral combination antibiotics and stay at hospital for 24 hours. The next day, if the score is still $\geq 21$, they are discharged and receive the same antibiotic at home. With this approach 50 of the 127 patients enrolled in the validation study were discharged (preliminary results as reported by Klastersky).\textsuperscript{176} An optimal strategy for the outpatient treatment of low-risk patients should be based
on a reliable risk stratification model and characterised by a low rate of readmission, low toxicity of chosen oral treatment, and no infection related mortality.

The role of glycopeptides
Glycopeptides are broad-spectrum antibiotics with activity against most gram-positive organisms, including methicillin-resistant staphylococci. Today, vancomycin is the most widely used glycopeptide. Teicoplanin, a relatively new glycopeptide, has demonstrated similar efficacy as vancomycin in the treatment of gram-positive infections. It requires less monitoring, and is more convenient to administer (once daily). However, these advantages may not motivate the higher cost of teicoplanin.

It has been demonstrated that most gram-positive organisms that are susceptible to vancomycin alone seldom cause rapid fatal infections, and patients infected with these microorganisms have not been adversely affected delaying the therapy until clinical and laboratory studies indicate its necessity. The utility of adding empirical glycopeptide in patients with persistent fever after monotherapy was analyzed in two placebo-controlled studies. The addition of teicoplanin or vancomycin did not result in any statistically significant improvement in any important end point including the number of patients who defervesced. Moreover, the indiscriminate and unnecessary use of glycopeptides is expensive and might lead to increased resistance among staphylococci and enterococci; their use needs to be restricted to patients with documented infections with organisms susceptible to vancomycin alone and patients with: (1) clinically suspected serious catheter related infections (e.g., cellulitis, bacteremia); (2) known colonisation with penicillin-and cephalosporin- resistant pneumococci and methicillin-resistant staphylococci; (3) positive result of blood cultures for gram-positive bacteria in a patients with a deteriorating condition before final identification and susceptibility testing; or (4) hypotension or other evidence of severe cardiovascular impairment.

Patients with overt mucositis, such as those receiving high dose cytarabine, are known to be at high risk for infection with oral viridans streptococci (OVS). These infections are usually indolent, but serious complications such as adult respiratory distress syndrome (ARDS) and/or septic shock develop in approximately 10% of these patients, despite adequate antibiotic therapy. Early broadening of the empirical antibiotic regimen for patients at high risk for OVS infection by the addition of glycopeptides is recommended by some investigators. However, the efficacy of this strategy is not proven. In these patients the addition of corticosteroids preemptively, for the prevention of development of ARDS, may be life-saving.

Empirical antifungal therapy
Due to difficulties in establishing a diagnosis of systemic mycosis in neutropenic patients, early empirical antifungal therapy has been introduced in patients with therapy-resistant fever or with pulmonary infiltrates and is recommended by many
authors and consensus groups. For about two decades, empirical antifungal therapy with conventional AmB (cAmB) or liposomal AmB was the standard of care in these patients. In spite of similar efficacy and markedly better tolerability of liposomal AmB, the empirical therapy with liposomal/lipid preparations of AmB is hampered by the high costs. Moreover, breakthrough fungal infections, infusion-related reactions, and nephrotoxicity still occur in patients receiving lipid preparations of AmB. Itraconazole has also been used as empirical antifungal therapy. However, the erratic bioavailability of its capsule formulation and the adverse gastrointestinal effects of its oral solution have limited its use. Moreover, experience with its new parenteral formulation is limited.

Two prospective randomised trials have demonstrated that fluconazole is an acceptable alternative to AmB as empirical antifungal therapy at institutions where mould infections and drug-resistant Candida species are uncommon. Patients who have symptoms of sinusitis or pulmonary infection or have received fluconazole as prophylaxis should not be considered for empirical fluconazole treatment as should not patients with previous Aspergillus infection.

Voriconazole and caspofungin were recently compared to liposomal AmB in two randomised, international, multicentre, prospective trials. Both were found to be as effective as AmB for empirical antifungal therapy in patients with neutropenia and persistent fever despite systemic antibacterial therapy for more than 96 hours. Interestingly, empirical treatment with voriconazole gave fewer breakthrough infections compared with AmB, but the number of patients discontinuing the drug because of toxic effects was similar in two groups. In the caspofungin study, which was double-blinded, caspofungin was found to be better tolerated, and more active in treating baseline fungal infections (including pulmonary aspergillosis) and candidemia than AmB.

Modification of initial antibiotic treatment
In an analyses of 488 episodes of febrile neutropenia, Elting et al. found that the median time to clinical response in hospitalised patients with cancer was 5-7 days. Some patients with microbiologically defined bacterial infections, even when adequately treated, may require ≥ 5 days of therapy before defervescence occurs. Therefore it would be unnecessary to change the initial regimen during the first 3-5 days, even if the patient remains febrile but otherwise is stable clinically. At the same time if the patient’s condition deteriorates or if a pathogen resistant to initial antibiotics is isolated, treatment should be modified promptly.

Subsequent treatment and length of treatment will depend on the nature of the infection (i.e. FUO, microbiologically or clinically documented), and on whether the patient is in a low-risk or high-risk subset. In patients with persistent fever after 3-5 days of empirical antibiotic therapy, a careful reevaluation of the patient is crucial before modifying the initial empirical regimen. A meticulous clinical examination may
Infections in patients with hematological malignancies

provide clues regarding possible cause of infection. Additional laboratory work-up may include special cultures, serology of specific pathogens, and imaging studies. Repeated blood cultures may be helpful in the diagnosis of breakthrough infections (see above). Possible causes of persistent fever in neutropenic patients are summarised in Table 6. If the reevaluation reveals a specific cause, treatment can be modified accordingly.

If the reassessment of the patient does not provide any new information, the patient is stable, and a rapid resolution of fever is expected, the initial antibiotic regimen can be continued. In other patients with persistent fever, prolonged neutropenia and/or deteriorating clinical condition more active measures need to be taken. Empirical change of empirical antibiotics from one broad spectrum antibiotic to another (e.g. switching from cephalosporins to carbapenems) is not supported by published evidence. Patients should be considered for the addition of glycopeptides if clinically indicated (see above) or empirical antifungal therapy. Studies in 1982 and 1989 suggested that up to one-third of febrile neutropenic patients who do not respond to a one-week course of antibiotic therapy may have systemic fungal infections. The Infectious Disease Society of America (IDSA) guidelines recommend introduction of an antifungal drug for patients who remain febrile after 5 days despite appropriate initial antibiotic treatment and for whom resolution of neutropenia is not imminent.

Table 6. Causes of persistent fever in neutropenic patients

- Resistant bacterial infection (e.g. VRE)
- Bacterial infection associated with tissue necrosis/mucositis
- Nonculturable cell wall-deficient bacteria
- Malignancy related fever
- Drug or transfusion related fever
- Fungal infection or other nonbacterial infection (e.g. virus, toxoplasmosis, AFB)

VRE: vancomycin-resistant enterococci; AFB: acid-fast bacteria

Duration of antimicrobial therapy

If defervescence is achieved and other clinical signs and symptoms of infection improve, a careful evaluation of all clinical, laboratory and socioeconomical aspects should be done. An individually tailored, feasible and safe approach should be chosen. Before hospital discharge adequate information should be given to the patient. Patients treated home with oral antibiotics should be instructed to return immediately to the hospital if they experience high fever, if their overall condition deteriorates or if they are unable to tolerate the medication. If the decision has been made to stop the use of antibiotics while the patient remains neutropenic, the patient must be monitored closely and intravenous antibiotics restarted immediately on the recurrence of fever or other evidence of bacterial infection.

If no specific etiology has been established (FUO), termination of all antibiotics 48 hours after defervescence may be considered regardless of whether the patient has
persistent neutropenia. Low-risk patients according to MASCC risk-index score can be considered for early discharge from hospital with oral antibiotic therapy 24 hours after defervescence. Oral antibiotics should be individually adjusted to the patient’s infectious disease and continued for at least 5 days. Finally, for high-risk patients with clinically or microbiologically documented infections, therapy can be adjusted to provide optimal coverage. Antibiotics should be administered until all symptoms and signs of infection are resolved and cultures become sterile. Then, it is recommended to continue intravenous antibiotics for 2 additional days if neutropenia has resolved (with a minimum of 7 days total antibiotic therapy) or for 7 days if neutropenia persists (Figure 3).

Granulocyte transfusions
Large numbers of granulocytes can now be obtained from a donor after administration of G-CSF, with or without dexamethasone. Some investigators believe that granulocyte transfusions can be useful in certain patients with profound neutropenia in whom documented bacterial or fungal infection cannot be controlled with optimal antibiotic therapy. However, there is no convincing evidence of the efficacy of this approach. Moreover, granulocyte transfusions may be associated with significant toxicity including transmission of CMV, alloimmunisation, graft-versus-host reactions (if the product is not irradiated), and platelet refractoriness. Granulocyte transfusion therapy should currently be regarded as an experimental clinical practice.

Colony stimulating factors
Colony stimulating factors (CSF) are cytokines that stimulate and accelerate the production of one or more cellular lines in the bone marrow. Granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF) are the most common stimulating factors studied in cancer patients due to their potent effect on neutropenia. The administration of G-CSF results in an increase in circulating neutrophils, while GM-CSF stimulates the growth of neutrophils, macrophages and eosinophils. Common side effects of CSF are bone and joint pain and flu-like symptoms. These side effects are usually mild and are more commonly reported in patients receiving GM-CSF.

Clinical trials have reported conflicting results when studying whether the CSFs improve outcome in patients with febrile neutropenia. In a recent meta-analysis of randomised controlled trials by Clark et al. (The Cochrane Collaboration) more than 8,000 references where screened and 13 studies were analyzed. This analysis showed that the use of the CSFs in patients with febrile neutropenia following chemotherapy reduces the amount of time spent in hospital and the neutrophil recovery period. The use of CSFs did not affect overall mortality. A possible beneficial effect of CSFs on mortality in the subgroup of patients with hematological malignancies was described. However, this beneficial effect was highly influenced by the results of one single trial in which three times more patients died in the control than in the treatment groups respectively. This finding was not reproduced in the other trials. Furthermore, despite repeated trials and meta-analyses, it is today still unclear whether the use of
CSFs reduces infection-related mortality.\textsuperscript{239, 241, 242} Thus, the routine use of G-CSF or GM-CSF in established febrile neutropenia cannot be recommended.

\textbf{Immunoglobulin prophylaxis in secondary hypogammaglobulinemia}
Secondary hypogammaglobulinemia is common in patients with hematological malignancies, in particular patients with B-cell chronic lymphocytic leukemia (B-CLL) and multiple myeloma.\textsuperscript{243} It is associated with increased risk of life-threatening infections usually caused by encapsulated organisms.\textsuperscript{244, 245} The etiology of hypogammaglobulinemia in these patients is poorly understood. Lymphopenia, and or defects in cellular immunity, such as functional abnormalities in T-cells resulting in dysregulation of monoclonal CD5- B-cells, may be responsible.\textsuperscript{246} Intravenous immunoglobulins (IVIG) may be used for the prevention of infections in patients with hypogammaglobulinemia. These are therapeutic preparations of normal human IgG that are obtained from a pool of more than 1000 healthy blood donors and contain a wide spectrum of antibacterial and antiviral specificities. The protective effect of IVIG, particularly for the prevention of upper and lower respiratory tract infections, in patients with B-CLL\textsuperscript{247-249} and multiple myeloma\textsuperscript{250} has been demonstrated. However, the use of IVIG is costly. It has been estimated that six million US dollars would be needed to achieve 1 quality-adjusted life year without an increase in life expectancy.\textsuperscript{251}

The high cost of IVIG, coupled with the potential of less expensive methods of prevention such as antibiotics, limits the role of IVIG in patients with hematological malignancies. The use of IVIG is warranted only in patients with hypogammaglobulinemia having recurrent severe sino/pulmonary bacterial infections.
Figure 3. Treatment algorithm in neutropenic patients with hematological malignancies 24 hours after fever defervescence

- **Patient afebrile for more than 24 hours**
  - **Low-risk at presentation (MASCC score ≥ 21)**
    - Consider outpatient treatment with oral antibiotics
  - **High-risk at presentation (MASCC score < 21)**
    - Clinically or microbiologically documented infection
      - FUO
      - Still neutropenic (ANC < 0.5x10⁹/L)
        - Continue iv antibiotics until 48 hours after fever defervescence
      - Neutropenia resolved (ANC > 0.5x10⁹/L)
        - Continue iv antibiotics for 2 more days

MASCC, Multinational Association of Supportive Care in Cancer risk-index score; iv, intravenous; ANC, absolute neutrophil count; FUO, fever of unknown origin
PURPOSE OF THE PRESENT INVESTIGATION

Infection remains an important cause of morbidity and mortality in cancer patients, in particular those undergoing chemotherapy for hematological malignancies. These studies were undertaken with the ultimate goal to improve the clinical management of infectious complications in these patients by addressing the following issues:

**Epidemiology and antibiotic resistance trends (I and IV)**

- To define the incidence and causative pathogens of bacteremia in neutropenic hosts not receiving antibacterial prophylaxis, and to assess antibiotic resistance and bacteremia-related mortality over time.

- To identify species distribution and triazole susceptibility of colonising yeasts isolated from patients treated for hematological malignancies, and to assess the impact of preceding fluconazole prophylaxis on emergence of resistant strains.

**Therapeutic studies (II and V)**

- To determine the efficacy and safety of cefepime by comparing it with that of imipenem-cilastatin in the management of febrile neutropenia in patients treated for hematological malignancies.

- To assess the safety and feasibility of early discontinuation of antibacterial therapy in patients with FUO, 48 hours after fever defervescence.

- To validate, in patients with hematological malignancies, the potential ability of the risk-index of the Multinational Association of Supportive Care in Cancer in identifying patients at low risk for the development of serious medical complications.

- To assess, 24 hours after fever defervescence, the feasibility and safety of early discharge of low-risk patients with febrile neutropenia with subsequent oral antibiotic therapy.

**Pneumococcal vaccination in splenectomised patients (III)**

- To determine the proportion of poor responders to pneumococcal polysaccharide vaccine among a well defined cohort of splenectomised patients with hematological disorders and to identify the clinical characteristics and pneumococcal infectious complications of these patients.
CHAPTER 2

EPIDEMIOLOGICAL AND ANTIBIOTIC RESISTANCE TRENDS (I, IV)

Bacteremia in hospitalised patients with malignant blood disorders (I)

Infectious complications are a major cause of morbidity and mortality in patients with hematological disorders, especially during chemotherapy-induced neutropenia. Bacteria remain the most common cause of severe infection, and in about one-third of episodes of febrile neutropenia, bacteremia is diagnosed. Before instituting empirical antibacterial treatment, it is essential to be aware of the spectrum of locally prevalent pathogens and their susceptibility pattern.

In this study (I) we retrospectively analyzed the results of all blood cultures taken in our hematology centre during the years 1988-2001. During this 14-year period a total of 18,731 blood culture specimens were drawn from 2,758 hematological patients. Blood cultures were performed with samples (usually two to three samples from different locations) of 10 ml blood inoculated into blood culture bottles. Excluding negative results, contaminants, and duplicate results during the same infectious episode, a total of 1402 episodes of bacteremia in 927 patients were identified. All patients were treated in the hematology ward and had an underlying hematological disorder with malignant lymphoma (39%), acute leukemia (27%) and multiple myeloma (19%) dominating. Gram-negative microorganisms constituted 45.3% and gram-positive microorganisms 54.7% of identified bacteria strains. The proportion of isolated gram-negative and gram-positive bacteria was essentially constant during the entire 14-year period (Figure 4). CNS was the most common cause of bacteremia (17.4% of all episodes), while E. coli was the most common gram-negative organism isolated (16%) (I; table 1).

![Figure 4. Annual incidence of gram-negative and gram-positive bacteremia](image)

Our results are somewhat different from those published by other investigators reporting epidemiological and therapeutic trials from the same time period. The well documented shift in the balance of predominant pathogens from gram-negative to gram-positive that occurred internationally during the 1980s, continued through 1990s, and gram-positive pathogens continued to be the more common causative agents in most hospitals (Figure 1). The reason for this shift of infecting pathogens is unclear. The selective pressure of widely used fluoroquinolone prophylaxis which is more active against gram-negative than against gram-positive bacteria, has most probably
played a significant role. Elting et al. showed that the use of fluoroquinolones was one of the factors significantly associated with development of streptococcal bacteremia.

Arguments against the use of fluoroquinolone prophylaxis include selection for gram-positive infections, the inability of clinical trials to demonstrate clinically significant reduction of such prophylaxis in the overall incidence of fever or reduction of mortality, the risk of selecting resistant pathogens, the potential of masking documented infections, and the promotion of fungal colonisation with possible increased risk of fungal infections. Therefore, antibacterial prophylaxis was not used in our centre and this may explain the remarkably stable ratio between gram-negative and gram-positive pathogens over the 14-year period.

Enterococci caused 7.7% of bacteremias with a clear increasing trend during the study period. This was entirely due to a continuously enhanced isolation frequency of *E. faecium* (Figure 5). *E. faecium* was frequently (87%) resistant to penicillin, but only one isolate was resistant to vancomycin. CNS strains were multidrug resistant, however all strains were fully susceptible to vancomycin (Figure 6). In all, 10% and 15% of isolated *E. coli* strains were resistant to piperacillin and cotrimoxazole, respectively. All *Pseudomonas* strains were sensitive to piperacillin, and ceftazidime. Only three isolates (4%) were resistant to imipenem and gentamicin (not tested for other aminoglycosides). Generally the rate of antibiotic resistance was low and stable over the entire 14-year period.

The emergence of antibiotic resistance, as described by many authors has become an important issue (see for review). Some examples of this problem are the increasing emergence of oxacillin (methicillin)-resistant Staphylococci; penicillin-resistant and macrolide-resistant *S. pneumoniae* and viridans group streptococci; glycopeptide-resistant enterococci; multidrug-resistant *Corynebacterium* species; *P. aeruginosa* resistant to beta-lactams, aminoglycosides and fluoroquinolones; increasing prevalence of intrinsically resistant species of *S. maltophilia*; and enterobacteriacae resistant to third generation cephalosporins. The early detection of such drug-resistant strains require frequent monitoring of local susceptibility patterns, especially at institutions treating a large number of patients with neutropenia. Moreover, institutional differences can be substantial, and reliance solely on national/international data can be misleading.
The 7-and -30 day mortality rates in bacteremic patients were 6.3% and 15.6%, respectively (I). The risk of death was especially high when bacteremia was caused by *P. aeruginosa*, *S. maltophilia*, or *E. faecium* (I; table 4). High acute mortality rates in association with these microorganisms have been described by other authors.255

*S. maltophilia* is an aerobic gram-negative bacillus. It has a limited invasiveness and low level of pathogenicity and it is rarely responsible for community acquired infections. In recent years it has been increasingly reported as a cause of life-threatening infections in immunocompromised, usually hospitalised, patients. In a study by Micozzi and co-workers the characteristics of 37 neutropenic patients with *S. maltophilia* bacteremia were evaluated and compared with patients having *P. aeruginosa* infection.256 Acute mortality rates associated with these infections were 24% and 21%, respectively. The majority of cases with *S. maltophilia* bacteremia presented as breakthrough infections and in many cases antibiotic treatment with a broad-spectrum antibacterial combination was ongoing. In both groups, profound neutropenia, long duration of neutropenia, hypotension and administration of inappropriate antibacterial treatment were factors associated with a high acute mortality. In a retrospective evaluation of 245 episodes of *P. aeruginosa* bacteremia in patients with cancer by Ioannis et al. the median time of documentation of *P. aeruginosa* infection and death was 2 days (range 0-40 days).257 These results indicate the seriousness of these infections and implicate that antibiotic regimens used in neutropenic patients should provide adequate coverage of *P. aeruginosa* and *S. maltophilia*.

In summary, the moderate predominance of gram-positive microorganisms remained essentially unchanged and no tendency to a shift from gram-negative to gram-positive microorganisms as cause of bacteremia was noted during a 14-year period in a relatively large hematology unit where antibacterial prophylaxis was not used routinely. Except for the significant increase of *E. faecium* bacteremia, the species distribution was essentially stable. The rates of antimicrobial resistance were low and stable. The overall 7- and 30- day mortality rates were 6.3% and 15.6%, respectively, but were significantly higher when *P. aeruginosa*, *S. maltophilia*, or *E. faecium* were the causative agent.

---

**Figure 6. Proportion (%) of drug-resistance among coagulase negative staphylococci during the period 1988-2001**

The 7-and -30 day mortality rates in bacteremic patients were 6.3% and 15.6%, respectively (I). The risk of death was especially high when bacteremia was caused by *P. aeruginosa*, *S. maltophilia*, or *E. faecium* (I; table 4). High acute mortality rates in association with these microorganisms have been described by other authors.255

*S. maltophilia* is an aerobic gram-negative bacillus. It has a limited invasiveness and low level of pathogenicity and it is rarely responsible for community acquired infections. In recent years it has been increasingly reported as a cause of life-threatening infections in immunocompromised, usually hospitalised, patients. In a study by Micozzi and co-workers the characteristics of 37 neutropenic patients with *S. maltophilia* bacteremia were evaluated and compared with patients having *P. aeruginosa* infection.256 Acute mortality rates associated with these infections were 24% and 21%, respectively. The majority of cases with *S. maltophilia* bacteremia presented as breakthrough infections and in many cases antibiotic treatment with a broad-spectrum antibacterial combination was ongoing. In both groups, profound neutropenia, long duration of neutropenia, hypotension and administration of inappropriate antibacterial treatment were factors associated with a high acute mortality. In a retrospective evaluation of 245 episodes of *P. aeruginosa* bacteremia in patients with cancer by Ioannis et al. the median time of documentation of *P. aeruginosa* infection and death was 2 days (range 0-40 days).257 These results indicate the seriousness of these infections and implicate that antibiotic regimens used in neutropenic patients should provide adequate coverage of *P. aeruginosa* and *S. maltophilia*.

In summary, the moderate predominance of gram-positive microorganisms remained essentially unchanged and no tendency to a shift from gram-negative to gram-positive microorganisms as cause of bacteremia was noted during a 14-year period in a relatively large hematology unit where antibacterial prophylaxis was not used routinely. Except for the significant increase of *E. faecium* bacteremia, the species distribution was essentially stable. The rates of antimicrobial resistance were low and stable. The overall 7- and 30- day mortality rates were 6.3% and 15.6%, respectively, but were significantly higher when *P. aeruginosa*, *S. maltophilia*, or *E. faecium* were the causative agent.
Triazole susceptibility of colonising yeasts in relation to fluconazole prophylaxis (IV)

Patients with severe neutropenia are at risk for life-threatening invasive fungal infections (IFI). The pathogenesis of IFI is not completely understood. Colonisation of the gastrointestinal tract and other body sites is likely to be the initial step preceding systemic yeast invasion. Improving the effectiveness of diagnostic procedures for IFI including non-cultural methods remain an unresolved task (see above). Moreover, IFI is still associated with a high case fatality rate and available treatments are costly and complex. Therefore, intense efforts are needed in identifying an optimal prophylactic approach. Several systemically absorbed antifungal agents have been used for this purpose.

Prophylaxis with fluconazole has in many studies been reported to markedly reduce oropharyngeal, rectal and urinary colonisation with yeasts other than C. glabrata and C. krusei. The usefulness of fluconazole prophylaxis has been documented in patients at high risk for developing IFI such as allogeneic HSCT recipients and patients with prolonged neutropenia following intensive chemotherapy for hematological malignancies (see for review). Antifungal prophylaxis in these patients reduces superficial and invasive fungal infection as well as mortality related to fungal infection.

A major concern with the use of antifungal prophylaxis has always been the potential for selection of resistant organisms that may cause subsequent superinfections. An increase in azole-resistant fungal colonisation and infection has been reported with prolonged or repeated exposure to antifungal agents especially in HIV patients. These infections particularly involve non-albicans Candida species such as C. krusei and C. glabrata in fluconazole recipients. However, the clinical relevance of the development of resistance during fluconazole prophylaxis in patients with hematological malignancies is still a matter of debate. Some studies have reported enhancement of the emergence of non-albicans yeast infection by the use of fluconazole. However, it should be noted that these studies were retrospective, uncontrolled analyses conducted in single centres, and could have been affected by the baseline prevalence of non-albicans Candida in the institution. In contrast, several prospective placebo-controlled studies could not demonstrate a predisposition toward the emergence of resistant yeast infections in fluconazole recipients.

In the light of these concerns, we prospectively analyzed the species distribution and triazole susceptibility patterns of colonising yeasts from our patients and assessed the impact of previous fluconazole prophylaxis on the colonisation of resistant yeasts.

Oropharyngeal and faecal surveillance cultures were taken once weekly from all patients having neutropenia as a result of anti-cancer chemotherapy. A total of 87 patients treated for hematological malignancies between March 2002 and February 2003 were included. Information on the dosage and duration of previous antifungal therapy and/or prophylaxis was obtained. Antifungal prophylaxis with fluconazole 50–100 mg orally once daily was recommended in patients with an expected duration of neutropenia (absolute neutrophil count < 0.5 x 10⁹/L) exceeding 7 days. Samples were
cultured on Columbia glucose agar plates supplemented with 2% horse blood and antibiotics (37°C), CHROMagar Candida plates (CHROMagar Co., Paris, France) (37°C), and Sabouraud’s glucose agar slants (30°C). Yeast species were identified by pigmentation observed on CHROMagar Candida plates (CHROMagar Co., Paris, France) and by ID 32C identification system (bioMerieux, Marcy l’Etoile, France). Antifungal susceptibility testing to fluconazole, itraconazole, and voriconazole was done using E-test (Figure 7). MICs were determined after 48 hours incubation at 35°C. Interpretive breakpoints according to NCCLS document M27-A2 were applied to fluconazole (resistance MIC ≥64 mg/L) and itraconazole (resistance MIC ≥1 mg/L) MICs. For comparison, microbiology reports of surveillance fungal cultures from patients treated between 1995 and 2001 were retrospectively reviewed.

Fluconazole prophylaxis was given to 26 (30%) of included patients. The median dosage of fluconazole was 50 mg (range 50–100 mg) once daily, with a median duration of prophylaxis of 16 days (range 3–70 days) per neutropenic episode. Of 87 patients 59 (69%) were colonised with one yeast species, while 28 (31%) were colonised with two or more yeast species resulting in a total of 123 clinical isolates. The annual number of isolated strains in this patient population was similar during the preceding 7 years: C. albicans (49–59% of the isolates), S. cerevisiae (12–24%) and C. glabrata (7–18%) were most frequently isolated. Fluconazole resistant C. norvegensis was isolated from 5 patients during 2002 compared to only 3 patients 1995–2001. Otherwise no major changes in the distribution of the isolated species were noted.

The distribution of yeast species did not differ significantly among isolates from patients who had received fluconazole prophylaxis as compared to those who were not given prophylaxis (IV; table 4). The fluconazole MICs for Candida species and S. cerevisiae isolates from patients in the prophylaxis group were ≥2 mg/L in 24 of 40 (60%) isolates compared with 26 of 83 (31%) isolates from patients previously not given prophylaxis (p= 0.002). Fluconazole resistance was found in 6 (15%) isolates from patients given prophylaxis and in 8 (9.6%) isolates from non-prophylaxis patients (p > 0.05). The fluconazole MICs were higher among isolates obtained after
administration of fluconazole than among isolates from patients who had not received prophylaxis, the geometric means 3.73 (95% confidence interval: 1.76-7.90) and 1.40 (95% confidence interval: 0.80-2.47), respectively ($p= 0.047$).

In the present study no tendency to a shift from *C. albicans* to non-albicans *Candida* species was noted during an 8-year period. Moreover, in accordance with many other studies (see above), previous exposure to fluconazole prophylaxis did not have a significant impact on the species distribution of colonising yeasts. In our department we have for many years been using a low dose of fluconazole prophylaxis in patients with severe chemotherapy-induced neutropenia and only during the neutropenic phase. With this regimen we have recorded a very low rate of superficial and invasive yeast infection.271

Thus, fluconazole MICs were significantly higher in yeast isolates from patients who had received fluconazole prophylaxis than in isolates from patients not so treated. Although only patients with an expected longer duration of neutropenia were selected to receive prophylaxis, this is unlikely to explain the higher MIC values noted in the prophylaxis group as no association is known between the duration of neutropenia and the development of azole resistance. The increased MICs were not reflected in increased resistance according to NCCLS breakpoints. However, these results document a trend toward more in vitro azole resistance in patients previously exposed to fluconazole prophylaxis.

In conclusion, fluconazole prophylaxis may contribute to emergence of less susceptible yeast strains in patients with hematological malignancies. Our results emphasise the need for continued surveillance of azole resistance and emerging cross-resistance in patients treated for hematological malignancies.
CHAPTER 3

THERAPEUTIC STUDIES (II, V)

Cefepime as monotherapy in the empirical treatment of febrile neutropenia following chemotherapy in patients with hematological malignancies (II)

One of the most challenging problems in antimicrobial chemotherapy is the optimal empirical treatment of infection in patients with neutropenia. Internationally, the rates of occurrence of pathogens are in a continuous periodic change under the selective pressure of broad-spectrum antimicrobial therapy and prophylaxis. Moreover, novel resistance mechanisms continue to emerge. Newer compounds with increased activity and spectrum may offer a greater inhibitory potential of empirical therapy among patients with neutropenia and infections.

Aminoglycosides and anti-Pseudomonas penicillin became standard therapy for neutropenic fever 30 years ago, and in the following decade many aminoglycosides (gentamicin, amikacin, tobramycin), and penicillins (ticarcillin, piperacillin, mezlocillin), and later combinations of beta-lactams and beta-lactamase inhibitors (piperacillin-tazobactam) were introduced. In the 1980s and early 1990s new generation cephalosporins (ceftazidime, cefepime), and carbapenems (imipenem, meropenem) became available, all having potent activity against aerobic gram-negative bacteria including P. aeruginosa, and activity against many strains of gram-positive cocci. Monotherapy with these antibiotics has therefore been and still is considered adequate.

Cefepime is a forth generation cephalosporin that posses a spectrum of action against gram-negative bacilli comparable to that of ceftazidime. Among the broad-spectrum agents used for the treatment of febrile neutropenia, the most active against gram-negative bacilli (lowest percentage of resistance) has shown to be imipenem (3.6-8.3%), followed by piperacillin-tazobactam (9.3-13.9%), cefepime (9.7-17.4%) and ceftazidime (12.8-17.0%). Moreover, cefepime has an excellent activity against viridans streptococci and pneumococci and its beta-lactamase stability is superior to that of piperacillin-tazobactam.

We conducted a prospective, open label, multicentre study to compare the efficacy and safety of cefepime with that of imipenem-cilastatin as monotherapy in the management of febrile neutropenia in patients with hematological malignancies. Furthermore, we assessed the safety of early discontinuation of antibiotic therapy in patients with fever of undetermined origin (FUO). Between September 1996 and December 1998, a total of 180 patients with 207 febrile episodes were randomised at start of fever (105 episodes with cefepime, 2 g iv q 8 hrs, 102 episodes with imipenem, 500 mg q 6 hrs). In patients with documented infection, the treatment was continued for five days after fever defervescence if the patient remained neutropenic (ANC < 0.5 x10^9 /l), and for at least two days if ANC exceed 0.5 x10^9 /l. In patients with FUO, treatment was recommended to be continued for another 48 hours after defervescence, regardless of the ANC level.
Infections in patients with hematological malignancies

The cefepime and imipenem groups were well comparable in terms of age, gender, underlying malignancy, prior transplantation, and presence central venous catheters. All patients were neutropenic at inclusion with a median ANC of 0.1 x10⁹/l (range 0-1 x10⁹/l), and ANC ≤ 0.1x10⁹/l in 77% of included patients. The mean duration of neutropenia, with ANC < 0.5x10⁹/l was 6.2 days. Febrile episodes were classified as microbiologically documented infection (47%), FUO (43%), or clinically documented infection (10%). At final evaluation 1-2 weeks after completion of antibiotic therapy, monotherapy success rates were 40% and 51% in the cefepime and imipenem-cilastatin groups, respectively (p =0.33). Relapse of fever within one week after end of antibiotic treatment occurred in the cefepime, and imipenem-cilastatin treated groups in 12 (11%) and 15 (14%) of episodes, respectively. Eradication of the causative pathogen was documented in 32/44 (72%) episodes in the cefepime group versus 40/54 (74%) episodes in the imipenem-cilastatin group (p = 0.79). No superinfections were reported. Three (2%) of the cefepime treated patients and four (3%) of the imipenem-cilastatin treated patients died as a result of infection (Table 6). Both cefepime and imipenem were well tolerated and adverse effects were uncommon (Table 7).

Table 6. Causes of infection related mortality according to treatment group

<table>
<thead>
<tr>
<th>Cefepime (n=3)</th>
<th>Imipenem (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- one PCP</td>
<td>- one septic shock</td>
</tr>
<tr>
<td>- one Pseudomonas pneumonia</td>
<td>- one pseudomembranous colitis (Clostridium difficile)</td>
</tr>
<tr>
<td>- one suspected invasive fungal infection</td>
<td>- two invasive fungal infections</td>
</tr>
</tbody>
</table>

The results of the current study support the notion that cefepime is a valuable alternative for the empirical therapy of neutropenic cancer patients with fever,¹³³, ²⁰⁵ and give strengthened support to its use in patients with more long-standing neutropenia. Moreover, assessment after 72 hours of treatment according to Pizzo¹⁹⁸ showed that 97 and 99% of the patients had responded satisfactorily to cefepime and imipenem-cilastatin, respectively. Finally, infection-related mortality was low and similar in the two groups.

The issue of which antibiotic should be used in the empirical therapy of febrile neutropenia remains debatable and there is a continuous publication of numerous studies in the field. The increasing resistance of common pathogens to antibiotics indicates that there are no antibiotic combinations of choice that can be applied universally. Recently, a meta-analyses showed that monotherapy with a suitable agent when compared with combination therapy was associated with a significant advantage in preventing treatment failure, fewer adverse effects, and similar superinfection rates.²⁰² Results from the current study together with results from previous studies involving cefepime monotherapy²⁷⁶-²⁷⁸ provide support for cefepime monotherapy being a valuable alternative in the initial treatment of febrile neutropenia.
In conclusion, the results of this study support the usefulness of cefepime as monotherapy for the empirical treatment of neutropenic fever in patients with hematological malignancies.

Table 7. Reported adverse events according to treatment group

<table>
<thead>
<tr>
<th>Adverse events, n</th>
<th>Cefepime</th>
<th>Imipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Skin rash</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>C. difficile (culture and/or toxin)</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

The safety and feasibility of early discontinuation of antibacterial therapy in neutropenic patients with FUO (II)

Despite the knowledge that patients with neutropenia and FUO do clearly better than other patients with febrile neutropenia, very little has been done to assess the feasibility and safety of applying more convenient, risk-adjusted and cost-effective therapeutic strategies in these patients. At start of fever, broad-spectrum antibiotic therapy has to be initiated in all neutropenic patients. However, if, after a few days, microbiological tests are negative, clinical signs of infection are absent and the patient has become afebrile, discontinuation of antibiotics may well be the most appropriate management.

In the above mentioned study (II), no cause of fever could be identified in 43% of the febrile neutropenic episodes (FUO). Study antibiotic treatment was discontinued prematurely because of persistent fever, adverse events, and/or clinical deterioration in 29 (32%) episodes of FUO (failure). Treatment with the study antibiotic was discontinued, according to the protocol, 48 hours after defervescence in 31 FUO episodes (34%). In this subgroup 23 patients had neutropenia when antibiotic treatment was stopped, only three of these patients became febrile again within a week. No death occurred (II, figure 1). In 29 patients with FUO the physician in charge decided to continue treatment with intravenous antibiotics for more than 48 hours after defervescence despite recommendations in study protocol. A total of 26 of these patients had neutropenia, 6 of whom became febrile again, and 2 died, one due to suspected but not verified invasive fungal infection and one due to progress of lymphoma. The two FUO subgroups were well comparable regarding risk factors such as age, frequency of acute leukemia, length of neutropenia, frequency of bacteremia, and pathological chest X-ray findings.

A few studies on pediatric cancer patients with neutropenia and FUO have reported that the discontinuation of intravenous antibiotics regardless of ANC or evidence of bone marrow recovery in these patients was safe and effective when the children had been afebrile for at least 24 hours and had been treated for a minimum of 72 hours.
Infections in patients with hematological malignancies

In the latest guidelines of the Infectious Disease Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO), different risk categories, in neutropenic patients with FUO could be identified according to the duration of neutropenia. DGHO recommend that antibiotic treatment should be continued for 7 days after defervescence in patients with persistent neutropenia. However, our clinical impression and hence our hypothesis was that patients who have had neutropenic fever, but become afebrile and stable and have negative blood cultures have been doing well also when iv antibiotics have been discontinued. The results of the present study support this view: In patients with FUO, the discontinuation of intravenous antibiotics 48 hours after defervescence regardless of the ANC-level at that time did not result in any higher incidence of fever relapse or mortality in comparison with patients with FUO and a more prolonged intravenous antibiotic therapy. This way of management of FUO has the advantage of providing better compliance, less antibiotic usage with reduced risks of side effects and emergence of antibiotic resistance in addition to cutting hospital costs.

In conclusion, the discontinuation of antibiotics regardless of the ANC-level in patients with hematological malignancies with FUO who have been afebrile for at least 48 hours is a promising alternative in the management of these patients, which should be assessed further in larger randomised trials.

Early hospital discharge with oral antimicrobial therapy in low-risk patients with febrile neutropenia (V)

The fatal consequences of infections among patients with prolonged and severe granulocytopenia was quantified by Bodey et al. at 1966. This work lead to the widespread practice of immediate hospitalisation and administration of intravenous broad-spectrum antibiotic therapy for all patients with febrile neutropenia. Since the publication by Bodey et al. additional criteria for determining immunocompromised patient’s risk of acquiring serious infection have been evaluated by the use of a wide variety of approaches. In general, researchers seek to identify low-risk patients who can safely be treated with short periods of hospitalisation. However, without a reliable means of identifying low-risk neutropenic patients at the onset of fever, early discharge of patients may put some patients at an unacceptable risk. Considering the low mortality of the standard approach, not even a single patient treated with an experimental strategy, i.e., oral therapy in an outpatient setting, should die because of this strategy.

The clinical application and reliability of different risk-assessment models and the use of alternative treatment strategies have faced many difficulties: (1) the power of many studies to detect small but clinically important differences in safety of applied treatment strategy has been limited; (2) more useful outcome measures than the conventional response to initial antibiotic, such as success of early discharge policy judged by low readmission rate, are often not used; (3) there is a significant variation in inclusion and exclusion criteria with clear differences in low-risk criteria as most
studies do not include patients with leukemia, and about half exclude patients with pneumonia, cellulitis and intravascular infections; (4) the expected duration of neutropenia, which may be difficult to predict in patients with hematological malignancies, is often used as a major criterion in the selection of low-risk patients. Interestingly, in the MASCC study by Klastersky et al. the expected duration of neutropenia was not found to predict final outcome, and it did not even correlate with the actual duration of neutropenia.181

In this study (V) we prospectively validated the usefulness of the MASCC risk-index score in identifying low-risk febrile neutropenia patients treated for hematological malignancies. This risk-index is designed and validated by the MASCC in a multinational, multicentre study involving more than 1100 patients with fever and neutropenia (see above).181 It is based on easily identifiable characteristics present at the onset of fever (Table 4). This makes the model applicable in daily clinical practice and, at the same time, allows standardisation of patient groups included in various studies.

All adult patients admitted to our centre from November 2003 through April 2005 for treatment of neutropenic fever after treatment with chemotherapy for a hematological malignancy were included in this study. Upon admission a history was taken, physical examination performed, and MASCC risk-index score calculated for each patient. After initial evaluation, all patients were hospitalised and initially received broad-spectrum intravenous antibiotics in accordance with local and international recommendations185, 232 until the fever subsided. The patients were monitored daily for clinical complications (V; table 8).

During the 18-month study period, 191 adult patients exhibiting a total of 279 episodes of fever and neutropenia following chemotherapy were treated at our unit. All of these patients were being treated for hematological malignancies, predominantly acute leukemia (50%). All patients demonstrated severe neutropenia at the time of onset of fever. The mean duration of neutropenia was 11 days (±10 days).

At the time of presentation 105 (38%) of the febrile episodes occurring in 81 patients were associated with low-risk according to the MASCC risk-index score and 174 (62%) episodes (in 132 patients) were high-risk. Serious medical complications were reported in association with 111 (63%) high-risk and 16 (15%) low-risk episodes (p< 0.0001) (V; table 8). Thus, the overall rate of misclassification was 28%. The specificity, sensitivity and positive and negative predictive values of the MASCC risk-index score regarding the development of medical complications were calculated to be 87%, 58%, 84% and 64%, respectively. Episodes classified as low-risk were also associated with a shorter duration of fever, higher rate of successful monotherapy and a relatively low incidence of infection-related mortality. Thus, this model of risk stratification appears to be of value in the identification of low-risk patients during management of febrile neutropenia following chemotherapy for hematological malignancies.
Different steps of modification of the initial gold standard of care for low-risk patients with febrile neutropenia have been developed and studied so far. They range from: (1) early hospital discharge before resolution of neutropenia, with continuation of intravenous antibiotic therapy, (2) therapy with oral instead of intravenous antibiotics from the very beginning of fever as inpatients, or outpatients, and (3) sequential approach with a short initial inpatient observation period with intravenous antibiotics followed by early hospital discharge with oral therapy. However, the general applicability of outpatient oral therapy has been challenged in view of the difficulties in identifying low-risk patients (as discussed above), the relatively high levels of gastrointestinal toxicity of the oral regimen and the high rate of use of colony-stimulating factors (CSFs) in these study populations.

An important factor to encourage home care has been the desire to achieve a higher quality of life during the cytopenic period after intensive chemotherapy. In addition, ever since the necessity of reducing health care costs has been felt, the exploration of the possibilities of treating patients with febrile neutropenia at home and the cost effectiveness of this strategy have been of interest. Outpatient treatment may also have the advantages of avoiding catheter complications, and reducing the risk for infection by resistant nosocomial microorganisms.

Treatment with oral antibiotics has been tested in hospitalised patients with neutropenia of short duration in two prospective randomised studies, which reported an efficacy and safety comparable to those of intravenous antibiotic treatment. However, the authors of both studies emphasised that their findings should not be interpreted as a recommendation that oral empirical therapy administered on an outpatient basis should be the new standard of treatment for low-risk patients. Importantly, in both studies patients were hospitalised until fever resolved and were strictly monitored during the entire period of febrile neutropenia. The most recent guidelines for antibiotic treatment of neutropenic patients with cancer by a working committee of the Infectious Disease Society of America (IDSA) are very cautious regarding the use of oral antibiotics alone. A careful selection of low-risk patients and limitation of this approach to adults is recommended.

In this study, we prospectively assessed the feasibility and safety of early hospital discharge of low-risk patients 24 hours after defervescence with subsequent oral antibiotic therapy. Most complications associated with febrile neutropenia occur during the first few days of each episode and, to date, no single risk stratification model has proven successful in the identification of such patients who may be treated safely with oral antibiotics. We preferred, therefore, the strategy of initial hospitalisation and intravenous antibiotic treatment of all patients followed by outpatient treatment of low-risk patients who were doing well and eligible for oral antibiotic therapy.

Patients who were initially scored as being at low-risk, but who later developed shock, hemodynamic instability, catheter-related infection, microbiologically verified infection with a multi-resistant microorganism (e.g., coagulase-negative staphylococci or E. faecium), or invasive fungal infection were not considered for oral therapy. Nor
were patients who experienced abdominal pain, nausea/vomiting, diarrhoea, and/or inability to swallow oral medications (Table 8). All other low-risk patients were switched from intravenous to oral antibiotic therapy 24 hours after their fever had subsided. The first dosage of oral treatment was administered at hospital, after which, if no acute complications arose, the patient was discharged and subsequently treated and monitored as out-patients. Oral antibiotic treatment was continued for five days, irrespective of the ANC level. Out-patients were instructed to return immediately to the hospital if they developed a fever, or were unable to tolerate the oral medication, or if their overall condition deteriorated. These patients had telephone access to the study team and the hematology unit during the day and to acute health-care facilities at all times. Three days after discharge, patients made a follow-up visit at the hematology day-care unit and final evaluation of the treatment outcome was carried out either four weeks after subsidence of fever or at the time of initiation of the next chemotherapeutic treatment.

The combination of ciprofloxacin and amoxicillin-clavulanate has been chosen for oral therapy in patients with febrile neutropenia by the majority of investigators. This combination is well absorbed and provides satisfactory coverage against gram-negative enteric bacilli and gram-positive cocci. However, as discussed previously, the widespread use of fluoroquinolones as treatment and prophylaxis has been associated with the development of drug resistance. Thus, oral antibiotics were tailored to findings such as the localisation of infection, type of infection, isolated infective pathogen, and the presence of neutropenia (V; table 3). We also considered local patterns of infection and antibiotic susceptibility in our centre. This approach probably reduces the risk of overuse of standard antibiotic combinations and consequently the development of antibiotic resistance, and improves treatment outcome.

In 38 low-risk episodes, patients were not eligible for oral antibiotic treatment and were excluded from this aspect of the study. The reasons for exclusion are summarised in Table 8. A total of 67 low-risk episodes were followed after discharge with oral antibiotic treatment 24 hours after defervescence. One patient had to be readmitted 2 days after discharge due to recurrence of fever (failure of oral treatment). This patient was treated for bacteremia caused by \textit{K. pneumoniae}, responded well to ceftazidime, but became febrile again upon receiving oral treatment with ciprofloxacin, despite the fact that, his causative bacteria were susceptible to this antibiotic. He was subsequently treated again with intravenous antibiotics and no superinfection was detected.

At clinical follow-up 2-4 days after discharge from the hospital, all remaining patients (99\%) were afebrile and exhibited reduced symptoms of infection. One patient had to discontinue her oral antibiotic treatment because she developed diarrhoea, but remained afebrile and did not require any further treatment. At the final evaluation 4 weeks after discharge, two patients had been readmitted to the hospital due to presence of new infections. Both of these patients experienced fungal infection (one with \textit{Pneumocystis jiroveci} pneumonia and the other invasive pulmonary aspergillosis) after their neutropenia had resolved and antibiotic treatment discontinued. All of the other 64 patients remained afebrile and, since there was no mortality, the success rate of oral
antibiotic treatment was 95%. The duration of hospitalisation and intravenous antibiotic treatment in these patients was shortened by 2.2 (±1.8) days. Thus, the total hospital cost per febrile episode was reduced by approximately 1600 €. The oral treatment with antibiotics was, in general, well-tolerated.

Table 8. Clinical conditions/reasons considered to render 38 of 105 low-risk patients ineligible for oral treatment with antibiotics

<table>
<thead>
<tr>
<th>Clinical condition/reason</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection with multi-resistant bacteria, verified microbiologically</td>
<td>11</td>
</tr>
<tr>
<td>Invasive fungal infection, clinically suspected or proven</td>
<td>8</td>
</tr>
<tr>
<td>Gastrointestinal complications and swallowing difficulties</td>
<td>4</td>
</tr>
<tr>
<td>Generally deteriorating condition</td>
<td>4</td>
</tr>
<tr>
<td>Central venous catheter infections</td>
<td>3</td>
</tr>
<tr>
<td>Deep abscess of soft tissue</td>
<td>2</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1</td>
</tr>
<tr>
<td>Previously included twice in the study</td>
<td>1</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>1</td>
</tr>
<tr>
<td>Refusal to take oral antibiotics</td>
<td>1</td>
</tr>
<tr>
<td>Unspecified</td>
<td>2</td>
</tr>
</tbody>
</table>

* Coagulase-negative staphylococci (n=9), Enterococcus faecium (n=1) and resistant Klebsiella species (n=1); # including one case of Pneumocystis jiroveci pneumonia, three cases of invasive pulmonary aspergillosis, and four cases of pneumonia in which fungal infection was suspected, never confirmed to be the cause.

In this study, we combined the MASCC risk-index score with easily attainable clinical and microbiological information concerning the appropriateness of oral antibiotic therapy. The low rate of re-admission, together with the low toxicity of the oral treatment and the absence mortality due to infection in the out-patients, confirm the safety and feasibility of this treatment strategy.

In conclusion, our present findings demonstrate that the MASCC risk-index is a valuable aid in the initial identification of patients suffering from hematological malignancies who run a low risk of complications in association with febrile neutropenia. Early discharge from the hospital 24 hours after defervescence and subsequent oral treatment with antibiotics was shown to offer a safe and cost-effective alternative to the conventional management of carefully selected low-risk patients.
CHAPTER 4

PNEUMOCOCCAL VACCINATION IN SPLENECTOMISED PATIENTS (III)

The spleen is an important site for antibody production and phagocytic clearance of blood-born bacteria which is facilitated by opsonization by specific antibodies. After splenectomy relatively higher levels of antibodies are required for maintenance of efficient phagocytosis in the macrophages of the liver. It is today well known that splenectomy is accompanied by a life-long risk for acquiring potentially fatal infections, mainly caused by polysaccharide encapsulated bacteria, such as Streptococcus pneumoniae. According to a recent review, the incidence of post-splenectomy septicemia and/or meningitis in adults varies from 2% to 11.6% per year, depending on age at splenectomy, cause of splenectomy and host immunity. Over the past decades, in the Western world, extensive programs have been launched to prevent overwhelming post-splenectomy infections (OPSI), such as immunisation, antibiotic prophylaxis, and patient education. However, despite the introduction of numerous preventive strategies, OPSI still pose a clinical challenge reflected in a yet high annual mortality rate of 1.0-3.8%.

Pneumococcal polysaccharide vaccine has been used for more than 20 years and is recommended for people over 65 years, as well as persons at high risk for pneumococcal infection due to comorbidity. This vaccine contains 23 different polysaccharides (PS) representing the pneumococcal serotypes that are most prevalent in invasive diseases covering about 90% of such infections. Its overall efficacy is quoted as “probably 60%” and this has been studied extensively (see 138, 139 for review). Recently performed systemic reviews of observational studies and randomised controlled trials have shown an efficacy against invasive disease of 53% and 38%, respectively. However, benefit from pneumococcal vaccination has shown to be clearly dependent on the baseline risk for infection and the characteristics of the given population. Previous studies on immunisation of patients with malignant diseases with or without chemotherapy have yielded large differences in both efficacy and immunogenicity.

We conducted this prospective study as a part of our ongoing program on pneumococcal vaccination/revaccination in splenectomised individuals. Other efforts in our program to prevent infection in splenectomised patients with hematological diseases include the development of educational programs for patients and health care professionals and the introduction of a warning system by providing a badge (similar to those carried by cardiac patients treated with pace maker and/or anticoagulants) for splenectomised and functionally asplenic patients. The main objective of the current study was to identify, in a well defined cohort of splenectomised patients with haematological diseases, the proportion of poor responders and their clinical characteristics and pneumococcal infectious complications.
Between 1994 and 2001, 76 adult splenectomised individuals with hematological disorders were recruited in this prospective study. The follow-up period extended from vaccination until July 2004, and the median follow-up time for surviving patients was 7.5 years (range 3.5-10.5 years). All patients were splenectomised before entry into the study. All patients were immunised subcutaneously with Pneumovax N®, which contains 25 μg of capsular PS per vaccination dose from each of 23 pneumococcal serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F (according to Danish nomenclature). The following defined algorithm was applied for decision-making regarding revaccination procedures: PS antibody levels were measured 1 year after vaccination and individuals with an antibody level <0.7 arbitrary units were revaccinated. In the remaining individuals the antibody level was monitored, in most cases annually. If the antibody level was <0.7 at 2 years or <1.5 at 3 or 4 years, revaccination was performed. After 5 years, all individuals were revaccinated, irrespective of PS antibody levels. PS antibodies were determined using an enzyme-linked immunosorbent assay before vaccination, at peak (4 weeks), and follow-up (one year). A data file with the unique personal identification numbers (obtained by each Swedish citizen shortly after birth or immigration) of these patients was linked with population-based Swedish Hospital Discharge Register (founded in the 1960s) run by the National Board of Health and Welfare, to identify recorded events (in- and outpatients) regarding pneumococcal infections potentially missing in the local files. In addition, the local computer systems (all installed in the late 1980s) at the Departments of Microbiology at Karolinska University Hospital were checked to identify positive culture results showing the growth of *S. pneumoniae* and its antibiotic resistance pattern.

Measurement of pneumococcal PS antibody levels at peak identified 21 patients (28%) as poor responders. In this group no increases in antibody levels were noted at one-year follow-up. The remaining 55 patients responded to the vaccine. The PS antibody level after 1 year declined below the predefined cut-off level (< 0.7 arbitrary units) in 5 of these patients, who in accordance with our pre-defined vaccination algorithm (see above) were revaccinated. Twenty of 21 (95%) of the poor responders showed no improved antibody response to revaccination. During the follow-up period, a total of five episodes of microbiologically verified pneumococcal infections were reported, all occurring among poor responders (annual risk 3.2% for 21 poor responders during the follow-up time of totally 156 person-years). All these episodes were also clinically documented pneumococcal pneumonias. The mean of antibody levels in these patients did not differ significantly from other poor responders (p= 0.33). The fact that all recorded pneumococcal infectious events during a long follow-up period occurred among individuals with poor PS antibody response indicates that peak levels of post vaccination PS antibody can be used to identify poor responders with continued risk for pneumococcal infections early after splenectomy. Furthermore, the vast majority (95%) of poor responders did not show any improvement in antibody responses when revaccinated and revaccination did not seem to prevent pneumococcal disease/infections in this group. These results reaffirm conclusions from previous studies that poor responders do not benefit from revaccination (Figure 8).
In 5 (9%) of good responders, antibody levels declined within one year after vaccination. Revaccination at this time resulted in good antibody responses and no pneumococcal infections were recorded among these individuals. This is a small sample for definite conclusions. However, the findings indicate that frequent revaccination is a useful method to keep PS antibody concentrations at a level with a higher probability to confer protection, irrespective of the type of underlying immunological defect (this is not true for the subgroup of poor responders). The good effect of revaccination in our patients supports the recommendations from the Centres of Disease Control and Prevention (revaccination every 6 years), the Advisory Committee on Immunisation Practice\textsuperscript{295} and the British Committee for Standards in Hematology (revaccination every 5-10 years or sooner).\textsuperscript{144} However, the results of the current study support the notion that revaccination should be performed with shorter intervals (1-5 years) if a primarily satisfactory antibody response is rapidly decaying. The fact that no severe reactions (e.g., anaphylactic reactions or localised Arthus-type reactions) were noted in this study indicates that this approach is safe and tolerable.

Several clinical factors, such as advanced age, hypogammaglobulinemia, advanced malignancy, previous chemotherapy or radiotherapy, have been reported to be associated with a poor antibody response to pneumococcal vaccination.\textsuperscript{290,296-299} Moreover, little is known about vaccination efficacy in elderly patients with hematological diseases. In the current study, poor PS antibody response was noted in 58\% of the included elderly patients (age > 65 years) indicating a probable additive negative impact of hematological diseases on the immunological response. However, none of the following factors could predict a poor antibody response: gender, disease activity or aggressiveness in hematological malignancies, previous radiotherapy and/or chemotherapy, time between splenectomy and pneumococcal vaccination, time between chemotherapy/radiotherapy and study pneumococcal vaccination (<1 year >), or the presence of hypogammaglobulinemia. This indicates the identification of poor responders through models based on clinical characteristics is not feasible.

In conclusion, a substantial proportion of splenectomised patients with hematological diseases mounted a poor PS antibody response and remained at risk for pneumococcal infections despite vaccination. In the absence of apt indirect clinical
predictors of antibody response, possibly with the exception of age, measurement of antibody levels seems to be a feasible method for early identification of this patient subgroup. Poor responders do not benefit from revaccination, and should be offered other prophylactic measures.
SUMMARY AND CONCLUSIONS

Epidemiological and antibiotic resistance trends

- The moderate predominance of gram-positive microorganisms remained essentially unchanged during a 14-year period in a relatively large hematology unit. The absence of the selective pressure of fluoroquinolone prophylaxis may have contributed to this finding.

- Except for the significant increase of *E. faecium* bacteremia, the species distribution was essentially stable. The rates of antimicrobial resistance were low and stable. Mortality was significantly higher when *P. aeruginosa*, *S. maltophilia*, or *E. faecium* were the causative agent implicating the importance of proper antibiotic coverage of these microorganisms.

- Previous exposure to fluconazole prophylaxis did not have a significant impact on the species distribution of colonising yeasts in patients treated for hematological malignancies. However, fluconazole prophylaxis was associated with the emergence of less susceptible yeast strains. These results emphasise the need for continued surveillance of azole resistance and emerging cross-resistance.

Therapeutic studies

- Cefepime was as safe and effective as imipenem-cilastatin when used as monotherapy in the empirical treatment of febrile neutropenia in patients with hematological malignancies.

- In FUO patients who have been afebrile for at least 48 hours, the discontinuation of antibiotics regardless of ANC-level appears to be a promising alternative in the management of these patients. Prospective large randomised trials are warranted.

- The MASCC risk-index is a valuable tool in the initial identification of hematological febrile neutropenic patients who run a low risk of complications.

- Early discharge from the hospital 24 hours after defervescence and subsequent oral treatment with antibiotics offer a safe and cost-effective alternative to the conventional management of low-risk patients with febrile neutropenia.

Pneumococcal vaccination in splenectomised patients

- A substantial proportion of splenectomised patients with hematological diseases mounted a poor antibody response to pneumococcal vaccination and remained at risk for pneumococcal infections. In the absence of apt indirect clinical predictors of antibody response, possibly with the exception of age, measurement of antibody levels seems to be a feasible method for early identification of this patient subgroup. Poor responders do not benefit from revaccination, and should be offered other prophylactic measures.
ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to all those who have supported me in my work. This thesis became possible through there never ending encouragement and enthusiasm. In particular I would like to thank:

Mats Kalin, Professor, main supervisor, for continuous scientific guidance throughout the whole study, never-ending enthusiasm, invaluable advices, and great patience.

Magnus Björkholm, Professor, co-supervisor, whose scientific and personal qualifications have been of the greatest importance for the realization of this study, for all scientific discussions, guidance and constructive criticism, and for his patience with my misspellings.

Martin Hjorth, Head of department of medicine in Lidköping Hospital, my tutor in internal medicine 1995-2001, for friendship, superb guidance, and for encouraging me to become an internist and introducing me to the interesting specialty of clinical hematology.

Eva Johansson, for all collaboration, practical advices, scientific discussions and for genuine friendship.

Ola Landgren, for all guidance through my first years in the field of clinical researches, for encouragement, friendship, and for all interesting discussions as room-mates about medicine, research, life, etc….

Jan Sjöberg, for being my neighbour in the corridor of Hematology Expeditions, for being there whenever I needed help with my works, for outstanding positivity, humanity and friendship.

Gunnar Grimfors, Previous head of the Division of Hematology. Karolinska University Hospital, for general support and for providing excellent work conditions.

Viktoria Hjalmar and Ana Petrescu for all support and for help with arranging our work schedule and managing it to allow me time to complete the last part of my thesis.

Per Ljungman, Head of Division of Hematology, Karolinska University Hospital, for his encouragement, invaluable advices when writing our guidelines for management of infectious complications, and for providing excellent working conditions.

Per Engervall, for his professional support and practical advices and for introducing me to his previous studies in the same field.

Bo Nilsson, Unit of Cancer Epidemiology, Karolinska University Hospital, for advanced statistical advices, and for fruitful discussions.
My co-authors, Göran Kronvall, Helle Bossen Konradsen, Peter Johansson, Robert Hast, Erja Chryssanthou and Björn Petrini for important discussions and constructive comments.

My colleges and friends at the Division of Hematology for genuine friendship and support essential for the realisation of this thesis.

Marinette Blücher, Sandra Brown, Marie-Louice Mountzoglu and Agneta Aronsson for highly professional and enthusiastic secretarial help.

My mother Nafisa, for love and kindness and for teaching me patience, loyalty and enthusiasm, the hornstones of life as a father, clinician and researcher.

My beloved wife Aseel, for love, encouragement, invaluable support and for giving me the self-confidence to accomplish this book.

And finally, our son Cherif and daughter Evin for being there and making everything worthwhile.

Thank you!

This study was supported by grants from the Swedish cancer society, Karolinska Institute Foundation, and the Stockholm County Council.
REFERENCES

Infections in patients with hematological malignancies


Infections in patients with hematological malignancies


Infections in patients with hematological malignancies

142. Landgren O, Bjorkholm M, Konradsen HB, et al. A prospective study on antibody response to repeated vaccinations with pneumococcal capsular polysaccharide in


Infections in patients with hematological malignancies


Infections in patients with hematological malignancies


