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Prevention of Bacterial and Fungal Infections in Granulocytopenic Patients

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Abstract—*Granulocytopenic patients are at high risk for infections caused by gram-negative bacteria mostly originating from the gastro-intestinal tract. Several antimicrobial prophylactic regimens are used for prevention of bacterial infections. Prophylaxis with absorbable antimicrobial agents such as trimethoprim–sulfamethoxazole or new fluorinated quinolones seems to be superior to non-absorbable drugs such as polymyxin, vancomycin and gentamicin. The most promising results are obtained with new quinolones. Use of prophylaxis in neutropenic patients leads to changes in the spectrum of infections from gram-negative towards gram-positive.*

INTRODUCTION

INFECTIONS are a frequent consequence of severe granulocytopenia in patients with acute leukemia [1]. During remission induction treatment these patients are especially susceptible to bacterial infections developed from either endogenous (belonging to the patients' own flora) or hospital-acquired organisms that colonize the alimentary tract, upper airway, urinary tract and/or skin [2, 3].

The most common organisms which cause infection in granulocytopenic patients are aerobic gram-negative bacilli such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella/Enterobacter* spp. and gram-positive bacteria especially *Staphylococcus aureus* and *Staphylococcus epidermidis*. Infections caused by anaerobic bacteria are relatively rare in neutropenic patients. The commonest infections in granulocytopenic patients are pneumonias, oropharyngeal infections, esophagitis, perianal and perirectal lesions, skin and soft tissue infections and septicemias.

Several factors predispose patients with acute leukemia to infection. The most important factor is the profound and prolonged granulocytopenia either due to the disease or to its treatment. Besides the myelosuppressive and mucosal effect on skin and mucous membranes of cytotoxic drugs, immunosuppression as a consequence of corticosteroids is also a factor that predisposes to infection. Medical procedures such as intravenous infusions, indwelling urinary and central venous catheters, which interrupt the skin and/or mucosal barrier, also contribute to the susceptibility of the patient to infections. Most of the infections occur during the period when the granulocyte counts are below 500/μl; the majority of severe and sometimes lethal infections are observed when granulocyte counts are below 100/μl [1, 3, 4].

Although there has been a dramatic decline in death rate associated with infections due to advances in antimicrobial therapy, extensive diagnostic procedures and a better supportive care, morbidity from infectious disease in granulocytopenic patients still remains a problem. Various methods to prevent infection in these patients have been studied. A rational approach for infection prevention in granulocytopenic patients is to suppress the potential pathogens already colonizing the patients and to reduce the acquisition of new microorganisms from the environment [5, 6].

The aim of this overview article is to compare the results obtained by different investigators using various antibiotics or combination of antibiotics in neutropenic patients nursed either under isolation or in open wards.

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This paper is a revised version of a chapter published previously [54].

RESULTS AND DISCUSSION

1. *Reverse single room or laminar airflow room isolation*

The effectiveness of simple protective isolation (single room treatment) or complete reverse iso-

lation with laminar air-flow alone is not convincing [7, 8]. Use of laminar air-flow rooms not only requires expensive equipment, but also a sterile supply of food, skilled nursing staff and other services. Besides, strict isolation procedures are a psychological burden to the patient.

2. *Total decontamination of the alimentary tract*

Since the alimentary tract has been recognized as an important reservoir of potential pathogens, total decontamination of the alimentary tract has been tried to prevent infections. The basic method of microbial suppression is the use of non-absorbable antibiotics such as gentamicin, vancomycin and nystatin, often in conjunction with topical antiseptics applied to the skin and orificia [5]. The results of the use of total decontamination of the gastrointestinal tract alone are controversial [5, 7, 9].

This procedure was only significantly effective in preventing infections in one study [10]. Poor compliance, usually due to the unpleasant taste of the oral nonabsorbable antibiotic regimens, can be a cause of significant rebound overgrowth of potential pathogens and acquisition of resistant strains from the hospital environment [5, 6].

The combination of oral non-absorbable antibiotics with nursing under strict isolation conditions has improved these results. A substantial reduction (about 50%) in the incidence of infections with this combined approach was obtained in a number of studies [7, 9–13]. However, in other studies results were less convincing [8, 14].

3. *Selective decontamination of the alimentary tract*

In the light of these problems another approach was developed by van der Waaij and co-workers [15–18]: the selective decontamination of the alimentary tract. This procedure aims to eliminate potentially pathogenic aerobic gram-negative rods from the alimentary tract, without affecting the anaerobic flora, and is based on the observation that most infections seen in neutropenic patients are caused by these potentially pathogenic, aerobic gram-negative rods and on the observation in mice that the anaerobic flora prevent the host from becoming colonized with bacteria from the environment (colonization resistance). With the anaerobic flora left intact, the resistance to colonization by aerobic gram-negative bacilli is considered to be maintained and subsequent infection prevented.

Antimicrobial agents such as nalidixic acid, colistin (polymyxin B) and trimethoprim–sulfamethoxazole selectively suppress aerobic flora and do not change the anaerobic flora [19]. Therefore these agents can be used for selective decontamination of the alimentary tract. These drugs are more palatable, leading to better compliance and are cheaper than gentamicin and vancomycin. Another advantage of this approach could be that there is no need for nursing the patient in a laminar airflow room. The results of infection prevention based on selective decontamination that have been evaluated are encouraging [20–23].

A. *Prophylactic use of trimethoprim–sulfamethoxazole*

Hughes *et al.* [24] were the first to report that children with leukemia and solid tumors had fewer episodes of bacterial sepsis when given trimethoprim–sulfamethoxazole as prophylaxis against *Pneumocystis carinii* infection than when given placebo. Enno *et al.* [25] extended these findings. An additional benefit of using trimethoprim–sulfamethoxazole was reported by these authors on patients already receiving the combination of framycetin, colistin and nystatin.

Trimethoprim–sulfamethoxazole offers several potential advantages as a single oral prophylactic antimicrobial agent [21, 24–32]. This drug combination is not only effective in the elimination of gram-negative bacilli from the gut but in addition it is well absorbed and gives therapeutic levels in the blood and tissues. Wade *et al.* [26] showed that the effect of the combination of trimethoprim–sulfamethoxazole and nystatin was comparable to that of the combination of gentamicin and nystatin, but the first combination resulted in the appearance of fewer resistant organisms and was better tolerated. Subsequent studies by Watson *et al.* [27] and Starke *et al.* [28] demonstrated also the equivalency or superiority of trimethoprim–sulfamethoxazole to non-absorbable antibiotics as prophylaxis. Results of the randomized study from the EORTC Gnotobiotic Project Group [29] showed superiority of trimethroprim–sulfamethoxazole + colistin when compared to only non-absorbable drugs colistin + neomycin. In the group of patients receiving trimethoprim–sulfamethoxazole + colistin the incidence of febrile days as well as the incidence of acquired infections was lower than in the group of patients receiving neomycin and colistin. The most striking differences were found in the occurrence of septicemias without localized infections. These studies indicate that absorbable drugs are better able to prevent infections than oral non-absorbable drugs, although both regimens are able to selectively decontaminate the gastro-intestinal tract. It raises the question whether not only selective decontamination but also tissue levels of the antibiotic are important for prevention of infection. This would be in line with findings published by Wells *et al.* [30, 31]. This group showed that bacteria may translocate from the gastro-intestinal tract to the mesenteric lymph nodes, where they can survive. These bacteria could then be an initial site of invasion into other tissues. Thus, elimination of the

flora from the gastro-intestinal tract by oral non-absorbable drugs does not eliminate bacteria from the lymph nodes, and foci of infection remain in existence.

One of the potential problems of using trimethoprim–sulfamethoxazole alone as a prophylactic agent is the emergence of resistant gram-negative bacilli which can colonize patients and can cause infections.

That means, that although trimethoprim–sulfamethoxazole does not affect the anaerobic flora it does affect the colonization resistance.

Dekker *et al.* [32] showed a decrease in the total number of acquired infections and fever in a group of patients with acute leukemia receiving trimethoprim–sulfamethoxazole. However, most of the infections caused by gram-negative bacilli in those patients were caused by bacteria resistant to this drug. Colonization of the alimentary tract with subsequent infections by resistant Enterobacteriaceae during treatment with trimethoprim–sulfamethoxazole has also been found in several other recent studies [26, 33–37]. Addition of colistin to trimethoprim–sulfamethoxazole significantly reduced the acquisition of resistant gram-negative bacilli and subsequent colonization of the lower alimentary tract with these bacteria leading to reduction of infections [38].

Another potential disadvantage of the prophylactic use of trimethoprim–sulfamethoxazole could be an increased duration of the granulocytopenic period which was shown in some studies [32, 37, 39, 40]. However, in other studies no prolongation of granulocytopenia was observed [29, 41]. It is possible that the effect of trimethoprim–sulfamethoxazole on the bone marrow is dependent on the intensity of the myelosuppressive therapy used. A serious problem observed in some patients receiving trimethorprim–sulfamethoxazole prophylactically is the development of hypersensitivity reactions, especially due to the sulfa component [29, 38, 42]. These adverse reactions to trimethoprim–sulfamethoxazole are not dose-dependent.

B. *Prophylactic use of new fluorinated quinolones*

The drawbacks associated with the use of trimethoprim–sulfamethoxazole encourage the search for more efficacious and safer antimicrobial prophylaxis in patients with prolonged and profound granulocytopenia. The development of the new quinolone derivatives holds some attractive promises. The orally well absorbed quinolones, norfloxacin and ciprofloxacin, exhibit broad activity against aerobic gram-positive and gram-negative bacteria, especially against Enterobacteriaceae and *Pseudomonas aeruginosa* [43, 44]. These antimicrobial agents show limited activity against anaerobic bacteria. Both drugs are well absorbed, and for most pathogens the plasma concentrations are above the inhibitory value [45, 46].

The effect of ciprofloxacin, given 500 mg twice daily to 15 patients, on the flora of the alimentary tract was investigated [47]. A rapid reduction in the number of Enterobacteriaceae in feces was observed within 3–5 days and thereafter cultures remained negative for Enterobacteriaceae. In contrast to rapid elimination of Enterobacteriaceae, no significant reduction in the number of anaerobic gram-negative bacilli and clostridium occurred although some effect was seen on anaerobic non-sporeforming gram-positive bacilli and anaerobic cocci. During this study period (mean duration of study 46 days) six resistant strains of *Pseudomonas* species were isolated from 186 fecal cultures, one resistant *Pseudomonas* species and two *Acinetobacter* species were isolated from oropharyngeal samples, but none of these bacteria colonized patients or caused infections. Most of the patients became colonized with *Staphylococcus epidermidis*. The mean peak concentration of ciprofloxacin in serum 2 h after administration of the drug was 1.6 mg/l with a range from 0.8 to 2.3 mg/l. All but one of the bacteriologically documented infections were caused by gram-positive cocci; no infections caused by gram-negative bacilli were observed. Ciprofloxacin was very well tolerated, compliance was excellent and no adverse reactions were seen. This study showed that ciprofloxacin was effective for selective decontamination of the alimentary tract and prevented infections caused by gram-negative bacilli.

The results of a randomized study by Dekker *et al.* [48] showed the superiority of ciprofloxacin, especially for prevention of infection caused by gram-negative bacilli in adult patients treated for acute leukemia over the combination of trimethoprim–sulfamethoxazole and colistin. In the group of patients receiving ciprofloxacin no infections caused by gram-negative bacilli occurred. Most of the acquired infections were caused by gram-positive bacteria. Ciprofloxacin also prevented colonization of the alimentary tract with resistant gram-negative bacilli. Ciprofloxacin was better tolerated leading to excellent compliance and showed less skin reactions when compared to the combination of trimethoprim–sulfamethoxazole + colistin. Other investigators [49–51] showed the benefit of prophylactic use of norfloxacin in patients with acute leukemia. Oral prophylaxis with norfloxacin suppressed infection caused by aerobic gram-negative bacilli during anti-leukemic therapy without significant effect on the incidence of infections caused by gram-positive bacteria.

CONCLUSION

It is possible that the use of trimethoprim–sulfamethoxazole and especially the effective new

quinolone derivatives for selective decontamination of the alimentary tract may lead to a change in the spectrum of infections seen in patients undergoing myelosuppressive therapy, from infections caused by organisms such as Enterobacteriaceae or *Pseudomonas aeruginosa* to *Staphylococcus epidermidis*, α-hemolytic streptococci and other gram-positive bacteria. *S. epidermidis* infections are often associated with the presence of long-term indwelling central venous catheters [52, 53]. Infections caused by α-hemolytic streptococci in patients from our center are frequently related to intensive cytotoxic treatment (e.g. amsacrine, high doses of cytarabine) which not only lead to profound and prolonged granulocytopenia but often also to ulcerations of the oropharynx and alimentary tract.

More studies are needed to ascertain the true efficacy of quinolone derivatives for infection prevention. It remains to be determined whether they should be used alone, or used in combination with additional agents active against gram-positive bacteria.

REFERENCES

1. Bodey GP, Buckley M, Sathe YS, Freirech EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966, **64**, 328–340.
2. Schimpff SC, Young VM, Greene WH, Vermeulen GD, Moody MR, Wiernik PH. Origin of infection in acute nonlymphocytic leukemia. Significance of hospital acquisition of potential pathogens. *Ann Intern Med* 1972, **77**, 707–714.
3. Bodey GP, Rodriquez V, Chang H-Y, Narboni G. Fever and infections in leukemic patients. A study of 494 consecutive patients. *Cancer* 1978, **41**, 1610–1622.
4. Gurwith MJ, Brunton JL, Lank BA, Ronald AR, Harding GKM. Granulocytopenia in hospitalized patients. I. Prognostic factors and etiology of fever. *Am J Med* 1978, **64**, 121–126.
5. Schimpff SC. Infection prevention during profound granulocytopenia. New approaches to alimentary canal microbial suppression. *Ann Intern Med* 1980, **93**, 358–361.
6. Pizzo PA, Schimpff SC. Strategies for the prevention of infection in the myelosuppressed or immuno-suppressed cancer patient. *Cancer Treat Rep* 1983, **67**, 223–234.
7. Yates JW, Holland JF. A controlled study of isolation and endogenous microbial suppression in acute myelocytic leukemia patients. *Cancer* 1973, **32**, 1490–1498.
8. Dietrich M, Gaus W, Vossen J, Van der Waaij D, Wendt F. Protective isolation and antimicrobial decontamination in patients with high susceptibility to infection. A prospective cooperative study of gnotobiotic care in leukemia patients. I. Clinical results. *Infection* 1977, **5**, 107–114.
9. Levine AS, Siegel SE, Schreiber AD *et al.* Protected environments and prophylactic antibiotics. A prospective controlled study of their utility in the therapy of acute leukemia. *N Engl J Med* 1973, **288**, 477–483.
10. Schimpff SC, Greene WH, Young VM *et al.* Infection prevention in acute nonlymphocytic leukemia. Laminar air flow room reverse isolation with oral, nonabsorbable antibiotic prophylaxis. *Ann Intern Med* 1975, **82**, 351–358.
11. Rodriguez V, Bodey GP, Freireich EJ *et al.* Randomized trial of protected environment—prophylactic antibiotics in 145 adults with acute leukemia. *Medicine* 1978, **57**, 253–266.
12. Buckner CD, Clift RA, Sanders JE *et al.* and the Seattle Marrow Transplant Team. Protective environment for marrow transplant recipients. A prospective study. *Ann Intern Med* 1978, **89**, 893–901.
13. Bodey GP, McCredie KB, Keating MJ, Freireich EJ. Treatment of acute leukemia in protected environment units. *Cancer* 1979, **44**, 431–436.
14. Lohner D, Debusscher L, Prevost JM, Klastersky J. Comparative randomized study of protected environment plus oral antibiotics versus oral antibiotics alone in neutropenic patients. *Cancer Treat Rep* 1979, **63**, 363–368.
15. Van der Waaij D, Berghuis-de Vries JM, Lekkerkerk-van der Wees JEC. Colonization resistance of the digestive tract in conventional and antibiotic treated mice. *J Hyg (Camb)* 1971, **69**, 405–411.
16. Van der Waaij D, Berghuis JM, Lekkerkerk JEC. Colonization resistance of the digestive tract of mice during systemic antibiotic treatment. *J Hyg (Camb)* 1972, **70**, 605–610.
17. Van der Waaij D, Berghuis-de Vries JM. Selective elimination of the Enterobacteriaceae species from the digestive tract in mice and monkeys. *J Hyg (Camb)* 1974, **72**, 205–211.
18. Van der Waaij D, Berghuis JM. Determination of the colonization resistance of the digestive tract of individual mice. *J Hyg (Camb)* 1974, **72**, 379–387.
19. Van der Waaij D. Colonization resistance of the digestive tract as a major lead in the selection of antibiotics for therapy. In: Van der Waaij D, Verhoef J, eds. *New Criteria for Antimicrobial Therapy: Maintenance of Digestive Tract Colonization Resistance.* Excerpta Medica, Amsterdam, 1979, 271–282.
20. Guiot HFL, Van Furth R. Partial decontamination. *Br Med J* 1977, **1**, 800–802.
21. Gurwith MJ, Brunton JL, Lank BA, Harding GLM, Ronald AR. A prospective controlled investigation of prophylactic trimethoprim/sulfamethoxazole in hospitalized granulocytopenic patients. *Am J Med* 1979, **66**, 248–256.

22. Sleijfer DT, Mulder NH, de Vries-Hospers HG *et al.* Infection prevention in granulocytopenic patients by selective decontamination of the digestive tract. *Eur J Cancer* 1980, **16**, 859–869.
23. Guiot HFL, van den Broeke JWM, Van der Meer JWM, Van Furth R. Selective antimicrobial modulation of the intestinal flora of patients with acute nonlymphocytic leukemia: a double blind placebo controlled study. *J Infect Dis* 1983, **47**, 615.
24. Hughes WT, Kuhn S, Chaudhury S *et al.* Successful chemoprophylaxis for *Pneumocystis carinii* pneumonitis. *N Engl J Med* 1977, **297**, 1419–1426.
25. Enno A, Catovsky D, Darrell J, Goldman JN, Hows J, Galton DAG. Cotrimoxazole for the prevention of infection in leukemia. *Lancet* 1978, **II**, 395–397.
26. Wade JC, Schimpff SC, Hargadon MT, Fortner CL, Young VM, Wiernik PA. A comparison of trimethoprim–sulfamethoxazole plus nystatin with gentamicin plus nystatin in the prevention of infections in acute leukemia. *N Engl J Med* 1981, **304**, 1057–1062.
27. Watson JG, Powles RL, Lawson DN *et al.* Cotrimoxazole versus nonabsorbable antibiotics in acute leukemia. *Lancet* 1982, **I**, 6–9.
28. Starke JD, Catovsky D, Johnson SA *et al.* Cotrimoxazole alone for prevention of bacterial infection in patients with acute leukemia. *Lancet* 1982, **I**, 5–6.
29. Kurrle E, Dekker AW, Gaus W *et al.* (EORTC Gnotobiotic Project Group Writing Committee). Prevention of infection in acute leukemia: a prospective randomized study on the efficacy of two different drug regimens for antimicrobial prophylaxis. *Infection* 1986, **14**, 226–232.
30. Wells CL, Maddaus MA, Reynolds CM, Jechorek RP, Simmons RL. Role of anaerobic flora in the translocation of aerobic and facultatively anaerobic intestinal bacteria. *Infect Immun* 1987, **55**, 2689–2694.
31. Wells CL, Maddaus MA, Jechorek RP, Simmons RL. Ability of intestinal *Escherichia coli* to survive within mesenteric lymph nodes. *Infect Immun* 1987, **55**, 2834–2837.
32. Dekker AW, Rozenberg-Arska M, Sixma JJ, Verhoef J. Prevention of infection by trimethoprim–sulfamethoxazole plus amphotericin B in patients with acute nonlymphocytic leukemia. *Ann Intern Med* 1981, **35**, 555–559.
33. Kaufman CA, Liepman MK, Bergman AG, Mioduszewski J. Trimethoprim–sulfamethoxazole prophylaxis in neutropenic patients. Reduction of infections and effect on bacterial and fungal flora. *Am J Med* 1983, **74**, 599–607.
34. Gualtieri RJ, Donovitz GR, Kaiser DL, Hess CE, Saride MA. Double blind randomized study of prophylactic trimethoprim–sulfamethoxazole in granulocytopenic patients with haematologic malignancies. *Am J Med* 1983, **74**, 934–940.
35. Wilson JM, Guiney DG. Failure of oral trimethoprim–sulfamethoxazole prophylaxis in acute leukemia: isolation of resistant plasmids from strains of Enterobacteriaceae causing bacteremia. *N Engl J Med* 1982, **306**, 16–20.
36. De Jongh CA, Schimpff SC, Wiernik PH. Antibiotic prophylaxis in acute leukemia. *Ann Intern Med* 1981, **95**, 783.
37. Jacoby GA. Perils of prophylaxis. *N Engl J Med* 1982, **306**, 43–44.
38. Rozenberg-Arska M, Dekker AW, Verhoef J. Colistin and trimethoprim–sulfamethoxazole for the prevention of infection in patients with acute non-lymphocytic leukemia. Decrease in the emergence of resistant bacteria. *Infection* 1983, **11**, 167–169.
39. Wade JC, de Jongh CA, Newman KA, Crowley J, Wiernik PH, Schimpff SC. Selective antimicrobial modulation as prophylaxis against infection during granulocytopenia: trimethoprim–sulfamethoxazole vs. nalidixic acid. *J Infect Dis* 1983, **147**, 624–634.
40. Pizzo PA, Robichaud K, Edwards B. Oral antibiotic prophylaxis in patients with cancer. A double blind randomized placebo controlled trial. *J Pediat* 1983, **102**, 125–133.
41. EORTC International Antimicrobial Therapy Project Group. Trimethoprim–sulfamethoxazole in the prevention of infection in neutropenic patients. *J Infect Dis* 1984, **150**, 372–379.
42. Young LS. Antimicrobial prophlaxis against infection in neutropenic patients. *J Infect Dis* 1983, **147**, 611–614.
43. Bauernfield A, Petermüller C. *In vitro* activity of ciprofloxacin, norfloxacin and nalidixic acid. *Eur J Clin Microbiol* 1983, **2**, 111–115.
44. Wise R, Andrews JM, Edwards LJ. *In vitro* activity of Bay 09867, a new quinolone derivative, compared with those of other antimicrobial agents. *Antimicrob Agents Chemother* 1983, **23**, 559–564.
45. Crump B, Wise R, Deut J. Pharmacokinetics and tissue penetration of ciprofloxacin. *Antimicrob Agents Chemother* 1983, **24**, 784–786.
46. Adhami ZN, Wise R, Weston D, Crump B. The pharmacokinetics and tissue penetration of norfloxacin. *J Antimicrob Chemother* 1984, **13**, 87–92.
47. Rozenberg-Arska M, Dekker AW, Verhoef J. Ciprofloxacin for selective decontamination of the alimentary tract in patients with acute leukemia during remission induction treatment: the effect on fecal flora. *J Infect Dis* 1985, **152**, 104–107.
48. Dekker AW, Rozenberg-Arska M, Verhoef J. Infection prophylaxis in acute leukemia: a comparison of ciprofloxacin with trimethoprim–sulfamethoxazole and colistin. *Ann Intern Med* 1987, **106**, 7–12.

49. Karp JE, Merz WG, Hendricksen C, Laughon B *et al.* Oral norfloxacin for prevention of gram-negative bacterial infections in patients with acute leukemia and granulocytopenia. A randomized, double-blind placebo-controlled trial. *Ann Intern Med* 1987, **106**, 1–7.
50. Winston DJ, Ho WG, Nakao SL, Gale RP, Champlin RE. Norfloxacin versus vancomycin/polymyxin for prevention of infections in granulocytopenic patients. *Am J Med* 1984, **80**, 884–890.
51. Bow EJ, Rayner E, Louie TJ. Comparison of norfloxacin with cotrimoxazole for infection prophylaxis in acute leukemia. *Am J Med* 1988, **84**, 847–853.
52. Blacklock HA, Hill RS, Clarke AG, Pillai MV, Mathews JRD, Wade JF. Use of modified subcutaneous right atrial catheter for venous access in leukemic patients. *Lancet* 1980, **1**, 993–994.
53. Lowder JN, Lazarus HM, Herzig RH. Bacteremias and fungemias in oncologic patients with central venous catheters. Changing pattern of infection. *Arch Intern Med* 1982, **142**, 1456–1459.
54. Rozenberg-Arska M, Dekker AW. Prevention of bacterial and fungal infection in granulocytopenic patients. In: Peterson PK, Verhoef J, eds. *Antimicrob Agents Ann.* Amsterdam, Elsevier, 1987, Vol. 2, 471–481.