Epidemiol. Infect (1992), **109**, 349–360

Selective decontamination in bone marrow transplant recipients

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SUMMARY

Patients undergoing bone marrow transplantation become immunocompromised for various reasons. Deep granulocytopenia, induced by conditioning (chemotherapy and total body irradiation), renders the patient at risk for serious bacterial and fungal infections. Our strategy for prevention of these infections by selective decontamination (SD) is the result of more than 15 years of clinical experience and research. The combination of antibiotics, used as standard SD (neomycin, polymyxin B, pipemidic acid and amphotericin B), with the application of local antimicrobial agents eliminates aerobic Gram-negative rods, *Staphylococcus aureus* and *Candida* spp. from the mucosal surfaces of the digestive tract, while the majority of the anaerobic flora persist and support colonization resistance (CR). The antibiotics used either are not resorbed or do not yield therapeutic serum concentrations. Antibiotics which induce therapeutic serum concentrations, such as ciprofloxacin and cotrimoxazole, are only used for SD on a limited scale. When Gram-negative rods persist despite intake of the standard regimen, ciprofloxacin is given until these persisting rods are eliminated. If the patients cannot swallow the oral regimen, i.v. cotrimoxazole is given temporarily. Streptococcal infections are prevented by the i.v. adminstration of penicillin for 14 days starting on the first day after cytotoxic treatment (conditioning for bone marrow transplantation). The combination of SD and systemic prophylaxis has been shown to be adequate; the major problem then remaining is a relatively mild catheter-associated infection with coagulase-negative staphylococci.

INTRODUCTION

The strategy for the prevention of infection described in the present contribution is the result of our experience with infections in bone marrow transplantation (BMT) recipients, the restrictive policy of antimicrobial therapy in our hospital and our views on colonization resistance (CR). With regard to the latter it has to be stressed that the digestive tract is colonized by high numbers of bacteria and yeasts. Treatment with antimicrobial drugs alters both the composition and the ecological balance of the microflora, as has been demonstrated in animals and man. The results of these studies [1] suggest that endogenous microflora form a complex ecological system which protects against both colonization by exogenous micro-organisms and unlimited growth of endogenous potentially pathogenic micro-organisms. This protection has been called 'colonization resistance' by

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Van der Waaij [2]. Although there is considerable evidence for the existence of CR, in our opinion CR is not the ultimate factor for determination of the composition of antimicrobial therapy. The efficacy of CR varies in both healthy persons and patients. This means that the administration of an antibiotic which is 'CR-friendly' does not always prevent colonization by resistant strains. Actually it is not possible to prove definitively that an antibiotic does not disrupt CR. This statement is based on our own observations in mice [1, 3, 4] that CR may differ substantially per bacterial species and even between strains (due to mutation of outer membrane proteins, unpublished data) or per individual mouse, so that absolute measurement of CR is not feasible.

In our opinion CR is the result of myriad interactions between the host, endogenous microbes and the environment. CR comprises 'colonization barriers', such as potential killing of bacteria by gastric acid and inhibition of bacterial growth by competition for nutrients, and 'colonization removal factors', which include washout activities in the intestinal tract in concert with bacterial adherence to mucosal receptors. None of these CR factors alone is absolutely effective, a fact which has to be realized, particularly when the patient involved has a decreased host defence, as in BMT recipients.

Infection in bone marrow transplantation

It is well known that patients undergoing bone marrow transplantation (BMT) are threatened by a wide variety of (potentially) pathogenic organisms, ranging from viruses (Herpes spp.) to multicellular parasites (*Strongyloides stercoralis*). After BMT the susceptibility of the patient to the pathogens varies, depending on the time after transplantation and the occurrence of non-infectious BMT-associated complications (Fig. 1) [5]. The focus of this contribution is prevention of bacterial and fungal infections during a relatively short episode of risk, i.e. the severe granulocytopenia 2–3 weeks after conditioning, and during extreme mucosal damage due to acute graft-versus-host disease (GVHD) [5, 6].

Soon after the first bone marrow transplantations were performed in the early 1970s bacterial and fungal infections were recognized as early complications. Twenty-two of the first 47 BMT recipients in Seattle developed septicaemia within the first 3 weeks [7]. As a consequence measures were taken to prevent bacterial and fungal infections. At present, two decades later, there is still no consensus on the optimum method for prevention of these early infections. Almost every centre for BMT has its own strategy, ranging from early empiric broad-spectrum therapy instead of prophylaxis to total decontamination in a sterile protective environment [8].

Antimicrobial modulation of the intestinal flora

Prevention of infection by means of antimicrobial modulation of the intestinal flora consists of the oral administration of antimicrobial drugs, which are nonabsorbable and active in the lumen of the digestive tract. This method is generally referred to as **antibiotic decontamination**. In the past most centres aimed at complete elimination of the intestinal flora, i.e. **total antibiotic decontamination** (TD). To prevent exogenous colonization, strict protective isolation and sterile food were required.

Buckner and colleagues [9] demonstrated the benefit of TD for BMT patients.

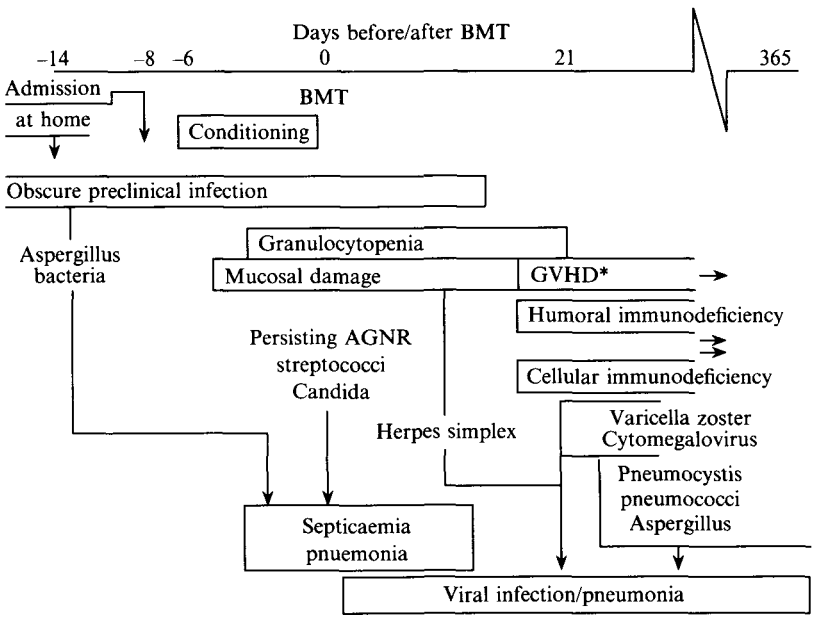

Fig. 1. Risk factors, compromised host defence and infections according to time before and after bone marrow transplantation (BMT), as described in reference 5. * GVHD: graft-versus-host disease.

Ten of 45 patients on a decontamination regimen, nursed in a laminar air flow room and fed with sterile food, developed septicaemia; of 44 patients of the control group, nursed in single rooms and receiving no antimicrobial prophylaxis, 23 developed septicaemia. The results were supported by the decreased number of febrile days, reduced need for antibiotic therapy and fewer platelet and granulocyte transfusions for TD patients in comparison to controls, but no differences in mortality were found. In a later study [10], the same investigators found significant differences in the survival of BMT recipients with aplastic anaemia when the TD group was compared with controls without decontamination nursed only in single rooms. In addition to a difference in the number of infections, a reduced incidence and a delayed onset of acute GVHD were found in the TD group in comparison to controls.

The first 12 BMT patients in Leiden (1967–74) were nursed in laminar-down flow isolators. They received sterile food and TD. The results of transplantation were poor due to non-infectious complications [11], such as acute toxicity as a result of conditioning, rejection of the bone marrow graft and acute GVHD. Adverse secondary reactions induced severe infection, such as septicaemia with Gram-negative rods or *Candida* spp. and pneumonia due to *Aspergillus* spp. It soon became clear that elimination of the patient's endogenous flora was almost impossible, and instead of the desired germ-free status overgrowth by resistant potentially pathogenic micro-organisms was often achieved. This was the reason for the initiation of selective decontamination [12]. Initially, the term partial antibiotic decontamination (PAD) was chosen to indicate that the antibiotics of the PAD regimen eliminated aerobic and facultative anaerobic Gram-negative rods, yeasts and *Staphylococcus aureus*, but not the major fraction of the anaerobic

Table 1. *Selective antimicrobial modulation (SAM)*

Drug	Daily dose	Directed against
Polymyxin B	400 mg orally	Gram-negative aerobes, especially *P. aeruginosa*
Neomycin	1000 mg orally	Gram-negative aerobes; staphylococci
Pipemidic acid	800 mg orally	Gram-negative aerobes, especially proteus and pseudomonas
Amphotericin B	1000 mg orally	Fungi
Orabase (Hoyt, Norwood, Mass.) containing polymyxin B 1%, neomycin 3%, and amphotericin B 3%	1 g applied to the mouth	Gram-negative aerobes; Gram-positive aerobes; and fungi colonizing the oral cavity

flora. Therefore we actually eliminated partly and not selectively because it was not feasible to culture all 300 species of anaerobic bacteria to demonstrate that the anaerobic flora was not disturbed [13, 14]. It was assumed that the persisting bulk of anaerobic bacteria and facultative Gram-positive cocci in the intestinal tract were responsible for a substantial part of the colonization resistance [2].

At present in Leiden the term PAD is still used, although selective antimicrobial modulation (SAM) [15, 16] and selective (gut) decontamination S(G)D are the current synonyms.

Selective decontamination: the Leiden regimen

In our BMT department SD is achieved by means of oral treatment with antimicrobial drugs that either are not absorbed or do not reach effective plasma levels after absorption because renal excretion is so rapid (pipemidic acid). This means that drugs that have to be resorbed to give adequate therapeutic serum levels are not used for SD, or only on a limited scale, to ensure that the risk of selection of resistant strains remains as low as possible. For adults, the dosage of the Leiden SD regiment is 250 mg neomycin, 100 mg polymyxin B and 250 mg amphotericin B, all given four times daily, and 400 mg pipemidic acid (formerly 1000 mg nalidixic acid) twice daily (Table 1). The first three antibiotics are mixed together in small capsules (4 × 3 capsules per day), pipemidic acid is given as tablets (two per day). This formulation has the advantage that various adaptations are possible, such as spread of intake over time, stepwise reduction in the dosage swallowed during nausea and the possibility of swallowing the drugs in suspension. Decontamination is combined with accessory measures, i.e. administration of orabase containing 3% (mg/ml) amphotericin B, 3% neomycin, and 1% polymyxin B to reduce the numbers of bacteria and yeasts in the oral cavity, supplemented with disinfection of the skin by means of providone-iodine (betadine) scrub or water containing 0·2% chlorhexidine, nursing in a protective environment and consumption of low-risk food. This means that either the food is intrinsically sterile (e.g. well-cooked, canned) or it contains limited numbers of bacteria with low virulence when present in the intestinal tract (*Lactobacillus* spp., *Bacillus* spp., coagulase-negative staphylococci). During the period of selective decontamination, weekly samples of faeces and urine as well as swabs from the

Table 2. *Septicaemia in selectively decontaminated patients during severe granulocytopenia following chemotherapy or bone marrow transplantation**

	Number of infections and causative micro-organisms								
	1983	1984	1985	1986	1987	1988	1989	1990	1991
No. of infections† per number of episodes‡	14/106	35/93	40/79	28/85	24/60	19/55	17/59	19/50	20/42
Percentage of infections	13·2	37·6	50·6	32·9	40	34	29	38	47
Entero-bacteriaceae	8	7	3	5	2	2	2	5	1
Pseudomonas aeruginosa	5	3	2	4	5	1	0	1	0
Alpha-haemolytic streptococci	6	17	26	5	9	8	4	3	3
Enterococci	6	7	4	2	3	0	1	0	0
Coagulase-positive staphylococci	4	5	0	4	1	2	5	2	4
Coagulase-negative staphylococci	7	3	12	8	7	4	6	9	6
Candida spp.	0	1	1	1	2	1	0	1	0
Aspergillus spp.	0	1	1	1	2	1	0	0	3
Miscellaneous	4	3	4	0	0	0	1	5	3

* Not including infections in BMT recipients 1990–1. † In some instances two or more micro-organisms were involved. ‡. Episodes of granulolcytopenia.

nose, oropharynx, axilla, groin and prepuce or vagina, are taken for surveillance cultures.

The efficacy of our regimen has been demonstrated in a double-blind, placebo-controlled study [16] and an open follow-up study [17]. The incidence of infections with aerobic Gram-negative rods, *S. aureus* and yeasts decreased from an incidence of 60% to less than 10%. The above-mentioned regimen was adequate until antileukaemic therapy was intensified. After 1983 the introduction of intermediate and high-dose cytosine-arabinoside (Ara-C, cytosar) therapy [18, 19] led to a gradual increase in the incidence of viridans streptococcal infections from 3% [17] to 48% [20]. Throughout the years 1983–5 *Streptococcal* species accounted for 30–50% of all species involved in bacterial infections (Table 2) [21]. Almost all septicaemias associated with high fever, bleeding and respiratory distress [20, 22] were caused by α-haemolytic streptococci originating in all probability from the oral cavity. These infections developed within 14 days of the last day of cytotoxic therapy. In 1986, to prevent these infections, a short course of prophylactic i.v. penicillin G (4×10^6 U daily) was given, beginning on the first day after conditioning (or chemotherapy) and ending 14 days later. This prophylactic therapy has significantly decreased the incidence of streptococcal septicaemias (Table 2). Between 1983 and 1987, the incidence of septicaemia due to Gram-negative rods and coagulase-positive and coagulase-negative staphylococci remained consistently low while the number of fungal infections was very low as

well (Table 2). This confirmed the adequacy of the regimen of selective decontamination for the control of infections with Enterobacteriaceae, *Pseudomonas aeruginosa*, staphylococci and fungi.

Alternative regimens for SD

During the 1980s several studies were performed in other haematological centres to study the efficacy of alternative regimens for SD. Elimination of the potentially pathogenic bacteria, while leaving the anaerobic flora intact, can also be achieved with cotrimoxazole [23]. Given alone, cotrimoxazole will soon select resistant Gram-negative rods [23]. Cotrimoxazole, combined with polymyxin B or colistin and amphotericin B, reduced the number of Enterobacteriaceae, *Pseudomonas* spp. and yeast and prevented the selection of resistant Gram-negative rods [24]. However, this prevention of selection of resistant strains was not observed in a later study by the same authors who compared the efficacy of infection prevention by cotrimoxazole and colistin with ciprofloxacin [25]. In that study, 12 of 28 patients receiving cotrimoxazole–colistin were colonized by cotrimoxazole-resistant Gram-negative rods; seven suffered infection. Moreover, our experience with cotrimoxazole in combination with polymyxin B (unpublished data) for patients on long-term SD therapy as out-patients (refractory to antileukaemic therapy) also does not confirm that selection of resistant strains is fully prevented. In half the number of these patients we observed colonization and subsequent septicaemia with cotrimoxazole-resistant Gram-negative rods, although still sensitive to polymyxin B. The explanation might be that cotrimoxazole is not only active in the lumen of the digestive tract but also systemically. Thus excretion of cotrimoxazole at sites where non-resorbable polymyxin is not present (e.g. wounds), or only transiently (oral cavity), might induce colonization of cotrimoxazole-resistant bacteria and subsequent infection with these micro-organisms.

At present many centres use ciprofloxacin or other new quinolones for infection prevention [26]. Unlike the old quinolones, nalidixic acid and pipemidic acid, most of the new quinolones yield therapeutically adequate plasma levels when administered orally. This means that SD with these drugs provides not only selective elimination of bacteria from the intestinal tract (SD) but also systemic prophylaxis. The secretion of resorbed ciprofloxacin by the mucosal membranes, like that of cotrimoxazole is accompanied by the risk of emergence of resistant bacteria. Although at present this risk is relatively low, we have seen failed SD with ciprofloxacin not only during experiments in mice [27] but in clinical situations in granulocytopenic patients too (unpublished data). Recently we encountered infections with ciprofloxacin-resistant *Escherichia coli* and *Serratia marcescens*. This resistance might well be based on the absence of a genotypically altered composition of outer membrane protein F, resulting in resistance to several non-related antibiotics [28]. The expectation that the threat of resistance will increase in the near future is fed by the present large-scale use and misuse of the new quinolones.

The choice between continuing with the old-fashioned Leiden regimen for SD, consisting of neomycin–polymyxin–pipemidic acid and amphotericin, and the modern trend toward one of the newer fluoroquinolones, is based on conceptual arguments as described above. SD only should consist of agents that are not

resorbable or do not induce adequate serum levels. Our decision to continue with the Leiden regimen is also supported by a study of Jansen and co-workers [29]. They performed a comparative study of 44 BMT recipients and 24 chemotherapy patients who received ciprofloxacin and 20 BMT recipients and 12 chemotherapy patients who received the Leiden regimen. None of the patients developed septicaemia with Gram-negative rods. Therefore the argument that ciprofloxacin is more effective than the Leiden regimen is not valid.

Developments in BMT and the interaction with SD

During the last two decades BMT has evolved from an experimental approach for leukaemic patients with refractory disease to approved antileukaemic therapy for patients in remission. Such acceptance is the result of a number of successive improvements. After the introduction of measures to prevent early bacterial and fungal infection GVHD became the main problem. Major contributions toward the prevention of GVHD have been improvement in histocompatibility matching, the introduction of cyclosporin A as immunosuppressive therapy and the development of monoclonal antibodies for the elimination from the bone marrow graft of T lymphocytes, which cells are responsible for GVHD. The reverse of depletion is a decreased acceptance of the bone marrow graft and an increased incidence of relapse of leukaemia. To solve these latter problems, conditioning regimens characterized by increased cytotoxicity were introduced, resulting in severe nausea, damage to the mucosal membranes and aggravation of the compromised host resistance. Decreased compliance to swallow SD and drugs and severe infections with Gram-positive bacteria [20, 22] and fungi were the result, leading to the introduction of various adaptations of infection prevention.

Current SD and additional measures

One week before admission the full dosage of SD (PAD capsules, pipemidic acid tablets, Table 1) is prescribed. At admission (Fig. 2) preparation of the patient is started: application of orabase to the oral cavity, introduction of mupirocin into the nares to treat carriership of *Staphylococcus aureus*, disinfection of the skin with povidone-iodine scrub and/or chlorhexidine, protective isolation (Fig. 2) and low-risk food. Before the start of the conditioning regimen, consisting of cytotoxic drugs and total body irradiation, the majority of patients have already been successfully decontaminated. During conditioning the SD regiment is reduced to half the dosage to improve compliance which usually decreases due to nausea and swallowing complaints. If the surveillance cultures still yield Gram-negative rods, pipemidic acid is replaced by either i.v. cotrimoxazole or oral ciprofloxacin, depending on the sensitivity of the isolated rods and/or the compliance of the patient. If the number of *Candida* spp. has increased, amphotericin is given, either as lozenges or as tablets in addition to the amphotericin in the capsules and orabase. After the last day of cytotoxic therapy prophylaxis against (viridans) streptococci is started and continued for two weeks. After recovery of granulopoiesis ($> 0{\cdot}3 \times 10^9$/l) isolation and decontamination are stopped unless the patient develops GVHD. About 1·5 months after BMT, when the patient is discharged, antibiotic prophylaxis against pneumococci and *Pneumocystis carinii* is started. This prophylaxis (cotrimoxazole: 1 tablet 800/160 per day) continues for one year.

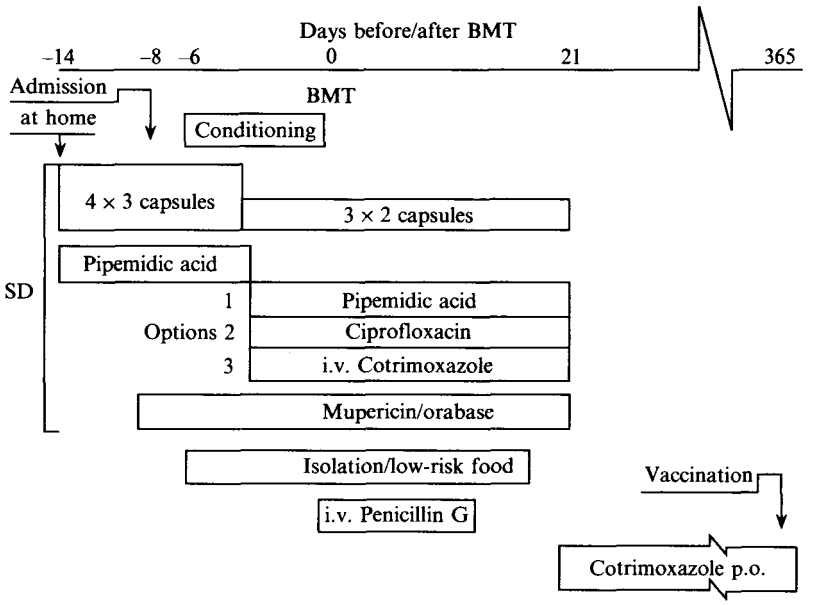

Fig. 2. Prophylactic measures according to time before and after bone marrow transplantation (BMT). Capsules contain a mixture of neomycin, polymyxin B and amphotericin in the dosages given in Table 1. Option 1, 2 or 3 is chosen on the basis of surveillance cultures and compliance of the patient, as is described in the section 'Current SD and additional measures'. Vaccination: polyvalent pneumococcal vaccine.

Ten to 11 months after BMT the patients are vaccinated with a polyvalent pneumococcal vaccine (Pneumovax® 23, Merck Sharp and Dohme, Haarlem, The Netherlands). Recent data have revealed that the efficacy of this vaccination is rather disappointing.

Present results in BMT

All transplantations performed in our hospital among adult patients during 1990–1 were evaluated. The data are presented by survival analysis curves which include the chronologic occurrence of major complications for allogeneic and for autologous BMT.

Ten of the 21 patients who received an allogeneic BMT (Fig. 3a) died, resulting in a 2-year actuarial survival of approximately 50%. This percentage is a current result for a non-selected group of patients with several risk factors [30, 31]. The risk factors were a relatively high age (median 34 years, range 12–51) with six patients over 40 years of age, unfavourable donor matching (4 patients) and unfavourable underlying diseases (6 patients) due to the high risk of relapse (secondary leukaemia after myelodysplasia, non-Hodgkin lymphoma). Major bacterial infection only occurred during the first 8 weeks (Fig. 2a); all except one were non-fatal catheter-associated bacteraemias (7 patients). The patient who died developed a fatal polymicrobial infection; *Staphylococcus epidermidis*, *Streptococcus mitis* and *Streptococcus bovis* were cultured from the blood simultaneously. Non-bacterial infections were caused by *Aspergillus* spp. (two patients survived, one died) and *Pneumocystis carinii*; the latter caused fatal pneumonia in a patient hypersensitive to cotrimoxazole who received pentamidine inhalation as prophylaxis. Infections covered by SD (Gram-negative rods, *S. aureus*, *Candida* spp.) were not encountered, whereas systemic prophylaxis against

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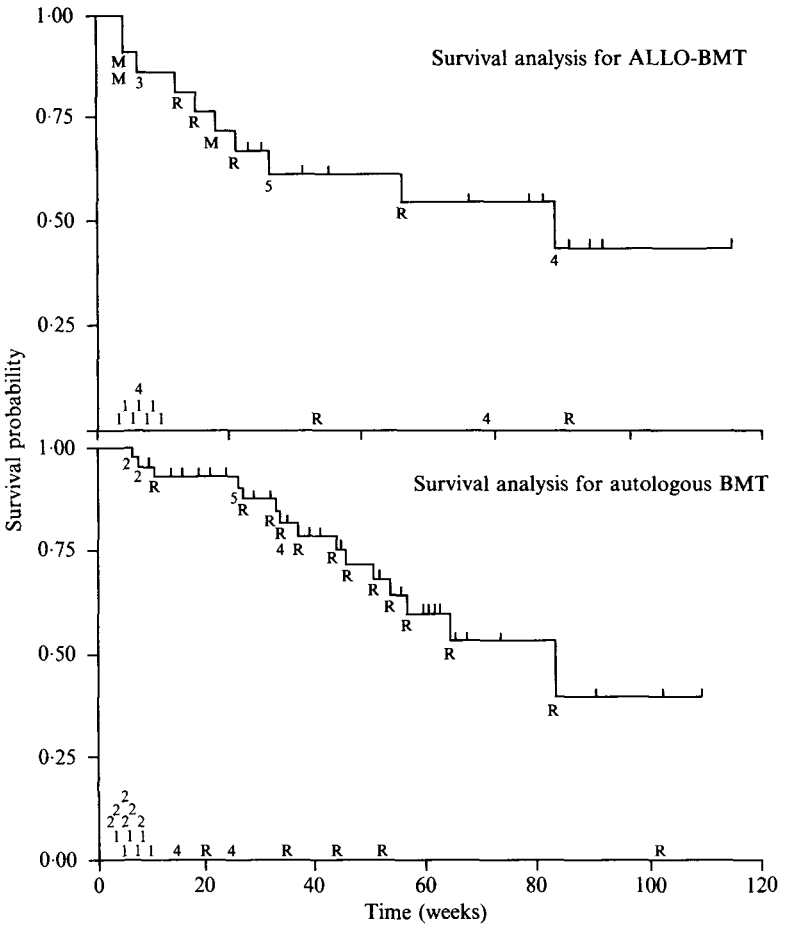

Fig. 3. Survival analysis for allogeneic and autologous BMT during 1990–1. Letters/numbers underneath the curve: fatal complications. Letters/numbers above the *x*-axis: non-fatal complications. (1), Coagulase-negative staphylococci (CNS); (2), *Streptococcus mitis*; (3), polymicrobial infections; (4), *Aspergillus* spp.; (5), *Pneumocystis carinii*; (M), miscellaneous; (R), relapse.

streptococci failed in one patient who received cotrimoxazole due to penicillin hypersensitivity.

Forty-four autologous bone marrow transplantations were performed during 1990–1. Since 1990 these patients were not yet considered to be at risk for infections with viridans streptococci; penicillin prophylaxis was only given to patients who underwent BMT in 1991. Fifteen patients died, resulting in a 2-year survival of approximately 40% (Fig. 3b). Infections covered by SD did not occur, in contrast to those not covered by SD. The latter were infections with *Streptococcus mitis* (8 patients), which caused the death of 2 patients, and non-fatal catheter-associated infections with coagulase-negative staphylococci (6 patients). Non-bacterial infections were due to *Aspergillus fumigatus* and were not fatal due to recovery from granulopoiesis in two cases and fatal in a patient with relapse of leukaemia. Infection with *Pneumocystis carinii* was diagnosed in one patient and probably triggered ARDS followed by fatal fibrosis of the lung.

In both patient groups relapse of the underlying disease was a major cause of

https://doi.org/10.1017/S0950268800050342 Published online by Cambridge University Press

failure. Among the allogeneic BMT patients relapse was the cause of death in four cases, whereas two patients in relapse are still alive at the probing date. Among the autologous BMT patients relapse occurred even more frequently, i.e. in 40% of the cases; 12 patients have already died, 5 are still alive at the probing date.

The efficacy of SD in both allogeneic and autologous BMT is clearly demonstrated by the virtual absence of infections with the target micro-organisms, i.e. Gram-negative rods, *Staphylococcus aureus* and *Candida* spp. For 60 of the 65 patients Gram-negative rods and *S. aureus* were not present in any of the surveillance cultures during the period of deep granulocytopenia ($< 0{\cdot}01 \times 10^9$/l). For only 5 of 65 patients did the number of *Candida* spp. temporarily exceed a critical level, i.e. more than 100 colony-forming units cultured from more than two sites of the body (e.g. oral cavity, faeces and genitourinary tract) which we consider as indicative of a substantial risk for systemic candida infection in our department. In 15 cases *Candida* spp. was not cultured from any site of the body.

Total or selective decontamination?

At present the majority of BMT centres use SD or no decontamination at all. In a few BMT centres total decontamination (TD) is applied, not only to prevent infections but also to mitigate GVHD. The increasing number of infections with micro-organisms not covered by SD and the discussion about prevention of GVHD by TD have given rise to the question of whether total or selective decontamination should be used for allogeneic BMT. Although animal experiments show that germfree animals suffer less from GVHD than conventional animals [32–34], clinical data on man are too scarce to convince the majority of haematologists. One study performed at the Department of Paediatrics in Leiden [35] demonstrated a lower incidence of GVHD grade II-IV in totally decontaminated children (median age 10 years) in comparison to those who were selectively decontaminated (median age 10 years). Our own randomized study [36, 37] showed less severe GVHD in adult patients, who initially received selective decontamination but additionally were given clindamycin (i.v.) and cephaloridine (p.o.) to eliminate residual anaerobic intestinal flora in comparison to patients who did not receive this additional decontamination. The problems of all studies in this field are the relatively small numbers of patients and the heterogeneous population with differences in donor matching, underlying diseases and age. In addition, classification of the severity of GVHD (class I-IV) is rather subjective but this approach is still the current standard instead of such objective parameters as the loss of serum proteins [6]. Probably the background noise of other factors involved in GVHD, such as autoreactivity due to tissues damaged by aggressive cytotoxic therapy [38], age, donor matching and the choice of GVHD prophylaxis, hinders unambiguous demonstration of the effect of modulation of the endogenous microflora on GVHD.

Irrespective of whether bacteria play an important role in GVHD, there is no need to eliminate the residual microflora in patients grafted with T-lymphocyte-depleted bone marrow from HLA-identical siblings because in these patients aGVHD only occurs as a very mild disease.

As far as the prevention of infections with micro-organisms not covered by SD is concerned, TD should prevent all bacterial and fungal infections – in theory. In

practice it has been found that TD seldom results in a germfree status of the patients, so that bacterial or fungal infections still occur. Especially in adults, persistent micro-organisms (resistant bacteria, *Candida* spp.) are a risk during TD because colonization resistance is extremely low. Analogous to TD, vancomycin therapy against catheter-associated CNS infection also eliminates a major part of the residual flora in patients on SD. In these patients elimination of candida becomes a problem. Without full compliance (intake of higher dosages of amphotericin) these patients will develop candida stomatitis, oesophagitis and even systemic candida infection.

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