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Selective Antimicrobial Modulation of the Intestinal Flora

Prophylaxis against Infection in Neutropenic Patients

In the last twenty years, cytotoxic regimens for the treatment of neoplastic diseases have become more and more aggressive. Because anti-neoplastic drugs lack specificity, the undesirable side-effects (bone marrow aplasia and mucosal damage) have become more severe. The price of the attempts to improve the rates of remissions by aggressive therapy has been paid, especially in bacterial and fungal infection. As a result, attention was directed to prevention of these infections. Sophisticated facilities for clinical protective isolation were developed in the late fifties and early sixties, with the isolation techniques used for germ-free animals being taken as the model. At first, single rooms (1) and plastic isolators (2-4) were used. Some years later, the laminar flow isolation systems were introduced (5). Protective isolation only prevents infections with exogenous micro-organisms; but as a rule, many opportunistic micro-organisms are present in the patient's endogenous micro-flora and can cause life-threatening infections in patients with decreased host defence. To solve this problem, protective isolation was soon combined with "antibiotic decontamination", i. e. the elimination or suppression of the micro-flora on the skin and mucosal surfaces with poorly resorbable antimicrobial agents administered orally.

One of the first prospective randomized controlled studies on protective isolation and antibiotic decontamination was done by Levine et al. (6) who compared patients with acute leukemia during remission-induction therapy randomly allocated to three groups: one given oral non-absorbable prophylactic antimicrobial agents and nursed in protective isolation (laminar air-flow rooms), one given the same antimicrobials but without isolation and a control group given neither prophylactic antimicrobials nor isolation. The decontamination regimen consisted of gentamicin, vancomycin and nystatin, and was aimed at complete eradication (total antibiotic decontamination = TAD) of the endogenous flora. Only the group of patients given prophylactic antimicrobials in a protective environment did better than the controls in terms of reduction of infection. Although the results of this study were conclusive concerning infection prophylaxis, the authors were reluctant to make recommendations for the routine use of prophylactic antimicrobials and a protective environment. They stated that only a few patients would profit from the prophylactic measures in terms of prolonged survival. Most patients either would not develop an infection, or infection would not be life-threatening when the patient was given adequate antimicrobial therapy. For the patients who did not respond to haematologic therapy,

the outcome would not be determined primarily by antimicrobial therapy or prophylaxis. Moreover, as Levine pointed out, the prophylactic measures might interfere with anti-tumour agents (7) and granulocyte recovery (8), and they are demanding for both the patients and the clinical staff. Thus, the actual benefit might be smaller than at first glance.

A number of other studies have confirmed the findings of Levine et al., i. e. TAD and protective isolation are effective in preventing infection, but not in improving remission rates or survival (9-11). Schimpff et al. (12) and Rodriguez et al. (13) reported a reduction of the incidence of infection and, in addition, an improved remission rate. However, the same objection holds for both studies, i. e. the patients given antimicrobial prophylaxis and the controls were not given the same anti-leukemic treatment. Fundamentally, prevention of bacterial and fungal infections in granulocytopenic patients can be realized at two levels: either *systemically* by applying infused granulocytes or antimicrobial agents, or *locally* by reducing the numbers of pathogenic micro-organisms on the mucosal surfaces and skin by applying nonabsorbable antimicrobial drugs and disinfectant agents. All of these methods have specific fundamental and practical advantages and drawbacks. Prophylactic granulocyte transfusion entails the risk of sensitization of the patient to future granulocyte and platelet transfusions (14) and the risk of pulmonary leukostasis and cytomegalovirus infection (15). Prophylactic systemic antimicrobial treatment involves the risk of the selection of resistant micro-organisms, as well as exposure to side-effects. Local treatment of the mucosal surfaces and skin with antimicrobial drugs and disinfectants intended to eradicate all colonizing micro-organisms (i. e. TAD) also involves the risk of selection of resistant micro-organisms, but in addition, the patient's compliance is a crucial factor. Once all of the micro-organisms have been eliminated, recolonization of the integument has to be prevented by nursing the patient in a sterile environment (protective isolation) and restricting his diet to sterile food. The practical application of TAD has proved to be difficult, the main drawbacks being failure to achieve a germ-free state, high costs, poor patient compliance and psychological stress due to isolation (16). These factors led to the development of

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another strategy for prophylaxis designed to circumvent the objectionable aspects of TAD.

It has proved possible to eliminate or suppress only those micro-organisms most frequently involved in infection and to preserve the anaerobes. Bodey et al. (17) showed that 90% of the severe infections in leukaemic patients are caused by aerobic and facultative anaerobic bacteria (*Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*) and *Candida* spp., whereas the anaerobes are relatively harmless. If these potentially pathogenic bacteria can be selectively eliminated, a significant reduction of acquired infections can in principle be expected. The advantage of this selective method is that due to the preservation of the anaerobic flora, the colonization resistance (CR) is not substantially disturbed. The term colonization resistance introduced by van der Waaij (18), refers to the resistance micro-organisms must overcome before they can colonize the body surfaces. A complex of factors, including host and microbial factors, help to hamper colonization by potentially pathogenic aerobic bacteria. Among the latter, the anaerobes of the large bowel exert a growth-controlling effect on aerobic and facultative anaerobic bacteria, probably via competition for nutrients (19). It has been shown that mice are more susceptible to oral challenge with *Salmonella* (20) if the intestinal flora has been disturbed by treatment with high doses of streptomycin. Ampicillin-treated mice are readily colonized by ampicillin-resistant gram-negative rods (18). Partial replacement of the endogenous micro-flora by resistant strains is also seen in hospitalized patients treated with broad-spectrum antimicrobials (21, 22).

The approach provided by selective elimination of the potentially pathogenic aerobic bacteria is called selective antimicrobial modulation (SAM) (synonyms: selective decontamination (SD) and, in our hospital, partial antibiotic decontamination (PAD). Compared with TAD, SAM might demand less stringent criteria for protective isolation. The fundamental aim of SAM is not to prevent all infections, which has been shown to be almost impossible with TAD, but to improve the cost-benefit ratio by reducing the number of serious infections at lower costs and with less effort.

Initially, SAM was studied in mice and monkeys (23). In recent years, interest in the use of SAM for patients with decreased host defence has been increasing. One of the first pilot studies explicitly designed to assess the application of SAM in man was published in 1977 (24). This report concerns nine patients with acute leukaemia or aplastic anaemia given an oral prophylactic regimen comprising a low-dose combination of neomycin, polymyxin B, nalidixic acid and amphotericin B, given orally. This regimen eliminated aerobic gram-negative rods from the intestinal microbial flora without appreciably disturbing the anaerobes (25). In 1979, Gurwith et al. (26) reported a prospective controlled study in which granulocytopenic patients given co-trimoxazole for prophylaxis were compared with patients without prophylaxis. Although the

study was not designed to assess the effect of a selective regimen, it showed that it is not obligatory to eliminate the anaerobes to obtain a significant reduction of infectious complications. In the same year, Bender et al. (27) published a prospective controlled study on the role of vancomycin as a component of an oral non-absorbable prophylactic antimicrobial regimen, with the idea that it might be advantageous to preserve the intestinal microbial ecology by the omission of vancomycin from the combination vancomycin, gentamicin, nystatin. Actually, Bender and his colleagues were the first to compare TAD (vancomycin, gentamicin, nystatin) with a kind of SAM (gentamicin, nystatin), and the results led them to conclude that SAM might be superior to TAD. Neither Guiot et al. (28) nor Sleijffer et al. (29), both sets of authors representing the Dutch groups that provided the initial impetus for the clinical use of selective prophylactic regimens, compared the effect of total and selective decontamination. They only assumed that SAM would be superior to TAD in terms of costs and the burden on both patients and nursing staff. Kurrle et al. (30) published a retrospective analysis of 50 totally decontaminated and 50 selectively decontaminated patients with acute leukaemia. The main conclusion drawn from this study was that in the TAD group most of the acquired infections were caused by aerobic gram-negative rods, whereas most of the infections in selectively decontaminated patients were caused by gram-positives. The incidence of infection was similar in the two groups, but the infections were less severe in the SAM group, as expressed by a reduction of the number of days with infection and days with fever. Kurrle et al. found that SAM without isolation was at least as effective as TAD with strict protective isolation.

The delicate micro-ecological balance of colonization resistance has often been mentioned as a limitation for successful selective decontamination. If infection occurs despite prophylactic measures, the patient must be treated systemically with antimicrobial drugs, and in many instances the drug of choice may disturb the intestinal anaerobic flora. This might mean that SAM is only effective in hospitals with a restrictive antimicrobial policy, and not in centres whose policy is to treat all patients suffering from a febrile granulocytopenic episode with a combination of high-dose broad-spectrum antimicrobial drugs. The risk of impairing colonization resistance can be partially avoided by selecting antimicrobial agents that do not affect the CR (31), by administering the antimicrobials intravenously and, if necessary, by restoring the anaerobic flora. This may be achieved by administering non-pathogenic faecal flora orally after treatment of the infection has been completed (25).

At present, two main trends can be distinguished in selective gut sterilization: the regimens based on non-absorbable multiple drugs, which are active locally in the lumen of the digestive tract, and regimens with co-trimoxazole (32), which is absorbable and therefore active both locally and systemically. Three aspects have to be taken into ac-

count here: the prophylactic efficacy, the unwanted side-effects and the costs. It seems probable that the non-absorbable multiple-drug regimens are less well tolerated and more expensive than co-trimoxazole as a "single" drug, but the former might be more effective in the elimination of potentially pathogenic bacteria from the intestinal mucosal surfaces. The differences between the two types of regimens with respect to both tolerance and costs is reduced by adding polymyxin B to co-trimoxazole to deal with *Pseudomonas* species, amphotericin B as an antifungal drug and folinic acid to diminish the chance of inhibition of bone marrow function by co-trimoxazole. This increases both the amount of drugs to be swallowed and the costs to approximately those of the SAM regimen used in our hospital, which consists of a combination of neomycin, polymyxin, amphotericin and nalidixic acid in low dosages (28). Although nalidixic acid is well absorbed, its systemic effect is negligible due to its pharmacokinetic properties (33) and, therefore, in this context the Leiden regimen is considered as non-resorbable and only active locally in the lumen of the intestinal tract.

The most striking difference between our regimen and co-trimoxazole as a single drug concerns the occurrence of resistant strains. Several reports have been published on infections associated with the selection of micro-organisms resistant to co-trimoxazole during prophylaxis (32, 34, 35). Neither selection of, nor infection with, bacteria resistant to the combination of antimicrobial drugs in our SAM regimen has been observed so far. Plasmid- or chromosome-mediated resistance to trimethoprim and/or sulfamethoxazole (36) might become a problem if co-trimoxazole is used prophylactically on a large scale in the future. The problem of the acquisition of resistant strains can be partially solved by adding another antimicrobial drug, e.g. polymyxin B, to co-trimoxazole. Even then, however, after resorption of co-trimoxazole, low concentrations of the drug excreted in saliva, urine and exudates of wounds (e.g. an intravenous catheter tract) can provide suitable conditions for recolonization with bacteria resistant to the drug. Unlike co-trimoxazole, the antimicrobial agents of the Leiden regimen are not commonly used for therapy, and therefore selection of resistant micro-organisms, if any, will not lead to the loss of a useful drug.

A fundamental difference between resorbable and non-resorbable drug regimens is that part of the reduction in the incidence of infection obtained with the former may be attributable to the early treatment of infection. This might be seen as a favourable aspect of co-trimoxazole prophylaxis. However, it is also possible that the systemic effect of co-trimoxazole has adverse aspects, i.e. blind, inadequate treatment of infection and delayed diagnosis (37, 38). Infection not yet clinically manifest might be even better treated with the drugs appropriate for the suspected micro-organisms. A detailed anamnesis, a thorough physical examination and other diagnostic procedures may yield information concerning the kind of mi-

cro-organisms most probably involved, and the results of surveillance cultures may assist decision-making. A recent evaluation of about 60 selectively decontaminated patients (to be published) showed that the occurrence of infection and the micro-organisms responsible can be predicted on the basis of the outcome of surveillance cultures. During periods of severe granulocytopenia, a correlation was found between colonization with – or persistence of – potentially pathogenic bacteria and the occurrence of infection. Thus, early treatment of infection does not have to be intrinsically blind.

Recently, Kurrle et al. (39) published the results of a study comparing the two regimens described above, i.e. the Leiden SAM regimen versus co-trimoxazole-polymyxin B. No differences were found in the number of serious acquired infections, but it was shown that the interval after which 50% of the patients had acquired new infections was shorter for patients on PAD than for those on co-trimoxazole-polymyxin B. Mainly for this reason, the authors suggested that the latter regimen might be slightly preferable to the former. It must be kept in mind, however, that this is only a suggestion and not an established truth, because it ignores the secondary aspects discussed above, which are of importance for decision-making.

The increasing interest in SAM has led the pharmaceutical industry to invest research funds in this field. It is to be expected that new antimicrobial drugs, such as norfloxacin and ciprofloxacin, will soon be evaluated for this purpose.

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