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Selective Antimicrobial Modulation of the Intestinal Microbial Flora for Infection Prevention in Patients with Hematologic Malignancies

Evaluation of Clinical Efficacy and the Value of Surveillance Cultures

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To confirm the results obtained in an earlier study, the incidence of infection was evaluated in 54 patients (62 periods of admission), nursed in conventional rooms and given a regimen of antimicrobial agents intended to modulate the intestinal flora selectively as a method to prevent infection during severe granulocytopenia. In 62 patients receiving selective antimicrobial modulation (SAM), 18% acquired major infections which was similar to 19% in patients on SAM in an earlier double-blind placebo controlled study and lower than 47% in the controls. Evaluation of a large number of surveillance cultures showed that the presence of specific potentially pathogenic aerobic bacteria was associated with the occurrence of major infection. If the bacterial species in question were not found in the cultures the chance of becoming infected was <5%, whereas the chance ranged between 42 and 62% depending on the species involved when these microorganisms were isolated.

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INTRODUCTION

Since the results of a double-blind placebo controlled study (1) on the effect of our regimen for selective antimicrobial modulation (SAM) in patients with acute myelogenous leukemia (AML) had shown that a reduction of the incidence of infection could be obtained with this treatment, it was decided to administer SAM routinely to all patients admitted to our hospital who were at risk of becoming severely granulocytopenic. Two years later, we wanted to know whether the incidence of infection among such patients was still of the same order of magnitude as that in the group of patients on SAM during the preceding study. To this end we compared the results obtained with SAM during the placebo controlled study (September 1977 to October 1981) and the follow-up study (October 1981 to January 1983). We also used the large series of bacteriological data to re-evaluate suggestions concerning the value of surveillance cultures, we had put forward in an earlier report (2). The usefulness of these cultures, either as a guide for changes in prophylactic measures or for the selection of antimicrobial drugs for treatment has been a controversial subject (3–7). Because of the high costs of this accessorrial procedure, the collection of more data in this field is a matter of prime importance.

PATIENTS AND METHODS

The patients involved, all adults at risk of becoming extremely granulocytopenic due to an underlying hematologic disorder and/or the appropriate remission induction therapy, were admitted to the Department of Internal Medicine of the University Hospital of Leiden between October 1981 and January 1983.
All patients were given SAM prophylaxis consisting of 4 capsules containing a mixture of neomycin, polymyxin B, and amphotericin B, given 4 times daily, and 1 tablet of nalidixic acid, given twice daily. The total dosage administered daily was 1 g neomycin, 1 g polymyxin B, 2 g nalidixic acid, and 400 mg polymyxin B. All patients were topically treated in the nose with a cream containing 0.5% neomycin and 0.1% chlorhexidine hydrochloride to prevent carriage of Staphylococcus aureus. No other topical antiseptics were used. Most of the patients were put on SAM within a few days after admission as soon as their granulocyte count dropped below 500/μl. SAM was withdrawn when the count rose above 500/μl and no further hematologic therapy was given, or if the attending physicians judged continuation useless on clinical or psychological grounds.

Protective isolation. The patients were nursed in conventional single-bed rooms and were only permitted to leave the room for examination elsewhere in the hospital or for a few days’ stay at home between 2 courses of cytostatic therapy. During the interim period the SAM regimen was continued at home. The patients were given conventional hospital food (1).

Definition of infections. Infections were classified as bacterial, fungal, viral, and protozoan. The bacterial and fungal infections were divided into minor infections (clinically manifest infection of the skin or mucosa without extension to the blood, deep tissue, or organs), and major infections (clinically manifest infection of deep tissue, or organs and septicaemia). Infections were called doubtful if the diagnostic procedures did not give conclusive results and no response to antimicrobial therapy was observed.

Acquired infections were defined as infections in which the first clinical signs appeared after the first week on SAM.

Management of infection. Systemic antibiotic treatment was not instituted until an infection was seriously suspected or proven (1). The choice of antibiotics was governed by the site of the infection and the suspected causative microorganisms. Whenever possible, antibiotic therapy was adjusted on the basis of the results of bacteriological investigation.

Fever. Each day on which a patient’s axillary body temperature was at least ≥38°C, was defined as a day with fever.

Granulocytopenic episodes. A period of 2 or more successive days with peripheral blood granulocyte counts of ≤100/μl was defined as a period of severe granulocytopenia. Each period of admission was split into episodes in which the granulocyte counts were ≤100/μl or >100/μl.

Bacteriological investigations. Bacteriological surveillance included cultures of feces and swabs taken from the nares, and the oropharyngeal, axillary, genitourinary, inguinal, and perineal regions. The samples were collected once a week on a fixed day, and plated on routine media (8). Each culture yielding an isolate belonging to the Enterobacteriaceae, Pseudomonas aeruginosa, and S. aureus, was considered positive for specific potentially pathogenic microorganisms (SPPM). The SPPM cultured from the surveillance cultures were stored at −20°C. In cases with a microbiologically proven infection, the SPPM strain involved was typed and compared with the related strain isolated from surveillance cultures. Enterobacteriaceae were biochemically typed (8) in addition to the determination of morphologic characteristics and sensitivity patterns (disc diffusion tests). P. aeruginosa and S. aureus were sent to the central laboratory for microbiology in the Netherlands (The National Institute of Health and Environmental Hygiene, Bilthoven) for typing by phage reactions and serologic and biochemical characteristics. Each granulocytopenic episode during which SPPM were cultured were called “SPPM-positive”.

RESULTS

Efficacy of SAM

Of 60 patients given SAM, 6 patients were excluded because their risk to become extremely granulocytopenic was overestimated and as a result they had received SAM for less than 14 days, which was considered too short for reliable assessment of the prophylactic efficacy. Most of the evaluable 54 patients had been treated for acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL) in relapse, chronic lymphoblastic leukemia (CLL) in blast crisis and severe aplastic anemia (Table I). Seven patients (miscellaneous, i.e. hairy-cell leukemia, non-Hodgkin’s lymphoma) were at least at less serious risk because they had only had a few days with a granulocyte count ≤100/μl. Six patients had been admitted twice and one 3 times, with breaks of at least one month. Thus, 62 periods of admission of these 54 patients were evaluated, representing 2294 days on
Table I. Patient characteristics and state of disease

AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia (blast crisis); AA = aplastic anemia; Miscellaneous: 2 patients with hairy-cell leukemia, and 5 patients with non-Hodgkin's lymphoma

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients (admissions)</th>
<th>Mean age, yrs (range)</th>
<th>Remission upon hematologic therapy yes/no</th>
<th>Mean no. of days with granulocytes ≤100/μl</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>43</td>
<td>45 (18–72)</td>
<td>26/17</td>
<td>25</td>
</tr>
<tr>
<td>ALL</td>
<td>5</td>
<td>45 (20–68)</td>
<td>4/1</td>
<td>17</td>
</tr>
<tr>
<td>CLL</td>
<td>3</td>
<td>61 (56–66)</td>
<td>1/2</td>
<td>22</td>
</tr>
<tr>
<td>AA</td>
<td>4</td>
<td>42 (20–50)</td>
<td>1/3</td>
<td>24</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>7</td>
<td>38 (18–61)</td>
<td>7/0</td>
<td>9.5</td>
</tr>
</tbody>
</table>

SAM prophylaxis. The total number of days of severe granulocytopenia (≤100/μl) was 1240, which amounts to a mean of 20 days per period of admission. 35 bacterial infections were diagnosed (Table II), 23 of which were acquired (12 minor infections, 11 major infections). The acquired major infections were septicemia with gram-negative rods in 7 patients, septicemia with S. aureus in 2 patients, and bacteremia associated with rectal abscesses (Streptococcus faecalis) or infiltration (β-hemolytic streptococci) in 2 other patients. In 5 patients, minor viral infections were observed, i.e. herpes simplex of the lip and oral cavity, and viral tonsillitis. No fungal or protozoan infections were diagnosed. In 7 patients the clinical condition seemed consistent with infection, but convincing evidence could not be found (doubtful infections). Eight patients died shortly after the period on SAM. All of them had been refractory for hematological therapy, and continuation of SAM was judged to be useless. In 3 of these 8 patients infection contributed to death (2 patients with S. aureus infection and 1 patient with S. aureus in combination with P. aeruginosa).

Comparison of the results of the follow-up and the placebo controlled study

Comparison of the results of the present retrospective follow-up study, performed during the period between October 1981 and January 1983, and those of the placebo controlled study

Table II. Occurrence of infections in the present study and the placebo-controlled study (data from reference 1)

<table>
<thead>
<tr>
<th></th>
<th>Present study</th>
<th>Placebo-controlled study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAM</td>
<td>Placebo</td>
</tr>
<tr>
<td>No. of patients</td>
<td>62</td>
<td>16</td>
</tr>
<tr>
<td>No. of days/patients with granulocyte counts ≤100/μl (range)</td>
<td>20 (0–82)</td>
<td>14 (0–31)</td>
</tr>
<tr>
<td>Infections*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of infections</td>
<td>35 (56%)</td>
<td>10 (62%)</td>
</tr>
<tr>
<td>Total no. of acquired infections</td>
<td>23 (37%)</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>No. of major acquired infections</td>
<td>11 (18%)</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>No. of major acquired infections with SPPM</td>
<td>9 (14%)</td>
<td>1 (6%)</td>
</tr>
</tbody>
</table>

* Within brackets: the percentage of patients infected
The results of surveillance cultures were also quite similar to those of the first study (1). The cultures of fecal samples showed SPPM only occasionally (Fig. 1); most of these

study performed between September 1977 and October 1981 shows that the results of SAM for both studies are similar (Table II). Thus, despite the longer period of granulocytopenia (<100/μl) in the patients of the follow-up study, a 50% reduction of the incidence of infections was obtained, relative to the placebo group of the former study.

Surveillance cultures and infection

Each dot represents a SPPM-positive culture being either from feces, or a skin swab (perineum, groins, axillae, vulva or prepuce) or an oral swab.

Fig. 1. Results of surveillance cultures. Each bar refers to a period of admission of 1 patient. Each dot represents a SPPM-positive culture being either from feces, or a skin swab (perineum, groins, axillae, vulva or prepuce) or an oral swab.
microorganisms being transient and all of them sensitive to at least one of the SAM drugs. SPPM were cultured regularly from the skin, i.e. axillary, genitourinary, and perineal areas; however, the oral cavity gave the highest yield. Not only transient gram-negatives and S. aureus were found there, but SPPM often persisted longer.

To examine the association between SPPM found in surveillance cultures and infections, each period of admission was divided into successive days with granulocyte counts above or below 100/µl. If SPPM were shown in the surveillance cultures during these periods the period was called "SPPM-positive".

No association was found between the occurrence of infection and the results of surveillance cultures during periods with granulocyte counts >100/µl, since there was only 1 case of infection of any importance, i.e. an axillary abscess. For periods with granulocyte counts ≤100/µl, there seemed to be an association. Of 38 granulocytic episodes with SPPM-positive surveillance cultures, 26 (68%) were associated with infection, versus 10 (35%) of 29 granulocytic episodes with surveillance cultures SPPM-negative ($\chi^2=7.62, p=0.06$). With respect to the microorganisms responsible for infections, it was found that infections with Enterobacteriaceae, P. aeruginosa and S. aureus occurred most frequently in patients with SPPM-positive surveillance cultures (Fig. 2). The incidence of infection with other microorganisms, such as streptococci and S. epidermidis, was similar for the granulocytic episodes with SPPM-positive surveillance cultures and those which were SPPM-negative (Fig. 2).

About 70% of the infections with SPPM were major infections versus 10% for infections with other bacteria (Fig. 2). With respect to the species, it was found that the presence of one species of the SPPM in surveillance cultures was often associated with infection caused by the same species (Table III). For example, S. aureus was found in the surveillance cultures of 23 patients during periods of severe granulocytopenia, and was not found in those of the other 39 patients, whereas infection with S. aureus occurred in 48% of the former versus 5% of the latter. This means a probability (95% confidence interval) to acquire infection with S. aureus between 27 and 69% for patients with positive surveillance cultures and between 0.6 and 17% for those with negative cultures. 62% of the patients with surveillance cultures positive for P. aeruginosa developed an infection with this species versus 2% for those negative for it. The probability (95% confidence interval) to acquire infection with P. aeruginosa lies between 25 and 91% if these bacteria are present in surveillance cultures; if not, the probability to acquire infection lies between 0 and 10%. Similar results were obtained for
Table III. Association between individual isolates of SPPM found in surveillance cultures and occurring in infections
Figures within brackets: acquired infections

<table>
<thead>
<tr>
<th>Surveillance cultures positive for</th>
<th>Patients with infections</th>
<th>Site of infection</th>
<th>Oral cavity</th>
<th>Skin</th>
<th>Pneumonia</th>
<th>Septicemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>12</td>
<td>6 (2)</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>3</td>
<td>1 (1)</td>
<td>1</td>
<td></td>
<td>3 (2)</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>11</td>
<td>1</td>
<td></td>
<td>2</td>
<td>5 (4)</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* One infectious episode with S. aureus and P. aeruginosa

species of Enterobacteriaceae; i.e. 42% of the patients with positive surveillance cultures acquired infection with these bacteria, versus 2% of the patients in those which were negative. The corresponding probabilities to acquire infection lies between 20 and 66% for the positive surveillance cultures and between 0 and 12% for the negatives.

In 13/28 of these infections, the association between presence in the surveillance cultures and infection was considered to be extremely clear because of the conformity between typing results of SPPM cultures from surveillance cultures and from the infection. One case report is given as an example below.

CASE REPORT

On August 13, an ulcerative lesion developed in the oral cavity of a 62-year-old patient being treated for AML. On August 23 and September 1 and 9, P. aeruginosa was cultured from oral swabs. The patient was not given local antimicrobial treatment in the oral cavity. On September 1, 4, 6, and 9, P. aeruginosa was cultured from the blood. All typing characteristics of these isolates were identical.

DISCUSSION

Patients and infection

The differences observed in a double-blind placebo controlled study on the prophylactic effect of SAM in patients suffering from AML (1) were significant, and the order of magnitude of reduction of the incidence of infection due to SAM seemed to be appreciable. However, the 95% confidence interval was 28%±30% (1), which means that the real effect of SAM on the incidence of acquired major infection might range from a minimum of -2% difference with the control group to a maximum of 58% difference. Thus, the substantial order of magnitude of the reduction of the incidence of infection we found in the patients given SAM might be fortuitous. The follow-up study presented in this paper was therefore performed to test the order of magnitude of the reduction.

The results show an 18% incidence of major acquired infection in 62 patients given
SAM. This is close to the results obtained in the placebo controlled study, where the incidence in 16 patients on SAM was 19%. The patients of the follow-up study were a heterogeneous group in contrast to the controlled study, but most of them were treated with the same antileukemic regimens for AML as those in the first study. Because the number of days with granulocyte counts $\leq 100/\mu l$ per patient was higher in the follow-up study than in both arms of the former study, we feel that SAM can give an appreciable reduction of acquired major infections.

**Surveillance cultures and infection**

The additional care given to patients with severely decreased host resistance is accompanied by high costs. Therefore, it is important to assess the benefit of each of the accessorrial procedures. One of the questions to be answered is whether it is valuable to perform surveillance cultures and, if so, how often and from what sites. The benefit of these cultures whether for the alteration of prophylactic measures or for the choice of antimicrobial drugs for therapy is still a subject of controversy (3–7). Our results show that most SPPM were isolated from cultures of oral swabs. This is not surprising since the patients were nursed in single rooms, fed normal hospital food and were not given local antimicrobial treatment in the oral cavity. It is reasonable to assume that under these conditions microorganisms can easily colonize the oral cavity, whose mucosal surfaces are affected by cytotoxic therapy (9), whereas in the lower parts of the digestive tract these microorganisms are eliminated by the antimicrobials of SAM and the additional effect of colonization resistance (10–12). Indeed, the number of SPPM found in feces were small. On the skin SPPM were present more often, but probably the skin is less sensitive to the cytotoxic treatment leaving its natural defense capacity in part unaffected.

No correlation was found between SPPM-positive surveillance cultures and infection during episodes of granulocytopenia as long as the number of granulocytes was higher than 100/µl, but the opposite was found during episodes of extremely low granulocyte counts ($\leq 100/\mu l$). The high incidence of infection with SPPM species cultures from oral swabs indicates that these cultures are important.

Whether the results of surveillance cultures should be taken into account in clinical practice may depend on several other factors, e.g. the patient's condition, granulocyte counts, the site of lesions or pain, the presence of fever, etc. All diagnostic data and the patient's recent history (e.g. the kind of infections during previous therapy) may contribute to the decisions. It must be kept in mind that even if the surveillance cultures are SPPM negative, in a small number of patients infection with SPPM may still occur. We have the feeling that in these cases the infections are often already present, either not yet clinically manifest or in a "closed" system (e.g. persisting soft-tissue infection), that prevents the bacteria in question from reaching the sites from which samples are taken for surveillance cultures.

The conclusion drawn from the present study is that the findings of surveillance cultures must be taken into account, either for additional prophylactic measures or for the treatment of infection.

**REFERENCES**


