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SELECTIVE INTESTINAL DECONTAMINATION IN DIFFERENT CLINICAL SITUATIONS

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INTRODUCTION

Infection continues to be a major problem in immunocompromised patient. Patients may run an increased risk of infections, basically for two reasons:

1. colonization at abnormal sites and/or in abnormal high numbers due to decreased colonization resistance (CR); i.e. the digestive tract may form a major source for both bacterial (Gram-negative and Gram-positive) and fungal infections,
2. decreased defense capacity:
   a. at the first line of defense: skin and mucosal lining,
   b. at the second line of defense: immune system.

The immunological system is very complex, however it is clinically useful to classify roughly host defense mechanisms into two separate systems: T cell dependent and a T cell independent immunity. Defects in the defense capacity of one of these systems increase the risk of infection by a specific group of microorganisms (*Peterson*, 1984).

Microorganisms which require T cell dependent mechanisms to control their intracellular multiplication are viruses - (herpesviruses) HIV, fungi, parasites (*Toxoplasma*, *Pneumocystis carinii*) and bacteria (mycobacteria, *Legionella*, *Listeria* and *Salmonella*). Although defects in the T cell independent system can be divided into defects in humoral defense system and defects in the polymorpholeucocyte system, defects in both systems are characterized by infections caused by aerobic bacteria like *Staphylococcus aureus* and other Gram-positive cocci, *Haemophilus influenzae* and aerobic Gram-negative rods (*Wade* and Schimpff, 1988).

These considerations will influence which antimicrobial agents will be used in different clinical situation as prophylaxis and empirical therapy.

A uniform regimen for prophylaxis to infections caused by T cell dependent microorganisms is difficult due to the heterogeneous aspects of the causative agents. Although some results have been obtained with the administration of prophylactic antimicrobials of these group of infections nowadays it will be impossible to cover in a rather easy way all these microorganisms. Prophylaxis for infections caused by T cell independent microorganisms on the other hand is much simpler.

COLONIZATION RESISTANCE AND SELECTIVE INTESTINAL DECONTAMINATION

Many of the T cell independent infections are caused by aerobic bacteria and yeasts which are generally regarded

as components of the normal microflora of the oropharynx or intestines.

Total bowel suppression to eradicate these microorganisms from the gastrointestinal tract (G.I. tract) is efficiently in reducing the number of severe infections, only when highly protective isolation measurements are employed (*Levine* et al., 1973; *Dietrich* et al., 1977).

Aerobic Gram-negative bacteria and staphylococci are the most common pathogens in the hospitalized immunocompromised patient. Disturbances of the integrity and microecology of the G.I. tract and skin play an important role in the pathogenesis of these microorganisms. In the normal situation these bacteria are a minority in the G.I. tract.

Van der Waaij (1974) demonstrated in animal studies that the inoculum necessary to colonize the digestive tract of conventional mice with bacteria was much higher than in germfree mice.

Suppression of growth of colonizing and newly ingested aerobic Gram-negative bacteria and yeasts is due to the hostile environment provided by the - predominantly anaerobic oropharyngeal and intestinal microflora; a flora selected and maintained by the host organism (*van der Waaij* et al., 1982). The host organisms contributes in this respect in two ways: 1. by selection of the bacteria which are "permitted" to colonize the mucosal surfaces of the G.I. tract immunologically (*van der Waaij*, 1988) and 2. by removing unwanted bacteria together with the by peristaltic movements. This combined action of host and resident microflora is called "colonization resistance" (CR) (*van der Waaij* and *de Vries*, 1974).

When the resident microflora of the G.I. tract is suppressed by antimicrobial agents, "bacterial of fungal overgrowth" may develop, either in the oropharynx, and the intestines. As a consequence of this overgrowth their is a good chance that invasion of sufficient severity occurs to cause an infection (*Tancrede* and *Andremont*, 1985).

This information leads to the obvious conclusion that infections in the high risk patient could be prevented if the existing colonization(s) at any of these sites in the digestive tract can be stopped and from then on, be prevented for the duration of the condition(s) of increased risk for infection.

By means of selective decontamination (SDD) the potentially pathogenic microorganisms (ppmo), in this case aerobic Gram-negative rods, *S. aureus* and yeasts are eliminated from their main reservoir the G.I. tract, in the meantime leaving the relatively harmless indigenous anaerobic flora intact.

So for SDD antimicrobial agents are used, which are not suppressive to the C.R. associated microflora but effectively eradicate these ppmo from the G.I. tract.

USE OF SDD IN DIFFERENT CLINICAL SITUATIONS

As cited above the eradication of the ppmo in the G.I. tract by means of SDD may be useful in clinical situations characterized by a relatively high incidence of infections with T cell independent infections, especially if this condition of a decreased T cell independent immunological system is temporary. The different clinical situations will be discussed here after.

1. Patients with chemotherapy for malignancies causing bone marrow suppression

Granulocytopenia secondary to cancer chemotherapy accounts for the

largest proportion of neutropenic patients in the hospital especially if neutropenia is lasting for more than ten days. This is plausible since chemotherapy causes in addition to severe granulocytopenia mucosal lesions.

Aerobic Gram-negative bacilli are the most common pathogens in this setting causing severe and often life threatening infections (*Wade* and *Schimpff*, 1988). In 1977 the antibacterial prophylactic effect of co-trimoxazole (TMP-SMZ) on Gram-negative infections was discovered in a study on the prevention of *Pneumocystis carinii* infections in leukemic children (*Hughes* et al., 1977). Since that time several studies have been undertaken that confirmed the prophylactic effect of TMP-SMZ. (*Gurwith* et al., 1979; *Kaufman* et al., 1983; Sleijffer et al., 1980; Dekker et al., 1981).

Dekker et al. (1981) showed that the use of TMP-SMZ can lead to an increased colonization of the G.I. tract with TMP-SMZ resistant Gram-negative rods during treatment of leukemic patients. The problem of the acquisition of resistant Gram-negatives was solved by the additional administration of polymixines (*Rozenberg-Arska* et al., 1983). *Candida* colonization and infections seem to be provocated by TMP-SMZ, like by many other antimicrobials. The addition of an oral antifungal drug like amphotericin B strongly reduced the incidence of *Candida* colonization and infection (Ezdinli et al., 1979; Dekker et al., 1981).

Since 1977, several studies have been published which showed the effect of SDD in neutropenic patients. In these studies different prophylactic regimens have been used. These studies have documented the fact that the application of SDD-antimicrobials, single or in combination, has significantly reduced the incidence of infections in patients with severe granulocytopenia (*Wade* et al., 1981; *Dekker* et al., 1987; *Karp* et al., 1987). One of the questions is whether a regimen including absorbable drugs like TMP-SMZ or quinolones, are superior -partly due to their systemic effect - to a regimen of non-absorbable drugs alone.

The EORTC Gnotobiotic Project Group investigated the combination colistin and neomycin versus colistin and TMP-SMZ. It appeared that the combination of colistin neomycin was less effective in preventing bacterial infection than did the colistin and TMP-SMZ combination (*Kurrle* et al., 1986).

The last years special attention has been paid to use of the new quinolones for SDD. Especially ciprofloxacin seems a promising drug for the prevention of infection in patients with granulocytopenia.

Advantages of ciprofloxacin versus TMP-SMZ were the good compliance, less adverse reactions and the absence of colonization with resistant Enterobacteriaceae (*Dekker* et al., 1987). On the other hand, TMP-SMZ has the advantage that if -besides granulocytopenia- an accompanying T cell defect exists, it protects the host against infections with organisms such as *Pneumocystis carinii*.

2. Patients in ICU units

The severely ill patients entering an intensive care unit (ICU) are prone to infections. This emphasises especially patients with long-lasting surgery and trauma patients (*Craven* et al., 1986; *Fife* and *Kraus*, 1988). There is a general agreement that injury brings about a suppression of host response defenses, and that this suppression is dose related (*Munster*, 1984). There is less agreement about which areas of immune response are the most important, and this may differ in different clinical situations.

The most common site of infection in mechanically ventilated patients is the respiratory tract. The mechanism of mechanical cleansing of the trachea and larynx by ciliar movement, which normally prevents colonization by ppmo, is interfered by the presence of an intratracheal cannula (*Johanson* et al., 1972). The use of antacids, to avoid stress ulcers and bleeding results in bacterial growth in the gastric juice. Retrograde pharyngeal colonization by organisms from the stomach may then under these circumstances contribute to the pathogenesis of nosocomial pneumonia (*Driks* et al., 1987; *Tryba*, 1987).

The second most common site of infection is the urinary tract, due to indwelling urinary catheters. Because many of these infections are caused by aerobic Gram-negative bacteria and staphylococci SDD may be beneficial in these group of patients.

Several studies have been performed to investigate this beneficial effect of SDD for respiratory tract infections. The first study by S*toutenbeek* et al. (1984) showed that there was remarkable reduction in hospital acquired pneumonia in the SDD treated patients compared to a historical control group, but additional systemic antibiotic prophylaxis was necessary to prevent early endogenous infections.

Although they clearly showed a reduction of the oropharyngeal colonization by ppmo, pneumonia and other infections by SDD treatment combined with systemic prophylaxis, there was no significant difference in the length of stay in the ICU nor on the mortality. Also other prospective studies with SDD in ICU settings did not show a difference in total mortality (*Unertl* et al., 1987; *Kerver* et al., 1987; *Ledingham* et al. 1988).

In conclusion it can be said that SDD in ICU patients, particularly in multiple trauma patients, may have benefit but needs further prospective investigation.

3. Transplantation patients

Transplantation patients are at increased risk for infection because of the immunosuppressive treatment given to prevent rejection of the transplant. All patients consequently have T cell suppression and are therefore at risk for T cell dependent infections. Within this category there are considerable differences in the incidence of an infection.

Most severely compromised transplant patients are those with allogeneic bone marrow (BM) transplantation (*Bortin* et al., 1983). They require strong immune suppression in order to mitigate or prevent graft versus host disease. Strong immune suppression involves increase risk for all T cell dependent infections enlisted above. However, the onset of such infections occurs usually not before the end of the first month after transplantation. By this time, the graft has repopulated the bone marrow and normal granulocyte counts may occur. In the first two weeks, however, severe granulocytopenia may exist as well as residual mucosal damage due to chemotherapy/irradiation for conditioning of the graft. This condition make these patients initially comparable to patients undergoing remission induction therapy for acute leukemia. SDD has been reported to be successful in infection prevention in BM-transplant patients (*Schmeiser* et al., 1988).

Of the remaining transplant patients, those with an implanted organ that is normally involved in the defense to infection, the liver, are the second in line regarding increased risk (*Kusne* et al., 1988).

Firstly the difficult operative procedure combined with abnormal bleeding often results in intra-abdominal haematoma.

Secondly it may take two to three weeks in these patients, before the Kupffer cells repopulate the terminal venules of the portal circulation and before the bile flow has restored. Regarding the latter, the patient is in general at lower risk if during transplantation an end to end anastomosis has been possible (the normal physiological situation) than if the gall bladder is connected to an ileum loop (Rough-Y anastomosis). In this case an open connection exists between the small intestines (jejunum) and the gall bladder; a condition which facilitates bacterial spread from the intestinal lumen into the bile duct system of the liver. An end to end anastomosis could be particularly important for the reduction of an infection risk in patients who have pretransplant enhanced PPMO-colonization in their small bowel. SDD prophylaxis has been reported to be successful in reducing Gram-negative infection (*Wiessner* et al., 1988).

4. Patients with extensive burns

Infection is supposed to be the primary cause of death in severely burned patients who survive the first 72 hours (*Monafo*, 1979; *Kagan* et al., 1985). Although bacteraemia mostly results from infected wounds, the principle infection leading to death is lower respiratory tract infection (*Goodwin* and *Yurt*, 1986; *Sittig* and *Deitch*, 1988). When there is beside the burnwound also lungdamage as a result of smoke inhalation, mortality due to pneumonia can be extremely high. Severely burned patients -like other trauma patients- suffer of an immunosuppression of nearly all components of the immune system. (*Munster*, 1984).

Several authors have investigated the close relationship between the microflora of the burnwound and the microflora of the G.I. tract (*Burke* et al., 1977; *Jarett* et al., 1978; *van Saene* and *Nicolai*, 1979; *Brook* and *Randolph*, 1981; *Manson* et al., 1990). SDD by means of aztreonam in experimentally burned mice decreased wound colonization during a 20 day period. *Jarrett* et al. (1978) using a non-absorbable regimen with erythromycin, neomycin and nystatin together with high hygienic policies showed a reduction in the colonization and infection rate of the patients compared with a control group.

Until now, only non-randomized studies have been undertaken which seem to show a beneficial effect of SDD with regard to the degree of bacterial colonization as well as to infectious complications (*Manson* et al., 1987).

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