Old Herborn University Seminar Monograph 3:
Consequences of antimicrobial therapy for the composition of the microflora of the digestive tract.
Editors: Carl Erik Nord, Peter J. Heidt, Volker Rusch, and Dirk van der Waaij.
Institute for Microbiology and Biochemistry, Herborn-Dill, Germany: 25-30 (1993).

EFFECT OF ANTIMICROBIAL DRUGS ON THE INTESTINAL MICROFLORA: CRITERIA FOR THEIR USEFULNESS FOR SELECTIVE DECONTAMINATION IN THE NEUTROPENIC PATIENT

HILLY G. DE VRIES-HOSPERS, RUDY H.J. TONK,
and DIRK VAN DER WAAIJ

Laboratory for Medical Microbiology, University of Groningen,
Groningen, The Netherlands

INTRODUCTION

Without prophylactic measures, neutropenic patients have a high chance to develop an infection, increasing with the depth and the duration of granulocytopenia (*Bodey* et al., 1966). Most infections in the granulocytopenic patient are caused by enteric bacteria, mainly Enterobacteriaceae- and Pseudomonadaceae-species (*Schimpff* et al., 1972; *Levine* et al., 1973; *Bodey* et al., 1978). In the past, the most frequently isolated Gram-positive microorganism was *Staphylococcus aureus*. However, there is an increasing number of infections caused by coagulase negative staphylococci and viridans streptococci (*Wade* et al., 1982; *Winston* et al., 1983; *Dekker* et al., 1987; *Kern* et al., 1987; *Peters* et al., 1988). The percentage of infections caused by anaerobes was and is still small, in the order of 1% of the total. As infections in granulocytopenic patients have a high mortality rate, infection prevention is worthwhile to be performed. This has been attempted by either total or selective decontamination. Total decontamination (TD) has the disadvantage of the need of strict isolation of the patient, who in addition should take sterile food and beverages. A disadvantage of TD is the elimination of microorganisms responsible for the Colonization Resistance (CR) (*van der Waaij* et al., 1971; *van der Waaij*, 1982a).

COLONIZATION RESISTANCE AND SELECTIVE DECONTAMINATION

The CR functions as a barrier against exogenous bacteria trying to colonize a certain tract. In the gastrointestinal tract especially the anaerobic bacteria play a major role in maintaining the CR. The majority of the infections in granulocytopenic patients is caused by aerobic bacteria, belonging to the normal gut flora. Elimination of these bacteria without affecting the CR is called selective decontamination of the digestive tract (SD). This method appeared to be efficacious in reduction of the infection frequency in granulocytopenic patients (*Sleijfer* et al., 1980; *Dekker* et al., 1981). Selective decontamination proved to be as efficacious as total decontamination in preventing Gram-negative infections, even without strict isolation procedures (*Kurrle* et al., 1986). SD is cheaper, less laborious and more comfortable for the patient as this method can be performed without strict isolation procedures.

ANTIMICROBIAL AGENTS FOR SELECTIVE DECONTAMINATION

SD can only be performed with antimicrobial agents (AMA) selected on the basis of their effect on the gastrointestinal microflora. An active concentration of the SD-drugs must reach the gastrointestinal tract (the site of action); this amount of SD-drugs must be:

a. not suppressive to the anaerobic CR-related microflora;

b. able to kill one or more of the potentially pathogenic microorganisms (PPMO), most frequently encountered in infections in granulocytopenic patients. These consists of aerobic Gram-negative bacilli as Enterobacteriaceae- and Pseudomonadaceae-species, *Staphylococcus aureus*, yeasts and fungi, coagulase negative staphylococci, and viridans streptococci.

Up to now there are no AMA which are active against coagulase negative staphylococci and viridans streptococci without affecting anaerobes. Yeasts and fungi can be eliminated by the polyenes amphotericin B and nystatin. Both antimycotics are not absorbed after oral administration and have no effect on bacteria.

Elimination of *S. aureus* from the digestive tract appeared to be possible with the absorbable drugs cephradine and co-trimoxazole. Aerobic enteric Gram-negative bacilli except *Proteus*-, *Morganella*-, and *Serratia*-species are highly susceptible to polymyxins, while anaerobes are resistant. Like the polyenes, polymyxin is not absorbed after oral administration. Polymyxin appeared an ideal drug for SD: the effect, elimination of susceptible Gram-negative bacilli is usually reached within three days after oral administration (*de Vries-Hospers* et al., 1981). The only disadvantage of polymyxin is the gap in the antibacterial spectrum. Fortunately, a number of absorbable antibiotics have been shown to be useful for SD. Elimination of Gram-negative bacilli from the digestive tract can be performed by oral administration of co-trimoxazole and nalidixic acid (*de Vries-Hospers* et al., 1981). Later on it was found that in volunteers the same effect could be obtained with the newer quinolones like norfloxacin and ciprofloxacin (*Pecquet* et al., 1986; *de Vries-Hospers* et al., 1987). Administration of these quinolones to neutropenic patients resulted in a reduction of the number of infections caused by Gram-negative bacilli (*Rozenberg-Arska* et al., 1985; *Winston* et al., 1986; *Karp* et al., 1987). Temocillin and aztreonam are β-lactam antibiotics with a small spectrum of activity against aerobic Gram-negative bacilli; both can be used for elimination of these bacteria from the digestive tract (*de Vries-Hospers* et al., 1984; *de Vries-Hospers* et al., 1985).

As mentioned above, anaerobic bacteria are involved in maintaining the CR. The animal experiments especially antimicrobial agents (AMA) with activity against Gram-positive bacteria, such as bacitracin and penicillin, appear to disrupt the CR significantly (*Wiegersma* et al., 1982). On the other hand, AMA like polymyxin, temocillin and aztreonam, which are only active against aerobic Gram-negative bacilli, appeared useful for SD, however, not in all cases: when aztreonam was administered orally to ten volunteers, elimination of aerobic Gram-negative bacilli was reached in eight of them with all three dosages tested (*de Vries-Hospers* et al., 1984). In the two volunteers who could not be decontaminated, aztreonam susceptible Gram-negative bacilli remained present in the faecal cultures during treatment with aztreonam. There was no measurable concentration of aztreonam in the faeces of these volun-

teers. The same phenomenon was found in volunteers who were treated with temocillin intramuscularly (*de Vries-Hospers* et al., 1985).

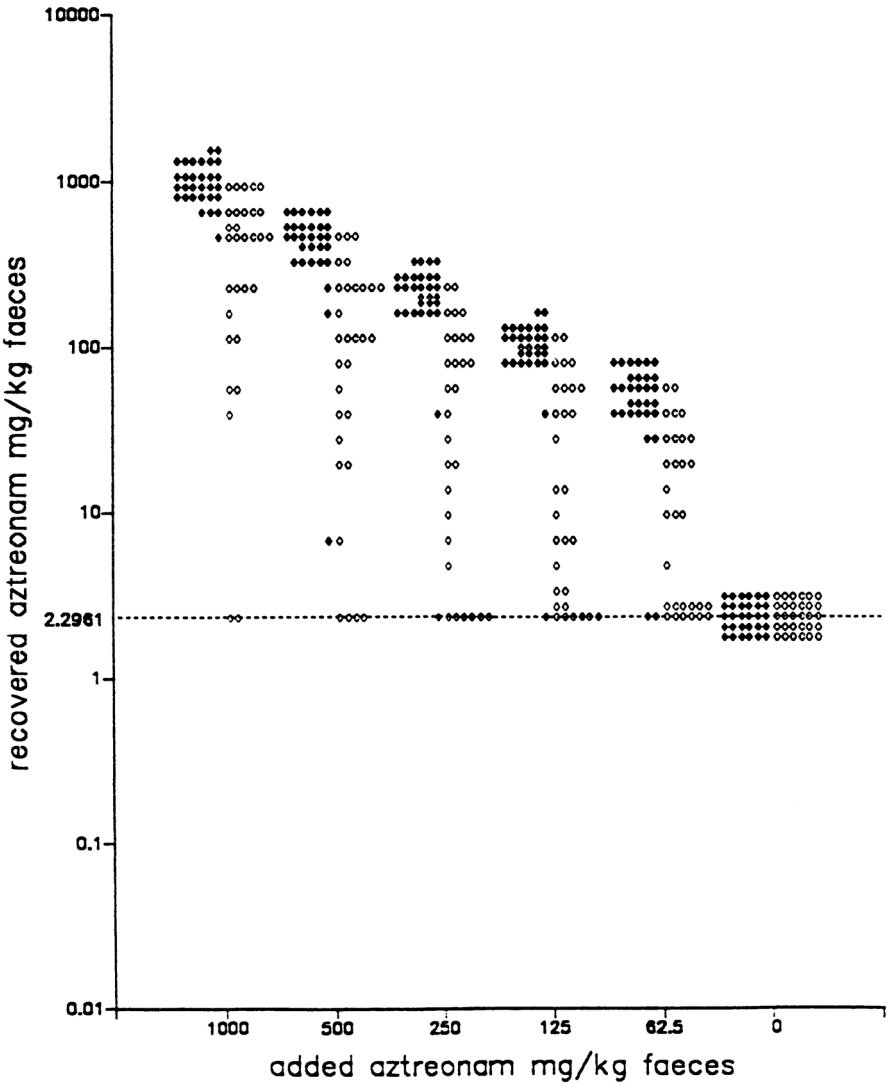

Figure 1: Recovery of microbiological active aztreonam in faecal samples derived from 30 healthy volunteers and mixed with different amounts of aztreonam. The concentration was determined either immediately after mixing (✦) or after 24 hours (✧) of incubation at 37°C.

INFLUENCE OF FAECES ON BIOLOGICAL ACTIVITY OF AZTREONAM AND TEMOCILLIN

To investigate why some of the volunteers treated with aztreonam or temocillin did not respond to antimicrobial treatment, another experiment was performed. Fresh faecal samples were collected from 30 healthy volunteers and

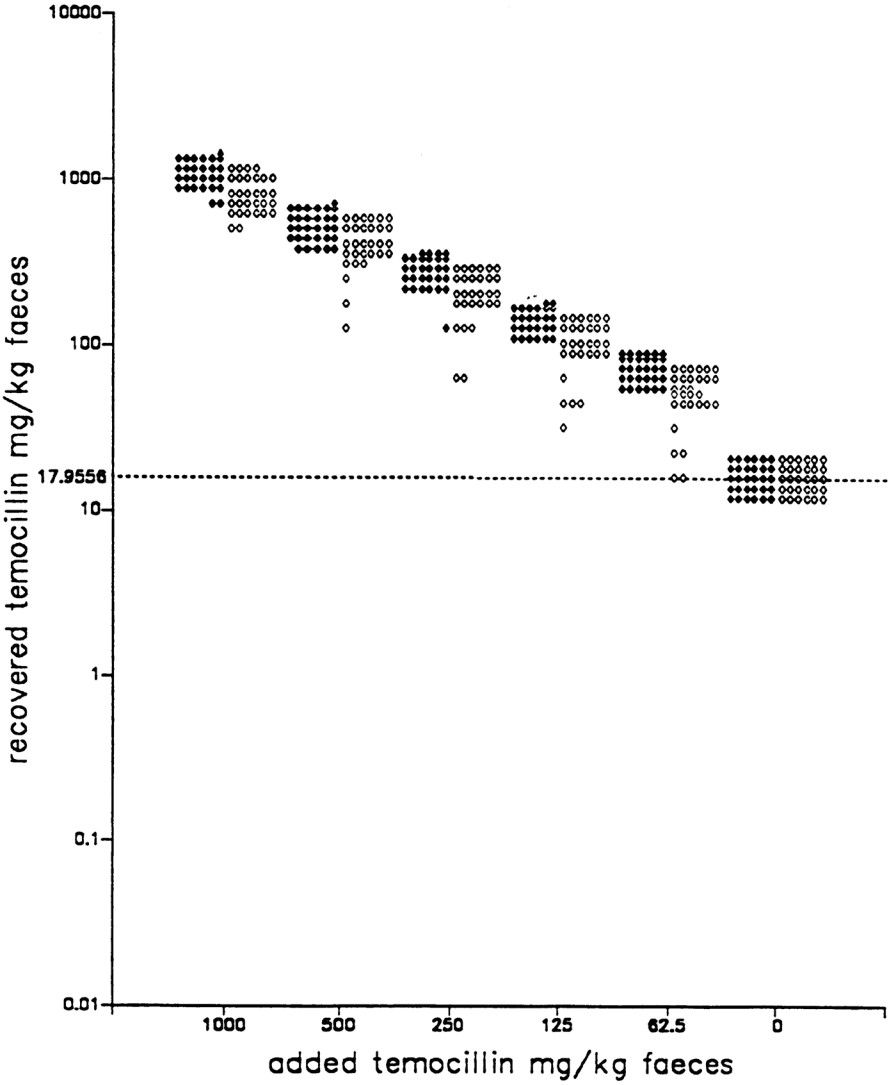

Figure 2: Recovery of microbiological active temocillin in faecal samples derived from 30 healthy volunteers and mixed with different amounts of temocillin. The concentration was determined either immediately after mixing (✦) or after 24 hours (✧) of incubation at 37°C.

mixed with different amounts of the antibiotics: 1000, 500, 250, 125, 62.5 and 0 mg/kg faeces. This mixtures were either immediately centrifuged or after 24 hours of incubation at 37°C. Then the microbiological active amounts of the antibiotics were determined in the faecal supernatants. The results are shown in Figures 1 and 2. It appeared that faeces had more influence on the microbiological activity of aztreonam than on that of temocillin, although there were interindividual differences. In some of the faecal samples, mixed with aztreonam, no microbiological activity was found after 24 hours of incubation with aztreonam (Figure 1). This was also the case in a few samples when the concentration of aztreonam was determined immediately after

mixing. This inactivation of aztreonam and other AMA in the presence of faeces may be due to (ir)reversible binding of antibiotics to faecal material. Another mechanism may be degradation of antibiotics by bacterial enzymes present in faeces, like has been described for aztreonam (*Welling* et al., 1987).

In conclusion: apart from the spectrum of antimicrobial activity and the pharmacokinetic properties of AMA, the influence of faeces on the microbiological activity of an antimicrobial agent must be taken into account, when AMA are screened for their usefulness for SD. When faeces renders AMA inactive, they cannot be used for SD or may be only when applied in relatively high dosages.

To predict the effect of AMA on the CR, and the usefulness for SD, a number of properties of the drug should be known:

a. the spectrum of antimicrobial activity;
b. pharmacokinetic properties;
c. the influence of intestinal contents on the activity of the AMA.

LITERATURE

Bodey, G.P., Buckley, M., Sathe, Y.S., and Freireich, E.J.: Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann. Intern. Med. 64, 328-340 (1966).

Bodey, G.P., Rodriguez, V., Chang, H.Y., and Narboni, G.: Fever and infection in leukemic patients. A study of 494 consecutive patients. Cancer (Philad.) 41, 1610-1621 (1978).

Chang, H.Y., Rodriguez, V., Narboni, G., Bodey, G.P., Luna, M.A., and Freireich, E.J.: Causes of death in adults with acute leukemia. Medicine 55, 259-268 (1976).

Dekker, A.W., Rozenberg-Arska, M., Sixma, J.J., and Verhoef, J.: Prevention of infection by trimethoprim-sulfamethoxazole plus amphotericin B in patients with acute nonlymphocytic leukemia. Ann. Intern. Med. 95, 555-559 (1981).

Dekker, A.W., Rozenberg-Arska, M., and Verhoef, J.: Infection prophylaxis in acute leukemia: a comparison of ciprofloxacin with trimethoprim-sulfamethoxazole and colistin. Ann. Intern. Med. 106, 7-12 (1987).

de Vries-Hospers, H.G., Sleijfer, D.T., Mulder, N.H., van der Waaij, D., Nieweg, H.O., and van Saene, H.K.F.: Bacteriological aspects of selective decontamination of the digestive tract as a method of infection prevention in granulocytopenic patients. Antimicrob. Agents Chemother. 19, 813-820 (1981).

de Vries-Hospers, H.G., Welling, G.W., Swabb, E.A., and van der Waaij, D.: Selective decontamination of the digestive tract with aztreaonam: a study in 10 healthy volunteers. J. Infect. Dis. 150, 636-642 (1984).

de Vries-Hospers, H.G., Hofstra, W., Welling, G.W., and van der Waaij, D.: Influence of temocillin on colonisation resistance and consequences for therapy. Drugs 29 (Suppl. 5), 227-233 (1985).

de Vries-Hospers, H.G., Welling, G.W., and van der Waaij, D.: Influence of quinolones on throat- and faecal flora of healthy volunteers. Pharmac. Weekblad Scientific Edition 9, S41-S44 (1987).

Emmelot, C.H., and van der Waaij, D.: The dose at which neomycin and polymixin can be applied for selective decontamination of the digestive tract in mice. J. Hyg. (Camb.) 84, 331-340 (1980).

Karp, J.E., Merz, W.G., Hendricksen, C., Laughon, B., Redden, T., Bamberger, B.J., Bartlett, J.G., Saral, R., and Burke, P.J.: Oral norfloxacin for prevention of Gram-negative bacterial infections in patients with acute leukemia and granulocytopenia. Ann. Intern. Med. 106, 1-6 (1987).

Kern, W., Kurrle, E., and Vaneck, E.: High risk of streptococcal septicemia after high dose cytosine arabinoside treatment for acute myelogenous leukemia. Klin. Wochenschr. 65, 773-780 (1987).

Kurrle, E., Dekker, A.W., Gaus, W., Haralambie, E., Krieger, D., Rozenberg-

Arska, M., de Vries-Hospers, H.G., van der Waaij, D., and Wendt, F.: Prevention of infection in acute leukemia: a prospective randomized study on the efficacy of two different regimens for antimicrobial prophylaxis. Infection 14, 226-232 (1986).

Levine, A.S., Siegel, S.E., Schreiber, A.D., Hauser, J., Preisler, H., Goldstein, I.M., Seidler, F., Simon, R., Perry, S., Bennet, J.E., and Henderson, E.S. Protected environments and prophylactic antibiotics: a prospective controlled study of their utility in the therapy of acute leukemia. N. Engl. J. Med. 288, 477-483 (1973).

Pecquet, S., Andremont, A., and Tancrede, C.: Selective antimicrobial modulation of the intestinal tract by norfloxacin in human volunteers and in gnotobiotic mice associated with a human fecal flora. Antimicrob. Agents Chemother. 29, 1047-1052 (1986).

Peters, W.G., Willemze, R., and Colly, L.P.: Results of induction and consolidation treatment with intermediate and high-dose cytosine arabinoside and m-Amsa of patients with poor-risk acute myelogenous leukemia. Eur. J. Hematol. 40, 198-204 (1988).

Rozenberg-Arska, M., Dekker, A.W., and Verhoef, J.: Ciprofloxacin for selective decontamination of the alimentary tract in patients with acute leukemia during remission induction treatment. The effect on fecal flora. J. Infect. Dis. 152, 104-107 (1985).

Schimpff, S.C., Young, V.M., Greene, W.H., Vermeulen, G.D., Moody, M.R., and Wiernik, P.H.: Origin of infection in acute nonlymphocytic leukemia. Significance of hospital acquisition of potential pathogens. Ann. Intern. Med. 77, 707-714 (1972).

Sleijfer, D.Th., Mulder, N.H., de Vries-Hospers, H.G., Fidler, V., Nieweg, H.O., van der Waaij, D., and van Saene, H.K.F. Infection prevention in granulocytopenic patients by selective decontamination of the digestive tract. Europ. J. Cancer 16, 859-869 (1980).

van der Waaij, D., Berghuis-de Vries, J.M., and Lekkerkerk-van der Wees, J.E.C.: Colonization resistance of the digestive tract in conventional and antibiotic treated mice. J. Hyg. (Camb.) 69, 405-411 (1971).

van der Waaij, D.: Colonization resistance of the digestive tract; clinical consequences and implications. J. Antimicrob. Chemother. 10, 263-270 (1982a).

van der Waaij, D., Hofstra, W., and Wiegersma, N.: Effect of b-lactam antibiotics on the resistance of the digestive tract of mice to colonization. J. Infect. Dis. 146, 417-422 (1982b).

van der Waaij, D., Aberson, J., Thijm, H.A., and Welling, G.W.: The screening of four aminoglycosides in the selective decontamination of the digestive tract in mice. Infection 10, 35-40 (1982c).

Wade, J.C., Schimpff, S.C., Newman, K.A., and Wiernik, P.H.: *Staphylococcus epidermidis*: an increasing cause of infection in patients with granulocytopenia. Ann. Intern. Med. 96, 1-10 (1982).

Welling, G.W., Groen, G., Welling-Wester, S., de Vries-Hospers, H.G., and van der Waaij, D.: Enzymatic inactivation of aztreonam by faecal enzyme preparations from healthy volunteers. Infection 5, 188-191 (1987).

Wiegersma, N., Jansen, G., and van der Waaij, D.: Effect of twelve antimicrobial drugs on the colonization resistance of the digestive tract of mice and on the endogenous potentially pathogenic bacteria. J. Hyg. (Camb.) 88, 221-230 (1982).

Winston, D.J., Dudnick, D.V., Chapin, M., Ho, W.G., Sale, R.P., and Martin, M.J.: Coagulase negative staphylococcal bacteremia in patients receiving immunosuppressive therapy. Arch. Intern. Med. 143, 32-36 (1983).

Winston, D.J., Winston, G.H., Nakao, S.L., Gale, R.P., and Champlin, R.E.: Norfloxacin versus vancomycin/polymyxin for prevention of infections in granulocytopenic patients. Am. J. Med. 80, 884-889 (1986).