Management of Fever in Cancer Patients with Acquired Neutropenia

P. Eggimann

Introduction

During the past few decades, substantial progress in multidrug immunosuppressive and cytotoxic chemotherapeutic treatments have greatly improved the prognosis of most cancer patients. However, infectious complications due to acquired neutropenia have become a major medical issue, often requiring intensive care management. The infections may be lethal if empiric broad-spectrum treatment is not instituted at the first sign of infection. Although this is now considered standard practice, the selection and evaluation of the efficacy of antibiotic agents has generated considerable controversy for nearly 25 years. After reviewing some particularities of infection in neutropenic patients, this paper will discuss the options and suggest a comprehensive algorithm for the non-infectious diseases specialist.

Particularities of Infection in Neutropenic Patients

Evaluation of the Infectious Risk

Among all the factors involved in the development of an infection in a patient with cancer, the most important is dysfunction of the immune system [1]. This immunosuppression may be subdivided into three types which predispose to the acquisition of distinct pathogens: These are granulocytopenia or neutropenia, defects of immune function related to the diminished capacity to opsonise microorganisms, and defects of cellular immunity related to T-cell functions (Table 1).

Neutropenic cancer patients are a heterogeneous group of patients, but the risk of infection is proportional to the granulocyte count and to the duration of immunosuppression. Although this risk substantially increases with granulocyte counts below 500/mm^3, many authorities consider that it becomes clinically relevant below 1 000/mm^3, and that severe infections and almost all bacteremias are observed below 100/mm^3 [2]. The presence of comorbidity, deep tissue infections, and the patient's underlying neoplastic disease are the other major factors. While the risk appears to be low for ambulatory patients with solid tumors, as many as 60% of leukemic patients will develop an infection during the aplastic phase of their treatment [3, 4].

J.-L. Vincent (ed.), *Yearbook of Intensive Care and Emergency Medicine*

Table 1. Common pathogens in immune dysfunction

Dysfunction of neutrophils (granulocytopenia)			
Bacteria:	*Staphylococcus epidermidis*	Fungi:	*Candida spp*
	Staphylococcus aureus		*Aspergillus spp*
	Viridans streptococci		*Mucorales*
	Escherichia coli		
	Pseudomonas aeruginosa		
Dysfunction of immune function (hypogammaglobulinemia)			
Bacteria:	*Streptococcus pneumoniae*		
	Haemophilus influenzae		
Dysfunction of cellular immunity			
Bacteria:	*Listeria monocytogenes*	Viruses:	*Cytomegalovirus*
	Salmonella spp		*Herpes simplex*
	Mycobacterium spp		*Varicella zoster*
	Legionella spp	Protozoa:	*Pneumocystis carinii*
Fungi:	*Cryptococcus neoformans*		*Toxoplasma gondii*
	Histoplama capsulatum		*Cryptosporidium*
	Coccidioides immitis	Helminths:	*Strongyloides stercoralis*

Significance of Fever

The lack of cells able to carry out the inflammatory response explains why paramount signs and symptoms of infection are often absent in neutropenic patients. Of these, fever, that may be related to the tumor, to some drugs or to transfusion products, is often the mainstay of an infection [5, 6]. Although not specific, the development of fever in such patients should be considered to be the first sign of a potentially life-threatening infection and requires prompt empiric initiation of broad-spectrum antibiotic treatment [2, 4, 7]. Until the validation of this concept late in the 1960s, almost all neutropenic cancer patients died before the results of blood cultures were available, but since then, continuous progress has been made in the management of these patients [3, 8].

Definition of Fever: Generally, a single temperature measurement of $\geq 38.3\,^{\circ}C$ orally, or $\geq 38.0\,^{\circ}C$ over at least 1 hour in the absence of obvious other causes is considered as

Table 2. Initial diagnostic work-up of neutropenic patients with fever

Complete comprehensive history

Detailed physical examination, without rectal examination

Complementary diagnostic work-up
- Blood culture (2 sets)
- Complete blood count
- Blood chemistry (electrolytes, creatinine, BUN, liver function test)
- Urine analysis and urine culture
- Chest roentgenogram
- Throat and sputum culture
- Other microbiological studies based on physical findings

fever [2]. Febrile neutropenic cancer patients require a complete diagnostic work-up (Table 2), and microbiological studies must be obtained before the start of any antimicrobial agents.

Etiology of Fever: According to the classification of the International Immunocompromised Host Society (ICHS), febrile episodes in neutropenic cancer patients are microbiologically documented in 30 to 40% of cases, including an episode of bacteremia in two thirds of them. The infection is clinically documented in 25 to 30% of episodes. The oral cavity, the oropharynx, the lungs, the digestive tract, the skin, particularly the anal region and the sites of catheter insertion are the most commonly infected sites. In 30 to 40% the origin of the fever remains, unknown. However, until formal demonstration of another origin (in only about 5 to 10% of cases), infection remains the most probable etiology of these episodes, known as unexplained fever [2].

Etiologic Agents

During the 1950s, *Staphylococcus aureus* was the primary documented pathogen. A shift occurred in the 1960s, and for more than two decades, Gram-negative microorganisms (*Escherichia coli*, *Klebsiella* spp and *Pseudomonas aeruginosa*) were responsible for more than two-thirds of microbiologically documented infections in febrile neutropenic cancer patients. Most empiric antibiotic regimens were specifically directed against these organisms and this strategy allowed a significant reduction of their related mortality [9, 10]. Within the past decade, Gram-positive microorganisms have emerged as increasingly important pathogens [7, 11]. Presently, coagulase-negative staphylococci, alpha-hemolytic streptococci, methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MSSA/MRSA) are responsible for the majority of episodes in most centers [12–15].

The factors responsible for this evolution are not completely understood, and the clinical data to establish them are scarce. The increasing use of venous access over long periods and indwelling catheters, which seem to promote bacteremia with microorganisms of the skin flora, is one factor [11,16]. Viridans streptococci are common in blood cultures of patients with extensive ulceration of the oral cavity, such as those treated with aggressive chemotherapy, and in those developing herpes gingivostomatitis [17, 18]. In leukemic patients receiving high dose cytarabine the course of streptococcal infections may be particularly fulminant with the development of acute respiratory distress syndrome (ARDS) [17, 19]. Finally, it is possible that the increasing use of oral quinolones as prophylaxis in neutropenic patients may have promoted the emergence of streptococci which are naturally resistant to them [20–23].

Fungal infections may occasionally be responsible for an initial febrile episode in a neutropenic host, but they present more commonly as superinfections occurring later in the course of a prolonged neutropenia. The risk appears to be particularly high if corticosteroids are associated, and their incidence has been reported to be as high as 15 to 30% [24–26]. The persistence of fever for more than 5 to 7 days, despite adequate broad-spectrum antibacterial coverage with a negative diagnostic

work-up, is their usual mode of presentation. When a fungal infection is suspected, the incubation time of blood cultures must be prolonged to detect the presence of *Candida* spp, and chest and sinus X-rays obtained in order to detect early signs of aspergillosis [27]. Outside endemic areas, *Histoplasma* spp, *Coccidioides* spp and other deep-sited mycoses are uncommon. Their treatment is mostly empirical and essentially based on amphotericin B since the advent of potent prophylaxis with triazole agents such as fluconazole or itraconazole [28–30].

Reactivation of the *Herpes simplex* virus group is very common in neutropenic cancer patients, and their morbidity justifies systematic prophylaxis by acyclovir for all seropositive patients [31]. This approach limits the development of *Herpes zoster* group infections, which may disseminate in these patients. *Cytomegalovirus* infections are characterized by multiorgan involvement and their severity is directly related to the degree of T-cell dysfunction. They occur in transplant recipients and in human immundeficiency virus (HIV) positive patients. Bone marrow transplant patients cumulate all risks, but the prognosis of these infections has improved dramatically with the advent of potent antiviral agents such as gancyclovir and forcarnet [32, 33].

Empiric Antimicrobial Therapy

It is difficult to provide precise guidelines for initial empiric antibiotic therapy for fever occurring during neutropenia, because the choice of a specific regimen must be adapted to local and institutional patterns in microorganism ecology, as well as to individual characteristics of the infected patients. However, some concepts are well-established. Initial empiric agent(s) must be characterized by

1) bactericidal serum levels rapidly reached after administration
2) broad-spectrum activity against most Gram-negative and some Gram-positive bacteria
3) a good tolerance for potential administration during a long period of time.

For 30 years, numerous authors have reported on the efficacy of empiric treatment [2, 34]. Presently, although data support the use of combination regimens, the advent of advanced-generation cephalosporins and the data from recent carbapenem studies may strongly argue in favor of monotherapy.

Combination Therapy

The combination of antibiotic agents as initial empiric therapy has been widely accepted as standard clinical practice. A rapid bactericidal effect, an enhanced killing of microorganisms afforded by synergism, and a reduction in the emergence of resistance were until recently the rationale for using such regimens [4, 35].

Combination of Two β-Lactam Agents: These combinations present the advantage of a low toxicity potential, but their coverage is less effective than that of a β-lactam plus an aminoglycoside, so that they are practically no longer used. The combination of more recent agents would be very costly, without broadening the coverage, and would probably increase the selection of resistant microorganisms [2, 7].

Anti-pseudomonal β-Lactam plus Aminoglycosides: The combination of an anti-pseudomonal β-lactam (anti-pseudomonal penicillin or third-generation cephalosporin) plus an aminoglycoside is the well established empiric initial treatment of fever in neutropenic cancer patients. A series of studies from the international antimicrobial therapy cooperative group (IATCG) of the European organization for research on treatment of cancer (EORTC) which each includes several hundreds of patients from 30 to 40 centers provided the essential data supporting this strategy [14, 15, 35–39]. The fourth study from this group [35] demonstrated the superiority of a long course (9 days) versus a short course (3 days) of the combination of an aminoglycoside (amikacin) with a third-generation cephalosporin (ceftazidime) in 872 febrile granulocytopenic cancer patients [39]. The eighth study showed, early in the 1990s, a similar efficacy for single daily doses of ceftriaxone plus amikacin as compared with ceftazidime plus amikacin three times a day, suggesting that aminoglycosides administered once daily are as effective and no more toxic than multiple daily doses. In order to adapt the β-lactam agent to the evolution of the spectrum of infecting agents to Gram-positive cocci, the ninth study [14] showed that a combination of piperacillin-tazobactam (an extended spectrum penicillin combined with a potent β-lactamase inhibitor) plus amikacin was more effective than ceftazidime plus amikacin [14].

Antipseudomonal β-Lactam plus Aminoglycoside plus Glycopeptide: In order to extend the coverage to Gram-positive cocci, including those resistant to methicillin, several authors reported that the addition of a glycopeptide (vancomycin/teicoplanin) to the combined regimens previously described enhanced their efficacy [40, 41]. Two large studies suggested however, that this addition may be safely delayed until there is strong clinical or microbiological evidence for it [38, 42]. In addition, the recent emergence of staphylococci and enterococci resistant to glycopeptides strongly argues against their widespread use [43, 44].

Monotherapy

The very broad spectrum of some third-generation cephalosporins (ceftazidime, cefepime), quinolones, and carbapenems (imipenem-cilastatin, more recently meropenem) incited many groups to study their efficacy in monotherapy as empiric initial treatment for fever in neutropenic cancer patients. The arguments favoring this approach are

1) a decrease in costs
2) reduced equipment for intra-venous administration
3) less frequent monitoring of drug levels
4) the absence of aminoglycoside, allowing a better safety profile when the administration of nephrotoxic drugs such as amphotericin or chemotherapy are needed [7, 12].

Third-Generation Cephalosporins: After an early trial conducted at the National Cancer institute, a meta-analysis indicated that except for profound neutropenia and Gram-positive bacteremia (< 50% failure), ceftazidime monotherapy could be considered as an alternative to the traditional combined regimens [4, 45]. Preliminary results

with extended spectrum cephalosporins, considered by some authors as fourth generation (cefepime) are promising, and large trials are in progress [46, 47].

Quinolones: The lack of activity aqainst streptococci of the old quinolones (ciprofloxacin, ofloxacin, pefloxacin) may explain why the fifth study of the IACTG of the EORTC [37] did not support sufficient efficacy of ciprofloxacin monotherapy. Newer generation quinolones (sparfloxacin, levofloxacin) with an extended spectrum against Gram-positive cocci should probably be reserved for some subgroups of low-risk patients for which recent preliminary data suggest that they may be managed ambulatory with oral therapy [48–51].

Carbapenems: The coverage of carbapenems extends to almost all Gram-negative and Gram-positive aerobic bacteria. They are the most potent agents against anaerobes, and their stability is preserved against most beta-lactamase producing species. This very broad spectrum and their low toxicity profile have contributed to their position as first line agents in many severe nosocomial infections, including those due to *Pseudomonas aeruginosa* or *Enterobacter cloacae*, as well as for intra-abdominal infections [9, 52]. Several studies demonstrated that carbapenem monotherapy is a valuable and realistic alternative for the empiric treatment of fever in cancer patients, and the eleventh study of the IACTG of the EORTC confirmed that this option is also applicable for patients with profound and prolonged neutropenia [12, 15, 53].

Of the 958 patients included, whose main duration of neutropenia was 16–17 days, 483 received meropenem (1 g every 8 hours) and 475 the combination (ceftazidime 2 g every 8 h plus amikacin 20 mg/kg once daily). Stringent ICHS consensus criteria were used, with success defined as the resolution of fever and clinical signs of infection and eradication of the infecting organism without modification of the initial empiric regimen [34]. The success rates were 270/483 (56%) for monotherapy and 245/475 (52%) for combination, and were comparable ($p = 0.20$). They were similar for all types of infection (single Gram-negative bacteremia, single Gram-positive bacteremia, clinically documented infections and possible infections), as were the modification rates of the allocated regimen (glycopeptide in 33% versus 37%; empirical antifungal therapy in 23% versus 25%) and further infection rates (12%). At 30 days, the overall mortality rate was 5% in both groups, and the mortality attributed to the presenting infection or to further infection was very low (1.7% versus 2.7%) [15].

Indeed, this study pointed out that the three main traditional arguments in favor of combined therapy are probably obsolete. The time to defervescence was similar in the group treated with meropenem monotherapy and in the group treated with a combination of ceftazime plus amikacin, suggesting that the aminoglycoside did not enhance the bactericidal effect. In the same way, the comparable efficacy in two subgroups in which synergism was previously demonstrated as important (patients with streptococcal bacteremia and those with profound neutropenia) suggests that enhancing the killing of bacteria by synergy is no longer necessary with carbapenems. Colonization with resistant organisms was not studied in this trial, but it was recently demonstrated that a combination of imipenem-cilastatin plus netilmicin for the treatment of severe ICU infections did not prevent colonization or superinfections with resistant microorganisms [52].

Duration of Treatment

The duration of antimicrobial therapy must be determined by the type of infection, and by the evolution of the patient's clinical condition. Unfortunately, there is no consensus in the literature. Short term treatments are associated with a high level of relapse, and prolonged antibiotic therapy is associated with an increased risk of superinfections [4]. For microbiologically documented infections, for those with a severe clinical course or if profound neutropenia persists, the treatment has to be prolonged for more than the traditional 14 days, and some authors prolong it until the time of recovery from neutropenia. For each episode of fever, the initial empiric regimen has to be re-evaluated after 72 hours, and eventually adapted or restricted to the identified causative agent. When the origin of the fever is not attributed to a documented infection (fever of unknown origin), the treatment can be stopped after 5–7 days without fever [2, 4, 7, 54].

Adjunctive Therapy

Numerous approaches aimed at enhancing the immune function of neutropenic patients have been studied.

White Blood Cell Transfusion: Despite positive results, complications including alloimmunization and transmission of infection have led us to abandon the transfusion of heterologous white blood cells which was one of the earliest approaches studied [55, 56].

Immunotherapy: After a long history and vigorous debate in septic shock patients, passive immunization with either polyclonal or monoclonal antibodies has no defined role in the treatment of neutropenic patients [57–59]. Patients in whom neutropenia is anticipated should to be actively immunized against numerous potentially infecting agents including pneumococci [60, 61].

Hematopoietic Growth Factors: Colony-stimulating factors (G-CSF and GM-CSF) produce a dose-dependent increase in neutrophil counts and some side effects such as bone pain and fever in almost all acquired and congenital granulocytopenias. They induce secondary cytokine production and there are theoretical concerns about the acceleration of disease in patients with myeloid disorders, but there is at present no evidence that these may be clinically relevant. Hence, they are presently widely used as adjuvant therapy for aggressive chemotherapy [62, 63]. This contributes to an intensification of many chemotherapeutic regimens, and will probably result in increased neutropenic episodes. However, despite impressive preliminary clinical data suggesting that, when combined with antibiotics in neutropenic febrile cancer patients, they may reduce the duration of neutropenia, hospital stay, and antibiotic therapy, there is presently no consensus about hematopoietic growth factor use in this indication [10, 64].

Prophylaxis of Infection in Neuropenic Cancer Patients

Physical measures, including rigorous respect of hospital hygiene rules are important. Systematic hand washing and disinfection, special clothes for patient handling, and systematically cooked meals are of paramount importance to limit colonization with potentially pathogenic microorganisms. A consensus on the efficacy of special isolation wards ventilated in positive pressure with filtered air has not been reached, and must be restricted to patients with an anticipated long and profound neutropenia such as bone marrow transplant recipients and acute leukemic patients [2, 65].

For two decades, oral chemoprophylaxis with either non-resorbable agents (neomycin/garamycin/polymixine/vancomycin) or antibiotics (trimethoprim-sulfamethoxazole) was shown to reduce the number of febrile episodes [66]. However, the rapid emergence of resistant species has motivated the use of more effective agents of which oral fluoroquinolones are the most studied. Their efficacy against most potentially pathogenic Gram-negative enterobacteria is excellent. Their complete absorption by the digestive tract is responsible for limitation of the lymphatic spread of microorganisms, and preservation of the anaerobic flora contributes, by competition for substrates, to limit the proliferation of potentially resistant species [22, 67]. The combination of quinolones with agents effective against streptococci (penicillin/rifampin) reduces the incidence of Gram-positive infections, but may be ineffective in reducing the overall incidence of febrile neutropenic episodes [21, 23]. Here again, the emergence of resistant species of *Escherichia coli* and viridans streptococci may limit their utilization [17, 68]. In summary, chemoprophylaxis remains very controversial and is actually not systematically recommended [65].

Practical Guidelines

The management of fever occurring in a neutropenic cancer patient requires prompt extensive evaluation in order to initiate early empiric broad-spectrum antimicrobial therapy. Several particularities must be taken into account to implement this strategy. The infectious risk is proportional to the degree and the duration of the immunosuppression. All infectious signs or symptoms other than fever may be absent. The choice of antibiotic agent(s) must be determined by the degree of immunosuppression, by clinical findings and by local epidemiologic data. The empiric regimen should be re-evaluated after 72 h. An algorithm is proposed as a practical guide for the clinician in Fig. 1, but the patient's clinical condition remains determinant and consulting with an infectious disease specialist may be required in difficult cases.

Conclusion

Severe infectious complications among cancer patients with acquired neutropenia remain a major medical issue, and as they may present with fever only, early empiric broad-spectrum antibiotic therapy is the cornerstone of their management. To adapt to the evolving spectrum of the infecting organisms to Gram-positive cocci and taking into account the most recent data from large clinical studies, empiric

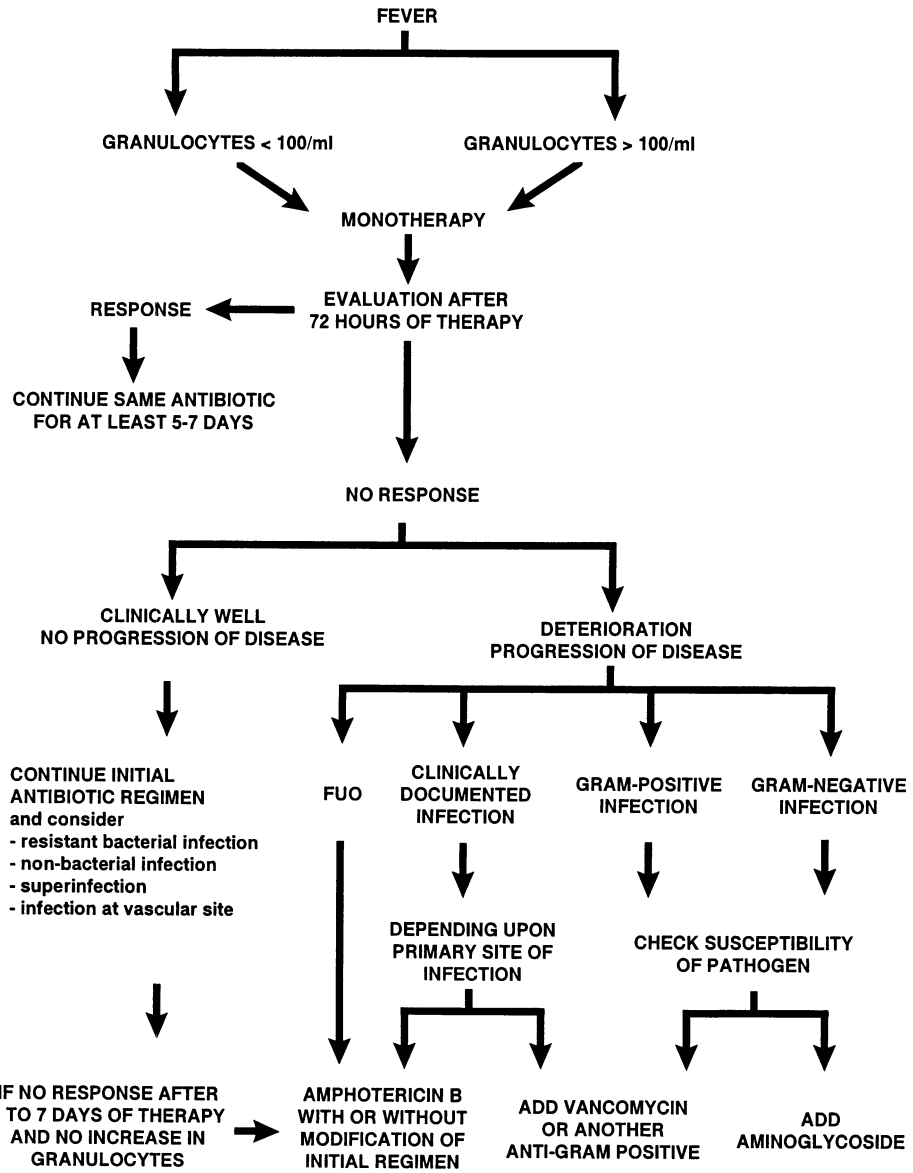

Fig. 1. Therapeutic algorithm for fever in neutropenic cancer patients. FUO: fewer of unknown origin

monotherapy with carbapenems may be chosen as first line treatment of fever in all neutropenic cancer patients including those high-risk patients with profound and persistent neutropenia. The combination of an anti-pseudomonal β-lactam with an aminoglycoside remains a well established alternative. For some particular subgroups of low-risk patients, preliminary data suggests that ambulatory management with oral therapy may be feasible.

References

1. Mcgeer A, Feld R (1994) Epidemiology of infection in immunocompromised oncological patients. In: Balliere's Clinical Infectious Diseases 1, pp 415–438
2. Hughes WT, Armstrong D, Bodey GP, et al (1990) Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. J Infect Dis 161:381–396
3. Bodey GP, Buckley M, Sathe YS, Freireich EJ (1966) Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 64:328–340
4. Schimpff SC (1995) Infections in cancer patients – diagnosis, prevention and treatment. In: Mandell GL, Douglas RG, Bennett JE (eds) Principles and practice of infectious diseases, 4th ed. Churchill Livingstone, New York, pp 2266–2275
5. Talcott GP, Siegel RD, Finberg R, et al (1992) Risk assessment in patients with cancer with fever and neutropenia: A prospective two-center validation of a prediction rule. J Clin Oncol 10:316–322
6. Talcott GP, Finberg R, Mayer RJ, et al (1988) The medical course of patients with cancer with fever and neutropenia. Arch Intern Med 148:2561–2568
7. Pizzo PA (1993) Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 328:1323–1332
8. Bodey GP (1986) Infection in patients with cancer: A continuing association. Am J Med 81 (suppl 1A):11–26
9. Calandra T, Cometta A (1991) Antibiotic therapy for Gram-negative bacteremia. Infect Dis Clin North Am 5:817–834
10. Hathorn JW, Lyke K (1997) Empirical treatment of febrile neutropenia: Evolution of current therapeutic approaches. Clin Infect Dis 24 (suppl 2):S256–S265
11. The EORTC International Antimicrobial Therapy Cooperative Group (1990) Gram-positive bacteraemia in granulocytopenic cancer patients. Eur J Cancer 26:569–574
12. Rolston KVI, Berkey P, Bodey GP, et al (1992) A comparison of imipenem to ceftazidime with or without amikacin as empiric therapy in febrile neutropenic patients. Arch Intern Med 152: 283–291
13. Coullioud D, Van der Auwera P, Viot M, Lasset C (1993) Prospective multicentric study of the etiology of 1051 bacteremic episodes in 782 cancer patients. Cemic (french-belgian study club of infectious diseases in cancer). Support Care Cancer 1:34–46
14. Cometta A, Zinner SH, De Bock R, et al (1995) Piperacillin-tazobactam plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. Antimicrob Agents Chemother 39:445–452
15. Cometta A, Calandra T, Gaya H, et al (1996) Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. Antimicrob Agents Chemother 40:1108–1115
16 Winston DJ, Dudnick DV, Chapin M, Ho WG, Gale RP, Martin WJ (1983) Coagulase-negative staphylococcal bacteremia in patients receiving immunosuppressive therapy. Arch Intern Med 143:32–36
17. Bochud PY, Eggimann P, Calandra T, Van Melle G, Saghafi L, Francioli P (1994) Viridans streptococcal bacteremias in neutropenic cancer patients: clinical spectrum and risk factors. Clin Infect Dis 18:25–31
18. Bochud PY, Calandra T, Francioli P (1994) Bacteremia due to viridans streptococci in neutropenic patients: a review. Am J Med 97:256–264
19. Dybedal I, Lamvik J (1989) Respiratory insufficiency in acute leukemia following treatment with cytosine arabinoside and septicemia with streptococcus viridans. Eur J Haematol 42:405–406
20. Karp JE, Merz WG, Hendricksen C, et al (1987) Oral norfloxacin for the prevention of gram-negative bacterial infections in patients with acute leukemia and granulocytopenia. Ann Intern Med 106:1–7
21. International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (1994) Reduction of fever and streptococcal bacteremia in granulocytopenic patients with cancer. JAMA 272:1183–1189
22. GIMEMA Infection Program (1991) Prevention of bacterial infection in neutropenic patients with hematologic malignancies: a randomized, multicenter trial comparing norfloxacin with ciprofloxacin. Ann Intern Med 117:7–12

23. Bow EJ, Mandell LA, Louie TJ, et al (1996) Quinolone-based antibacterial chemoprophylaxis in neutropenic patients: Effect of augmented gram-positive activity on infectious morbidity. Ann Intern Med 125:183–190
24. Anaissie E (1992) Opportunistic mycoses in the immunocompromised host: experience at a cancer center and review. Clin Infect Dis 14 (suppl 1):S43–S53
25. EORTC International Antimicrobial Therapy Cooperative Group (1989) Empiric antifungal therapy in febrile granulocytopenic patients. Am J Med 86:668–672
26. Bodey G, Bueltmann B, Duguid W, et al (1992) Fungal infections in cancer patients: an international autopsy survey. Eur J Clin Microbiol Infect Dis 11:99–109
27. Schaffner A (1994) Prophylaxis and treatment of fungal infections in cancer patients. In: Balliere's Clinical Infectious Diseases 1, pp 499–522
28. Winston DJ, Chandrasekar PH, Lazarus HM, et al (1993) Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial. Ann Intern Med 118:495–503
29. Menichetti F, Del Favero A, Martino P, et al (1994) Preventing fungal infection in neutropenic patients with acute leukemia: fluconazole compared with oral amphotericin B. Ann Intern Med 120:913–918
30. Powderly WG, Finkelstein D, Feinberg J, et al (1995) A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. N Engl J Med 332:700–705
31. Novakova I, Donnelly JP, De Pauw B (1991) Ceftazidime as monotherapy or combined with teicoplanin for initial empiric treatment of presumed bacteremia in febrile granulocytopenic patients. Antimicrob Agents Chemother 35:672–678
32. Gold D, Corey (1987) Acyclovir prophylaxis for herpes simplex virus infection. Antimicrob Agents Chemother 31:361–367
33. Reusser P (1994) Prophylaxis and treatment of herpes virus infections in immunocompromised cancer patients. In: Balliere's Clinical Infectious Diseases 1, pp 523–544
34. Jones RN, Thornsberry C, Barry AL (1984) In vitro evaluation of HR810, a new wide-spectrum aminothiazol α-methoxyimino cephalosporin. Antimicrob Agents Chemother 25:710–718
35. EORTC International Antimicrobial Therapy Cooperative Group (1987) Ceftazidime combined with a short or long course of amikacin for empirical therapy of Gram-negative bacteremia in cancer patients with granulocytopenia. N Engl J Med 317:1692–1698
36. Klastersky J, Zinner SH, Calandra T, et al (1988) Empirical antimicrobial therapy for febrile granulocytopenic cancer patients: lessons from four EORTC trials. Eur J Cancer Clin Oncol 24:535–545
37. Meunier F, Zinner SH, Gaya H, et al (1991) Prospective randomized evaluation of ciprofloxacin versus piperacillin plus amikacin for empiric antibiotic therapy of febrile granulocytopenic cancer patients with lymphomas and solid tumors. Antimicrob Agents Chemother 35:873–878
38. The EORTC International Antimicrobial Therapy Cooperative Group (1991) Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. J Infect Dis 163:951–958
39. EORTC International Antimicrobial Therapy Cooperative Group (1993) The efficacy and toxicity of single daily dose of amikacin and ceftriaxone versus multiple daily doses of amikacin and ceftazidime for infection in patients with cancer and granulocytopenia. Ann Intern Med 119:584–593
40. Karp JE, Hick JD, Angelopulos C, et al (1986) Empiric use of vancomycin during prolonged treatment induced granulocytopenia. Am J Med 81:237–242
41. Rubin M, Hathorn JW, Marshall D, Gress J, Steinberg SM, Pizzo PA (1988) Gram-positive infections and the use of vancomycin in 550 episodes of fever and neutropenia. Ann Intern Med 108:30–35
42. Ramphal R, Bolger M, Oblon DJ, et al (1992) Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime: a randomized prospective study. Antimicrob Agents Chemother 36:1062–1067
43. Edmond MB, Wenzel RP, Pasculle AW (1996) Vancomycin-resistant staphylococcus aureus: perspectives on measures needed for control. Ann Intern Med 124:329–334
44. Coque TM, Tomayko JF, Ricke SC, Okhyusen PC, Murray BE (1996) Vancomycin-resistant enterococci from nosocomial, community, and animal sources in the united states. Antimicrob Agents Chemother 40:2605–2609

45. Sanders JW, Powe NR, Moore RD, et al (1991) Ceftazidime monotherapy for empiric treatment of febrile neutropenic patients: a metaanalysis. J Infect Dis 164:907–916
46. Eggimann P, Glauser MP, Aoun M, Meunier F, Calandra T (1993) Cefepime monotherapy for the empirical treatment of fever in granulocytopenic cancer patients. J Antimicrob Chemother 32 (Suppl B):151–163
47. Ramphal R, Gucalp R, Rotstein C, Cimino M, Oblon D (1996) Clinical experience with single agent and combination regimens in the management of infection in the febrile neutropenic patient. Am J Med 100:83S–89S
48. Malik IA, Khan WA, Karim M, Aziz Z, Khan MA (1995) Feasibility of outpatient management of fever in cancer patients with low-risk neutropenia: Results of a prospective randomized trial. Am J Med 98:224–231
49. Freifeld AG, Pizzo PA (1996) The outpatient management of febrile neutropenia in cancer patients. Oncology 10:599–612
50. Escalante CP, Rubenstein EB, Rolston KV (1997) Outpatient antibiotic therapy for febrile episodes in low-risk neutropenic patients with cancer. Cancer Invest 15:237–242
51. Freifeld A, Pizzo P (1997) Use of fluoroquinolones for empirical management of febrile neutropenia in pediatric cancer patients. Pediatr Infect Dis J 16:140–146
52. Cometta A, Baumgartner JD, Lew D, et al (1994) Prospective randomized comparison of imipenem monotherapy with imipenem plus netilmicin for treatment of severe infections in non-neutropenic patients. Antimicrob Agents Chemother 38:1309–1313
53. The meropenem study group of Leuven (1995) Equivalent efficacies of meropenem and ceftazidime as empirical monotherapy of febrile neutropenic patients. J Antimicrob Chemother 36: 185–200
54. Santolaya ME, Villarroel M, Avendano LF, Cofre J (1997) Discontinuation of antimicrobial therapy for febrile, neutropenic children with cancer: a prospective study. Clin Infect Dis 25:92–97
55. Clift RA, Sanders JE, Thomas ED, Buckner CD (1978) Granulocyte transfusions for the prevention of infection in patients receiving bone-marrow transplant. N Engl J Med 298:1052–1057
56. Strauss RG, Conett JE, Gale RP, et al (1981) A controlled trial of prophylactic granulocyte transfusions during initial induction chemotherapy for acute myelogenous leukemia. N Engl J Med 305:597–638
57. Cohen J, Heumann D, Glauser MP (1995) Do monoclonal antibodies and anticytokines still have a future in infectious diseases? Am J Med 99:45S–52S
58. Cohen J, Carlet J (1996) Intersept: an international, multicenter, placebo-controlled trial of monoclonal antibody to human tumor necrosis factor-alpha in patients with sepsis. International sepsis trial study group. Crit Care Med 24:1431–1440
59. Fisher CJ Jr, Agosti JM, Opal SM, et al (1996) Treatment of septic shock with the tumor necrosis factor receptor:fc fusion protein. The soluble tnf receptor sepsis study group. N Engl J Med 334:1697–1702
60. Gardner P, Schaffner W (1993) Immunization of adults. N Engl J Med 328:1252–1258
61. Fedson DS (1994) Adult immunization. Summary of the national vaccine advisory committee report. JAMA 272:1133–1137
62. American society of clinical oncology (1994) Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 12: 2471–2508
63. Boogaerts M, Cavalli F, Cortes-Funes H, et al (1995) Granulocyte growth factors: achieving a consensus. Ann Oncol 6:237–244
64. Freifeld A, Pizzo P (1995) Colony-stimulating factors and neutropenia: intersection of data and clinical relevance. J Natl Cancer Inst 87:781–782
65. Pizzo PA (1995) Empiric therapy and prevention of infection in the immunocompromised host. In: Mandell GL, Bennett JE, Dolin R (eds) Principles and practice of infectious diseases. 4th ed. Churchill Livingstone, New York, pp 2686–2696
66. EORTC International Antimicrobial Therapy Cooperative Group (1984) Trimethoprim-sulfamethoxazole in the prevention of infection in neutropenic patients. J Infect Dis 150:372–379
67. Maschmeyer G (1993) Use of the quinolones for the prophylaxis and therapy of infections in immunocompromised hosts. Drugs 45 (Suppl 3):73–80
68. Cometta A, Calandra T, Bille J, Glauser MP (1994) Escherichia coli resistant to fluoroquinolones in patients with cancer and neutropenia. N Engl J Med 330:1240–1241