

## Review

# The relationship between gut-derived bacteria and the development of the multiple organ dysfunction syndrome

GRARD A. P. NIEUWENHUIJZEN<sup>1</sup>, EDWIN A. DEITCH<sup>2</sup> AND R. JAN A. GORIS<sup>1</sup>

<sup>1</sup>Department of Surgery, Academic Hospital Nijmegen, The Netherlands, and <sup>2</sup>Department of Surgery, University of Medicine and Dentistry, Newark, New Jersey, USA

(Accepted 17 July 1996)

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### ABSTRACT

Abnormal colonisation, infections of gut origin and bacterial translocation are all signs of gut failure that have been hypothesised as being implicated in the pathogenesis of the multiple organ dysfunction syndrome (MODS). We have summarised published experimental and clinical studies that have tried to correlate the occurrence or prevention of these phenomena with the development of MODS. We conclude that in some patients loss of intestinal barrier function or the onset of infection precedes the development of MODS. In other patients, however, this relationship is not so clear and it seems that these are epiphenomena of critical illness and may reflect a failure of the host's immune and mechanical defence systems. The causal relationship between these phenomena and the development of MODS is complex and needs further clarification.

*Key words:* Gastrointestinal tract; nosocomial infections; bacterial translocation; selective decontamination of the digestive tract.

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### INTRODUCTION

Despite major advances in critical care, the multiple organ dysfunction syndrome (MODS) still develops in about 15% of patients admitted to an intensive care unit (ICU) and remains the major cause of death in critically ill patients (Knaus & Wagner, 1989). Under various pathological conditions in critically ill patients, gut function may fail and serves as an initiator and stimulator of a generalised systemic inflammatory response, acting as the motor of sepsis and MODS (Meakins & Marshall, 1986; Border et al. 1987).

Some questions must be answered if gut failure is an important phenomenon in MODS. First, infections of gut origin should be a significant problem in critically ill patients. Secondly, these infections should be related to gut barrier failure or to an abnormal colonisation of the gut. Lastly, interventions to reduce this auto-intoxication of the host by the gut should reduce morbidity and mortality.

In this review we will discuss the issues of nosocomial infections, bacterial translocation and the results of selective decontamination of the digestive tract (SDD), trying to correlate the development of MODS with gut barrier failure.

### NOSOCOMIAL INFECTIONS

Because of their impaired host defences, multiple invasive procedures in which normal epithelial barriers are disrupted, and the extensive use of broad-spectrum antibiotics, patients in the ICU are at increased risk of developing nosocomial infections (Donowitz et al. 1982). Nosocomial or ICU-acquired infections are those infections that are caused by the specific microbiological environment in the ICU. These develop at least 48 h after admission to the ICU and are caused mainly by potentially pathogenic microorganisms, such as the gram negative *P. aeruginosa*, *Serratia marcescens* and *Acinetobacter* spp.,

enterococci, *S. epidermidis* and *aureus* and yeasts such as *Candida albicans* (Donowitz et al. 1982; Eickhoff, 1982; Daschner, 1985; Bartlett et al. 1986; Chandrasekar et al. 1986; Craven et al. 1988; Emmerson, 1990; Marshall & Sweeney, 1990; Nathens et al. 1992), which are frequently resistant to many antibiotics.

The reported incidence of nosocomial infections in ICU-patients varies considerably between studies, ranging from 7.2% to 41.4% (Northey et al. 1974; Daschner et al. 1982; Donowitz et al. 1982; Brown et al. 1985; Daschner, 1985; Chandrasekar et al. 1986; Craven et al. 1988; Marshall & Sweeney, 1990), in which surgical ICUs seem to have a higher incidence of infection. Furthermore, infection rates tend to increase with the length of stay in the ICU (Northey et al. 1974). The development of a nosocomial infection may be related to an increased mortality. It has been calculated that the relative risk of death following the development of a nosocomial infection increased 3.5-fold for a mixed ICU population (Craven et al. 1988). Lower respiratory tract infections are the leading cause of death from nosocomial infections (Gross et al. 1980), and crude infection rates ranging from 4.6% to 21.3% have been reported in ICU patients (Johanson et al. 1972; Daschner et al. 1982; Donowitz et al. 1982; Langer et al. 1987; Craven et al. 1988; Fagon et al. 1989; Chevret et al. 1993). The incidence varies with the method of diagnosis: when the diagnosis of pneumonia was made by bronchoscopy or protected brush specimens, the incidence was 23.1% whereas if the diagnosis was based on clinical criteria the incidence was 30.6% (Selective Decontamination of the Digestive Tract Trialists' Collaborative Group, 1993). The risk of developing nosocomial pneumonia increases with the length of stay in the ICU, the actuarial risk being 6.5% after 10 d and 28% after 30 d (Fagon et al. 1989). Overall crude mortality rates for patients with nosocomial pneumonia ranged from 20–55% but increased to 70–80% when *P. aeruginosa* was the infecting microorganism (Stevens et al. 1974; Gross & van Antwerpen, 1983; Craven et al. 1986; Fagon et al. 1989; Leu et al. 1989; Meduri, 1990; Chevret et al. 1993). Several studies have documented that the development of nosocomial pneumonia is associated with an increased mortality. In a case-control study it was concluded that the mortality attributed to pneumonia was 33% (Leu et al. 1989); the development of nosocomial pneumonia seemed to increase the length of stay in the ICU by a week (Freeman et al. 1979). However, others demonstrated in ICU patients who required continuous mechanical ventilation, that although the development of pneu-

monia was one of the variables in the univariate analysis that was associated with mortality after logistic regression, pneumonia was not an independent factor after multivariate analysis (Craven et al. 1986). Colonisation of the proximal gastrointestinal (GI) tract with potentially pathogenic microorganisms, especially gram negative bacteria, appears to be associated with the development of nosocomial pneumonia (Le Frock et al. 1979) and this colonisation precedes the appearance of gram-negative bacteria in the trachea (Atherton & White 1978; Kerver et al. 1987; Marshall et al. 1993). Because colonisation of the GI tract with *Candida*, *P. aeruginosa* and *S. epidermidis* was associated with high multiple organ failure (MOF) scores, it was suggested that the proximal GI tract could be viewed as the undrained abscess of MODS (Marshall et al. 1993).

In the late 1970s it was hypothesised that MODS was causally related to uncontrolled infection (Polk & Shields, 1977; Fry et al. 1980). This hypothesis was confirmed by others, demonstrating a good correlation between MOF scores and the incidence of ICU-acquired infections (Marshall et al. 1988a). Others, however, have disputed this hypothesis since a focus of uncontrolled infection was identified in only about half of the patients developing MODS (Goris et al. 1985; Waydhas et al. 1992). Furthermore, drainage of confirmed intra-abdominal abscesses did not reverse the course of MODS or increase survival (Norton, 1985). Although patients with infection have a higher mortality, and infection is found in an appreciable number of those who die, outcome appeared to be influenced more by the host's response to this infection than by the infection itself (Marshall & Sweeney, 1990). Hence, it has been postulated that in some patients infection is the expression of failing host defences, and that many critically ill patients die with, rather than because of, infection (Deitch, 1992). Clearly in some patients infection seems to be directly related to the development of MODS and mortality, but in most patients it is a secondary phenomenon and a symptom rather than a cause of MODS.

#### BACTERIAL TRANSLOCATION

Gut barrier failure, leading to the passage of viable enteric bacteria and endotoxin across the intestinal mucosal barrier to the mesenteric lymph nodes (MLN) and distant organs, has been termed bacterial translocation (BT) (Wolochow et al. 1966; Berg & Garlington, 1979). The mechanism by which microorganisms reach the lamina propria of the gut has

been hypothesised to be paracellular (Deitch et al. 1988, 1989*b*; Ma et al. 1989) or transcellular, the latter suggesting that the enterocyte has an active, energy-consuming, role (Alexander et al. 1990*a*; Wells et al. 1990). Subsequently, macrophages might transport bacteria from the gut to the MLN (Wells et al. 1987*b*, 1988), and the route by which the bacteria reach the systemic circulation could be by both the lymphatic system and by direct invasion of the capillaries with subsequent transport through the portal system to the liver. The lymphatic route, however, seems to be the primary path for bacterial translocation (Deitch, 1990*a*; Mainous et al. 1991).

Pathophysiologically, BT seems to be promoted by 1 of 3 factors: disruption of the normal ecology of the indigenous microflora resulting in bacterial overgrowth; impaired host immune defences; and physical disruption of the mucosal barrier of the gut. In critically ill or severely injured patients most of these factors are implicated. Experimentally, BT is promoted by various conditions such as the administration of oral antibiotics (Berg, 1981; Deitch et al. 1985; Wells et al. 1987*a*, 1991), the use of total parenteral nutrition (Alverdy et al. 1988; Mainous et al. 1991), elemental diets (Spaeth et al. 1990*a, b*) or protein malnutrition (Li et al. 1989; Deitch et al. 1990*b*), haemorrhagic shock (Baker et al. 1988; Koziol et al. 1988; Sori et al. 1988; Flanagan et al. 1990; Arden et al. 1993), burns (Maejima et al. 1984*a, b*; Alexander et al. 1990*b*; Jones et al. 1990; Fukushima et al. 1992; Herndon & Ziegler, 1993), surgical trauma and anaesthesia (Salman et al. 1992), abdominal irradiation (Guzman-Stein et al. 1989), intestinal obstruction (Deitch et al. 1990*a*), and obstructive jaundice (Deitch et al. 1990*c*; Slocum et al. 1992). The induction of a generalised inflammatory response by endotoxin (Deitch et al. 1987, 1989*a*; Deitch, 1991) or zymosan (Mainous et al. 1991; Deitch et al. 1992*a*; Mainous et al. 1993), as well as the induction of a generalised immunosuppressed state with prednisolone or cyclophosphamide (Berg et al. 1988) or the induction of impaired cell-mediated immunity (Owens & Berg, 1980, 1982) have also been reported to promote BT.

BT could explain the paradoxical observation that bacteraemia with enteric bacteria was regularly found without an identified infectious focus in trauma patients (Garrison et al. 1982; Border et al. 1987), patients with extensive burns (Jarret et al. 1978) or patients dying of MODS and sepsis (Goris et al. 1985). Because it has been shown experimentally that alterations in the flora of the GI tract (Wells & Balish, 1979; Marshall et al. 1988*b*) and translocation of

bacteria and endotoxin by itself (Deitch et al. 1991; Sullivan et al. 1991) can alter the host's immune response, it has also been postulated that BT by itself could initiate, exaggerate and perpetuate the systemic inflammatory response that leads to MODS and could be viewed as the motor of MODS (Meakins & Marshall, 1986).

Animal studies that have tried to correlate BT with mortality and MODS have given conflicting results. In a zymosan-induced animal model of MODS, mortality was significantly lower in germ-free animals but organ damage was still present in all animals, suggesting that BT has only a partial role in the development of MODS (Goris et al. 1986). The correlation between survival and BT seems to be related to the magnitude of the inflammatory insult since in another study of low-dose zymosan peritonitis, mortality was reduced by cefoxitin, but this effect was lost when higher doses of zymosan were given (Deitch et al. 1992*b*). It has recently been shown that elimination of macrophages in this model of MODS led to an increase in systemic BT but also, surprisingly, to an improvement in survival (Nieuwenhuijzen et al. 1993). Bacteraemia and survival therefore do not always correlate, particularly in systemic inflammatory states. On the other hand, an elegant study, in which gavaged *E. coli* labelled with carbon-14 oleic acid were used, showed that after severe haemorrhagic shock all animals with positive blood cultures died compared with only 17% of the animals with no bacteraemia, suggesting a positive correlation between BT and mortality (Sori et al. 1988).

Human data on gut barrier function and BT are limited and conflicting. Loss of gut mucosal barrier function, as measured by an increased permeability, has been described in burn patients, with a good correlation with septic complications (Ziegler et al. 1988; Deitch, 1990*b*; LeVoyer et al. 1992). Recently, increased intestinal permeability has been reported after severe trauma and haemorrhagic shock in man, but no causal relationship could be shown between increased intestinal permeability and the severity of the insult, infectious complications, or MOF scores (Roumen et al. 1993). Although early translocation of endotoxin has been demonstrated in burn patients (Winchurch et al. 1987), it was also shown that neutralising circulating endotoxin with polymyxin B did not reduce either sepsis score or mortality (Munster et al. 1993). Although endotoxaemia has been shown to be associated with septic shock (van Deventer et al. 1988; Danner et al. 1991), in a large multicentre randomised double blind placebo-controlled trial, treatment of patients with septic shock

with anti-endotoxin could only decrease mortality in a subgroup of patients with gram-negative bacteraemia (Ziegler et al. 1991).

Data on BT in man are sparse. BT to the MLN has been demonstrated in patients with Crohn's disease (Ambrose et al. 1984), simple intestinal obstruction (Deitch 1989) and abdominal trauma (Moore et al. 1991). Brathwaite et al. (1993) sampled MLN and portal venous blood at laparotomy for blunt abdominal trauma. All macrophages within the MLN were positive for *E. coli*  $\beta$ -galactosidase, while only 5% were positive with conventional culturing techniques, suggesting that most of the bacteria that reached the MLN were ingested and killed by macrophages (Brathwaite et al. 1993). This is in line with a study on patients with abdominal trauma in which regular culture techniques demonstrated that only 6% of the MLN contained bacteria, while with electron microscopy this number rose to 81% (Reed et al. 1994).

Peitzman et al. (1991) observed, however, that all MLNs cultured at laparotomy from patients with abdominal trauma were sterile as were three quarters of those from patients operated for gastrointestinal disease. A recently published study in multiple organ donors, in which specimens of MLN, liver, spleen, lung, and gut were harvested during explantation, has demonstrated that translocation of bacteria and endotoxin occurs in patients with an anatomically intact GI tract (van Goor et al. 1994). Bacteria were recovered from 79% of the MLN specimens, 14% of the liver specimens and half of the lung specimens. Positive blood cultures were found in 7% of the donors and elevated systemic endotoxin concentrations in 19%. These studies clearly show that BT definitely occurs in various human pathological conditions and that the variability of the incidence could be the result of different bacterial determination techniques. No single study, however, could correlate septic complications or mortality with BT.

Although BT has been associated with mortality and septic complications in various animal models, the question still remains whether it is an important pathophysiological event in human disease or just an epiphenomenon of severe disease, since results are quite variable. BT may be seen as a normal biological process functioning to sample antigens from the gut and to prime the host's immune response. In this perspective it is interesting that the enterocyte has an active role in BT (Alexander et al. 1990a; Wells et al. 1990). On the other hand, an explanation for these variable results may be that intestinal bacteria or endotoxins do not necessarily need to reach the portal

circulation to induce or contribute to a systemic inflammatory state. It has been demonstrated that the gut can be a cytokine-generating organ after haemorrhagic shock and that gut-derived cytokines can be liberated even in the absence of detectable bacteria or endotoxin in the portal circulation (Deitch et al. 1994). This and other studies have indicated that the gut can produce important amounts of immunoinflammatory factors and that intestinal injury predisposes to distant organ injury, even in the absence of detectable bacteria or endotoxin in the portal or systemic circulations (Schmeling et al. 1989; Pogetti et al. 1992; Gerkin et al. 1993). This suggests that the potential relationship between gut barrier failure function and MODS may be more complex than initially assumed.

#### SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT

Selective decontamination of the digestive tract (SDD) is a method designed to suppress selectively potentially pathogenic microorganisms in the oropharynx and upper GI tract with topically applied, nonabsorbable antibiotics, which leave the anaerobic flora intact. Its rationale is based on the concept of colonisation resistance, which describes the role of anaerobic colonisation of the GI tract, preventing competitive overgrowth by potentially pathogenic gram-negative microorganisms (van der Waaij et al. 1971). Since the development of ICU-acquired pneumonia and mortality have been associated with oropharyngeal colonisation with gram-negative microorganisms (Kerver et al. 1987; Marshall et al. 1993), it was hypothesised that prevention of overgrowth of oropharyngeal and intestinal bacteria by potentially pathogenic microorganisms by SDD might reduce the incidence of ICU-acquired infections and mortality.

The use of SDD in critically ill patients in the ICU was introduced by Stoutenbeek et al. (1984), who used SDD in trauma patients that required mechanical ventilation for more than 5 d. A regimen of polymyxin E, tobramycin and amphotericin B as topical non-absorbable antibiotics was used together with systemic cefotaxime for the first 48 h to prevent the occurrence of primary gram-negative pneumonia when SDD was not fully established (Stoutenbeek et al. 1984, 1987). This protocol significantly reduced gram-negative colonisation of the oropharynx and the gut. The total infection rate was reduced significantly from 81% to 16%, with an overall decrease in the respiratory tract infection rate from 59% to 8%, and a decrease in the

secondary respiratory tract infection rate from 20% to zero. A significant reduction in mortality, however, was not achieved (Stoutenbeek et al. 1984). The results of this study are debatable, because historical controls were used.

Since then some 40 studies have been published in which the clinical efficacy of SDD was evaluated in different groups of patients in the ICU, with different goals and study designs (see Fig.). Ten nonrandomised studies (Ledingham et al. 1988; Brun-Buisson et al. 1989; Hunefeld, 1989; Konrad et al. 1989; Thülig et al. 1989; McClelland et al. 1990; Sydow et al. 1990; Hartenauer et al. 1991; Winter et al. 1992; Tetteroo et al. 1993) and 21 randomised studies (Unertl et al. 1987; Kerver et al. 1988; Brun-Buisson et al. 1989; Ulrich et al. 1989; Godard et al. 1990; Rodriguez-Roldan et al. 1990; Aerdt et al. 1991; Blair et al. 1991; Pugin et al. 1991; Cerra et al. 1992; Cockerill et al. 1992; Ferrer et al. 1992; Gastinne et al. 1992; Hammond et al. 1992; Jacobs et al. 1992; Palomar et al. 1992; Rocha et al. 1992; Sanchez-Garcia et al. 1992; Verhaegen, 1992; Winter et al. 1992) were performed in surgical, medical, and mixed surgical and medical ICUs. Seven studies were randomised, double-blind, placebo-controlled trials (Rodriguez-Roldan et al. 1990; Pugin et al. 1991; Cerra et al. 1992; Gastinne et al. 1992; Hammond et al. 1992; Rocha et al. 1992; Sanchez-Garcia et al. 1992). Nine studies have been done in specific homogeneous groups such as patients with multiple injuries (Stoutenbeek et al. 1984, 1987; Hammond et al. 1994), cardiopulmonary bypass surgery (Flaherty et al. 1990; Fox et al. 1991; Martinez-Pellús et al. 1993), liver transplantation (Rolando et al. 1993), burns (Mackie et al. 1992), oesophageal resection (Tetteroo et al. 1990), neurosurgery (Korinek et al. 1993), or neurological disorders (Hammond & Potgieter, 1993). Controls consisted of historical, consecutive (with or without cross over) or concurrent groups. The SDD antibiotic protocols showed a great variability. Most commonly polymyxin, tobramycin and amphotericin B and systemic antibiotic prophylaxis with cefotaxime were used. However, other nonabsorbable antibiotic regimens were also used. Furthermore, the type and dose of systemic antibiotic prophylaxis differed widely among the clinical trials. Ten studies did not use any systemic antibiotic prophylaxis (Stoutenbeek et al. 1984; Brun-Buisson et al. 1989; Hunefeld, 1989; Godard et al. 1990; Rodriguez-Roldan et al. 1990; Cerra et al. 1992; Gastinne et al. 1992; Korinek et al. 1993; Martinez-Pellús et al. 1993; Hammond et al. 1994). These studies did not show any unfavourable results of not using systemic antibiotic prophylaxis,

leaving its use highly debatable. Based on the comparable clinical results with different antibiotics, the optimal antibiotic protocol still remains to be established.

Inclusion criteria also differed widely among the studies. Some studies included all patients admitted to the ICU (Ledingham et al. 1988; Godard et al. 1990; Rodriguez-Roldan et al. 1990; Tetteroo et al. 1990; Pugin et al. 1991; Mackie et al. 1992; Martinez-Pellús et al. 1993; Rolando et al. 1993), others included only patients with a prolonged ICU-stay or patients requiring chronic mechanical ventilation. This is important because it takes 4–5 d for SDD to establish oropharyngeal decontamination and at least 10 d before reductions in the rectal flora are seen consistently. Furthermore, patients with primary infections were not excluded consistently, thereby further compounding interpretation of the data. Only one study excluded patients having an infection on admission (Cockerill et al. 1992).

The goal of most studies was to compare the efficacy of SDD in reducing nosocomial infections, particularly lower respiratory tract infections, and mortality. The diagnosis of respiratory tract infection, however, was based on different criteria in different studies. Most studies used clinical and radiological criteria, combined with cultures of the tracheal aspirate. Only 7 studies used the more accurate method of culturing protected catheter specimens to diagnose pneumonia (van der Waaij, 1983; Hunefeld, 1989; Rodriguez-Roldan et al. 1990; Sydow et al. 1990; Pugin et al. 1991; Verhaegen, 1992; Hammond et al. 1994).

All studies reported that SDD caused a significant reduction in the colonisation rates of gram-negative bacteria of the oropharynx and trachea within 48 h. Rectal decontamination of gram-negative organisms, however, took longer, usually 10–12 d. In addition, decontamination of the rectal flora was often incomplete and tended to decrease with long term use (Stoutenbeek et al. 1984, 1987; Ledingham et al. 1988; Hunefeld, 1989; Ulrich et al. 1989; Pugin et al. 1991; Hammond et al. 1992; Rocha et al. 1992; Winter et al. 1992; Hammond et al. 1994).

To date, there have been published 4 excellent meta-analyses of randomised clinical trials with SDD (Vandenbroucke-Grauls & Vandenbroucke, 1991; Selective Decontamination of the Digestive Tract Trialists' Collaborative Group, 1993; Heyland et al. 1994; Kollef, 1994). All 4 showed significant reductions in the incidence of respiratory tract infections by SDD with relative risks ranging from 0.12 to 0.46. Although these reductions were consistent in all

**Published Trials with Selective Decontamination of the Digestive tract (SDD)**

Study characteristics				RTI rate				Mortality rate		
Patients	Study Design	SDD regimen		PCS	Controls	SDD	p	Controls	SDD	p
<b>Non-Randomized trials</b>										
Ledingham 1988	Mixed	Cons	PTA/ C		10	3	<0.01	24	24	NS
Sydow 1988	Mixed	His	PTA/ C		75	7	<0.001	15	0	<0.05
Brun-Buisson 1 1989	Mixed	Cons	PNeNa/J-	X	21	19	NS	20	22	NS
Hunefeld 1989	Mixed	Conc	PTA/-		55	37	NS	94	63	<0.001
Konrad 1989	Mixed	Conc	PTA/ C		27	6	<0.001	21	30	NS
Thülig 1989	Mixed	Cons	PTA/ C		46	10	<0.001	47	38	NS
McClelland 1990	Mixed	His	PTA/ C		42	7	<0.05	42	40	NS
Hartenuer 1991	Surg	DBPC	PTA/ C		45	10	<0.001	47	38	NS
Winter 1 1992	Mixed	His	PTA/ Ceftr	X	13	3	NS	40	36	NS
Tetteroo 1993	Mixed	Obs Coh	PTA/ C		52	8	<0.001	44	18	<0.05
<b>Randomized trials</b>										
Unertl 1987	Mixed	RConc	PGA/-		70	21	<0.01	30	25	NS
Kerver 1988	Mixed	RConc	PTA/ C		40	6	<0.001	32	28	NS
Brun-Buisson 2 1989	Mixed	RConc	PNeNa/J-	X	12	8	NS	24	22	NS
Ulrich 1989	Mixed	RConc	PNA/ Tr		44	6	<0.001	54	31	<0.05
Godard 1990	Mixed	DBPC	PTJ/-	X	8	0	<0.05	18	12	NS
Rodriguez-Roldan 1990	Mixed	RDBPC	PTA/-		73	0	<0.001	30	33	NS
Aerdtz 1991	Mixed	RConc	PNA/ C		62	6	<0.001	10	12	NS
Blair 1991	Mixed	RConc	PTA/ C		22	7	<0.01	19	15	NS
Pugin 1991	Mixed	RDBPC	PNeV		78	16	<0.001	27	26	NS
Cerra 1992	Surg	RDBPC	NNy/-		100	56	<0.001	48	52	NS
Cockerill 1992	Mixed	RConc	PGNy/ C		16	4	<0.05	21	15	NS
Ferrer 1992	Mixed	RConc	PTA/ C	X	24	23	NS	28	29	NS
Gastinne 1992	Mixed	RDBPC	PTA/-	X	19	14	NS	36	40	NS
Hammond 1992	Mixed	RDBPC	PTA/ C		19	15	NS	17	18	NS
Jacobs 1992	Mixed	RConc	PTA/ C		9	0	NS	50	31	NS
Palomar 1992	Mixed	RConc	PTA/ C	X	53	21	<0.01	29	29	NS
Rocha 1992	Mixed	RDBPC	PTA/ C		46	15	<0.001	44	21	NS
Sanchez-Garcia 1992	Mixed	RDBPC	PGA/ Ceftr		43	24	<0.01	46	39	NS
Verhaegen 1 1992	Mixed	RConc	PTA/ C		22	16	NS	18	20	NS
Verhaegen 2 1992	Mixed	RConc	OA/ O		22	11	<0.05	18	21	NS
Winter 2 1992	Mixed	RConc	PTA/ Ceftr	X	18	3	<0.05	43	36	NS
<b>Specific patient groups</b>										
Stoutenbeek 1984	Trauma	His	PTA/ C		20	0	<0.001	8	0	NS
Flaherty 1990	CPB	RConc	PGA/Cefa		27	12	<0.05	-	-	
Tetteroo 1990	ER	RConc	PTA/ C		14	2	<0.05	5	3	NS
Fox 1991	CPB	Cons	PTA/ Cep		50	66	NS	67	17	<0.05
Mackie 1992	Burns	Obs Coh	PTA/ C		27	7	<0.05	21	3	<0.05
Hammond 1993	Neuro	RDBPC	PTA/ C		5	15	NS	15	15	NS
Martinez-Pellus 1993	CPB	RConc	PTA/- <sup>o</sup>		-	-		8	3	NS
Korinek 1993	Neurosurg	RDBPC	PTA/-	X	42	24	<0.04	18	13	NS
Rolando 1993	LiverTx	RConc	CoTA/Ce		10	6	NS	55	36	NS
Hammond 1994	Trauma	RDBPC	PTA/-		18	26	NS	9	13	NS

**Abbreviations in study design**

His= Historical controls  
 Conc= Concurrent controls  
 Cons= consecutive controls  
 Obs Coh= Observational cohort  
 DB= Double blind  
 PC= Placebo controlled  
 R= Randomized

PCS= protected catheter specimen  
 RTI = Respiratory tract infection

**Abbreviations in SDD regimen**

**Oropharyngeal and intestinal regimen/ systemic antibiotics**

A= Amphotericin B      N= Norfloxacin  
 C= Cefotaxime          Na= Nalidixic acid  
 Ce= Cefuroxim          Ne= Neomycin  
 Cefa= Cefazolin          Ny= Nystatin  
 Ceftr= Ceftriaxone      O= Ofloxacin  
 Cep= Cephadrin          P= Polymyxin  
 Co= Colistin              T= Tobramycin  
 G= Gentamycin          Tr= Trimethoprim  
 J= Povidone-Iodine      V= Vancomycin

Fig. Main characteristics of published studies with SDD.

subgroups analysed, the results of the studies were extremely heterogeneous, suggesting that systematic methodological variations existed. This was particularly true for the definition of pneumonia (Selective Decontamination of the Digestive Tract Trialists' Collaborative Group, 1993; Heyland et al. 1994), so effects of SDD on respiratory tract infections should be interpreted cautiously. Furthermore, when subgroups were analysed, there was a less dramatic effect when adequate criteria were used to assess respiratory tract infection (protected brush specimen or bronchoscopy) or when mortality in the control group was less than 20%. This is in accordance with the earlier observation that SDD seems to be more effective in ICUs in which the infection rate is high (Bonten et al. 1993a).

SDD had no significant favourable effect on the length of hospital stay (15.5 d in SDD patients compared with 17 d in control patients) (Heyland et al. 1994). Only 3 studies demonstrated that SDD reduced the length of ICU stay or the number of days on the ventilator (Cerra et al. 1992; Cockerill et al. 1992; Tetteroo et al. 1993). On the other hand, SDD seemed to reduce the requirements for parenteral antibiotics because of the reduced incidence of nosocomial infections (Unertl et al. 1987; Kerver et al. 1988; Ledingham et al. 1988; Flaherty et al. 1990; McClelland et al. 1990; Tetteroo et al. 1990; Aerdt et al. 1991; Blair et al. 1991). When the costs of microbiological surveillance were taken into account, a significant reduction in the overall costs/patient was calculated after SDD had been established in the ICU (Miranda et al. 1983). This was disputed by other studies that did not observe a reduction in the therapeutic use of systemic antibiotics (Ulrich et al. 1989; Godard et al. 1990; Gastinne et al. 1992). Others confirmed the reduction in the use of systemic antibiotics, however, the average costs/patient/day were 1.4 times higher in the SDD group, due to the extra costs of SDD (Rocha et al. 1992).

None of the 4 meta-analyses demonstrated a significant mortality reduction by SDD, with relative risks ranging from 0.70 to 0.93. On testing these results for heterogeneity no significance was shown. Thus with regard to this effect of SDD, methodological differences were of less importance. Some interesting observations can also be made from subgroup analyses. Although no significant effects were found in any subgroup, the largest difference between relative risks was observed in studies with or without the use of systemic antibiotics. This was greater than the effect of SDD alone, suggesting that if any effect had been observed, the administration of

early systemic antibiotics could have had the largest impact on mortality. One meta-analysis detected a significant effect of SDD on infection-related mortality, but this was mainly from the results of one single study (Ulrich et al. 1989; Kollef, 1994).

Regarding the long term adverse effects of SDD, the possible emergence of bacterial resistance needs further attention. Recently, resistance of *S. aureus* and *Acinetobacter* spp. against tobramycin and cefotaxime, both components of SDD regimens, has been demonstrated (Rocha et al. 1992; Nardi et al. 1993). Furthermore, the introduction of SDD in one ICU has been shown to be associated with the appearance of methicillin-resistant *S. aureus* (Kaufhold et al. 1992) and an increase in gram-positive infections (McClelland et al. 1988; Bonten et al. 1993b).

A striking paradox is the difference between the effect of SDD on lower respiratory tract infections and mortality. This could be the result of an inaccurate diagnosis of pneumonia. For example, as non-protected tracheal aspirates can easily be contaminated by bacteria in the oropharynx, the overdiagnosis of lower respiratory tract infections could be reduced in patients receiving SDD as a result of the reduction in oropharyngeal colonisation. Another possibility is that systemic and topical antibiotics, by inhibiting bacterial growth in culture media, would make the usual microbiological criteria for diagnosing infection less reliable. This concept is consistent with the observation that SDD is associated with substantial concentrations of antibiotics in tracheal and bronchial aspirates (Gastinne et al. 1991). It could also be that the wrong patient groups have been studied, and that SDD could be only of value for certain subpopulations in the ICU. For example, if only infection-related deaths were examined, the effect of SDD on survival appeared to be more favourable. It is also possible that there is no relationship whatsoever between infection and mortality in patients in the ICU with MODS. This hypothesis is strengthened by the observation that after multivariate analysis in patients receiving continuous mechanical ventilation, pneumonia was not a variable associated with death (Craven et al. 1986). The development of nosocomial infection in these patients could be an expression of the failure of the host's immune system and therefore viewed as part of the sequential organ system failure in MODS.

It is remarkable that the incidence of MODS was not reduced by SDD in any clinical study in which it was assessed. A few animal studies have tried to correlate SDD with survival in models of MODS. Two regimens of SDD with trimethoprim or strep-

tomyacin, respectively, were used in an animal model of MODS induced by intraperitoneal inoculation of zymosan (Goris et al. 1991). Organ damage was present in all groups, but overall mortality was significantly lower in the streptomycin group compared with the trimethoprim group and the controls, despite the fact that trimethoprim achieved a far better decontamination than streptomycin. Thus in this study it seems that SDD is not related to mortality and that other factors, such as the influence of streptomycin on macrophage function may be more important (Goris et al. 1991). Another study with zymosan peritonitis showed that a regimen of tobramycin and polymyxin E reduced endotoxin concentrations and 4 d mortality. Unfortunately no information about late mortality or organ damage was given (Rosman et al. 1992).

In conclusion, studies on SDD vary considerably in design and methods, but it seems to be clear that SDD reduces nosocomial colonisation and respiratory tract infections. The beneficial effect on mortality, cost reduction, length of stay in the ICU, days on the ventilator and mortality, is less clear and should be determined in well conducted, prospective, double blind, placebo-controlled studies. From a risk benefit point of view no legitimate argument can be made to implement SDD routinely on an ICU with mixed groups of patients, although certain homogenous subpopulations may benefit.

#### CONCLUSIONS

Experimentally and clinically it has been established that BT occurs under various pathological conditions, but its relationship to mortality and the development of MODS remains uncertain. Although the GI tracts of critically ill patients in the ICU are rapidly colonised by potentially pathogenic micro-organisms and nosocomial infections caused by them are an important cause of morbidity on the ICU, the results of studies that have tried to correlate infection rate with mortality or the development of MODS are conflicting. Furthermore, interventions directed at eliminating this occult reservoir of microorganisms, for example by SDD, have shown that although it seems to reduce the rate of respiratory tract infection, it does not have any impact on the duration of ICU stay, mortality, or the development of MODS.

In conclusion, it seems that the causal relationship of abnormal colonisation, infection, or BT to the development of organ function or MODS is complex. Clearly, in some patients, these phenomena reflect a

failure of the host's immune defence systems and can be viewed as epiphenomena of critical illness. Recognition that the development of BT or infection after the onset of MODS is of no importance supports this concept. On the other hand, there is a clinical subgroup of patients in whom loss of intestinal barrier function or the onset of infection precedes the development of MODS. In many of these patients, early control of infection is associated with clinical recovery. Lastly, there is also a third group of patients in which it is difficult to assess the contribution of bacteria to organ failure. The relative percentage of ICU patients in each of these 3 groups varies from ICU to ICU and is related, at least to some extent, to the type of patient and the underlying disease processes.

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