Hematological Malignancies

Chapter 5

Acute Myelogenous Leukemia and Febrile Neutropenia

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Abstract Aggressive chemotherapy has a deleterious effect on all components of the defense system of the human body. The resulting neutropenia as well as injury to the pulmonary and gastrointestinal mucosa allow pathogenic micro-organisms easy access to the body. The symptoms of an incipient infection are usually subtle and limited to unexplained fever due to the absence of granulocytes. This is the reason why prompt administration of antimicrobial agents while waiting for the results of the blood cultures, the so-called empirical approach, became an undisputed standard of care. Gram-negative pathogens remain the principal concern because their virulence accounts for serious morbidity and a high early mortality rate. Three basic intravenous antibiotic regimens have evolved: initial therapy with a single antipseudomonal β-lactam, the so-called monotherapy; a combination of two drugs: a β-lactam with an aminoglycoside, a second β-lactam or a quinolone; and, thirdly, a glycopeptide in addition to β-lactam monotherapy or combination. As there is no single consistently superior empirical regimen, one should consider the local antibiotic susceptibility of bacterial isolates in the selection of the initial antibiotic regimen. Not all febrile neutropenic patients carry the same risk as those with fever only generally respond rapidly, whereas those with a clinically or microbiologically documented infection show a much slower reaction and less favorable response rate.

Once an empirical antibiotic therapy has been started, the patient must be monitored continuously for nonresponse, emergence of secondary infections, adverse effects, and the development of drug-resistant organisms. The average duration of fever in serious infections in eventually successfully treated neutropenic patients is 4–5 days. Adaptations of an antibiotic regimen in a patient who is clearly not responding is relatively straightforward when a micro-organism has been isolated; the results of the cultures, supplemented by susceptibility testing, will assist in selecting the proper antibiotics. The management of febrile patients with pulmonary infiltrates is complex. Bronchoscopy and a high resolution computer-assisted tomographic scan represent the cornerstones of all diagnostic procedures, supplemented by serological tests for relevant viral pathogens and for aspergillosis. Fungi have been

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found to be responsible for two thirds of all superinfections that may surface during broad-spectrum antibiotic treatment of neutropenic patients. Antibiotic treatment is usually continued for a minimum of 7 days or until culture results indicate that the causative organism has been eradicated and the patient is free of major signs and symptoms. If a persistently neutropenic patient has no complaints and displays no evidence of infection, early watchful cessation of antibiotic therapy or a change to the oral regimen should be considered.

Keywords Neutropenic fever • Empirical antibacterial therapy • Unexplained fever • Immunodeficiency • Invasive fungus

1. Introduction

Only 50 years ago, dealing with a patient with a disseminated malignant disease was relatively simple. There were no curative options and information on the inevitable dismal prognosis was not shared with the patient or his family. The mid sixties of the twentieth century witnessed the first successes of chemotherapeutic agents. This encouraged investigators to explore this route further, thereby escalating the dosage of the cytostatic drugs in the expectation of better results. It became rapidly clear that the destructive effects of cytotoxic compounds were not limited to malignant cells. Infection has emerged as a prominent complication of chemotherapy, which was particularly worrisome in the sixties, a decade without powerful broad-spectrum antimicrobial agents. Since a possible cure of the cancer was seen as the primary goal, complications of rigid cytotoxic regimens were taken for granted and when they occurred, treatment was more or less improvised. This situation remained unchanged until Bodey [1] pointed out that patients in remission of their underlying disease could die suddenly of an overwhelming infection during cytotoxic therapy-induced neutropenia. Neutropenia was and remains defined as an absolute neutrophil count of less than 0.5×10^9/l (500/mm^3) or a count less than 1.0×10^9/l (1,000/mm^3) expected to fall below 0.5×10^9/l (500/mm^3) [1]. He even showed a positive correlation between the severity and duration of neutropenia and the risk of acquiring a life-threatening bacterial infection. This risk appeared even more pronounced in individuals who were treated for an acute leukemia or lymphoma as these disorders interfered directly with vital components of the immune system. Next to gram-negative bacilli, *Staphylococcus aureus* earned a notably bad reputation [2]. A few years later, Schimpff and co-workers demonstrated convincingly that early administration of antimicrobial agents covering the above suspected pathogens while waiting for the results of the blood cultures saved lives. His so-called empirical approach became an undisputed standard of care [3]. However, better options to manage infections encouraged hematologists to intensify their antileukemic regimens further in an attempt to improve the remission rates in previously refractory cases. These intensifications, in turn, inspired more thorough clinical research into potentially more effective antimicrobial regimens, which was facilitated by the booming development of new antimicrobial agents such as broad-spectrum synthetic penicillins, third and fourth generation cephalosporins, fluoroquinolones, and carbepenems in conjunction with a keen eagerness of the respective pharmaceutical companies to put

their compounds to test in large clinical trials that were usually conducted by cooperative trial groups [4, 5]. A cycle of several subsequent rounds of broader-spectrum antibiotics and further intensification of chemotherapeutic regimens has eventually lessened the mortal risk of neutropenia to only one of many problems in today's clinical practice.

Modern anti-leukemic therapy is inherently associated with ulceration of the pulmonary and gastrointestinal mucosa thereby allowing micro-organisms originating from the damaged mucosal tracts easy access to the body [6, 7]. These pathogens may be part of the original indigenous flora but are commonly acquired during hospitalization [8]. In the 1970s, it was considered logical to prevent invasion of the body by indigenous flora by prophylactic administration of anti-infective agents. Since such prophylactic agents were mainly targeted against the gram-negative enterobacteriaceae, a shift from gram-negative to gram-positive micro-organisms, including coagulase-negative staphylococci, viridans streptococci, and enterococci, as the primary cause of fever in neutropenic patients was seen [9–15]. In the meantime, therapeutic regimens in the treatment of hematological malignancies have become so complex that use of surgically implanted venous access devices became universal in spite of the risk of catheter-associated infections and thrombosis [16, 17]. An epidemiological survey among hospitalized patients treated for hematological malignancies between 1995 and 2001 in the United States showed that approximately 70% (64% in 1995 and 76% in 2001) of all microbiologically confirmed febrile episodes were due to gram-positive bacteria and 18% (22% in 1995 and 14% in 2001) due to gram-negative bacilli [18]. This change in pathogens was facilitated by increased use of central venous catheters and other medical devices.

Introduction of immunomodulatory monoclonal antibodies into the therapeutic arena has extended the treatment-related immunodeficiency to T-cell functions and innate immunity. This, in turn, has brought viral and fungal infections, including *Pneumocystis jeroveci*, into play, particularly when impaired cellular immunity coincided with prolonged, severe neutropenia [19, 20]. The modern chemotherapeutic regimens designed to treat acute lymphoblastic leukemia incorporate high doses of corticosteroids. As a result, patients treated with such regimens are at increased risk of infections typically related to an impaired cellular immunity. In addition, allogeneic bone marrow transplantations have become a fully accepted treatment modality for many hematological malignancies. Nowadays, infections still account for substantial morbidity and mortality among patients who undergo myeloablative therapy for a hematological malignancy. In spite of all changes in the spectrum of infectious agents, gram-negative pathogens remain the principal concern because their virulence accounts for serious morbidity and high early mortality rate [21, 22].

2. Management of New Fever and Infections

2.1. Principles

Administration of potentially curative chemotherapy is the starting point in treating acute leukemias. Giving cytotoxic drugs is relatively straightforward since internationally accepted antitumor protocols have defined the optimal dosages. Once the chemotherapy has been administered, the hematologist

must wait patiently for the desired outcome a few weeks later. However, while the scientist in the hematologist has completed this first task, the general clinician in him or her has to step forward to monitor the patient, as the natural host defense system gradually disintegrates. Close surveillance of the patients with attention to the emergence of infectious complications is mandatory. Management of infections during this time of danger must be individualized because fixed protocols and algorithms are of limited usefulness given the complexity of infectious diseases management [23, 24]. It is here that the science and art of medicine meet; listening to the patient's complaints and meticulous physical examinations constitute the crucial factors for timely therapeutic interventions and eventual success. This applies to both patients who are treated with intensive chemotherapeutic regimens and to recipients of a stem cell transplant. During this period of neutropenia, appropriate coordination of information coming from different sources is important, since, next to the patient, family members, nurses, microbiologists, pulmonologists, radiologists, and pathologists can assist in the timely discovery of an emerging complication. Different cancer centers approach these tasks in different ways but it occurs to us that the hematologist who is responsible for treating the underlying hematological disease must also act as the captain of the ship. This coordinating role obliges him or her to have at least some basic knowledge of likely infection problems and, perhaps even more importantly, to have fine communication skills to keep all parties on board as well as incorrect on the same course. Since the symptoms of an incipient infection are usually rather subtle due to the absence of granulocytes, teamwork is crucial to ensure that antibiotics are administered at the first signs or symptoms of infection [25]. In most cases, fever defined as a single oral temperature of more than 38,3°C (101°F) or a temperature of more than 38,0°C (100,5°F) for more than 1 h, will serve as a trigger for action. At the onset of fever, attempts to identify the cause of fever deserve absolute priority (see Table 5-1), immediately followed by institution of appropriate broad-spectrum antibiotic therapy preferably within one hour of fever [22]. Fever in a neutropenic patient is a warning sign that should be taken very seriously because self-limiting infection is virtually

Table 5-1. Diagnostic procedures at the onset of fever.

- Short history of the patient with recent complaints
- Physical examination with special attention to:
  - o Vital signs
  - o Gastrointestinal tract: abdomen, perineum
  - o Respiratory tract: oropharyngeal area and lungs
  - o Skin, including bone marrow aspiration sites, vascular access sites, and tissue around the nails
- Cultures of blood (minimal 15 ml) and any clinical suspicious body site, including urine
- CT scanning of the chest
- Check medication list, results of surveillance cultures, compliance with prophylaxis, course of the leukocyte count
- Consider determination of CRP, galactomannan antigen, and viral serology

nonexistent in neutropenic patients irrespective of whether they have been treated for acute leukemia or lymphoma or received a stem cell transplantation. In anticipation of the results of the diagnostic evaluation, fever denotes infection until proven otherwise. Absence of phagocytic cells in combination with a damaged skin and mucosal surfaces allows micro-organisms residing at a superficial site of infection easy access to the bloodstream. Under these circumstances, a relatively small inoculum, that easily can escape detection when limited volumes of blood are sampled for culturing, can cause a serious septic syndrome [3]. Therefore, withholding antibiotics while waiting for a blood culture to become positive is a bad idea, even though fever can be of noninfectious origin [26]. A sudden onset of fever accompanied by chills, tachycardia with or without a drop in blood pressure, and tachypnea is associated with a higher rate of positive blood cultures. Shock at the onset of fever is an ominous clinical sign but neither clinical manifestations nor the pattern of fever during neutropenia can serve as an indicator of a particular causative agent, not even when the most notorious pathogens such as *Pseudomonas aeruginosa* or *Staphylococcus aureus* are involved [19, 27]. A substantial minority of patients with true infections will have an insidious onset of fever. Although more frequently related to noninfectious causes than acute fever, a slow rise of temperature does not exclude an infectious origin, although gram-negative rods, viridans streptococci, and *Staphylococcus aureus* are less prevalent amongst these patients. Acute fever following transfusion is often related to the presence of irregular blood group antigens or to cytotoxic antibodies acquired during previous transfusions or a pregnancy [28]. Of note, relative bradycardia in patients who did not receive antiarrhythmic medication suggests either a viral or noninfectious origin of the fever. A possible relation between fever and frequently used drugs such as allopurinol, antibiotics, bleomycin, and cytarabine or with the underlying disease process itself should always be kept in mind [29, 30]. A dysfunctional immune system is presumed to be responsible for the high rate of drug allergy in patients with active acute leukemia; the allergy may abate when complete remission is achieved [29]. This phenomenon is well known in patients with infectious mononucleosis or acquired immunodeficiency syndrome.

Until recently, coagulase-negative staphylococcal bacteremia was thought to be entirely related to the use of central venous catheters but recent work points at mucosal sites as important portals of entry [31–33]. The clinical spectrum of catheter-related infections ranges from asymptomatic bacteremia as a manifestation of intraluminal colonization or a process confined to the site of insertion to marked inflammation of the tunnel tract and septicemia with metastatic emboli in the skin and other organs. Suspicion of a tunnel or exit line infection should arise when the catheter tract becomes painful, red, or swollen or when signs of inflammation are visible at the exit site. Malfunction of the catheter, illustrated by problems drawing blood through the line, is a common first warning of a possible lumen infection [16, 17].

2.2. Selection of Antimicrobial Agents for the Empiric Phase

2.2.1. Basic Regimens

In the selection of the initial antibiotic regimen, one should consider the type, frequency of occurrence, and antibiotic susceptibility of bacterial isolates recovered from other patients at the same hospital. In addition, the use

of certain antibiotics may be limited by special circumstances, such as drug allergy, liver function disturbances, or renal insufficiency. Despite numerous clinical studies, since the 1970s, no single empirical antibiotic regimen has been shown to be superior for initial treatment of patients who become febrile during a neutropenic episode after therapy with chemotherapy drugs for hematological malignancies (see Table 5-2) [4, 9, 34–44]. However, there is world-wide consensus that any initial antibiotic regimen should include drugs with reliable activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella* species, other enterobacteriaceae, and *Staphylococcus aureus* [22]. Three basic intravenous antibiotic regimens have evolved: initial therapy with a single β-lactam, the so-called monotherapy; a combination of two drugs, a β-lactam with an aminoglycoside, a second β-lactam or a quinolone but without a glycopeptide; and, thirdly, a glycopeptide in addition to β-lactam monotherapy or combination. Numerous extensive studies have shown that traditional combinations, consisting of an antipseudomonal β-lactam and an aminoglycoside, are not more effective than monotherapy in the empiric treatment of uncomplicated episodes of fever in neutropenic patients. A third or fourth generation cephalosporin, a carbapenem, as well as piperacillin–tazobactam, have been found to be effective single agents in the majority of cases [43, 45]. It appears appropriate to reserve two-drug regimens for complicated cases or if antimicrobial resistance is a potential problem. The major disadvantages of an aminoglycoside are nephrotoxicity and ototoxicity, and the necessity to monitor serum levels [46–48]. Combination of drugs such as amphotericin B, cyclosporine, and cisplatinum with an aminoglycoside is best avoided because of their additive renal toxicity, whereas high sodium content may limit the simultaneous use of two β-lactam antibiotics in elderly patients. An extensive study by European Organization for Research and Treatment of Cancer – National Cancer Institute of Canada [11] showed unambiguously that vancomycin can be withheld and not administered empirically for persistent fever despite appropriate initial monotherapy or combination antibiotic treatment until the results of the cultures indicate the need for vancomycin. Vancomycin must be included in an initial empiric regimen for patients known to be colonized with penicillin- and cephalosporin-resistant pneumococci, viridans streptococci, or methicillin-resistant *Staphylococcus aureus* or in situations where β-lactam resistance is likely such as a catheter-associated cellulitis where coagulase-negative staphylococci predominate .

The choice to implement a particular antibiotic regimen is, at least partly, based on the results of clinical trials as reported in the literature. Yet, the results of such trials should be interpreted with great caution. Definitions for response as well as inclusion and exclusion criteria for clinical study protocols are usually very rigid and quite different from common clinical practice [23, 24].

2.2.2. Specifically Tailored Regimens

Conduct of clinical trials in febrile neutropenic patients was a booming business in the mid-seventies and eighties when many new broad-spectrum antibiotics became available. The data derived from these trials expanded our knowledge of the possible infectious complications tremendously. For instance, analyses of these studies revealed that only half of the patients who develop fever during neutropenia will have a clinically or microbiologically

Table 5-2. Efficacy of antibacterial regimens in the treatment of neutropenic patients with fever.

Study	No of evaluable episodes (patients)	Treatment	Favorable responses/documented infections	Favorable responses/bacteremia
Wade et al. [33]	121 (92)	Piperacillin + Amikacin	22/38 (58%)	5/15 (33%)
		Ticarcillin + Amikacin	19/34 (56%)	6/11 (55%)
Duprez and Michaux [34]	(118)	Piperacillin + Amikacin	26/34 (76%)	9/14 (64%)
		Cefotaxime + Amikacin	27/37 (78%)	15/20 (75%)
Winston et al. [35]	297 (244)	Piperacillin + Amikacin	38/53 (72%)	16/25 (64%)
		Carbenicillin + Amikacin	48/66 (73%)	20/36 (56%)
Winston et al. [36]	272 (219)	Piperacillin + Moxalactam	45/61 (74%)	17/23 (74%)
		Moxalactam + Amikacin	41/50 (82%)	13/18 (72%)
EORTC [9]	(872)	Azlocillin + Amikacin full course	75/138 (54%)	12/47 (26%)
		Ceftazidime + Amikacin short.	69/118 (58%)	12/35 (34%)
		Ceftazidime + Amikacin full course	95/145 (66%)	19/41(46%)
Winston et al. [37]	(187)	Piperacillin + Cefoperozone	39/50 (78%)	22/29 (76%)
		Piperacillin + Moxalactam	31/38 (82%)	16/22 (73%)
Sage et al. [38]	174 (225)	Piperacillin + Netilmicin	12/15 (80%)	1/2 (50%)
		Ticarcillin + Netilmicin	11/14 (79%)	1/2 (50%)
		Mezlocillin +Netilmicin	11/18 (61%)	1/5 (20%)
		Cefoperozone + Netilmicin	4/10 (40%)	0/2 (0%)
Feliu et al. [39]	170 (118)	Piperacillin + Amikacin	24/44 (55%)	9/21 (43%)
		Ceftazidime +Amikacin	30/51 (59%)	14/23 (61%)
De Pauw et al. [4]	784 (696)	Ceftazidime	127/367 (35%)	33/118 (28%)
		Piperacillin + Tobramycin	117/335 (33%)	25/132 (19%)
Cometta et al. [13]	706 (475)	Piperacillin–tazobactam + Amikacin	210/342 (61%)	40/50 (50%)
		Ceftazidim + Amikacin	196/364 (54%)	35/101 (35%)
De Pauw et al. [40]	304 (225)	Meropenem	54/110 (44%)	37/79 (47%)
		Ceftazidime	35/105 (41%)	24/79 (30%)
Cometta et al. [14]	483 (475)	Meropenem	270/483 (56%)	47/113 (42%)
		Ceftazidime + Amikacin	245/475 (52%)	34/114 (30%)
Feld et al. [41]	409 (471)	Meropenem	33/77 (54%)	14/31 (45%)
		Ceftazidime	33/82 (44%)	22/43 (51%)
Del Favero et al. [42]	(733)	Piperacillin–tazobactam	67/186 (36%)	42/140 (30%)
		Piperacillin–tazobactam + Amikacin	60/176 (34%)	44/137 (32%)
Bow et al. [43]	(528)	Piperacillin–tazobactam	71/265 (27%)	11/81 (14%)
		Cefepime	54/263 (21%)	7/86 (8%)

documented infection, the majority being pulmonary infiltrates and bacteremias (see Table 5-3) [49, 50]. Furthermore, it was obvious that neutropenic patients without a documented infection generally defervesced within a few days, whereas those with a clinically or microbiologically documented infection showed a much slower and less frequent fever defervescence rate [19, 27, 51]. This very consistent observation suggests that it might be prudent to select different antibiotic regimens for patients with different symptoms. Although there is no statistically valid evidence to support a more individually tailored approach, it appears reasonable to assume that patients might benefit from timely administration of the antibiotics with the highest intrinsic potency against a given micro-organism. A known or suspected focus of infection, if present at the time of initial fever, could help in the selection of additional case-specific anti-infective agents because the location of an infection is, at least to a certain extent, predictive of specific infective pathogens (see Table 5-4)[52]. Likewise, results of surveillance cultures and knowledge of

Table 5-3. Classification of febrile neutropenic episodes.

FUO-fever of unknown origin	New fever, not accompanied by clinical or microbiological evidence of infection
Clinically documented infection	Fever accompanied by a clinical infection, but pathogens cannot be identified, e.g., cellulitis, pneumonia
Microbiologically documented infection	Fever accompanied by a localized infection and microbiologically plausible evidence, or fever without a localized infection, but infectious agents can be demonstrated in a (blood) culture

Table 5-4. Sites of infection and prevalent causative micro-organisms.

Site	Prevalent pathogens	Preferred antimicrobial agents
Upper respiratory tract	Streptococci	Amoxicillin, clindamycin
Lower respiratory tract	Gram-negative bacilli	Combination therapy <<?>>
	Streptococci	Amoxicillin, clindamycin, macrolides
	Moulds	Consider antifungal agents in an early phase
	Diffuse infiltrates	Antiviral agents
	Cytomegalovirus	Trimethoprim–sulfamethoxazole
	Pneumocystis jeroveci	
Skin and soft tissue	Staphylococci	Glycopeptides
	Streptococci, anaerobes	Amoxicillin, clindamycin, macrolides, glycopeptides
Abdominal	Anaerobes	Metronidazole, glycopeptides
Perianal abscess	Gram-negative bacilli	Combination therapy <<?>>

the common complications associated with particular antileukemic regimens may offer valuable input to individualizing appropriate initial treatment of a neutropenic patient with fever.

2.2.2.1. Gastrointestinal Tract

A damaged integument probably plays a major etiologic role in virtually all infections that occur following aggressive cytoreductive therapy for a hematological malignancy but its involvement is most obvious in infections of the skin and gastrointestinal tract. The use of high-dose cytarabine in conjunction with the occurrence of diarrhea were found to be independent risk factors for streptococcal infections among 513 patients evaluated during first episodes of neutropenic fever [53]. It has been recognized that bacteremias due to oral *Streptococcus mitis* and *Streptococcus oralis* may result in serious complications such as sepsis or adult respiratory distress syndrome, which carry high mortality [54–56]. Similarly, bacteremias due to *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Clostridium* species as well as candidemias are more frequently encountered in patients with acute leukemia who suffer from neutropenic enterocolitis or typhlitis, the most serious disturbance of the delicate balance between mucosal damage and microbial flora in the setting of prolonged exposure to antibiotics after intermediate or high-dose cytarabine chemotherapy. The signs and symptoms of chemotherapy-induced enterocolitis or typhlitis vary considerably from patient to patient and include nausea, vomiting, abdominal cramps, and severe abdominal pain with virtually no formed bowel movements but accompanied by profuse, watery diarrhea. Many patients are in such pain that they only gain relief from narcotic analgesics which, in turn, induce constipation by reduction of bowel movements. This may create a very alarming situation as the clinical picture in severe cases resembles that of gut perforation, acute pancreatitis, or even toxic megacolon. Because there is a high mortality rate for surgical interventions in neutropenic and thrombocytopenic patients with acute leukemia, it is essential for physicians to be aware of the existence of neutropenic enterocolitis/typhlitis with the accompanying symptoms. Ultrasonography or CT, showing pathological thickening of the bowel walls, may be useful to establish the diagnosis of typhlitis. Patients treated for acute myeloid leukemia with a bowel wall thickness of more than 10 mm had a significantly higher mortality rate than did those with a bowel thickness of less than 10 mm [57]. Disproportional bacterial overgrowth in the gastrointestinal tracts of neutropenic patients with damaged mucosa can serve as a source of bacteremia for the endogenous gastrointestinal flora as well as for otherwise exclusively enteric pathogens such as *Clostridium septicum* [58, 59] and *Bacteroides fragilis*. In contrast, *Salmonella* species are rarely found in the stool or blood of granulocytopenic patients; these organisms are obviously not major players in this field. This is also true for pathogens like *Campylobacter* and *Shigella* species. Therefore, an adequate antibiotic regimen for patients with abdominal symptoms should cover gram-negative rods but due consideration should be given to the use of compounds with activity against anaerobes. Next to glycopeptides and carbapenems, metronidazole is an attractive adjunct to a standard monotherapy/combination regimen under these circumstances. Pseudomembranous colitis caused by *Clostridium difficile* [60–64] constitutes a related but distinct entity that can be severe and even fatal. The stool should be tested immediately for *Clostridium difficile* toxin if the diagnosis is suspected. Enteric *Clostridia* infections

necessitate oral antibiotic therapy with either vancomycin or metronidazole. Relapses are frequent and may follow cancer chemotherapy or courses with antibiotics such as clindamycin. Relapse is harder to document because toxin may persist in the stool of successfully treated patients.

Diagnostic problems account for underestimating enteric viruses as causative agents in gastrointestinal infections. Although a compromised cell-mediated immunity is known to predispose for parasitic and protozoan infections, their incidence is surprisingly low in patients who are treated for a hematological malignancy [65, 66].

2.2.2.2. Skin

Folliculitis and cellulitis are the most common manifestations of infectious processes in the skin. Sometimes it is difficult to differentiate infectious lesions from drug-induced toxic skin eruptions. Infection-associated erythema and swelling are usually mild but, if left untreated, infiltration and abscess formation will involve extensive areas of the skin with necrosis and gangrene. Since the lesions associated with the various organisms are rather alike, a simple needle aspiration or biopsy should be performed to establish an accurate diagnosis as early as possible in the course of the disease. Causative micro-organisms include streptococci, staphylococci, and, less commonly, gram-negative bacilli and fungi [67–70]. Localized infections of the skin, particularly in the face, are usually caused by gram-positive bacteria that arise more frequently in carriers of organisms like *Staphylococcus aureus*. None of the standard empiric regimens is the optimal choice for treating skin infections caused by the prevalent but usually indolent non*S. aureus* gram-positive cocci that are often methicillin-resistant, but the morbidity from these infections should not be underestimated either. *Pseudomonas aeruginosa* acquired in a hot Jacuzzi may cause a folliculitis that occasionally progresses to a destructive ecthyma gangrenosum [71]. This characteristic entity should be distinguished from similar lesions caused by other rare pathogens, such as actinomyces, *Stenotrophomonas maltophilia* [68] and fungi [69, 70] as well as from pyoderma gangrenosum, a noninfectious cutaneous process in patients with a myeloid malignancy [72, 73]. Sweet's syndrome, a dense, tender infiltration by neutrophils of the dermis on the head, neck, and upper extremities is associated with a leukocytosis [74]. Varicella zoster is the leading dermatologic complication in patients with impaired cell-mediated immunity [75–77]. If skin or mucous membrane lesions due to herpes simplex or varicella-zoster viruses are present, even if they are not the cause of fever, treatment with valacyclovir or another suitable antiviral is indicated with the intention to speed healing of lesions that could become potential portals of entry for bacteria and fungi.

The results of several prospective studies do not indicate a general need for a glycopeptide as part of the front-line therapeutic regimen unless one has a particular reason to suspect the presence of methicillin-resistant *Staphylococcus aureus* or penicillin-resistant *viridans* Streptococci on the basis of local patterns of resistance or surveillance cultures. Nevertheless, most physicians intuitively prefer an up-front glycopeptide-containing regimen to cover catheter-related infections as these are frequently due to coagulase-negative staphylococci, although early glycopeptide treatment does not contribute to improved survival from these usually indolent infections. Hence, when coagulase-negative staphylococci are involved, a few days of watchful waiting for a possible clinical response and the results of the cultures will have no detrimental impact.

Most catheter-associated infections will respond to antibiotic therapy without the removal of the catheter. Rotation of antibiotics through each lumen of multilumen catheters to avoid microbial sequestration in one of the lines and the use of antibiotic-containing heparin lock solutions to supplement systemic therapy have been proposed by some investigators but such practices remain controversial. Pulling the catheter is most likely to be required for the cure if a concurrent venous thrombosis is found, the tunnel tract appears involved, or if the infection, regardless of the etiology, is recurrent, or if after several days of therapy an eventual response to antibiotics appears doubtful [78].

2.2.2.3. Upper Respiratory Tract

Gingivostomatitis and periodontal lesions occur frequently in patients with acute leukemia [79]. Oral mucositis is characterized by pain, edema, erythema, superficial lesions, pseudomembranous formation in conjunction with excessive mucous production, reduced saliva secretion, and bleeding. A wide array of pathogens can be found and include *Herpes simplex*, gram-negative bacilli, streptococci, anaerobes, and *Candida* species [80]. With the introduction of aggressive chemotherapeutic regimens, hitherto unusual pathogens such as *Stomatococcus* and *Aerococcus* are increasingly seen in patients with mucositis. Mixed and polymicrobial infections are more or less standard [80, 81]. Given the range of prevalent pathogens, there is little need to deviate from one of the standard regimens, although, on theoretical grounds one might prefer to select a carbapenem, fourth generation cephalosporin, or extended-spectrum penicillin given their superior intrinsic activity against viridans streptococci and pneumococci. The course of *Herpes simplex* stomatitis is usually prolonged in patients treated for leukemia or lymphoma, and relapses are common [82]. *Herpes simplex* lesions are most commonly white painful plaques with or without serpiginous borders on the gums, tongue, buccal mucosa, or oropharynx and may be difficult to discriminate from oropharyngeal candidiasis and, indeed, co-infections do occur. Swallowing can be so painful that saliva is expectorated and intake of food and fluids drastically reduced. It is not uncommon for oropharyngeal *Herpes simplex* and *Candida* infections to extend to the esophagus. Although neither herpes nor candidiasis belong to the category of diseases that requires an empiric approach, it is generally accepted that early treatment with valacyclovir and fluconazole, respectively, is important to prevent extension into the esophagus and further dissemination, particularly among bone marrow transplant recipients. When the paranasal sinuses are involved in the infectious process, moulds have to be considered as possible causes. Direct inspection of the nasal turbinates and a computer-assisted tomographic scan of the sinuses can be helpful to establish or reject the diagnosis.

2.2.2.4. Lower Respiratory Tract

Management of pulmonary infiltrates that are responsible for 70% of all fatal infections in febrile neutropenic patients is complex [83–85]. The importance of classic clinical complaints of cough, pain, and dyspnea should not be neglected but bronchoscopy and radiological examination of the chest by a computer-assisted tomographic scan represent the cornerstones of all diagnostic procedures. Typically, chest radiographs performed early in the evolution of infection in patients with profound granulocytopenia fail to show infiltrates. It may take more than 3 days for the infection to generate enough necrosis with

hemorrhage and edema to produce a visible infiltrate. The critical decision faced by the clinician at the bedside of patients with pulmonary infiltrates is whether to undertake invasive procedures such as bronchoscopy with or without bronchoalveolar lavage, transbronchial biopsy, transthoracic aspiration, thoracoscopy-guided biopsy, or open lung biopsy. The exact role of these diagnostic procedures in the optimal management of patients is still controversial because the yield depends on the collaboration and skills of various specialists. Moreover, concurrent thrombocytopenia precludes simple invasive diagnostic procedures such as transbronchial biopsies in many patients.

The radiologic pattern of a possible infiltrate is often suggestive of its cause. A diffuse opacity, usually of both lungs, is seldom of bacterial or fungal origin. Although viruses and *Pneumocystis jeroveci* typically cause diffuse, bilateral pulmonary infiltrations, it should be kept in mind that a similar picture of pneumonitis can be seen secondary to radiation, fluid overload, cytotoxic drugs such as methotrexate, cytarabine and bleomycin, and in pulmonary hemorrhage. *Pneumocystis jeroveci* pneumonia is manifested in patients with deficient cellular immunity as fever, progressive hypoxemia with dry cough, and dyspnea, typically beginning after discontinuation of corticosteroid therapy given for other reasons [85]. High-dose trimethoprim–sulfamethoxazole with adjuvant corticosteroids for hypoxemic patients ($PO_2 < 70$ mmHg) has become the preferred therapy for these infections [86]. Alternatives include intravenous pentamidine, oral dapsone in combination with trimethoprim, or oral atovaquone suspension alone.

Antiviral drugs are indicated only if there is clinical or laboratory evidence of viral disease. With the exception of a cytomegalovirus-related pneumonitis in allogeneic bone marrow transplant recipients with graft-versus-host disease, there appears to be no need for empiric coverage of respiratory viruses, such as respiratory syncytial virus, influenza [87, 88], and adenoviruses. Ganciclovir, valganciclovir, and foscarnet have established activity in the treatment of cytomegalovirus infection and their timely use might be lifesaving. *Mycoplasma pneumoniae* with or without cold agglutinins is remarkably infrequent in patients treated for leukemia. In more acutely ill patients, the possibility of acute lung injury following transfusion of a cellular blood product or respiratory distress syndrome related to streptococcal sepsis should be considered.

Patients with an infection by *Streptococcus mitis,* which has been linked with severe mucositis and high-dose cytarabine are at particular risk [53, 54]. The incidence of acute respiratory distress syndrome in such cases is more than 20% and mortality is substantial. The pathophysiology of adult respiratory distress syndrome following streptococcal bacteremia in a neutropenic patient is poorly understood. Probably several factors are involved, such as deleterious effects of sepsis superimposed on preexisting tissue damage. Even patients who had received appropriate antimicrobials at the onset of fever were reported to experience shock and death [54–56]. Therefore, in addition to antibiotics, corticosteroids should be considered in the management of patients affected by ARDS and streptococcal bacteremia.

Bacterial infections of the lung, accompanied by bacteremia in about 50% of cases, usually create infiltrates on a computer-assisted tomographic scan that are confined to one or more lobes. Pneumonias caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus* do have a bad

reputation but enterobacteriaceae [89, 90], *Haemophilus influenzae* and *Streptococcus* species are hardly less dangerous. Given the uniformly poor outcomes of pulmonary infections in clinical trials, the empiric use of a combination of antibiotics is recommended with the addition of vancomycin in centers that face resistance of *S. pneumoniae* to penicillin and macrolides. Outbreaks of *Legionella pneumophila,* an infection characterized by patchy interstitial or nodular pulmonary infiltrates and sometimes accompanied by headache or gastrointestinal symptoms, have been observed among compromised patients in units with contaminated water systems [91]. Therefore, if a case of legionellosis is encountered, other patients with similar symptoms on the same ward should be treated with a macrolide or a fluoroquinolone from the start of antimicrobial therapy.

A nodular pattern of pulmonary infiltrates should lead the physician to consider the possibility of atypical pneumonia or, more commonly, a pulmonary fungal infection. In the latter case, diagnostic procedures rather than immediate institution of antifungal drugs should be given priority. Especially in patients with concomitant impairment of the cell-mediated immunity, pulmonary aspergillosis has to be distinguished from tuberculosis. Infections with *Mycobacterium tuberculosis* in patients with impaired cell-mediated immunity are manifested as either localized pulmonary disease or devastating miliary tuberculosis. Nontuberculous mycobacteria are still rather rare in patients with acute leukemia, but the introduction of purine analogues such as cladribine and fludarabine, which cause severe and prolonged depression of cellular immunity, may change this picture in the near future [92].

2.2.2.5. Other Foci of Infection

Urinary tract infections are astonishingly uncommon in patients who are treated for leukemia or lymphoma and, since gram-negative bacteria are the predominant urinary tract pathogens, the choice for a single broad-spectrum β-lactam is fully justified.

Malignant otitis externa is a very serious infectious complication that can emerge after administration of aggressive chemotherapy for a hematological malignancy. At the outset, the patient will complain of a painful, discharging ear, and physical examination will reveal a reddened edematous ear canal. Local maceration and humid conditions favor the growth of *Pseudomonas aeruginosa* which, indeed, can be isolated frequently from swabs taken from superficial lesions of the external canal. Untreated, the infection will penetrate into underlying soft tissues, threatening the retromandibular and parotid area. Likewise, spread to the middle ear, the mastoid air cells, and adjacent temporal bone is possible. Once osteomyelitis becomes established, extension to the base of the skull with invasion of the cranial nerves and local thrombosis poses a direct danger to the patient's life. A computer-assisted tomographic scan may be helpful to identify tissue damage in the early phase. Prolonged antibiotic therapy with ceftazidime, ciprofloxacin, or other antipseudomonal antibiotics in combination with surgical debridement constitutes the treatment of choice [93]. Occasionally, a similar clinical picture can be the result of an infection by *Staphylococcus aureus* or *Aspergillus fumigatus*. In such cases, surgery should be combined with an antistaphylococcal penicillin or vancomycin, or with voriconazole, respectively.

An insidious onset of fever accompanied by headache and confusion might be indicative of meningitis when causation by leukemia or lymphoma has been excluded by cytologic examination of the cerebrospinal fluid. In cases of infection, the cerebrospinal fluid is usually clear with moderate protein elevation. The prevalent pathogens are *Listeria monocytogenes, Cryptococcus neoformans,* and *Toxoplasma gondii* [65]. Recovery of one of *Listeria monocytogenes* [94] and *Cryptococcus neoformans* from blood cultures should, provided that no intracranial hypertension is detected, always prompt a lumbar puncture even in the absence of neurological symptoms. Considering their low incidence and the relatively reliable diagnostic possibilities, there is no need to cover for these infections with a specific empiric regimen.

2.2.3. Management on an Out-Patient Basis

Outpatient management of infections in patients with hematological malignancies is discussed in more depth in Chap. 6. When potent oral broad-spectrum antibiotics became available in the late eighties, many clinicians felt tempted to use these drugs in the treatment of febrile neutropenic patients. Several groups around the world assessed the options and limitations of this seemingly revolutionary approach [95–97] systematically. These analyses showed that it is possible to define risk factors that can be used to classify patients into low or high-risk categories. In fact, these studies offered nothing more than identification of objective parameters that corroborate the gut's feeling of the experienced clinician. Since the time of Bodey [1], it was already obvious that patients with absolute neutrophil count between 0,1 and 0.5×10^9/l (100–500/ml) carry a minor risk compared to those with a granulocyte count of less than 0.1×10^9/l (100/ml). But now other risk factors have been identified. Patients with concurrent mucosal damage or impaired cellular immunity, as well as those with clinically documented infections or unstable vital signs, are at high risk and deserve increased vigilance. Patients with these additional risks cannot be considered candidates for antibiotic treatment on an out-patient basis. The vast majority of patients with acute leukemia are considered high-risk patients and should continue to receive intravenous broad-spectrum antibiotics in the hospital or similar setting. The remaining low-risk patients, namely those with unexplained fever who are clinically stable, may be safely treated with oral antibiotics provided that they have been seen at a qualified medical center promptly after the onset of fever [95, 96]. The possible use of antibiotic prophylaxis does not pre-empt the need for a thorough check-up but limits the choice of drugs that can be used for treatment. Patients with increasing granulocyte counts are considered to be better candidates for outpatient therapy than are patients without an indication of bone marrow recovery. Among the oral regimens that have been evaluated are ofloxacin, ciprofloxacin, and ciprofloxacin plus amoxicillin–clavulanate. It is crucial to make sure that the patient is informed about the risk of unremitting fever during a neutropenic episode and that he or she fully understands the importance of seeking immediate medical advice in case any unexpected incident occurs. Vigilant observation at home by a relative or professional health care worker and prompt access to appropriate medical care must be available 24 h per day, 7 days a week [98–101]. As an alternative to initial outpatient therapy, early discharge with continued outpatient therapy for selected patients may be considered after a brief admission during which intravenous therapy is initiated, fulminant infection is excluded, and appropriate culture specimens are taken [102, 103].

Two studies have demonstrated that children who lack signs of sepsis and severe mucositis, who are afebrile for >48 h, who have neutrophil counts of >100 cells/mm^3 (>0.5 × 10^9/l), and who are at low risk for complications may have their intravenous antibiotic treatment safely stopped to be substituted by oral cefixime [104, 105].

3. Management of Fever After the Empiric Episode

3.1. Principles

After starting empiric antibacterial treatment, fevers will persist or return in about one third of patients. The average duration of fever in serious infections, in eventually successfully treated neutropenic patients is 4–5 days (Table 5-2, Fig. 5-1) [4, 9, 13, 14, 34–44]. Although fever can be inconvenient for the patient, it is important to realize that it is part of the body's defense system [106]. Indeed, some retrospective studies have suggested that fever is associated with improved survival and shortened disease. Uncontrolled studies have reported an association of increased mortality with the absence of fever in polymicrobial or gram-negative sepsis and in elderly patients with community acquired pneumonia [107, 108]. So, when the body temperature remains above normal during 3 or 4 days on apparently effective broad-spectrum antibiotics, this should not be considered a complete waste of time, particularly not if the time is used for an appropriate diagnostic work-up. It should be kept in mind that empiric administration of antibiotics is only meant as an immediate cover for rapidly fatal bacteria such as gram-negative rods and *Staphylococcus aureus*, thereby, so to say, buying time for consideration of the next therapeutic interventions and for waiting for the results of the diagnostic procedures. When the results of the cultures become available and the infection has had time to blossom clinically, there is a more solid basis for decisions on necessary adjustments of an antibiotic regimen.

Unfortunately, all large, randomized clinical trials on empiric antibiotic therapy in the febrile neutropenic patients during the past 30 years have been pharmaceutical company-driven for purposes of attaining governmental agency approval [23, 24]. As a consequence, the design of these studies focused primarily on the efficacy of a particular drug in comparison with another drug

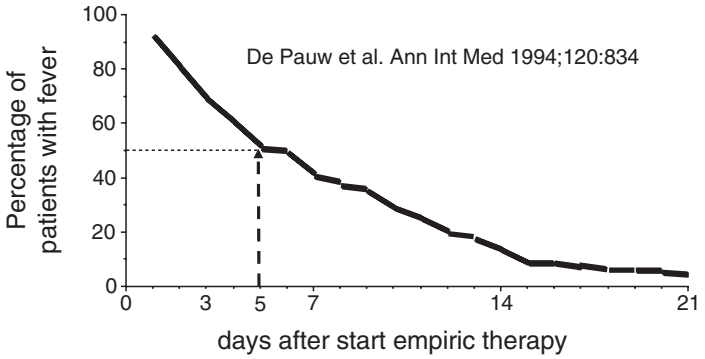

Fig. 5-1. Typical course of fever after institution of empiric antimicrobial therapy in neutropenic patients.

or combination of drugs. According to the protocols for these trials, only patients who survived the febrile episode without a change in the allocated regimen could be labeled as successes, whereas any change in therapy, independent of the trigger, was denoted a failure, even if the patient survived unscathed and the infection was eradicated. Therefore, modification of the test regimens was discouraged, which constitutes a rather artificial situation, as clinicians are inclined to adjust an antibiotic regimen for no other reason than a subjective feeling of unease with the original choice of antibiotics. Changes often reflect impatience, nervousness, and lack of confidence on the part of the clinician concerned over the still febrile neutropenic patient rather than any deficiency in the original antibiotic regimen used. When restrictions surrounding a clinical trial do not apply, juggling antibiotics against an undulating line on a temperature chart is a well-known frequent occurrence on a ward full of patients suffering with hematological malignancies. Indeed, in daily practice, many modifications are not based on objective criteria and are made outside office hours, i.e., by less experienced physicians on call [103, 109]. However, it is generally recognized that exposure to many different antibiotics as a result of haphazard changes of regimens enhances the risk of drug-related adverse events and seldom improves the outcome of the patient under treatment. Moreover, such a policy of endless therapeutic trials of antibiotic changes might wrongly decrease the perceived need for further diagnostic procedures in poorly responding patients. Since there is evidence from clinical trials on what to do after the empiric phase, some experts have been promoting the so-called algorithms of planned progressive antibiotic therapy to treat neutropenic patients with fever. A planned progressive strategy involves adjustment of therapy every 2–3 days, until the patient becomes febrile or until all the potential causes of infection are covered by the best available microbial agents, irrespective of the development of additional symptoms. It is clear that algorithms featuring planned progressive therapy are destined to lead to overtreatment with unnecessary expenses and drug exposures [108]. It appears more intellectually attractive not to rely on fixed algorithms but to weigh several different, patient-specific parameters, including fever and clinical response, as a guide for modification of an empiric regimen. It goes without saying that spending time at the bedside is crucial for those who feel attracted to the role of attending physician because careful observation often provides early clinical clues for a rational adaptation of the original empirical antibiotic regimen. The need for individualization is not only dictated by variations in the signs and symptoms of the patient that accompany persisting fever but also by differences in skills and expertise amongst attending specialists in various centers. For example, centers with excellent and interested departments of medical microbiology and pathology will rely more heavily on their findings than do centers with poorly functioning departments, whereas units with an active radiology service may benefit from the locally available know-how in this particular field.

3.2. Modifications in Poorly Responding Patients

3.2.1. Case-by-Case Modification of an Initial Empiric Regimen

Once an empiric antibiotic therapy has been started, the patient must be monitored continuously for nonresponse, emergence of secondary infections,

adverse effects, and the development of drug-resistant organisms. This implies that the start of antibacterial agents cannot be seen as an impetus to stop diagnostic procedures. Daily blood cultures are certainly justified as long as patients remain febrile and when a new temperature peak occurs because breakthrough bacteremia or fungemia may develop. Close monitoring of sites that are prone to infection should start before the onset of fever and has to be continued after empirical antibacterial therapy has commenced. Subtle changes must bring diagnostic tools into play to confirm or exclude the presence of an infectious focus. Regular CT-scans of the chest, preferably in combination with serological monitoring for *Aspergillosis* antigen, have an established value in patients who are at increased risk of fungal infections [92].

As a rule, approximately 65% of patients without a focus of infection, which includes 30% overall with positive blood cultures, will show some clinical improvement after 3 days of broad-spectrum empiric coverage in spite of persisting fever. In most cases, defervescence will follow rapidly. Elements that should be incorporated in clinical decision making include the course of fever and clinical condition with special attention to the vital signs, evolving symptoms of infection in relation to the granulocyte count, C-reactive protein levels, antigen monitoring, and risk for relapses of latent viral infections determined by pretreatment antiviral titers. The results of all cultures taken at the onset of fever have to be assessed and it is recommended to analyze surveillance cultures, if any, to identify possibly colonizing resistant organisms. Without clinical deterioration or proof of an infection caused by a micro-organism resistant to the initial antibiotic regimen, persisting fever after 72–96 h of empiric therapy in and of itself is an unsatisfactory basis for changing the original empirical antibacterial regimen. It is better to alter the regimen only when there are objective reasons to do so: deterioration of vital signs, isolation of a resistant pathogen without clinical improvement, persistence of a pathogen, antibiotic-related adverse events, occurrence of a new focus of infection or progression of an existing focus in the absence of granulocyte recovery, unexplained fever persisting for more than 5 days, new fever, a new pathogen or recognition of a local outbreak with a resistant organism (Tables 5-5 and 5-6). In most patients, antimicrobial therapy can be adjusted objectively on the basis of clinical or microbiologic findings but such an individually tailored approach requires careful daily assessment of all possible parameters collaborating with consulting specialists, including microbiologists, pulmonologists, and radiologists. In contrast to the moment of the onset of fever, there is ample time for deliberation and contemplation in a situation where the patient's fever persists for 3 or more days while on antibiotics because the origin of fever is obviously not a rapidly fatal micro-organism that needs immediate treatment. Fever that persists for more than 3 days suggests that the patient has a nonbacterial infection, a resistant bacterial infection, a second infection, or a drug fever [22, 110].

Despite extensive cultures, only around 30% of all febrile patients will be shown to have microbiologically defined infections. In 30% of patients, organ involvement is already apparent with the initial fever and an additional 10% will show clinically defined infection within the next 72 h (see Fig. 5-2). Others have neither a focus of infection, nor a positive culture and are defined as unexplained fevers. Using clinical well-being as a leading parameter, there are

Table 5-5. Reasons to modify an empirical antibiotic regimen.

- Deteriorations of vital signs
- Development of a new clinical focus
- Progression of an existing focus
- Persistence of a presumed causative pathogen
- Isolation of an in vitro resistant organism in the absence of clinical improvement
- Occurrence of a new fever
- Isolation of a new pathogen
- Adverse event attributable to one of the current antibiotics
- Known local outbreak with an unusual micro-organism such as Legionella

Table 5-6. Possible causes for the lack of response to antibiotics.

- A bacterial infection resistant to the antibiotics
- Cell wall-deficient bacteremia
- Infections at a avascular site (e.g., abscesses or catheters)
- Inadequate serum and tissue levels of the antibiotics
- Slow response to the drugs in use
- The emergence of a second infection
- A nonbacterial infection
  - o Fungal
  - o Viral
  - o Posttransplant lymphoproliferative disease (in allogeneic stem cell transplant recipients)
  - o Parasitic
- Pyrogenic substances
  - o Cytokines
  - o (Auto)immune reactions
  - o Blood product antigens
  - o Toxins
  - o Drugs (antibiotics)
  - o Tissue (tumor) products

roughly three possible situations after 3 days of treatment: the patient's condition is (a) improving (approximately 55% of cases); (b) stable (approximately 35%); or (c) deteriorating (10%; see Fig. 5-3 and Table 5-7). Patients belonging to each of these three categories may have either a microbiologically documented infection, a clinically documented infection, or an explained fever. All these factors that are partly subjective and partly objective can be exploited to steer the modification of an empiric regimen when there is a perceived need to do so. Ultimately, only 15–20% of patients with a persisting unexplained fever should require a continued empirical rather than a clinical or microbiologically directed approach after 72 h of broad-spectrum antibacterial therapy.

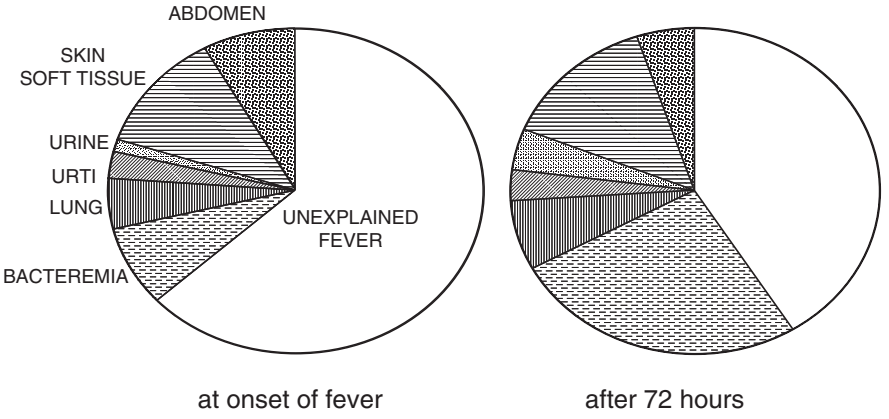

Fig. 5-2. Identified causes of infection at the onset of fever and at the end of the empiric episode.

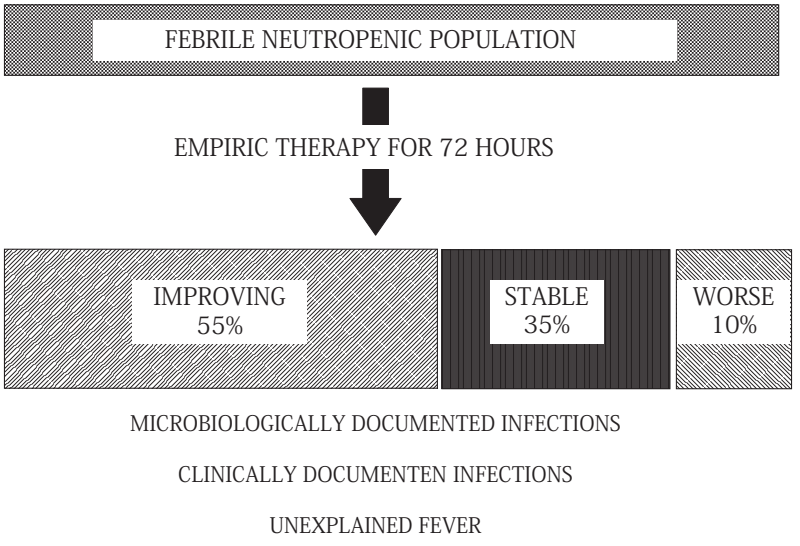

Fig. 5-3. Evolution of clinical condition during the first 72 h of empiric antimicrobial therapy.

Whichever modification is planned, it cannot be overemphasized that maintenance of appropriate antigram-negative cover is mandatory as long as a patient is febrile and neutropenic.

3.2.1.1. Microbiologically Documented Infections

When the patient is improving or stable, there appears to be no imminent need to adjust an antibiotic regimen. Depending on the micro-organism isolated, a change to an oral regimen could be considered with caution. When a gram-negative isolate is identified, broad-spectrum antibiotic coverage should be maintained in full dose. Whereas the clinical relevance of a blood culture

Table 5-7. Considerations for modification of antibiotic regimens in febrile neutropenic patients.

Improving clinical condition
• Microbiologically documented infection
o Maintain gram-negative coverage
o Consider adjustment on the basis of susceptibility pattern
o Consider switching to an oral regimen
• Clinically documented infection
o Continue existing regimen
• Unexplained fever
o Maintain gram-negative coverage
o Consider switching to an oral regimen
Stable clinical condition
• Microbiologically documented infection
o Maintain gram-negative coverage
o Consider adjustment on the basis of susceptibility pattern
o Consider switch to an oral regimen
• Clinically documented infection
o Continue existing regimen
o Consider change on the basis of organ- or syndrome-specific pathogens
• Unexplained fever
o Maintain gram-negative coverage
o Consider further diagnostic procedures
Deteriorating clinical condition
• Microbiologically documented infection
o Maintain gram-negative coverage at maximally tolerated doses
o Consider adjustment on the basis of susceptibility patterns
• Clinically documented infection
o Maintain gram-negative coverage at maximally tolerated doses
o Broaden coverage of organ- or syndrome-specific pathogens
• Unexplained fever
o Cover relevant potential gaps in the spectrum of the existing regimen
o Consider further diagnostic procedures
o Consider institution of intravenous antifungals

positive for gram-negative bacilli is never a matter of controversy, the implication of recovery of particular gram-positive cocci is less clear. Single blood cultures positive for *S. aureus*, *S. pneumoniae*, or *Enterococcus faecalis* in neutropenic patients should be regarded as significant and indicative of the need for further treatment. Viridans group streptococci, with an average mortality of 15–20%, are perhaps the most feared among the bacteremias today [54–56]. Although viridans streptococci are common blood contaminants in the general population, positive blood cultures in patients with oral mucositis

should not be disregarded, certainly not when *S. mitis* or related streptococci are isolated [53, 54]. Isolation of rare micro-organisms should prompt evaluation of the appropriateness of the starting antibiotic regimen, especially when the patient is not responding optimally. On the other hand, isolation of in vitro resistant organisms such as coagulase-negative staphylococci and, more rarely, *Stenotrophomonas maltophilia,* from the blood of a clinically, evidently improving patient, pose an interesting challenge. Many would be inclined to modify the initial regimen but in many cases other bacteria that were not recovered on the culture plate may have been the culprits in the current fever. A blood culture that yields *Candida* species or another fungus should be taken very seriously and dictates immediate institution of antifungal therapy [111–113]. The availability of the candins has extended the therapeutic options [114–116].

Adaptations of an antibiotic regimen in a patient who is clearly not responding is relatively straightforward when a micro-organism has been isolated; the results of the cultures, supplemented by susceptibility testing, will assist in selecting the proper antibiotics.

3.2.1.2. Clinically Documented Infections

All clinical trials so far have demonstrated consistently that patients diagnosed with a clinically documented infection respond much slower and remain febrile for a longer time than those without a focus of infection [19, 27, 51]. Moreover, due to problematic penetration into avascular sites, infections associated with abscesses or prosthetic devices usually respond poorly to antimicrobial therapy. Attending physicians should, therefore, be more hesitant to change antibiotics in patients who are not deteriorating. On the other hand, there are indications that early addition of specific agents might be useful for more rapid control of clinically documented infections. For instance, considering the probable involvement of anaerobes, switching to a carbapenem, if not given initially, or addition of metronidazole to a standard anti-gram-negative regimen, appears a logical choice when fever is accompanied by abdominal symptoms. In cases with a clinically documented site who do not improve or stabilize, coverage of micro-organisms known to prevail at the involved site of infection (see Table 5-4) appears appropriate. Clinically documented infections that emerge later during the course of febrile neutropenia carry a dismal prognosis and are presumed to be related to the occurrence of resistant micro-organisms, including invasive fungi, in combination with persisting immunodeficiency often as a result of a refractory underlying disease.

3.2.1.3. Persistent Unexplained Fever or Fever of Unknown Origin

If the patient with an unexplained fever clinically improves or remains stable after 72 h of empirical treatment and re-evaluation by physical examination and diagnostic tests yields no new information, and no isolate was found, the initial antibiotic regimen can be continued or can be switched to an oral compound. The latter option is more reasonable clinically if neutropenia is expected to resolve within the ensuing days. If vancomycin is a component of the initial antimicrobial regimen, withdrawal of the drug should be considered if the results of the cultures do not support its use.

Deteriorating cases without any microbiological or clinical sign of infection pose a dilemma. Unexplained fever accompanied by deterioration can imply that the patient has a nonbacterial infection or a noninfectious cause of fever,

but foremost, a resistant bacterial infection or the emergence of a second infection should be taken into account [19, 110]. An initial response rate of about 35% may be expected in patients with shock, compared with 70% in patients without shock, which suggests the possible presence of an undetected toxin-producing pathogen in the former. Addition to the original empirical antibacterial regimen is mandatory in critically ill patients, independent of the level of fever. Escalation might include filling theoretical gaps in antibiotic spectrum and enhanced monitoring for any changes in the patient's condition. Under these circumstances, the selection of agents should be guided by knowledge of locally prevalent virulent pathogens and actual susceptibility patterns, which implies the necessity of close cooperation with the local microbiology laboratory. Addition of vancomycin appears reasonable in view of the fact that the spectrum of antibacterial drugs in traditional empiric regimens usually does not cover coagulase-negative staphylococci, methicillin-resistant *Staphylococcus aureus*, enterococci, and some strains of penicillin-resistant *S. pneumoniae* and viridans streptococci. On the other hand, liberal use of vancomycin has confronted the medical community with vancomycin-resistant enterococci and staphylococci, which has led to increasing use of new agents like quinupristin-dalfopristin and linezolid in the treatment of febrile neutropenic patients. When the starting regimen consists of a single, broad-spectrum β-lactam, addition of an aminoglycoside is an attractive option to provide a better coverage when infections by resistant gram-negative rods are suspected. However, it has to be emphasized that development of resistance during therapy is extremely rare and that aggressive gram-negative organisms typically cause the infection to deteriorate rapidly to a stage beyond cure within a few days after first fever in most cases. Hence, if the local resistance pattern or a particular concern in an individual patient prompts the use an aminoglycoside for resistant gram-negative bacteria, then aminoglycosides should be prescribed from the start in optimal doses with monitoring of the peak and trough serum levels. Clinical deterioration in a persistently neutropenic patient with unexplained fever is an important but rather rare event in daily practice and applies to only a quarter of the overall 10% of cases that deteriorate while on broad-spectrum antibacterial treatment. Moreover, it is noteworthy that the success rate of empiric modifications is less than 20%, whereas more than 50% of cases will respond to specifically customized modifications [41].

3.3. Specific Considerations

3.3.1. Invasive Fungal Disease

Invasive fungal infections are encountered in up to 40% of autopsies in patients with hematological malignancies. Fungi have been found to be responsible for two thirds of all superinfections, which surface during broad-spectrum antibiotic treatment of neutropenic patients. More than 20 years ago, when diagnostic capabilities were virtually nonexistent and the choice of effective antifungal agents limited, two prospective, randomized trials laid the scientific foundation for the addition of systemically active antifungals even though neither study was adequately powered to reach a statistically valid conclusion [111, 112]. This strategy appeared to reduce the incidence of invasive fungal infections in patients without any further sign of a clinically documented

infection. Solid statistical evidence to support the validity of this empiric approach was never obtained subsequently in further placebo-controlled trials because empirical antifungal treatment had become widely accepted as the standard of care. This so-called empiric antifungal therapy has remained popular as it seemed to make life easy for clinicians. The lack of reliable diagnostic tools combined with very poor outcomes of invasive fungal infections that were not timely treated contributed greatly to this popularity [117–119]. However, in most cases in 2007, antifungals prescribed empirically for fever alone are unnecessary because invasive fungal infection is present in a minority of cases. A better understanding of the pathophysiology of invasive fungal disease in combination with use of better diagnostics allows for a more individualized approach [117, 120]. An optimal diagnostic work-up in conjunction with careful clinical observation will likely render routine empiric antifungal therapy superfluous in most cases because appropriate application of presently available diagnostic tools enables timely pre-emptive institution of appropriate antifungal therapy by experienced clinicians [121–123]. The most common initial presentation of invasive aspergillosis is unremitting fever despite broad-spectrum antibacterial treatment, accompanied eventually in most patients by pulmonary infiltrates or sinusitis. Clinicians should suspect the diagnosis in a patient with pleuritic pain, hemoptysis, or a localized pleural rub. The halo sign (a dense central nodule with surrounding less dense infiltrate) on a computer-assisted tomographic scan of the chest, though not pathognomonic, is highly suggestive of an early phase of pulmonary aspergillosis or other mould pneumonia in immunosuppressed patients [124–126]. Even when gram-negative pathogens, including *Pseudomonas aeruginosa* and *Enterobacter cloacae*, are isolated from the sputum or blood of such patients, aspergillosis should be the leading consideration when nodular chest CT findings are present. If no infiltrate is found in a high-risk patient with persisting fever, the investigation should be repeated within a few days, preferably supported by bronchoalveolar lavage if indicated and additional assays such as screening for the presence of galactomannan in the blood [121]. Even in patients with aspergillosis who are responding adequately to antifungals, the computer-assisted tomographic chest scan will usually show some enhancement of the lesion when the neutrophils return with eventual development of cavitation within the infiltrate, the so-called air-crescent sign [124–126]. This finding is suggestive of aspergillosis, although mucormycosis and other moulds may cause an identical picture. Whether the increased incidence of non *Aspergillus* mould is due to more extensive use of the new azoles like voriconazole or to the use of more intensive immunosuppressive treatment schemes remains to be seen [127, 128]. Isolation of an *Aspergillus* species from sputum or bronchoalveolar lavage specimens connotes either invasive infection or bronchial colonization, the latter conferring high risk for invasive aspergillosis. When voriconazole or posaconazole have been used as prophylaxis, it is sensible to select an antifungal compound with a different mode of action when therapy becomes mandatory [129, 130]. Surgery is indicated for patients in whom lesions near the pulmonary hilus pose a direct threat of invasion of a major vessel with the risk of fatal hemorrhage or for debridement of dead tissue after a period of antifungal therapy [126]. Low risk patients who test negative for *Aspergillus* in all diagnostic procedures do not need to be started on intravenous antifungals. Treatment should be stopped for those patients started on

antifungals pending diagnostic test results. A more conservative wait-and-see approach can be implemented successfully once clinicians learn to accept that negative diagnostic results constitute sufficient evidence that there is no fungal infection in many persistently febrile neutropenic patients [121, 123].

Fluconazole given as prophylaxis has virtually eliminated infections with *Candida albicans*. However, *Candida* species or other fungi are still occasionally identified as causes of disseminated infections in humans, albeit with a shift from *Candida albicans* to nonalbicans species [131, 132]. A candidemic patient typically presents with an irregular fever sometimes accompanied by polymyalgia and polyathralgia. In about 10% of cases, characteristic pinkish-purple, nontender subcutaneous nodules may arise anywhere on the body. Biopsy specimens should be cultured and histologically screened at multiple levels in an attempt to establish a final diagnosis. *Candida* ophthalmitis is seldom seen in leukemic patients since the distinctive retinal exudates are the result of an inflammatory response that involves granulocytes. Upon the return of the neutrophils or tapering of corticosteroids, complaints of abdominal discomfort and elevation of alkaline phosphatase levels with or without hepatosplenomegaly may emerge. At this stage, an abdominal ultrasound or computer-assisted tomographic scan will display rather distinctive multiple abscesses in the liver and/or spleen, known as "bull's-eyes" [133, 134]. Mortality from an invasive yeast infection may be as high as 40%, particularly when the start of antifungal therapy has been delayed. Trichosporonosis and fusariosis can produce a clinical syndrome identical to candidemia [135–137].

3.3.2. Biological Response Modifiers

Up to now, empirical antimicrobial therapy has been the backbone of improving survival of febrile neutropenia in leukemic patients. Hematopoietic growth factors have been studied as adjunctive therapy for febrile neutropenic patients in several randomized, controlled trials. G-CSF (filgrastim) and granulocyte-macrophage colony-stimulating factor (sargramostim) when used as part of the treatment of febrile neutropenic patients were shown to consistently shorten the duration of neutropenia defined as a neutrophil count below 0.5×10^9/l (500/ml). However, the duration of absolute neutropenia, i.e., count of less than 0.1×10^9/l (100/ml), was not influenced, which might help to explain why neither a decrease in infection-related mortality rates nor a significant effect on morbidity, including duration of fever and use of anti-infectives, were observed [138, 139]. Therefore, the use of growth factors should be restricted to complicated cases for which there appears to be no rational alternative therapeutic option [140–142]. This concept also applies to the use of granulocyte transfusions. Transfusion of high numbers of granulocytes harvested after administration of G-CSF, with or without dexamethasone, to a donor is done by some clinicians without there being any unequivocal evidence of its efficacy. Patients with prolonged profound neutropenia and an uncontrolled clinically documented infection, such as severe cellulitis or sinusitis, appear to be the primary candidates for treatment with granulocyte transfusions, whereas administration of a colony-stimulating factor (G-CSF) should be preferred when a return of the neutrophils is imminent. Significant toxicities in granulocyte-transfusion recipients include transmission of cytomegalovirus, alloimmunization associated with fever, graft-versus-host reactions if granulocytes are not irradiated, progressive platelet refractoriness, and, possibly,

respiratory insufficiency associated with concomitant administration of amphotericin B. New approaches with agents designed to protect the mucosa, like recombinant human interleukin 11 and keratinocyte growth factor palifermin, show promising results in terms of reducing severity of mucositis and occurrence of fever and bacteremia in neutropenic patients [143–145].

4. Cessation of Antimicrobial Therapy

4.1. Antibacterial Therapy

It is widely believed that antibiotic treatment should be continued for a minimum of 7 days or until culture results indicate that the causative organism has been eradicated, infection at all sites has resolved, and the patient is free of major signs and symptoms. Ideally, the neutrophil count should be >500 mm^3 (0.5×10^9/l) before treatment is stopped [146]. When no infection has been identified after 3 days of treatment and the patient has become afebrile for 48 h in association with a neutrophil count that has exceeded 500 cells/mm^3 (0.5×10^9/l), antibiotic therapy may be stopped. In addition, if a persistently neutropenic patient has no complaints and displays no clinical, radiological, or laboratory evidence of infection, cessation of antibiotic therapy or a change to oral antimicrobials should be considered after 4 days without symptoms. If antibiotics are discontinued while the patient is still neutropenic, the patients must be monitored closely and intravenous antibiotics restarted immediately with recurrence of fever or any other evidence of bacterial infection, since the initial infection may have only been suppressed, not eradicated. One should consider continuous administration of antibiotics throughout the neutropenic period in patients who have profound neutropenia, mucous membrane lesions of the gastrointestinal tract, or any other identified risk factor. Some experts suggest, in patients in whom hematological recovery cannot be anticipated, a change from the therapeutic regimen to a prophylactic scheme after 2 weeks of therapy with intravenous antimicrobials. When the suspicion of a noninfectious cause of the fever is high, interruption of antibiotic therapy after ~4 days seems warranted in clinically well patients without any evidence of infection apart from persisting fever. Under these conditions, meticulous monitoring has to be maintained to guarantee the patients timely protection against subsequent infections that are likely to occur.

4.2. Antifungal Therapy

The decision to start antifungals may appear complex but is not as difficult as the decision to discontinue. If a systemic fungal infection has been identified, the course of antifungal therapy will be determined by the causative agent and the extent of the disease. In patients with pulmonary infiltrates or other suspicious lesions, it is essential to see a clinical and, preferably, a radiological response before one ponders cessation of antifungal therapy. However, if no fungal infection is found, it is not clear how long antifungal drugs should be administered [147]. For clinically well patients with prolonged neutropenia, it is suggested that antifungal agents can be stopped after 2 weeks of treatment, provided that no conspicuous lesions can be found by clinical evaluation or by computer-assisted tomographic scanning of the chest and the abdominal

organs. In the patient who appears ill or is at high risk, continuation of antifungal therapy throughout the neutropenic episode is recommended. Conversely, when neutropenic fever subsides, the patient is clinically well and computer-assisted tomographic scan of the abdomen and chest reveals no suspicious lesions; antifungals may be discontinued, particularly when the criterion for commencing antifungal therapy had been simply fever unresponsive to antibiotics. This approach also applies when the presumptive diagnosis becomes questionable during the course of granulocytopenia. When a patient diagnosed with and treated for a proven or probable invasive fungal disease requires further chemotherapy or bone marrow transplantation, protection against the offending pathogen has to be provided, even if the patient responded completely to initial antifungal therapy. The risk of relapse of invasive fungal disease is so high that secondary prophylaxis is warranted, requiring that a full dose of the most effective antifungal is administered [148, 149]. After introduction of routine CT scanning it became apparent that solitary lesions caused by invasive fungal disease are rare and this observation reduced the enthusiasm for surgical interventions. However, if the number of lesions is limited or a difficult-to-treat pathogen, such as a zygomycosis, has been found, surgical excision has to be considered, especially when the lesions are located close to a large vessel [150].

5. Concluding Remarks

Modern chemotherapy offers hope of a cure to many cancer patients, but it confronts the medical community with new challenges continuously. Infection remains an inevitable side-effect of the myeloablative therapy for acute leukemia and is the principal cause of morbidity and mortality amongst these patients. Optimal care can be delivered only by those who pay scrupulous attention to the patient's clinical condition and are aware of the evolving therapeutic and diagnostic modalities. It cannot be denied that time remains an important factor in the management of infectious complications but we must try to distinguish more accurately between patients truly in need of immediate therapy and those who are not. Fixed treatment algorithms are only acceptable if they allow individual interpretation and reasonable deviations. Maintaining guidelines that dictate second line treatment of a population in which more than half of the patients do not have true infection is not justifiable in view of potential adverse events and the economical burden. The demand for an alternative strategy, built on clinical skills, modern and more accurate laboratory tests and imaging techniques, has become apparent and a broad application of this principle may change the approach to antimicrobial treatment in neutropenic patients completely. Overuse of antimicrobial agents, both antibacterial and antifungal, has become all too common in the belief that broader coverage will benefit the patient. Unfortunately, prescription of antimicrobials according to a preset scheme may give a false sense of security with reduced or delayed diligence in pursuing a diagnosis. Diagnostic considerations should prevail whenever patients do not respond satisfactorily to an antibacterial regimen. In addition, neutropenia can no longer be seen as the major compass to steer antimicrobial therapy in a febrile patient because neutropenia is not the one and only factor predisposing for infection. A damaged integument and impairment of T cell-mediated immunity have altered the incidences of

causative micro-organisms. This change not only has consequences for the selection of antimicrobial agents but may also foster development of totally different future treatment modalities such as biological response modifiers that might reduce the need for antimicrobial agents. Undoubtedly, unwarranted widespread use of antibiotics has contributed to the development of resistance amongst micro-organisms. Resistance of previously susceptible pathogens to drugs like penicillins, cephalosporins, glycopeptides, fluoroquinolones, and azoles has become all too familiar of extended spectrum macrolides, carbapenems, and other agents . The primary purpose of prophylactic or empiric use of antimicrobial agents is not to make the physician's life easier but rather to help patients most at risk survive a difficult and dangerous episode.

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