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Selective Antimicrobial Modulation of Human Microbial Flora: Infection Prevention in Patients with Decreased Host Defense Mechanisms by Selective Elimination of Potentially Pathogenic Bacteria

Henri F. L. Guiot, Jos W. M. van der Meer, and Ralph van Furth

To reduce the frequency and severity of bacterial infection, selective antimicrobial modulation (SAM) was applied in 39 patients with severely decreased host defense mechanisms. The objective was to eliminate potentially pathogenic aerobic microorganisms with minimal disturbance of the normal anaerobic bacterial flora. Elimination of potentially pathogenic aerobic microorganisms was easily accomplished in patients not infected at hospitalization. The anaerobic flora seemed to be undisturbed, and selection of or overgrowth with resistant microorganisms did not occur. The microbiologic results of the SAM regimen correlated with the incidence of infection. Only three major infections occurred in 23 patients who were free of potentially pathogenic microorganisms; 10 major infections occurred in 16 patients who were not free of potential pathogens. Seven of these 10 infections were present at hospitalization. The incidence of major infections was 47% in the patients on the SAM regimen and 82% in a group of control patients with a similar risk of infection.

Infection is one of the most serious complications in patients with severe bone-marrow failure. The severity and duration of granulocytopenia in these patients are correlated with the incidence of severe bacterial and fungal infection [1, 2]. The organisms causing infection in granulocytopenic patients belong to the resident flora or are acquired from the hospital environment. It would seem logical to prevent such infections by total elimination of the resident flora with antibiotics (total antibiotic modulation) and by nursing the patients in strict protective isolation [3]. However, apart from such negative aspects as discomfort for the patient and high costs, attempts to eliminate all microorganisms often fail and may lead to overgrowth with multiresistant, potentially pathogenic strains. Moreover, much effort is required to eliminate all bacteria and fungi from the patient, whereas in granulocytopenic patients most of the severe infections are caused by only a few species of the normal resident flora: members of the family Enterobacteriaceae, Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans. Although anaerobes outnumber aerobes and facultative anaerobes by a factor of 100–10,000, anaerobes are responsible for <10% of severe infections in patients with bone-marrow failure [4].

It has been shown that anaerobes have an inhibitory effect on the growth of aerobic microorganisms. (The latter are defined here as being both obligate aerobes and facultative anaerobes.) This effect is called colonization resistance [5–9]. If the anaerobic flora is disturbed by treatment of the patient with antibiotics, colonization resistance is decreased. Under these conditions, overgrowth with potentially pathogenic aerobic bacteria or fungi and selection of multiresistant microorganisms may occur, and the chance of nosocomial infection will increase. The concept of colonization resistance and the fact that it is almost impossible to make a patient totally germ-free led us to change our approach to infection prevention. A combination of antibiotics with activity against aerobes and fungi but not against anaerobes was
chosen for administration to patients with a high risk of infection; this regimen has been titled selective antimicrobial modulation (SAM) [10].

The present report describes the results of a clinical trial with SAM in patients with severe granulocytopenia. The anaerobic flora in the feces of patients on the SAM regimen was compared with that of healthy individuals to assess the extent of disturbance caused by the regimen.

Patients and Methods

Patients. Between 1975 and 1978, 50 patients were admitted to the isolation ward of the University Hospital in Leiden, The Netherlands. These patients were treated for diseases associated with bone-marrow failure and were placed on a regimen of SAM and protective isolation as additional care. Most of these patients were assigned to this special ward because their risk for infection was expected to be extremely high. Of this group, 39 patients with severe granulocytopenia (<100 granulocytes/mm$^3$) for more than seven days are included in the present report (SAM group). Seven patients have already been described [10].

During the first six months of 1976, 31 other patients were treated for diseases associated with bone-marrow failure. They could not be assigned to the special isolation ward and were not placed on the SAM regimen. Their only protection consisted of conventional isolation in single rooms. In these patients the quantitative relationship between circulating leukocytes and infection was previously described by van der Meer et al. [2]. Only the 14 patients in this group who had severe granulocytopenia (<100 granulocytes/mm$^3$) for more than seven days are briefly discussed herein for purposes of comparison (control group).

Therapy for hematologic disorder. In the SAM group, 15 patients with acute myeloid leukemia (AML) were treated with the LAM V remission-induction regimen. Eleven patients underwent bone-marrow transplantation (BMT) [11] for treatment of AML, acute lymphocytic leukemia (ALL), or severe aplastic anemia (AA). Thirteen patients with AA were treated with antithymocyte globulin [12]. In the control group, 11 patients were treated with the LAM V regimen for AML, two patients with androgens for AA, and one with corticosteroids for AA.

Isolation of patients on the SAM regimen. The first six patients of the SAM group were nursed in strict protective isolation (including sterile food) in laminar down-flow isolators or other equivalent systems. The isolation measures for the next 13 patients were progressively reduced. The last 20 patients were isolated in “open” systems: one of the plastic curtains of the laminar-flow system was constantly kept open about 75 cm. The patient was allowed to leave the isolator while he or she was wearing a well-fitting mask to take some exercise or a shower and to have contact with nonsterilized dry and clean articles (daily newspaper, letters, and cigarettes). Of these 20 patients, 10 were placed on the SAM regimen at home during short periods (four to 14 days) of partial hematologic remission. The last 20 patients were given food with a low bacterial level. The isolation units were disinfected with 70% alcohol twice a week. The shower was rinsed with hot water before use, dried carefully after use, and disinfected with 70% alcohol twice a week because bacteriologic control suggested that contamination of the skin with $P. aeruginosa$ could occur there. Sterile nursing was initially (first six patients) performed by two nurses but was later changed to aseptic handling by one nurse. Clothes for the nursing staff were not sterilized but were washed in the central hospital laundry at 90°C.

Isolation of control patients. The control patients were conventionally isolated in single rooms, without laminar-flow air. They were given the normal hospital food.

SAM regimen. Four times a day the nasopharyngeal region was sprayed with an aqueous solution of 3% gentamicin. One gram of an ointment composed of 3% amphotericin B, 3% neomycin, and 1% polymyxin B in oral protective paste (Orabase®; Squibb B.V., Rijswijk, The Netherlands) was applied to the mouth. The ointment was used as a toothpaste with menthol flavoring and applied with a toothbrush. The SAM regimen of the gastrointestinal tract consisted of 250 mg of neomycin, 250 mg of amphotericin B, 100 mg of polymyxin B, and 1,000 mg of nalidixic acid.
acid, all given orally four times a day. The skin was washed daily with either povidone-iodine soap (even days) or water containing 0.02% chlorhexidine (odd days). The prepuce or vulval and vaginal region was treated with a cetyl-based cream containing the same composition of antibiotics as the ointment used for the mouth. For macroscopically detectable \( C. \) \textit{albicans} persisting in the mouth, a gentian violet solution was used. Persisting potential pathogens on the skin were treated daily with silver sulfadiazine.

In 15 patients the complete SAM regimen was not followed during short periods (eight to 14 days); either lower dosages were given during cytotoxic therapy (because of nausea) or nalidixic acid was omitted temporarily if hypersensitivity due to the drug was suspected.

### Management of infections.

In both the SAM patients and controls, systemic antibiotic treatment was not instituted until infection was seriously suspected or proven. The choice of antibiotics was governed by the site of the infection and the suspected causative microorganisms. Initial therapy almost always consisted of a combination of two antibiotics given iv. Whenever possible, antibiotic therapy was adjusted on the basis of the results of bacteriologic investigations.

### Definition of infections.

Infections were divided into bacterial, fungal, viral, and protozoan infections. The bacterial and fungal infections were divided into minor infections—clinical infections on the skin or mucosa without extension to deep tissues (stomatitis, gingivitis, sinusitis, and pharyngitis), whether microbiologically proven or not—and major infections—clinical infections with extension to deep tissue or organs (pneumonia and pyelonephritis) and sepsis, whether microbiologically proven or not. Infections were called doubtful if all diagnostic procedures did not give conclusive results and only the patient's clinical condition (fever) was suggestive of infection.

### Microbiologic investigation.

A bacteriologic inventory of the SAM patients was carried out twice a week. Samples of feces and urine and swabs from the nose, oropharynx, axilla, groin, and prepuce or vagina were cultured on selective and nonselective media (Oxoid, London, England, and Difco Laboratories, Detroit, Mich.). Samples from infected areas were cultured by standard bacteriologic methods. During periods of fever (axillary temperature, >38°C), at least two blood samples were cultured daily, both aerobically and anaerobically. The microbiologic surveillance has been described in detail by Guiot and van Furth [10].

### Anaerobic flora.

Gram-stained smears of fecal samples obtained twice a week were examined with a microscope. In addition, the anaerobic fecal flora of 22 patients on the SAM regimen was compared with that of 21 healthy individuals (nurses, physicians, and technicians) to obtain quantitative and qualitative information about the composition of the anaerobic flora during SAM. The fecal flora was investigated after the patient had been on the SAM regimen for at least four weeks. Only patients without diarrhea (graft-vs-host disease [11]) and receiving no antibiotics except those in the SAM regimen were investigated. Only one fecal sample of each individual was obtained. For this purpose, about 1 g of feces was suspended and homogenized in 9 ml of prereduced anaerobic brain-heart infusion broth (Oxoid) (adapted by the method of Holdeman and Moore [13]). From this suspension a series of 10-fold dilutions was prepared. For half of the patients and healthy individuals, cfu counts were performed \(10^7, 10^8, \) and \(10^9\) dilutions) on aerobic sheep blood agar (Oxoid), Eugon agar (Becton, Dickinson and Co., Cockeysville, Md.), Schaedler agar (Bio-Mérieux, Charbonnières-les-Bain, France), and anaerobic brain-heart infusion broth. For the other half of both groups, suspension cultures were made of all dilutions \(10^{-7}-10^{-12}\). Anaerobic conditions were obtained with the GasPak\textsuperscript{®} system (Becton, Dickinson and Co.) and the open-tube technique [13]. Isolates were identified on the basis of morphologic characteristics; the production of volatile fatty acids, lactic acid, succinic acid, gas, \( \text{NH}_3 \), indole, and catalase; and the fermentation of glucose, lactose, ribose, and starch [13].

### Pattern of volatile fatty acids in feces.

In addition to the bacteriologic inventory, the metabolic activity of the anaerobic flora was investigated. For this purpose, about 5 g of feces from patients on the SAM regimen and from healthy individuals was suspended in 10 ml of water. The suspension was mixed thoroughly and centrifuged for 15 min at 4.95 g. The supernatant was decanted and filtered through a coarse paper filter, and 1 ml of ether and 0.5 ml of 2 n HCl were added. The tube
was stoppered and kept at 4°C for about 30 min before it was centrifuged at 4.95 g for 15 min. This sample was kept at −20°C until the remaining water froze. Estimation of the amounts of volatile fatty acids was performed by gas chromatography with a glass column (length, 175 cm; diameter, 0.2 cm) filled with Chromosorb® W-AW (Sulpeco, Bellefonte, Pa.). The temperature of the column was 120°C, that of the injector and detector ports, 150°C and 170°C, respectively. The carrier gas was N₂ under a pressure of 0.8 kg/cm². Five micro­liters of the ether supernatant was injected for gas chromatography.

**Fecal flora for anaerobic reconstitution.** For reconstitution of anaerobic flora, 5 g of feces from a decontaminated patient without gastrointestinal complaints and with a fecal flora of normal appearance by microscopy was suspended in 0.85% NaCl. The suspension was homogenized by shaking for 30 sec and then centrifuged at a low speed (5 min at 1 g). The supernatant was filtered through a layer (3–5 cm) of cotton wool to remove the coarse particles and then centrifuged at a higher speed (15 min at 4.95 g). The pellet was suspended in 5 ml of 0.85% NaCl, and 1 ml of this suspension was mixed into 100 ml of chilled chocolate milk that was then swallowed by the patient within 1 hr of preparation.

**Results**

**Clinical details of the group of patients on the SAM regimen.** Clinical details concerning the SAM group are given in table 1. The mean ages of the patients with AML and AA were similar, whereas the mean age of the patients with BMT was considerably younger. The mean number of granulocytopenic days was about the same for the patients with AML and AA, whereas the patients with BMT had a shorter period of granulocytopenia.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute myeloid</td>
<td>Aplastic anemia</td>
<td>Bone-marrow</td>
</tr>
<tr>
<td></td>
<td>leukemia (n = 15)</td>
<td>(n = 13)</td>
<td>transplantation (n = 11)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.3</td>
<td>35.8</td>
<td>22</td>
</tr>
<tr>
<td>Mean</td>
<td>37</td>
<td>33</td>
<td>20.5</td>
</tr>
<tr>
<td>Median</td>
<td>19–55</td>
<td>15–84</td>
<td>16–44</td>
</tr>
<tr>
<td>No. of granulocytopenic days &lt;100 granulocytes/mm³</td>
<td>35.3</td>
<td>34.5</td>
<td>26.8</td>
</tr>
<tr>
<td>Mean</td>
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<td>30.5</td>
<td>20</td>
</tr>
<tr>
<td>Median</td>
<td>14–68</td>
<td>18–76</td>
<td>18–62</td>
</tr>
<tr>
<td>Range</td>
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<td>58</td>
<td>38.5</td>
</tr>
<tr>
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<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Minor</td>
<td>2</td>
<td>3*</td>
<td>0</td>
</tr>
<tr>
<td>Major</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No. of newly acquired infections</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Minor</td>
<td>5*†</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Major</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
<td>1</td>
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</tr>
<tr>
<td>Bacterial infection</td>
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<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other causes‡</td>
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<td>1</td>
<td>3</td>
</tr>
<tr>
<td>No. of patients with partial hematologic cure</td>
<td>9</td>
<td>6</td>
<td>11</td>
</tr>
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</table>

* Two patients died.
† Two patients died of infections that originated from minor local infections present at hospitalization.
‡ There were no fatal cases of fungal infection.
Infections present at hospitalization. Seven patients were admitted with minor infections: five localized in the oral region and one in the rectal area plus one case of furuncles. Two of these patients (both with AML) developed fatal septicemia shortly after their first course of remission-induction therapy, presumably originating from the local smoldering infection (determined at autopsy to be pharyngitis due to *P. aeruginosa* and rectal infiltration with *Escherichia coli*). The other minor infections were cured with narrow-spectrum antibiotics without further problems. Of the five patients hospitalized with a major infection, four had septicemia (two due to *P. aeruginosa* and two due to *E. coli*), and one had pneumonia (unknown etiology). Two of these patients, both with AA, died of septicemia before hematologic therapy could even be started. The other major infections (in patients with AML) were cured with systemic antibiotic treatment within a few days; the fifth patient (with AA) needed four weeks to become free of infection.

Infections acquired after hospitalization. The six minor infections that developed after hospitalization were all localized in the oral region. These infections were caused by the anaerobic flora of the mouth and responded rapidly to penicillin G. Of the eight major infections that developed after hospitalization, two originated from smoldering minor infections that had been present at hospitalization (described in the foregoing), and six were newly acquired. Five of the latter started as skin infections: one case of cellulitis and one of eczema gangrenosum (both exogenous skin infections with *P. aeruginosa* followed by sepsis [14]); one iv catheter infected with *E. coli* (which persisted, even though the organism was sensitive to the antibiotics included in the SAM regimen); one case of an extensive lesion due to herpes simplex virus secondarily infected with *Proteus mirabilis* (which persisted because the patient had not been given nalidixic acid); and one case of anaerobic infection of a rectal fistula (the SAM regimen was successful, however, with only anaerobes and streptococci persisting in the feces). A major infection occurred in a patient who was refractory to therapy for leukemia; her death was the result of bleeding, infection, and leukemia. The death of this patient is classified as due to other causes in table 1 and due to a combination of infection and bleeding in figure 1. Except for the last case, all of these infections responded rapidly to systemic antibiotic treatment directed against the causative agents.

Fever. Figure 1 shows the relationship between some clinical parameters by superimposition of separate diagrams for the number of patients on the SAM regimen (<500 granulocytes/mm³ most of the time), the number of patients with severe granulocytopenia (<100 granulocytes/mm³), and the number of patients with severe granulocytopenia and fever (axillary temperature, >38 C).
mm³), the number of patients with fever (axillary temperature, >38°C), and the number of patients with fever and infection. During the study, the number of patients with fever decreased from 13 of 39 patients given SAM in the first week to eight of 36 in the third week, although the number of patients with severe granulocytopenia (<100 granulocytes/mm³) increased during that period from 13 of 39 to 26 of 36 patients on the SAM regimen. After the first three weeks, the association between severe granulocytopenia and fever stabilized: about half of the patients on the SAM regimen had severe granulocytopenia, and about 30% had fever. Bacterial infection as the main cause of death was only seen in the first three weeks, although 50% of the patients had <100 granulocytes/mm³ for more than four weeks.

The reduction in fever due to bacterial or fungal infection in severely granulocytopenic patients is shown in detail in figure 2. After the first week, <25% of the patients with severe granulocytopenia had fever due to or probably due to infection.

Mortality. Four patients died as the result of a bacterial infection (table 1). Other causes of death (six patients) were graft-vs.-host disease, noninfectious interstitial pneumonia after total-body irradiation, endogenous viral infection, and bleeding due to persisting bone-marrow failure. None of the patients hospitalized without an initial infection died of a bacterial or fungal infection.

Microbiologic results related to occurring infections. The SAM regimen was not totally successful in the patients who were already infected at hospitalization; only three of 12 patients infected at hospitalization were free of aerobic potential pathogens within one week (tables 2 and 3). In the other nine patients, either a potentially pathogen-free state was not reached (five patients) or a longer period was required to accomplish reduction of pathogens with SAM. Major infections as well as fatal infections were significantly more common in patients who were not free of potential pathogens within one week (P < 0.004; table 2). The persisting, potentially pathogenic aerobic strains (table 3) in particular were involved in infection. These strains persisted although they were sensitive to the antibiotics used in the SAM regimen. They were mainly isolated from oral or skin swabs, often in small numbers and not from all samples.

Comparison of SAM group to control group. The control group consisted of 14 patients whose
microscopy. Because animal experiments and experience with patients have indicated that successful oral implantation of anaerobic flora is possible [15], the effect of reconstitution was only controlled on the basis of fecal smears.

The taste and appearance of the chocolate milk were not distinguishable from those of normal chocolate milk.

Discussion

The data presented in this report were obtained in a trial of SAM in patients with severe granulocytopenia (<100 granulocytes/mm³). Patients with less than seven days of severe granulocytopenia were excluded from the study. Infection at hospitalization was not a reason for exclusion. The effect of SAM was evaluated by comparison of a group of patients who were on the SAM regimen to a control group of patients who were not. For clarity, the SAM group will be discussed as a whole, although the patients with BMT probably had less risk of developing an infection than those with AML or AA because this subgroup had a lower mean age and fewer granulocytopenic days. A reduction in the number of major and fatal infections was accomplished in the SAM group, but this reduction holds when only patients with AML are compared. The meaning of this reduction becomes clearer when it is taken into account that in the SAM group death due to infection occurred within the first three weeks after hospitalization and only in patients who were infected at hospitalization (figure 1). The reduction in the number of days with fever in the SAM patients is consistent with the finding of reduced infectious complications. It must be noted that in the SAM group fever not related to infection occurred more frequently because of complications associated with BMT and treatment with antithymocyte globulin. Therefore, the decrease in the number of days with fever due to infection in the first four weeks of the SAM regimen is remarkable because the number of patients with severe granulocytopenia increased during that time (figures 1 and 2).

The microbiologic results of the SAM regimen correlated with the incidence of infection (tables 2 and 3). A state in which the patient was free of potentially pathogenic aerobic bacteria was less easily achieved when there was an infection at the beginning of the SAM regimen. If a potential pathogen-free state was achieved, the incidence of major infection was relatively low from that time on. In most instances when the SAM regimen was successful, the potentially pathogenic aerobic bacteria (table 3) were definitely eliminated within one week, and the anaerobic flora was not disturbed. The persisting anaerobic flora was probably involved in a few minor infections and one major infection.

Clearly, even when the SAM regimen is successful, vigilance to detect the onset of an anaerobic infection (oropharyngeal and perirectal areas) continues to be very important. Besides the anaerobic flora, *Staphylococcus epidermidis*, *Streptococcus faecalis*, other streptococci, and *C. albicans* persisted. These microorganisms were present in normal or subnormal numbers and were not involved in major infections. Because the persistence of potentially pathogenic aerobic bacteria seems to have been correlated with infection in our patients, we are now inclined to administer a systemic narrow-spectrum antimicrobial agent directed against the persisting strains during a limited time, even if infection cannot be conclusively diagnosed and particularly when the patient has severe granulocytopenia.

It may be that the numbers of anaerobic bacteria were normal because no significant differences were found between the level of anaerobic bacteria in fecal samples of patients on the SAM regimen and those of healthy individuals. Therefore, the risk of severe gastrointestinal complications due to disturbance of the flora [16-20] induced by the antibiotics in the SAM regimen probably is very small. It is not clear why the levels of acetic acid and n-butyric acid in feces were lower in the patient group. Small changes in the patient's bacterial flora, not detectable with the methods we used, may have conceivably contributed to this decrease. On the other hand, decreased appetite due to cytotoxic therapy in the SAM group may have contributed to the reduction of acid in the feces.

Some investigators [7, 8] have suggested that volatile fatty acids are the main factors responsible for the selective inhibition of aerobic and facultative anaerobic bacteria in the intestine. Probably there is competition for nutrients (authors' unpublished observation) that contributes to the selective
inhibition that has been called colonization resistance by van der Waaij and Berghuis [9]. If this hypothesis is correct, one might expect that the colonization resistance of patients on the SAM regimen would not be dramatically reduced because both volatile fatty acids and large numbers of anaerobes were demonstrated in fecal samples of patients on the SAM regimen. Indeed, the microbiologic condition of most of the SAM patients was stable; overgrowth with multiresistant, potentially pathogenic aerobic microorganisms did not occur except in the two patients with AA hospitalized with septicemia who were completely colonized by P. aeruginosa before the SAM regimen was started.

Most of the patients tolerated the SAM regimen rather well. Complaints of a bad taste or nausea were mild, and difficulty in swallowing the antibiotic capsules or nalidixic acid tablets mainly occurred during periods of intensive cytotoxic treatment.

As a result of the reduction in isolation measures, most of the patients felt relatively comfortable. There was no indication, with exception of the two patients with exogenous P. aeruginosa infections on the skin, that the reduced isolation measures had an unfavorable effect on the bacteriologic or clinical results. These two cases of P. aeruginosa infections had probably originated from small lesions on the skin of the foot, which became contaminated while the patients were showering. Since that time disinfection of the shower has been included in our isolation measures. The extent to which further reduction of isolation is permissible is difficult to determine. Dietrich et al. [21] demonstrated a reduction in pulmonary infection in isolated patients; remarkably, none of our patients in the SAM group developed a bacterial or fungal pulmonary infection after hospitalization.

Although there have been many trials of infection prevention, the outcomes of several large-scale, prospective, controlled studies [21–23] were not consistent, and further studies have been undertaken in other centers. If stringent methods such as strict protective isolation and total antimicrobial modulation (with or without systemic antibiotics) are to be recommended, there must be proof not only that the clinical effect is favorable, but also that unfavorable effects such as discomfort, psychological stress [24, 25], nausea, and costs are in proportion to the final prolongation of survival. Probably the benefit of strict infection-control procedures will be hard to show for patients with a poor prognosis, like those with AML. On the basis of divergent arguments, several other centers continued clinical research in this field, resulting in very aggressive methods of infection prevention [26] or more moderate methods similar to the SAM regimen [27–29]. The SAM regimen seems to be an adequate method for infection prevention in our hospital, but it remains to be proven that SAM can have the same favorable effect in hospitals with restricted facilities for protective isolation and bacteriologic control.

References


