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Selective decontamination in neutropenic patients

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INTRODUCTION

It is well known that severe neutropenia, as usually seen in patients with acute leukaemia, aplastic anaemia or secondary to aggressive chemotherapy, predisposes to infections with Gram-negative enteric bacilli, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and to fungal infections. Infection with anaerobes, in contrast, is rare in patients with haematologic malignancy [1]. The spectrum of bacterial pathogens in this patient population has recently broadened, and now includes coagulase-negative staphylococci, viridans group streptococci, and, occasionally, coryneforms and other rather unusual opportunistic organisms. All these microorganisms originate either from the patient's own microflora, especially from the digestive tract, or from the hospital environment after having colonized the patient during the hospital stay [2]. Studies have shown that the incidence of fever during periods of severe neutropenia approaches 100%, and most of these fever episodes actually represent bacterial infection. For more than 20 years, methods for the prevention of bacterial and fungal infections have been under investigation in patients with profound neutropenia. These included decontamination trails, oral or systemic antimicrobial prophylaxis, strict reverse isolation and maintenance of germ-free conditions [3–8], prophylactic granulocyte transfusions [9], and, more recently, the application of haemopoietic growth factors [10, 11]. The method which remains the most widely used is oral antimicrobial prophylaxis, especially with agents for so-called selective decontamination of the intestinal tract.

PRINCIPLES OF SELECTIVE DECONTAMINATION

The human microflora of the digestive tract is mainly composed of anaerobic bacteria. The aerobic flora which comprises the potentially pathogenic microorganisms relevant for infections is of minor concentration, though of primary clinical relevance. Therefore, it seemed to be a logical consequence to suppress only the aerobic flora of the digestive tract, including yeasts, for the prevention of infections. There was also some evidence from experimental animal studies reported by van der Waaij [12] that an intact anaerobic flora may prevent the colonization of the intestinal tract with exogenous potentially pathogenic microorganisms. Antimicrobial therapy that leaves the anaerobic flora intact should maintain the so-called colonization resistance of the host. These

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Table 1. *Oral antimicrobial agents commonly used for selective decontamination in neutropenic patients*

Antibacterials, non-absorbable	polymyxin B colistin neomycin gentamicin
Antibacterials, absorbable	trimethoprim-sulphamethoxazole nalidixic acid norfloxacin ciprofloxacin ofloxacin
Antifungals	nystatin amphotericin B

considerations led to the concept of 'selective decontamination' (SD) also called 'selective decontamination of the digestive tract', 'partial antibiotic decontamination' or 'selective antimicrobial modulation'. The aim of SD is to reduce the risk of infection in neutropenic patients by the suppression or elimination of aerobic potentially pathogenic microorganisms from the digestive tract, especially of Enterobacteriaceae, *Pseudomonas* species, staphylococci, and yeasts, without affecting the anaerobic flora.

An important step for the clinical application of SD was the identification of antimicrobial drugs which might fulfil the microbiological prerequisites. These drugs should only suppress aerobic potentially pathogenic microorganisms and have no, or only minor, influence on the anaerobic flora. Such properties were found with a variety of oral agents (Table 1) [13–25]. Some of these agents, notably trimethoprim-sulphamethoxazole and the newer quinolones, are not only active in the gastro-intestinal tract. They are well absorbed, have a systemic antibacterial activity, and are excreted in saliva, sputum and urine. For antifungal prophylaxis polyenes (nystatin, amphotericin B) or, more recently, ketoconazole and fluconazole have been added.

Newer fluorinated quinolones are the most recently studied agents used for SD in neutropenic patients. Their antimicrobial spectrum makes this class of antimicrobial drugs of special interest for SD. Nalidixic acid was employed in early studies of SD, [26–28]. When the newer quinolones such as norfloxacin, ciprofloxacin and ofloxacin became available this group of drugs was tested for application in SD. Studies in healthy volunteers and in patients indicated that quinolones readily eliminate Gram-negative aerobic bacilli from the digestive tract. The anaerobic flora appeared only little affected and there was no overgrowth by yeasts [18–25].

CLINICAL TRIALS OF SELECTIVE DECONTAMINATION

The clinical efficacy of SD for the prevention of infection in severely neutropenic patients has been studied in numerous trials. In a first series of prospective randomized studies SD was compared to control groups which received no measures of infection prevention. Most of these studies were performed in patients with acute leukaemia. Some of these trials also included patients with other

Table 2. *Effect of selective decontamination on the incidence of fever episodes and infection in patients with severe neutropenia. Results of randomized studies*

Author (reference)	Number of patients	Prophylactic drugs*	Diagnosis	Incidence of fever and infection (% of untreated control groups)
Hughes [29]	160	TMP/SMZ	AL and others	52
Gurwith [30]	111	TMP/SMZ	AL and others	37
Sleijfer [26]	113	TMP/SMZ or NA or colistin	AL and others	39
Weiser [31]	14	TMP/SMZ	AL	95
Dekker [32]	52	TMP/SMZ	AL	57
Guiot [27]	33	NA + colistin + neomycin	AL	61
Kauffman [33]	55	TMP/SMZ	AL and others	97
Gualtieri [34]	47	TMP/SMZ	AL and others	74
de Jongh [35]		TMP/SMZ	Lung cancer	38
Estey [36]	147	TMP/SMZ	AL	63
EORTC [37]	139	TMP/SMZ	AML	75
	203	TMP/SMZ	Other	52
Henry [38]	43	TMP/SMZ	AL	100
Karp [39]	68	Norfloxacin	AL	100
Hartlapp [40]	42	Ofloxacin	Testicular cancer	19

* TMP/SMZ: trimethoprim/sulphamethoxazole, NA: nalidixic acid, AL: acute leukaemia.

haematological malignancies and with solid tumours who were given intensive chemotherapy. Fourteen major prospective randomized studies have been published to date, the results of which are summarized in Table 2. The interpretation and comparison of the data of these studies are rather difficult, since these studies differed in the selection of patients, in the antibacterial and antifungal regimens, and in the definitions of fever episodes and infections.

In the study of Sleijfer and colleagues [26] the antibacterial drugs used for SD, i.e. trimethoprim-sulphamethoxazole, nalidixic acid or colistin, were selected according to the *in vitro* susceptibility of the bacteria isolated from the digestive tract of individual patients. This procedure significantly reduced the incidence of all infections to 39% as compared to the untreated control group. In all other trials fixed drug regimens were studied. Trimethoprim-sulphamethoxazole was applied in ten studies [29–38]. Six of these studies showed a significant reduction of the risk of all infections and fever episodes to 38–63% as compared to the control groups. In the trial of the EORTC a significant reduction of infection could not be demonstrated in patients with acute non-lymphocytic leukaemia but could with other diseases [37]. In three studies SD failed to reduce the overall incidence of febrile episodes but reduced significantly the incidence of Gram-negative [33], of clinically documented [38] or of microbiologically documented infections [34]. One trial of trimethoprim-sulphamethoxazole failed to show the efficacy of SD using this agent [31]. Guiot and co-workers [27] studied a combination of neomycin, nalidixic acid, colistin and nystatin. This drug regimen significantly reduced the incidence of infection to 61%. In two further studies the quinolones norfloxacin and ofloxacin were tested. Norfloxacin reduced significantly the

incidence of Gram-negative infections to 29% [39] and ofloxacin the overall incidence of infections to 19% [40]. Taken together all but one of these 14 prospective studies of SD demonstrated a significant reduction of the risk of either all infections or at least of subgroups of infections as compared with untreated control groups.

The failure of some trails using trimethoprim-sulphamethoxazole to show a substantial reduction of the overall incidence of infections in neutropenic patients might be due to the fact that a relatively high incidence of resistance to this drug has emerged in Gram-negative bacteria. It seems to be important to monitor the quality of decontamination by the use of surveillance cultures in order to recognize the emergence or persistence of resistant strains. Rozenberg-Arska and co-workers suggested that the addition of colistin to trimethoprim-sulphamethoxazole should improve the elimination of Gram-negative bacteria from the digestive tract, and that this combination should be more effective in the prevention of Gram-negative infections than trimethoprim-sulphamethoxazole alone.

In a further series of trials trimethoprim-sulphamethoxazole alone or with a polymyxin was compared with other antimicrobial drugs or drug combinations. The Gnotobiotic Project Group compared the combination of trimethoprim-sulphamethoxazole plus colistin with neomycin plus colistin [42]. Both groups received additional antifungal prophylaxis with oral amphotericin B. The data from this study indicated that the combination of trimethoprim-sulphamethoxazole plus colistin was significantly more effective than the non-absorbable drug combination in the prevention of severe infections, especially of bacteraemia. These results which are in good agreement with the data from other trials [28, 43–46] indicate that the systemic activity of trimethoprim-sulphamethoxazole might be of relevance.

Several of the more recently available fluoroquinolones have now also been studied for SD and infection prevention in neutropenic patients. Although norfloxacin has been shown to be useful for SD, studies have shown that ciprofloxacin and ofloxacin are clinically more effective [47, 48], presumably due to a better systemic antibacterial activity. Quinolones have also been compared with non-quinolone antibacterial agents. In trials in which trimethoprim-sulphamethoxazole was used as the control regimen the quinolones were unequivocally superior with respect to the quality of decontamination and the incidence of infections, especially of Gram-negative infections. Quinolones also had fewer side effects, above all fewer allergic reactions, than trimethoprim-sulphamethoxazole [49–54]. Interestingly, in these recent studies both trimethoprim-sulphamethoxazole and quinolones failed to prevent infections with Gram-positive bacteria such as coagulase-negative staphylococci and viridans group streptococci. Results of comparisons of ciprofloxacin with trimethoprim-sulphamethoxazole plus colistin were not unequivocal. In the study of Dekker and colleagues [55] ciprofloxacin was superior whereas in a second study not yet published in detail the combination of trimethoprim-sulphamethoxazole plus colistin appeared to have a better efficacy [56]. In two studies norfloxacin or ofloxacin were compared with the combination of oral vancomycin and polymyxin B [57, 58]. In both studies the quinolones were superior with respect to the

elimination of Gram-negative bacilli, the incidence of infections and side effects. However, neither quinolones nor the control regimen appeared effective in eliminating colonization or preventing infection with streptococci, coagulase-negative staphylocci or other Gram-positive microorganisms.

CONCLUSION

A series of randomized studies in neutropenic cancer patients has demonstrated that SD reduces significantly the risk of infection, mainly of infections caused by Gram-negative bacilli. However, none of the above-mentioned trials was able to demonstrate convincingly a reduced infection-related mortality following the application of SD. Disadvantages of SD are side-effects of the antimicrobial drugs used, above all allergic reactions and gastrointestinal intolerance. The criticism has also been made that SD with absorbable agents might simply reduce the ability to document the microbial causes of fever but has no significant effect on the frequency and duration of fever, and on total consumption of therapeutic antimicrobials. Despite these problems many experts consider SD to be useful in patients with malignant disorders who receive intensive cytotoxic therapy and who are or will become severely neutropenic for a longer period of time.

Two principal procedures for SD have been used in the past. Either the antimicrobial drugs for SD were selected according to the antimicrobial susceptibility, or fixed drug combinations were applied. Under both circumstances, it would appear important to perform regular surveillance cultures since the elimination of the relevant microorganisms from the microflora is the basic prerequisite for an effective infection prevention.

Trimethoprim-sulphamethoxazole has been used most frequently as yet, but can no longer be considered the drug of choice in many parts of the world due to high rates of resistance of the target organisms. While some centres may prefer the addition of a polymyxin to trimethoprim-sulphamethoxazole in order to reduce the emergence of resistant isolates, others will use one of the newer quinolones as a more convenient and at least as effective, if not superior, regimen for SD. Disadvantages of trimethoprim-sulphamethoxazole have included frequent skin rashes. There was also concern about a possible prolongation of neutropenia in patients receiving the agent although the results of trials are contradictory on this aspect [28, 32, 42, 43].

Obviously, the most useful alternative to trimethoprim-sulphamethoxazole appear to be the newer quinolones, especially ciprofloxacin, ofloxacin, and perhaps pefloxacin and others. Compared with trimethoprim-sulphamethoxazole these drugs seem to be clearly superior in the prevention of Gram-negative infections [48–55]. However, it should be considered, that quinolones will not prevent infections caused by *Pneumocystis carinii*. There is also clearly a concern about the development of bacterial resistance to quinolones. Quinolones should not be used in children since animal experiments have demonstrated deposits of these drugs in cartilage.

A major unsolved problem of SD is infection caused by Gram-positive cocci. Neither trimethoprim-sulphamethoxazole nor quinolones appear to be particularly useful at reducing the incidence of infections caused by coagulase-

negative staphylococci or of viridans group streptococci. The main reasons for this failure are the poor antibacterial activity of these drugs in these microorganisms and the rapid emergence of resistant strains. The increasing use of long-term central venous catheters prone to get colonized by staphylococci and other organisms is clearly another reason for the failure of any regimen of chemoprophylaxis. A newer approach for the prevention of at least some Gram-positive infections in neutropenic patients is the combination of quinolones with macrolide antibiotics such as erythromycin or roxithromycin or the combination of quinolones with oral penicillin [59–62]. Whether or not such regimens are of benefit remains to be determined.

Recently, haemopoietic growth factors have been shown to shorten the duration of neutropenia after intensive cytotoxic chemotherapy and thereby to reduce the risk of infection [10, 11]. It is, however, unclear as yet whether such factors can be applied safely in patients with haematological malignancy because of a potential to stimulate the growth of malignant cells. Whether or not colony stimulating factors are more effective than SD or whether the combination of both procedures is more effective than one procedure alone has to be investigated in further clinical trials.

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