Prevention of lower respiratory tract infection in mechanically ventilated patients : study of the effect of a novel regime of selective decontamination in combination with short-term systemic antibiotic prophylaxis

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PREVENTION OF LOWER RESPIRATORY TRACT
INFECTION IN MECHANICALLY VENTILATED PATIENTS

Tekening omslag: Willemijn Aerdt

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PREVENTION OF LOWER RESPIRATORY TRACT INFECTION IN MECHANICALLY VENTILATED PATIENTS

Study of the effect of a novel regime of selective decontamination in combination
with short-term systemic antibiotic prophylaxis

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE RIJKSUNIVERSITEIT LIMBURG TE MAASTRICHT,
OP GEZAG VAN DE RECTOR MAGNIFICUS, PROF. DR. F.I.M. BONKE,
VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN
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Aan Piep, Willemijn en Tim

Abbreviations

DFI	Dutch Florin
ICU	Intensive Care Unit
MCR	Microbial Colonization Resistance
MIC	Minimum Inhibitory Concentration
PCR	Physiological Colonization Resistance
PTA	Polymyxin E, Tobramycin and Amphotericin B
SDD	Selective Decontamination of the Digestive tract

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Introduction

The incidence of infection in patients treated in Intensive Care Units (ICU's) is high [Donowitz,1982; Daschner,1982; Chandrasekar,1986]. In patients admitted for five days or more, the incidence of unit acquired infection may exceed 70% [Stoutenbeek,1984; Kerver,1987].

In patients requiring prolonged intubation and mechanical ventilation, infections of the lower respiratory tract are particularly troublesome and occur in about 60% of the cases [Stoutenbeek,1984; Kerver,1987].

Once a cycle of lower respiratory tract infection, reduced host defense, septicemia and organ failure is established, conventional management is clearly inadequate and mortality may exceed 50% [Stevens,1974; Watt,1984]. This stresses the need for adequate prevention of infection.

Early lower respiratory tract infections, that occur in the first days after admission, are frequently caused by microorganisms that are part of the commensal oropharyngeal flora. However, late infection, chiefly caused by Gram-negative bacilli, constitutes the main problem.

Gram-negative bacilli, which hardly ever colonize the oropharynx or stomach of healthy individuals, frequently colonize these sites in critically ill patients. By aspiration of small quantities of oropharyngeal or gastric contents past the cuff of the endotracheal tube – a frequent event in mechanically ventilated patients – these microorganisms spread to the lower airways, and infection may result. In this sequence of events, the occurrence of microbial colonization of oropharynx and stomach plays a pivotal role [Johanson,1984].

It is reasonable to postulate that prevention of colonization of oropharynx and stomach might provide prophylaxis against mechanical ventilation associated pneumonia. However, until recently, attempts to eliminate colonization by the administration of antibiotics failed and resulted in colonization with new, resistant, strains of bacteria.

In the 1970's it became clear that the autochthonous anaerobic flora of the digestive tract plays an important role in the prevention of colonization of the digestive tract with Gram-negative bacilli [Clasener,1987]. This concept did not only explain the development of colonization and super-infection with resistant strains which follows the use of those antibiotics which disturb the anaerobic intestinal flora, but also resulted in the development of Selective Decontamination of the Digestive tract (SDD) as a novel method of infection prevention. This technique implies the application of antibiotics to the digestive tract. The antibiotics used eliminate Gram-negative bacilli and yeasts from the gastrointestinal tract, but do

not affect the anaerobic flora, so leaving the limiting effect that parts of this anaerobic flora have on the growth of aerobic microorganisms intact [Van der Waaij,1974]. SDD has already proved effective in the prevention of infection in neutropenic patients.

In 1984, SDD, in combination with short-term systemic antibiotic prophylaxis, was first shown to reduce the incidence of lower respiratory tract infection in mechanically ventilated patients [Stoutenbeek,1984]. However, in this study as well as in others [Kunnen,1989; Ledingham,1988], the infection rates were compared to those in historical control groups. Furthermore, the experience was limited to the use of one regime of SDD.

In this thesis the results of a prospective, randomized study of the effect of a novel regime of SDD will be presented. The regime of SDD consisted of norfloxacin, polymyxin E and amphotericin B in combination with short-term systemic cefotaxime prophylaxis and was applied to patients that were mechanically ventilated for at least five days. The incidence of microbial colonization of the oropharynx and of the stomach, and the incidence of lower respiratory tract infection in a group of patients receiving this regime, were compared with the incidences in two control groups. In neither of the two control groups the patients received antibiotic prophylaxis; antibiotics were administered only in case of clinical evidence of infection. However, in the first control group infections were treated with antibiotics which affect the autochthonous anaerobic flora, whereas in the second control group the use of antimicrobial agents was confined to agents which lack this effect, such to evaluate the effect of two different policies of antibiotic therapy on the incidence of colonization and infection.

In chapter I, the concept of an anaerobic intestinal flora which limits the growth of aerobic microorganisms will be elucidated, as will be the clinical consequences of this concept.

In chapter II, the literature on the pathogenesis and prevention of lower respiratory tract infection in mechanically ventilated patients will be reviewed.

In chapter III the design of our study will be specified.

In chapter IV, colonization of oropharynx, stomach and rectum in the three groups will be described, as will be the role this colonization played in the development of lower respiratory tract infection.

In chapter V, the clinical results are given, with the emphasis on lower respiratory tract infection.

Chapter VI provides a cost-effectiveness analysis of the use of our regime of SDD in mechanically ventilated patients.

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CHAPTER I

Microbial colonization resistance of the digestive tract: clinical implications

In the last fifteen years it has become clear that parts of the autochthonous anaerobic intestinal flora play an important role in limitation of the growth of aerobic microorganisms in the digestive tract of man. This concept of a growth-limiting flora explains the occurrence of superinfections following the use of antibiotics that affect the anaerobic intestinal flora, and has far-reaching consequences for the antibiotic policy. This concept has further led to the development of Selective Decontamination of the Digestive tract (SDD), a novel technique of infection prevention.

This important development, that has recently been reviewed by Clasener et al., will be summarized in this chapter [Clasener, 1987].

The flora of oropharynx and lower digestive tract

Bacterial microorganisms can be categorized in many different ways. According to the role microorganisms play in the etiology of ICU-acquired infection, we divided microorganisms colonizing the intestinal tract of man into the following three categories:

1 *Autochthonous flora*

This flora, that is present in all individuals, consists mainly of anaerobic microorganisms, which are present in high concentrations (10^{7-9} /ml saliva in the oropharynx and 10^{9-11} /g faeces in the lower digestive tract). The anaerobic flora not only has important physiological functions [Mackowiak, 1982], it also contributes to the defense against colonization of the digestive tract by aerobic microorganisms [Van der Waaij, 1977]. Anaerobic microorganisms have a low pathogenicity: although the number of anaerobic microorganisms in oropharynx and lower digestive tract is about 1,000,000 times greater than the number of aerobes, anaerobic infections are rare compared to aerobic infections.

2 *Commensal flora*

This flora consists of aerobic microorganisms that, although not always present, are considered to be normal inhabitants of the oropharynx, or of the lower digestive tract. The most frequent commensal bacteria in the oropharynx are: *Strepto-*

coccus viridans, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Branhamella catarrhalis*. The most important members of the commensal flora of the lower digestive tract are *Escherichia coli* and *Enterococcus faecalis*. Commensal microorganisms play an important role in the etiology of community-acquired infections, and also in the etiology of infections acquired in the first days of admission at the ICU [Stoutenbeek,1987; Ruiz-Santana,1987].

3 Gram-negative bacilli

Gram-negative bacilli hardly ever colonize the oropharynx of healthy individuals [Johanson,1969], and Gram-negative bacilli other than *E.coli* are only seldom present in the digestive tract in concentrations above the limit of detection (10^2 microorganisms/g faeces). However, hospitalized patients – even if only moderately ill – frequently acquire Gram-negative bacilli in their oropharynx [Johanson,1969]. In the lower digestive tract of hospitalized patients, *E.coli* is often supplanted by non-coli bacilli as predominant Gram-negative bacilli [Le Frock,1979]. Gram-negative bacilli are responsible for more than 50 percent of the infections in the ICU [Massarani,1986], and for more than 80 percent of the infections occurring after the first week of admission [Stoutenbeek,1987]. Gram-negative bacillary colonization of oropharynx and stomach, and non-coli bacillary colonization of the lower digestive tract is the initial step in virtually all these infections.

Commensal flora and Gram-negative bacilli together are responsible for almost all infections at the ICU. Microorganisms from these two categories will be referred to as potentially pathogenic microorganisms.

In the present chapter, factors influencing colonization of the lower digestive tract will be reviewed. Understanding of these factors is important, because Gram-negative bacillary colonization of the lower digestive tract is a major source of infection as well as of cross-infection [Selden,1971]. Furthermore, the lower digestive tract is probably the most important ecological niche in the human body where resistant microorganisms are selected and where resistance against antibiotics is transferred by cell-to-cell contact.[Van der Waaij,1982].

Colonization resistance of the lower digestive tract

Working with germ-free animals, Van der Waaij et al found that an organism such as *Escherichia coli* would colonize the alimentary canal when as little as 10 to 100 microorganisms were given orally. On the contrary, conventional animals required about 10^7 or more organisms via oral inoculation for the digestive tract to be colonized. This indicates that the intestinal flora has the capacity to prevent

colonization by new organisms. This capacity was originally called Colonization Resistance [Van der Waaij, 1971; 1979]. Subsequent studies in mice and man learned that the microorganisms responsible for colonization resistance are part of the anaerobic flora [Van der Waaij, 1977]. Not much more is known about the limiting flora in man, except then that it is obligatory anaerobic, and that it is probably associated with the mucus of the large intestine. There are probably several mechanisms by which the anaerobic flora limits the colonization by aerobes: shielding of mucosal receptors, production of toxic substances such as volatile fatty acids and competition for food. However, colonization resistance does not only depend on microbial factors, but also on physiological factors like peristalsis, secretion of mucus, secretion of immunoglobulin A, etc. We therefore used the term Microbial Colonization Resistance (MCR) for that part of colonization resistance that depends on the anaerobic flora.

Microbial colonization resistance and antibiotic policy.

From the beginning of the antibiotic era, superinfections have represented the failure of treatment that initially seemed successful: adequately instituted therapy eliminated the infecting microorganism, but this microorganism was suddenly succeeded by a resistant microorganism, usually of another species [Weinstein, 1977]. Superinfections have occurred with considerable frequency after administration of penicillin (especially at higher dosages) [Tillotson, 1968], methicillin [Sabath, 1962], tetracycline [Louria, 1962], chloramphenicol [Louria, 1962], and ampicillin [Price, 1970; Bingen, 1982].

The occurrence of superinfections during or after treatment with some antibiotics may be explained as follows. The administration of an antibiotic affecting that part of the anaerobic intestinal flora that is responsible for MCR, results in susceptible *E.coli* (normal concentration 10^5 /g of faeces) being replaced by resistant Gram-negative bacilli in a much higher concentration (usually $\pm 10^9$ /g of faeces). This resistant Gram-negative bacillus may be an *E.coli*, but usually it is a *Klebsiella*, *Serratia*, *Enterobacter* or *Pseudomonas*. These microorganisms may already be present in the intestine in low concentrations, but are also regularly supplied via the food or transmitted from other patients. In any case, a substantial increase in the number of resistant Gram-negative bacilli in the lower digestive tract occurs. This situation greatly increases the probability of superinfection.

Maintenance of the autochthonous anaerobic intestinal flora, and thus of MCR, seems the surest way of preventing colonization with resistant Gram-negative bacilli and thus super-infection. Therefore, it is advisable to use antimicrobial agents that do not affect MCR. Consequently all antibiotics should be tested for their influence on MCR.

Two factors determine the effect of an antimicrobial agent on MCR [Van der Waaij, 1982].

- (1) The concentration of antibiotic at the site of the limiting anaerobic flora (presumably the mucus of the large intestine). This concentration conceivably is determined by the following factors:
 - a. the degree of resorption after oral antibiotic administration,
 - b. the degree and site (e.g. saliva, bile, mucus) of excretion of resorbed antimicrobial agents,
 - c. the degree and site of excretion of parenterally administered antimicrobial agents.
- (2) The effect of the antimicrobial agent on that part of the anaerobic intestinal flora that constitutes MCR.

The fact that the composition of this flora is not exactly known, renders direct determination of the effect of antibiotics on this flora impossible. There are several indirect methods to determine this effect.

- (1) The increase in the concentrations of Gram-negative bacilli in the lower digestive tract, together with the high incidence of superinfections in patients treated with some antibiotics, were the original indications that these antibiotics disturb the MCR. However, as colonization resistance may already be reduced by underlying disease, patients are not very suitable to determine the effect of an antibiotic on the MCR.
- (2) Animal experiments of the effect of antibiotics on MCR may yield more useful results than patient studies. An additional advantage of animal experiments is that they offer the possibility to perform a challenge test with bacteria resistant to the antibiotic tested. The challenge strain is administered both before and during antibiotic administration. If the rate of elimination of the challenge strain is not diminished by the administration of a certain dose of antibiotic, this antibiotic in this dose (and administered in this way) has no influence on MCR. However, it is difficult to extrapolate the dose of antibiotic used in animals to the dose used in humans.
- (3) Therefore, challenge experiments in human volunteers are the method of choice to study the influence of antimicrobial agents on MCR and are now becoming an established procedure. A major difficulty in this approach is finding, for the use as challenge strain, Gram-negative bacilli that at the same time should be apathogenic, and resistant to the sometimes high faecal concentrations reached by the antibiotics to be tested.

The evidence presently available regarding the effect of some important antibiotics on MCR has recently been reviewed [Vollaard, 1989]. It is on this review that the tables I and II are based.

Table 1 *Antimicrobial agents and Microbial Colonization Resistance (MCR). The effect of intravenous administration.*

<i>Antimicrobial agent</i>	<i>Effect on MCR</i>	<i>Remarks</i>
Penicillins		
amoxicillin	disturbance	effects MCR less than ampicillin e.g. flucloxacillin, dicloxacillin. ≥10 ⁶ U tid, lower dose unknown.
ampicillin	disturbance	
azlocillin	disturbance	
isaxozolylpenicillins	disturbance	
penicillin G	disturbance	
piperacillin	disturbance	
ticarcillin	disturbance	
Cephalosporins		
cefotaxime	none	≤ 4 g daily, higher doses disturb MCR. ≤ 750 mg tid, higher doses disturb MCR.
cefoxitin	disturbance	
cephradine	none	
ceftazidime	none	
ceftriaxone	disturbance	
cefuroxime	none	
Aminoglycosides		
All aminoglycosides	none	
Quinolones		
ciprofloxacin	none	
pefloxacin	none	
Other agents		
chloramphenicol	disturbance	oral vancomycin severely disturbs MCR
clindamycin	disturbance	
cotrimoxazole	none	
doxycycline	none	
erythromycin	none	
imipenem	unknown	
lincomycin	disturbance	
metronidazole	none	
trimethoprim	none	
vancomycin	none	

Table II Antimicrobial agents and Microbial Colonization Resistance (MCR). The effect of oral administration.

No known effect on MCR	Disturbing MCR
cefactor	aminoglycosides (all except tobramycin)
colistin*	amoxicillin
cotrimoxazole*	ampicillin
doxycycline	clindamycin
erythromycin	isaxozolylpenicillins
metronidazole	phenethicillin
nitrofurantoin	tetracycline
quinolones (all)*	vancomycin
roxithromycin	
tobramycin*	
trimethoprim*	

* agents that may be used for selective decontamination (mostly in combination with other agents).

Selective decontamination of the digestive tract

Antimicrobial agents that do not disturb MCR, can be administered safely, that is without increasing the risk of colonization and super-infection with resistant strains. This offers the opportunity to eliminate potentially pathogenic microorganisms from the digestive tract, without the risk of overgrowth by resistant microorganisms. The technique of eliminating potentially pathogenic microorganisms while leaving the autochthonous anaerobic flora intact has been named Selective Decontamination of the Digestive tract (SDD) [Van der Waaij, 1974].

Patients with cytostatic-induced leucopenia have such a serious reduction of resistance to infection that infections already develop with the normal concentrations of aerobic intestinal flora. Elimination of these potentially pathogenic microorganisms by means of SDD prevents infection in these patients [Sleijfer, 1980; Karp, 1987; Dekker, 1987].

More recently, the successful application of SDD has also been described in non-neutropenic patients, particularly in those patients whose physiological colonization resistance is disturbed by disease or by medical intervention (e.g. transurethral catheterization [Vollaard, 1989] or endotracheal intubation [Stoutenbeek, 1984]).

This thesis describes the effect of a regime of SDD – in association with short-term systemic antibiotic prophylaxis – on the colonization of the oropharynx and of the stomach with potentially pathogenic microorganisms and on the frequency of lower respiratory tract infection in patients requiring prolonged mechanical ventilation.

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Lower respiratory tract infection in mechanically ventilated patients

PATHOGENESIS AND POSSIBLE MODES OF PREVENTION

Introduction

Patients receiving mechanical ventilation are at high risk of developing lower respiratory tract infection. This risk increases when mechanical ventilation is prolonged. In several studies, the incidence of respiratory tract infection increased to 50% or more after the first week of mechanical ventilation [Cross, 1981; Ruiz-Santana, 1987; Stoutenbeek, 1984; Kerver, 1987].

Respiratory tract infection in critically ill patients is associated with a considerable increase in morbidity. It is followed by secondary septicaemia in 36% of the cases [Daschner, 1982; Caplan, 1979], and prolongs ICU-stay [Craig, 1984]. Adequate treatment of lower respiratory tract infection often is not possible, and death may result, especially if Gram-negative bacilli are involved. ICU-acquired lower respiratory tract infection was reported to be associated with an important increase in mortality [Craig, 1984; Craven, 1986; Ruiz-Santana, 1987]. However, a direct relationship between pneumonia and increased mortality could not be established [Craven, 1986]. Although contaminated respiratory equipment has been eliminated as source of lower respiratory tract infection [Pierce, 1970; Comhaire, 1981] the incidence of these infections in patients who are intubated and mechanically ventilated still remains unacceptably high. This review will focus on the pathogenesis of lower respiratory tract infection in mechanically ventilated patients, and on the potential strategies for its prevention. The emphasis will be laid on selective decontamination of the digestive tract.

Etiology

Respiratory tract infections that occur in the first days of mechanical ventilation often have the same etiology as community-acquired infection [Woodhead, 1987; White, 1981]: they are predominantly caused by *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* [Ruiz-Santana, 1987; Stoutenbeek, 1987].

Later during ICU-stay Gram-negative bacillary infection is increasingly impor-

tant, accounting for more than 80% of the lower respiratory tract infections which occur after more than three days of mechanical ventilation [Stoutenbeek, 1987; Ruiz-Santana, 1987]. *Pseudomonas aeruginosa*, *Klebsiella sp.* and *Escherichia coli* are the most commonly isolated organisms, but other Gram-negative bacilli e.g. *Enterobacter sp.*, *Proteus sp.* and *Serratia sp.* also play a role [Daschner, 1982; Sanford, 1986].

Pathogenesis

Bacteria may reach the lower respiratory tract in three different ways: by haematogenous spread, by inhalation, or by aspiration of oropharyngeal or gastric contents.

Aspiration is the most important way of spread of bacteria to the lower airways in hospital-acquired pneumonia [Laforce, 1981; Podnos, 1985]. Microorganisms colonizing the oropharynx may be introduced to the lower airways by aspiration of oropharyngeal contents at the onset of acute disease [Langer, 1987] or at endotracheal intubation [Nair, 1986]. Later during intensive care stay aspiration of oropharyngeal secretions and gastric contents continues to be the major cause of pneumonia. Aspiration is enhanced by depressed consciousness [Huxley, 1978; Langer, 1987], a condition that is present in a great majority of mechanically ventilated patients, caused either by disease itself or by sedation. Aspiration is further facilitated by the presence of endotracheal or tracheostomy tubes [Cameron, 1973; Spray, 1976]. Small quantities of oropharyngeal secretion may pass the cuff of the endotracheal tube, especially if high volume cuffed tubes are used [Seegobin, 1986; Pavlin, 1975]. In critically ill patients, the concentration of Gram-negative bacilli in the oropharyngeal secretions is usually high and may exceed 10^7 organisms per milliliter [Van Uffelen, 1984]. This means that even aspiration of only 0.001 ml will introduce a bolus containing more than 10^4 organisms into the tracheobronchial tree. Antibacterial defense mechanisms of the lung perform less well when presented with bacteria in a fluid bolus than when bacteria are deposited as a small particle aerosol: in experimental animals, intratracheal instillation of a fluid bolus containing 10^4 microorganisms produced clinical signs of respiratory tract infection, whereas aerosol challenge of 10^7 did not result in clinical illness [Berendt, 1978]. Moreover, pulmonary antibacterial defense mechanisms are known to be compromised by shock, acidosis, pulmonary oedema and hypoxia [Green, 1977] all of which are common in critically ill patients. Under these circumstances aspiration of even a minute quantity of oropharyngeal or gastric contents may give rise to lower respiratory tract infection [Johanson, 1984]. Colonization of the oropharynx and of the stomach with Gram-negative bacilli play a pivotal role in the pathogenesis of these infections.

Colonization of the oropharynx

In normal persons oropharyngeal colonization with Gram-negative bacilli doesn't occur: only 2 % of healthy individuals harbor Gram-negative bacilli in their oropharynx, and then only transiently [Johanson,1969]. Inoculation of even large numbers of Gram-negative bacilli into the mouths of healthy subjects does not cause colonization. La Force et al. studied the elimination of Gram-negative bacilli from the oropharynx after gargle challenge: when suspensions of Gram-negative bacilli (*Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*) were gargled by normal volunteers, bacterial counts rapidly decreased and less than 1% of the original inoculum was recoverable after 3 hours. Even pilated *E.coli* (which adhered well to buccal cells in vitro) was rapidly cleared from the oropharynx [La Force,1976].

This finding suggests the presence of highly effective mechanisms to exclude Gram-negative bacilli from the normal upper respiratory tract. These mechanisms, which prevent colonization of the oropharynx with potentially pathogenic microorganisms, will be referred to as colonization resistance. Several factors contribute to colonization resistance:

- (1) mechanical factors,
- (2) factors that influence bacterial adherence,
- (3) the autochthonous oropharyngeal flora.

- (1) Mechanical factors, such as salivary flow and swallowing, rapidly clear about 90% of the Gram-negative bacilli before they can get attached to oropharyngeal epithelial cells [La Force,1976]. The approximately 10% of bacteria that are not immediately cleared from the oropharynx mechanically, normally do not adhere to the oropharyngeal mucosa.
- (2) Adherence is influenced by several factors. The most important is fibronectin, a high-molecular weight glycoprotein which covers the oropharyngeal cell surface, and so modulates the oropharyngeal flora. Fibronectin promotes the adherence of certain Gram-positive cocci (e.g. *Streptococcus pyogenes*) but prevents the colonization with Gram-negative bacilli [Woods,1981; Abraham,1983]. Fibronectin is cleared from the cell surface by the excess proteolytic enzyme activity that occurs in the oropharyngeal secretions of severely ill patients [Woods,1981,A]. The loss of cell surface fibronectin is associated with increased adherence of Gram-negative bacilli to buccal epithelial cells in vitro, and with an increase of the incidence of oropharyngeal colonization in vivo [Woods,1981; Woods,1983]. In their study in patients undergoing elective cardiac surgery, Dal Nogare et al recently demonstrated that most of the fibronectin digestive activity is due to elastase derived from polymorphonuclear cells [Dal Nogare,1987], which are the principal cells in the saliva (other than desquamated squamous cells).

Salivary IgA also exerts inhibitory activity on the adherence of bacteria to the

mucous membrane [Williams,1972]. Degradation of IgA by polymorphonuclear cell elastase was described in patients with chronic tracheostoma [Niederman,1986].

The normal inflammatory response of the respiratory tract to the presence of bacteria may therefore actually enhance Gram-negative bacillary colonization by degradation of both cell surface fibronectin and of IgA.

- (3) The autochthonous oropharyngeal flora is another important factor preventing colonization with Gram-negative bacilli.

It has been supposed that aerobic oropharyngeal bacteria, primarily α -haemolytic streptococci, protect the oropharynx against Gram-negative bacillary colonization, because suppression of oropharyngeal α -haemolytic streptococci with penicillin was associated with colonization with Gram-negative bacilli [Sprunt,1969], and this colonization did not occur in patients carrying penicillin resistant streptococci in their oropharynx [Sprunt,1971]. However, the inhibiting flora might as well be the anaerobic oropharyngeal flora, which is also influenced by the administration of penicillin. Several anaerobic bacteria isolated from the oropharynx of healthy volunteers, particularly *Bacteroides melaninogenicus*, have been shown to inhibit the growth of most Gram-negative bacilli in vitro [Murray,1976]. Like the anaerobic flora of the lower digestive tract (chapter I), the autochthonous anaerobic flora of the oropharynx is considered to play an important role in the defense against colonization with Gram-negative bacilli [George,1982].

Mechanisms by which the autochthonous flora limits colonization by Gram-negative bacilli are not well known but may include: the shielding of mucosal receptors, production of toxic substances such as volatile fatty acids, and competition for food [Clasener,1987].

Like in the lower digestive tract, the role of the autochthonous flora in the prevention of colonization with Gram-negative bacilli will be referred to as Microbial Colonization Resistance (MCR), whereas the mechanical clearance of bacteria and the factors which prevent bacillary adherence will together be called Physiological Colonization Resistance (PCR). PCR and MCR together normally offer a highly effective protection against colonization of the oropharynx with Gram-negative bacilli.

However, in critically ill patients, Gram-negative bacillary colonization of the oropharynx readily occurs. Johanson et al found that, whereas Gram-negative bacillary colonization of the oropharynx was present only in 2% of healthy individuals, it occurred in 35% of moderately ill patients and in 73% of critically ill patients [Johanson,1969]. This colonization occurred soon after admission and played an important role in the pathogenesis of lower respiratory tract infection. Respiratory tract infection occurred in 23% of the ICU-patients with oropharyngeal colonization with Gram-negative bacilli but only in 3.3% of the non-coloni-

zed patients [Johanson,1972]. The following clinical factors appeared to be associated with an increased risk of oropharyngeal colonization: coma, hypotension, endotracheal intubation and azotaemia. The use of some antibiotics probably also promoted colonization [Johanson,1972]. The importance of the association between antibiotic therapy and oropharyngeal Gram-negative bacillary colonization was further emphasized by other authors [Le Frock,1979,A; Nord,1984; Rose,1975]. Other conditions associated with an increased risk of colonization of the upper respiratory tract are diabetes, ethanol abuse [Mackowiak,1978], advanced age and disability [Valenti,1978].

Of these conditions intubation and coma, which both are present in virtually all mechanically ventilated patients, are of paramount importance, because these two factors are not only associated with increased risk of colonization but also with an increased risk of pneumonia [Johanson,1972].

Colonization of the stomach

The acid environment of the stomach is normally sterile [Wilson,1983]. However, in critically ill patients colonization of the stomach with potentially pathogenic microorganisms frequently occurs. In his study of ten mechanically ventilated patients, Atherton observed colonization of the stomach with predominantly Gram-negative microorganisms in nine. Tracheal colonization was observed in all ten patients, six of whom carried the same microorganisms in the trachea as in the stomach [Atherton,1978]. Gastric colonization increases if the gastric pH is increased by the use of antacids or H₂-blockers. Several authors have correlated high levels of gastric pH with logarithmic increases in the concentrations of Gram-negative bacilli in gastric aspirates [Hillman,1982; Du Moulin,1982; Donowitz,1986], and have demonstrated the development of retrograde colonization from the stomach to oropharynx and lower airways [Du Moulin,1982; Daschner,1988]. Recent studies have shown that the use of sucralfate – a cytoprotective agent that does not effect gastric pH – results in a lower rate of gastric colonization and of ICU-acquired pneumonia than does the use of antacids or H₂-blockers [Driks,1987; Tryba,1987; Daschner,1988]. However, Gram-negative bacillary colonization of the stomach was not entirely prevented and the decrease of the incidence of pneumonia was not significant [Driks,1987]. Enteral feeding can also play a role in the pathogenesis of gastric colonization, directly by administration of contaminated feeding or indirectly by increasing the pH [Pringleton,1986].

Sources of microorganisms colonizing oropharynx and stomach

Microorganisms colonizing oropharynx or stomach might derive either from the patient's own digestive tract (endogenous) or from other sources (exogenous).

Endogenous sources

The most important endogenous source of microorganisms causing colonization and ICU-acquired infection is the patient's own faecal flora.

Le Frock et al observed Gram-negative bacilli other than *Escherichia coli* (*Klebsiella*, *Enterobacter* and *Proteus*) as predominant in the faecal flora of 60% of all hospitalized patients [Le Frock,1979]. This occurred even in patients who were only moderately ill and did not receive antibiotics. The Gram-negative bacilli which appeared in the oropharynx were nearly always the same as those in the faecal flora, pointing to the latter as the origin of newly appearing oropharyngeal strains [Le Frock,1979,A]. Transmission of faecal microorganisms occurs mostly by faecal-oral contact, either via the hands of the patient, or via the hands of medical personnel [Maki,1978]. Theoretically, the retrograde spread of microorgan-

Fig. 1 The central role of faecal microorganisms in the development of ICU-acquired infections.

isms from the intestines to the stomach is also possible, especially when peristalsis is impaired.

The use of antibiotics that disturb the autochthonous anaerobic intestinal flora does increase the faecal concentration of Gram-negative bacilli, thereby increasing the risk of contamination and infection from this source (chapter 1) [Clasener, 1987].

Figure 1 illustrates the central role that faecal microorganisms play in the development of infection in critically ill patients.

Exogenous sources

Exogenous sources of colonization potentially include every human or inanimate object in the hospital. The most important exogenous source of microorganisms, however, is faecal material, deriving from other patients, as was found by Selden et al in their study of endemic infection with multi-resistant *Klebsiella* [Selden, 1971]. Respiratory secretions or urine from infected patients can also be the source of microorganisms [Penn, 1981]. The most important mode of transmission of microorganisms from patient to patient, is the spread via the hands of personnel. [Maki, 1978; Knittle, 1975; Casewell, 1977].

Microorganisms transmitted from patient to patient may either directly colonize oropharynx or stomach, or may first colonize the patient's own lower digestive tract and subsequently colonize oropharynx and stomach via faecal-oral contamination.

Contaminated respiratory equipment normally does not give rise to microbial colonization of oropharynx or stomach, but to direct introduction of potentially pathogenic microorganisms in the lower respiratory tract [Kerver, 1987].

Prevention

In the past twenty years much attention has been given to the prevention of ICU-acquired pneumonia caused by contaminated respiratory equipment or by cross-infection. The decontamination of humidifiers and ventilators, and the changing of respiratory tubing every 48 hours have reduced lower respiratory tract infection from these sources to a minimum [Craven, 1987]. Proper hand washing and other hygienic measures [Simmons, 1983] are now well established in most ICU's.

However, despite infection-control measures directed at eliminating reservoirs and interrupting modes of transmission of Gram-negative bacilli, colonization of oropharynx and stomach, with subsequent aspiration and lower respiratory tract infection, still frequently occurs.

Possible further strategies for the prevention of lower respiratory tract infection involve: prevention of aspiration, enhancement of lung defenses and the prophylactic administration of antimicrobial agents.

Aspiration of small quantities of pharyngeal secretion is probably unavoidable in

seriously ill patients, especially if the patient carries an endotracheal or tracheostomy tube.

Immunization may enhance lung defenses, but not immediately and only for the vaccinated strains [Polk, 1973; Maki, 1978].

The prophylactic use of systemic antibiotics has not been successful in the past: it has been found not to reduce the infection rate, and to cause superinfection with resistant strains [Lepper, 1954; Petersdorf, 1957; Price, 1973], and is, therefore, generally rejected [Caplan, 1979]. Topical application of antibiotics in upper and lower airways was studied by several groups, but did not reduce the respiratory tract infection rate [Feeley, 1975] and resulted in resistance against the antibiotics used [Klastersky, 1974].

Selective decontamination of the digestive tract

In the early 1970's Van der Waaij et al performed a series of experiments on irradiated mice. In these experiments, that were recently reviewed [Clasener, 1987], it appeared that the most effective prevention of infection in irradiated mice was the oral administration of antibiotics that eliminated the potentially pathogenous aerobic microorganisms (predominantly Gram-negative bacilli) from the digestive tract. The anaerobic intestinal flora, that was demonstrated to have a limiting effect on the growth of potentially pathogenic aerobic microorganisms, was spared [Van der Waaij, 1974]. This technique – elimination of aerobic Gram-negative bacilli from the digestive tract, while sparing the autochthonous anaerobic flora – is called Selective Decontamination of the Digestive tract (SDD) (chapter I). The value of SDD in the prevention of infection in neutropenic patients has been established in prospective controlled studies [Sleijfer, 1980; Gurwith, 1979; Karp, 1987].

In 1984 SDD was first applied in mechanically ventilated patients. Stoutenbeek et al studied 63 trauma patients who required mechanical ventilation for more than five days [Stoutenbeek, 1984]. The patients received a regime of SDD consisting of polymyxin E (colistin), tobramycin, and amphotericin B (the PTA-regime), administered to the stomach via the nasogastric tube and to the mouth in a sticky paste. They were further given systemic cefotaxime (50-60 mg/kg/d). Systemic cefotaxime was added to the regime because, in a pilot study, SDD alone did not prevent early lower respiratory tract infection [Stoutenbeek, 1987]. In the group of patients so treated the incidence of lower respiratory tract infection was eight percent. A retrospective control group of 59 patients who had been admitted to the same intensive care unit three years earlier, had a 59% incidence of respiratory tract infection; a highly significant difference ($p < 0.001$). The two groups had similar hospital trauma indices. There were five infection-related deaths in the

control group and none in the treatment group. Several other studies of the use of SDD in mechanically ventilated patients have been published with similar effect on the infection rate [Van Griethuizen, 1987; Van Uffelen, 1987; Kunnen, 1989; Ledingham, 1988]. However, in all studies the infection rates were compared to those in retrospective control groups. Only recently, the results have been published of a prospective randomized study of the effect of SDD in surgical patients requiring prolonged mechanical ventilation [Kerver, 1988]. In the control group (n=47) a restrictive antibiotic policy was followed, whereas patients in the study group (n=49) received the PTA-regime of SDD throughout admission, in combination with systemic cefotaxime prophylaxis (50-70 mg/kg/d) during the first five to seven days. Application of this regime reduced the overall incidence of ICU-acquired infection from 81% in the control group to 39% in the SDD group ($p<0.001$). The patients in the control group together acquired 40 lower respiratory tract infections, versus six lower respiratory tract infections in the SDD group ($p<0.001$). SDD appeared to be especially effective in the prevention of Gram-negative infections and of mixed Gram-positive/Gram-negative infections. The incidence of Gram-positive infections was not significantly reduced.

All but one author [Van Griethuizen, 1987] studying the effect of SDD in mechanically ventilated patients have used the PTA-regime which has been described above, mostly in combination with systemic cefotaxime. Although effective, this regime has two major disadvantages. It is expensive (DFI 65/day to which DFI 115 has to be added for every day of systemic cefotaxime prophylaxis [Vollaard, 1984]. More important is that the orally administered tobramycin, although poorly resorbed, may give rise to detectable serum levels, which – especially in patients with impaired renal function – might even exceed the level of ototoxicity and nephrotoxicity [Sciarrà, 1988].

Further prospective studies are required, both to confirm the effectiveness of the concept of SDD in mechanically ventilated patients and to develop safer and less expensive regimes of SDD.

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Selective decontamination and short-term systemic antibiotic prophylaxis in mechanically ventilated patients: study design.

Aims of the study

The major aim was to assess, in a prospective, controlled randomized study, the effect of a new regime of selective decontamination and systemic antibiotic prophylaxis in patients requiring prolonged mechanical ventilation. We studied the influence of this regime on the colonization of oropharynx, stomach and rectum with potentially pathogenic microorganisms and on the incidence of lower respiratory tract infection in these patients.

In the first control group we followed conventional antibiotic use, i.e. administration of antibiotics only in case of infection. In this control group we adhered to the antibiotic policy previously used in our unit which involved the use of antibiotics known to disturb the autochthonous anaerobic flora and thus disturbing MCR. The use of these antibiotics might influence the colonization and infection rate (chapter 1). This necessitated the institution of a second control group, in which, like in the first control group, we followed conventional antibiotic use, but in which infections were treated only with antibiotics that do not affect MCR. This permitted us to compare the influence of antibiotics disturbing and those not disturbing MCR on the colonization and infection rate.

The role of oropharyngeal and gastric colonization in the pathogenesis of lower respiratory tract infection was also subject of study.

Study design

Study population

All patients admitted to the ICU of the Nijmegen University Hospital from May 1986 to September 1987 were eligible for the study. The criterion for inclusion was the expected need for mechanical ventilation for at least five days, regardless of the disease necessitating mechanical ventilation. All patients were included within 24 hours after admission.

Exclusion criteria were: age less than 16 years, pregnancy, and allergy to one of the antibiotics used for selective decontamination or to cefotaxime. Informed consent was obtained from patients or their relatives. The study protocol was approved of by the hospital's institutional review board for human studies.

Randomization

As soon as possible after admission, the severity of acute illness was assessed using the APACHE II score [Knaus,1985]. Using this score each patient was entered into one of four categories: APACHE II score less than 10, 10-19, 20-29 and 30 or more. Within these strata, patients were randomly allocated to one of the treatment groups by means of the permuted block method.

Treatment groups (Table I)

In control Group I, the patients did not receive any antibiotic prophylaxis. Antibiotic treatment was instituted only on clinical evidence of infection, in which case antibiotics known to disturb MCR were used (see Table I&II, chapter I).

Table I Study design

	Group I	Group II	Group III
Antibiotic therapy	antibiotics affecting MCR	only antibiotics without influence on Microbial Colonization Resistance (MCR)	
Prophylaxis	no antibiotic prophylaxis		Selective decontamination and short-term systemic cefotaxime

Table II Treatment of infections of unknown etiology (i.v.)

	Group I	Group II and III
aerobic infection	ampicillin 1 g qid (or piperacillin 1 g qid) in combination with gentamicin 80 mg tid	cefotaxime 1 g qid (or cefuroxime 750 mg tid) in combination with gentamicin 80 mg tid
anaerobic infection	lincomycin 600 mg bid	metronidazole 500 mg tid

Dosages are for adults of 70 kg.

Infection of unknown etiology was treated with intravenous therapy with ampicillin 1 g qid (or piperacillin 1 g qid) in combination with gentamicin 80 mg tid (Table II).

In control Group II, the patients received, like in the other control group, antibiotic treatment only on clinical evidence of infection. However, if antibiotic therapy was necessary, only antibiotics without influence on MCR were used (see Table I&II, chapter I). Infection of unknown etiology was treated with intravenous therapy with cefotaxime 1 g qid (or cefuroxime 750 mg tid) in combination with gentamicin 80 mg tid (Table II).

In Group III: the patients started with SDD and systemic antibiotic prophylaxis immediately after randomization. SDD was continued until extubation, systemic prophylaxis was administered only during the first five days of admission. When infection occurred it was treated, like in group II, with antibiotics without influence on MCR.

Patients in all three treatment groups occasionally received short-term perioperative systemic antibiotic prophylaxis, but only with antibiotics consistent with the trial protocol.

Selective decontamination and systemic prophylaxis (group III)

Selective decontamination: polymyxin E (colistin) 200 mg, norfloxacin 50 mg and amphotericin B 500 mg, were administered four times daily via the nasogastric tube to decontaminate the stomach and the lower digestive tract. When gastric suction had to be applied, this was discontinued for 1 hour after administration of the antimicrobial agents. A sticky paste containing the same agents (polymyxin E 2%, norfloxacin 2% and amphotericin B 2% in hydroxypropylmethylcellulose 4,000 cP 20% in white petrolatum) was used to decontaminate the oropharynx. One gram of this paste was applied to the oral mucosa four times daily with a gloved finger or a cotton swab.

Systemic prophylaxis consisted of cefotaxime 500 mg intravenously three times daily, during the first five days of mechanical ventilation.

Justification of the regime used

Selective decontamination of the digestive tract

Norfloxacin was the main constituent of our regime of SDD. This quinolone is active against most Gram-negative bacilli, but has only slight activity against anaerobic microorganisms [Wolfson, 1985]. Emergence of resistance to norfloxacin is not common [Wolfson, 1985]. Norfloxacin is absorbed incompletely from the digestive tract and therefore reaches high faecal concentrations: at an oral dose

of 200 mg daily, we measured a norfloxacin concentration of 100 μ g per gram faeces (unpublished observations). This exceeds the MIC 90 of even the least susceptible strains of Gram-negative bacilli [Wolfson, 1988], but does not affect most of the anaerobic microorganisms in the concentrations in which they are present in the digestive tract [Goldstein, 1987]. This makes norfloxacin very suitable for SDD. Norfloxacin, administered orally in a daily dose of 200 mg, eliminated all Gram-negative bacilli from the intestinal tract of healthy volunteers, without signs of disturbed MCR [De Vries-Hospers, 1985]. The effectiveness of SDD with norfloxacin has been proved in three randomized studies in neutropenic patients [Winston, 1986] [Karp, 1987] [Winston, 1987].

To reduce the risk of colonization with Gram-negative bacilli less susceptible to norfloxacin, (e.g. *Pseudomonas* sp. other than *Pseudomonas aeruginosa* and *Acinetobacter* sp.), polymyxin E was added to the regime. Moreover, the use of a combination of agents decreases the risk of the development of resistance to the agents used for SDD. Amphotericin B was used to prevent colonization with yeasts.

The use of systemic cefotaxime

In a pilot study, SDD alone did not reduce the incidence of those lower respiratory tract infections which develop during the first days of mechanical ventilation [Stoutenbeek, 1987]. This failure is explained by the fact that, on admission, oropharyngeal microorganisms often have already gained access to the lower airways (chapter II), and cannot be reached by antibiotics that are administered to the upper respiratory tract.

Furthermore, the antibiotics used for SDD are directed mainly against Gram-negative bacilli, and not against the Gram-positive cocci that play an important role in early lower respiratory tract infection. This necessitates the administration of a systemic antibiotic during the first days of mechanical ventilation. Cefotaxime is a suitable agent for this purpose because it is active against the commensal oropharyngeal flora, as well as against most Gram-negative bacilli. Cefotaxime (50-100 mg/kg/day intravenously) has now been used for this purpose for more than three years, with good clinical results, and without emergence of resistance [Stoutenbeek, 1987, A]. However, the dose of cefotaxime that was used seems rather high. At lower doses of cefotaxime, serum and sputum levels still exceed the minimum inhibitory concentrations for *Haemophilus influenzae*, *Streptococcus pneumoniae* and most Gram-negative bacilli [Carmine, 1983]. This, and the synergistic activity of cefotaxime and its metabolite desacetyl-cefotaxime against *Staphylococcus aureus* and most other susceptible microorganisms [Chin, 1984], justifies a lowering of the cefotaxime dose to 500 mg tid. Clinical results of the treatment of lower respiratory tract infection with this dose of cefotaxime have been very satisfactory [Perkins, 1982] [Simon, 1988].

Bacteriology

To monitor colonization at these sites, cultures of gastric aspirate and of oropharyngeal and rectal swabs were performed at admission and thereafter twice weekly. Aspirate of the gastric contents was obtained by suction to the nasogastric tube. The first 10 ml of gastric aspirate were discarded, the second 10 ml (obtained with a new syringe) were cultured.

Cultures of the rectum were obtained by sampling at about 5 cm proximal from the anus, with a sterile cotton swab moistened with sterile saline.

The oropharynx was sampled with a dry cotton swab.

Cultures of the tracheal aspirate were performed on admission, and thereafter thrice weekly, the tracheal aspirate was collected by suctioning material directly from the lower respiratory tract via the endotracheal tube.

Urinary cultures were performed on admission and thereafter once weekly. All patients in our ward had indwelling urinary catheters, from which the urine was obtained by aseptic puncture with a sterile syringe.

Cultures from other sites (blood cultures, cultures from wounds, drains etc.) were taken as clinically indicated.

All samples were immediately plated on the following media: Eosin methylene-blue lactose sucrose agar (Merck, D6100 Darmstadt, F.R.Germany), 7% sheep blood in blood agar base special (Mast Lab. Ltd., Boothe, England) and Sabouraud dextrose agar (Difco Lab., Detroit, Mich., US) with chloramphenicol 40 mg/L. The oropharyngeal swab and the tracheal aspirate were also plated on Haemophilus selective agar base (Merck) with bacitracine 10 U/ml.

Sabouraud plates were incubated at 29°C for seven days. All other plates were examined after overnight incubation at 37°C in 7% CO₂.

The tracheal aspirate and oropharyngeal and rectal swabs were inoculated using the four quadrant method. Semiquantitative estimation of the bacterial concentration was made on a scale of 0 to +4 according to the density of growth on the agar plates. Growth in only the first quadrant was reported as +1, in the second quadrant as +2, etc..

Serial 1/10 dilutions of the gastric aspirate were made in Thioglycolate medium. One- μ L volumes of each dilution were inoculated on the solid media. The solid media were also inoculated with 100 μ L of the first 1/10 dilution of gastric aspirate, lowering the limit of detection to 100 microorganisms/ml of gastric aspirate. Concentrations were expressed as the logarithms to the base of 10 of the counts per ml of gastric aspirate, rounded down to whole numbers (Fig. 1).

Microorganisms isolated were identified and antibiotic sensitivity profiles were determined by standard methods.

Colonization

Colonization was defined as the presence of the same microorganism in two or

Figure 1 Quantitative tenfold serial dilution method of gastric aspirate (reproduced with permission from: F.K.L. Spijkervet. Irradiation mucositis and oral flora [Dissertation]. Groningen, 1989).

more consecutive samples from the same site, without clinical signs of infection. Microorganisms isolated from samples obtained during the first 24 hours after admission were considered to have been present on admission. Colonization that first occurred afterwards was considered acquired.

To establish the possible influence of the different antibiotic policies in both control groups on the intensity of colonization, we compared the concentrations of Gram-negative bacilli in oropharynx and stomach in patients in groups I and II before and after the start of the first course of antibiotic therapy. The concentrations of Gram-negative bacilli in oropharynx and stomach were determined immediately before the institution of antibiotic therapy, and further between one and four days and between five and eight days after the institution of antibiotic therapy. Patients that had received antibiotic therapy before admission on our ICU were excluded from this part of the study.

Infection criteria

All infections that were not present on admission, but developed afterwards, were considered intensive care acquired.

Lower respiratory tract infection was diagnosed if the following three bacteriological criteria were met: (1) positive culture of the tracheal aspirate, (2) Gram stain showing many polymorphonuclear leucocytes as well as (3) the causative organism. This in combination with at least two of the three following clinical findings: (1) purulent aspect of the tracheal aspirate, (2) peripheral leucocytosis of more than 12.000 cells per cubic millimeter, and (3) fever (rectal temperature above 38.0°C). The last two criteria were considered to be signs of lower respiratory tract infection only if they could not be explained otherwise. The diagnosis of a respiratory tract infection was made by a chest-physician (J.Festen) who had no knowledge of the patient's treatment group.

The term lower respiratory tract infection denotes pneumonia or purulent tracheobronchitis. Pneumonia was diagnosed if the criteria mentioned above were met, and the chest roentgenogram (judged by an independent chest-physician) showed a new infiltrate. The emergence of lower respiratory tract infection without these radiographic findings was defined as purulent tracheobronchitis [Unertl, 1987].

A lower respiratory tract infection was called endogenous if it was preceded by colonization of the oropharynx, the stomach or both with the causative micro-organism. All other lower respiratory tract infections were considered exogenous.

Urinary tract infection was defined as the presence of $\geq 10^5$ colony forming units per ml of urine. All patients had indwelling catheters.

Septicaemia was diagnosed if one blood culture was positive (in the case of *Staphylococcus epidermidis* if at least two blood cultures yielded the same strain) in combination with fever (rectal temperature $>39^\circ\text{C}$), or hypothermia (temperature $<36^\circ\text{C}$).

The diagnosis of wound infection was based on purulent discharge from a wound in combination with signs of inflammation and a positive culture.

Institution of antibiotic treatment

The decision to start antibiotic treatment was not taken by the investigators but by the responsible physicians in the ICU. The infection criteria used by the responsible physician were not necessarily the same as those mentioned above. However, antibiotic treatment was determined by clinical evidence of infection together with microbial findings, and was not based on the results of surveillance cultures.

Statistical analysis

The data were analyzed with the chi-squared test, or Fisher's exact test for categorical data, or the test of Kruskal-Wallis, Wilcoxon's sum test and Wilcoxon's signed rank test otherwise. A p-value of 0.05 or less was considered statistically significant.

In the planning stage, it was assumed that the incidence of lower respiratory tract infection in group III would probably be about ten percent, whereas in the other groups this incidence could well exceed 50%.

This assumption was based on the results of a similar study [Stoutenbeek, 1984]. This means that, with a type I error of 0.05 and a type II error of 0.10, 20 patients per group would be needed.

Note: in the context of this document, "there was a difference" implies a significant difference, unless stated otherwise. P-values and 95% confidence intervals that are not mentioned in the text are available from the author.

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CHAPTER IV

Selective decontamination and short-term systemic antibiotic prophylaxis in mechanically ventilated patients: results of the colonization study.

Results of the colonization study

Study population

Eighty-eight patients who were expected to require mechanical ventilation for at least five days were randomized on admission (Table I). Twenty-four patients (11 in group I, five in group II and eight in group III) were excluded from the study because mechanical ventilation was discontinued before the 5th day: sixteen patients improved, and eight patients died before that day (none of these early deaths were caused by infectious disease). Eight additional patients were withdrawn from the study: five (four in group II and one in group III) because of the necessity to use antibiotics not in accordance with the treatment group, two

Table I Study population

<div style="text-align: center;"> 88 ├── Group I │ 30 └── Group II 30 ├── Group III │ 28 </div>			Number of patients randomized
Group I	Group II	Group III	Number of patients randomized per group
30	30	28	
4	2	2	Number of patients who died before the 5th day of mechanical ventilation
7	3	6	Number of patients extubated before the 5th day of mechanical ventilation
1	4	3	Number of patients withdrawn for other reasons (see text)
18	21	17	Number of patients completing the study

patients (group I and group III) because, although randomized, they were mistakenly not enrolled in the study protocol, and one (group III) because the trial medication had to be discontinued because of severe nausea.

The remaining 56 patients (18 in Group I, 21 in Group II and 17 in Group III) completed the study. The three groups were comparable with respect to age, sex, duration of intubation, duration of intensive care stay, and APACHE II score (Table II). Some important elements of the APACHE II score (temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation score and chronic health points) were separately screened for differences between the groups. No differences were found.

The control and test groups were comparable in terms of diagnostic category on admission (Table III) and incidence of infection on admission (Table IV).

Table II Patient characteristics

	Group I (n=18)	Group II (n=21)	Group III (n=17)
Age (years)	49 ± 22	46 ± 21	45 ± 24
Sex (m/f)	11/7	15/6	12/5
ICU-stay (days)	30 ± 17	25 ± 11	23 ± 13
Intubation (days)*	25 ± 23	22 ± 16	16 ± 16
Number of death	4	2	2
APACHE II score	22.6 ± 8.6	23.4 ± 7.7	20.5 ± 5.9

Figures are expressed in numbers or in means ± standard deviation.

* Not normally distributed and therefore given as the median duration ± the inter-quartile range.

Table III Diagnostic categories on ICU-admission

	Group I	Group II	Group III
Multiple trauma (including head trauma)	8	6	9
Other neurologic disease	1	5	3
Respiratory insufficiency	3	2	3
Cardiovascular surgery	1	3	1
Septicaemia	2	2	1
Miscellaneous	3	3	0
Totals	18	21	17

Table IV Infection on admission

	Group I (n=18)	Group II (n=21)	Group III (n=17)
Lower respiratory tract	1	4	3
Septicaemia	2	3	0
Peritonitis	1	2	1
Urinary tract infection	1	2	1
Other sites	1	1	0
Number infected on admission	6	9*	4*

* In Group II and Group III some patients were admitted with infection at more than one site.

OROPHARYNX GRAM-NEGATIVE BACILLI

Figure 1 Colonization of the oropharynx with Gram-negative bacilli.

Colonization of the oropharynx

Gram-negative bacilli

On admission, Gram-negative bacillary colonization of the oropharynx was present in about 40% of the patients in all three groups (Fig. 1). In group I the Gram-negative bacillary colonization rate increased to more than 70%, whereas in group

Table V Intensive care acquired colonization of the oropharynx

	Group I (n=18)	Group II (n=21)	Group III (n=17)
Number of patients acquiring new colonization oropharynx†	15 (83%)	19 (90%)	2 (12%)
95% confidence interval	59-96%	70-99%	1-36%
MICROORGANISMS INVOLVED*			
Gram-positive bacteria	3 (10%)	9 (25%)	1 (-)
Enterococcus faecalis	1	1	-
Staphylococcus aureus	1	4	-
Other Streptococci	1	4	1
Gram-negative bacilli	21 (72%)	18 (50%)	0
Acinetobacter sp.	1	2	-
Citrobacter sp.	1	1	-
Enterobacter sp.	2	4	-
Escherichia coli	9	-	-
Klebsiella sp.	2	1	-
Morganella morganii	1	-	-
Proteus mirabilis	1	1	-
Pseudomonas aeruginosa	4	6	-
Pseudomonas maltophilia	-	2	-
Serratia marcescens	-	1	-
Other Gram-negative bacteria			
Haemophilus influenzae	1 (3%)	6 (17%)	0
Yeasts	4 (14%)	3 (8%)	1 (-)
Total*	29	36	2

* Several patients acquired more than one species of microorganisms.

† Overall $p < 0.001$. Difference between Group I & II not significant ($p=0.85$), between Group I & III $p=0.0001$, between Group II & III $p<0.0001$.

II it remained about 40% throughout ICU-stay. In group III, SDD and systemic antibiotic prophylaxis resulted in rapid elimination of all Gram-negative bacilli from the oropharynx.

In group I and group II, 83% and 90% of the patients respectively acquired microbial colonization – mainly with Gram-negative bacilli – of the oropharynx during their stay at the ICU (Table V). In group III, acquisition of new microorganisms – none of them Gram-negative bacilli – occurred only in 12% of the patients.

The effect of antibiotic therapy on colonization could be studied in 12 of the 18 patients of group I and in 18 of the 21 patients of group II.

In the 12 patients in group I, antibiotic therapy consisted of: ampicillin (seven patients), high dose penicillin (two patients) or flucloxacillin (three patients). All patients concurrently received gentamicin. In the first four days of antibiotic therapy

OROPHARYNX

Figure 2 The influence of antibiotic therapy on the concentrations of Gram-negative bacilli in the oropharynx in Group I and Group II. The increase in concentration in Group I is statistically significant ($p=0.012$), in Group II the concentration did not change.

py, the concentration of Gram-negative bacilli did not change. However, cultures obtained five to eight days after the start of antibiotic therapy showed a significant increase of the concentration of Gram-negative bacilli in the oropharynx (Fig. 2). In the 18 patients of group II antibiotic therapy consisted of cefuroxime (11 patients), cefotaxime (three patients), cephadrine (two patients) or cotrimoxazole (two patients). Cotrimoxazole was prescribed as monotherapy, the cephalosporins were combined with gentamicin on nine occasions. Administration of these antibiotics did not result in a change of the oropharyngeal concentration of Gram-negative bacilli (Fig. 2).

Commensal oropharyngeal flora

Haemophilus influenzae was isolated from the oropharynx on admission in 44% of the patients in group I, in 29% in group II and in 24% in group III. In group I and group II, the rate of colonization with *Haemophilus influenzae* slightly decreased during ICU-stay. In all patients in group III, *Haemophilus influenzae* was eliminated from the oropharynx in a few days, that is, before the second culture (Fig. 3).

Figure 3 Colonization of the oropharynx with *Haemophilus influenzae*.

Only three patients (two in group II and one in group III) carried *Streptococcus pneumoniae* in their oropharynx on admission.

On admission, *Staphylococcus aureus* was cultured from the oropharynx in four patients in group I (22%), two patients in group II (10%) and five patients in group III (30%). Cefotaxime and SDD eliminated *Staphylococcus aureus* from the oropharynx within six days after admission in all five patients in group III.

Yeasts

On admission, yeasts were cultured from the oropharynx of 48% of the patients in group I, 57% in group II and 47 % in group III. In group I and group II, this percentage slightly increased during admission at the ICU. In group III, yeasts were eliminated from the oropharynx in virtually all patients. Antibiotic therapy did not change the concentration of oropharyngeal yeasts in any of the groups.

Colonization of the lower respiratory tract

Colonization of the -normally sterile- lower respiratory tract was frequently present on admission. Microorganisms were cultured from the lower respiratory tract in nine of the 17 patients admitted without lower respiratory tract infection in group I (53%), in nine of the 17 patients in group II (53%) and in nine of the 14 patients in group III (64%). The microorganisms involved are listed in Table VI. *Staphylococcus aureus*, *Haemophilus influenzae* and, to a lesser extent, *Streptococcus pneumoniae* were most frequently involved. Gram-negative bacilli played a secondary role. In all patients with microbial colonization of the lower respiratory tract on admission, the colonizing microorganism could, at the same time, be cultured from the oropharynx. This suggests that aspiration of oropharyngeal contents frequently occurs in an early phase of acute disease.

Table VI Microorganisms colonizing the lower respiratory tract on admission.

	Group I	Group II	Group III	Total
<i>Haemophilus influenzae</i>	1	4	2	7
<i>Staphylococcus aureus</i>	3	2	5	10
<i>Streptococcus pneumoniae</i>	—	2	—	2
Gram-negative bacilli	5	3	—	8
Other microorganisms	—	1	2	3

Note: some patients were colonized by more than one microorganism.

Lower respiratory tract colonization was eliminated by the short course of cefotaxime in all patients in group III. In both control groups, colonization of the lower respiratory tract frequently persisted. In seven cases (three in group I and four in group II) a microorganism that already colonized the lower respiratory tract on admission later gave rise to lower respiratory tract infection.

Colonization of the stomach

Gram-negative bacilli

The percentage of patients carrying Gram-negative bacilli in the stomach on admission was 50% in group I, 19% in group II and 29% in group III (no significant differences). In both group I and group II, the rate of Gram-negative bacillary colonization of the stomach increased to more than 50% during admission (Fig.4).

STOMACH GRAM-NEGATIVE BACILLI

Figure 4 Colonization of the stomach with Gram-negative bacilli.

In group III, nearly all Gram-negative bacilli were eliminated from the stomach and the acquisition of new Gram-negative bacilli was prevented, except in one patient to whom the antibiotics used for SDD were not properly applied. Table VII gives the newly acquired microorganisms in the three groups.

Antibiotic therapy in group I was followed by a significant increase of the concentration of Gram-negative bacilli in the stomach. Like in the oropharynx, this increase in concentration became manifest five to eight days after the start of anti-

Table VII Intensive care acquired colonization of the stomach.

	Group I (n=18)	Group II (n=21)	Group III (n=17)
Number of patients acquiring new colonization of the stomach†	17 (94%)	19 (90%)	4 (24%)
95% confidence interval	73-100%	70-99%	7-50%
MICROORGANISMS INVOLVED*			
Gram-positive bacteria	8 (20%)	9 (26%)	4 (-)
Enterococcus faecalis	8	9	4
Gram-negative bacilli	27 (66%)	20 (59%)	1 (-)
Acinetobacter sp.	1	3	1
Enterobacter sp.	4	4	-
Escherichia coli	10	1	-
Klebsiella sp.	5	4	-
Morganella morganii	-	1	-
Proteus mirabilis	2	-	-
Pseudomonas aeruginosa	4	5	-
Serratia marcescens	-	1	-
other Gram-negative bacilli	1	1	-
Yeasts	6 (15%)	5 (15%)	1 (-)
Candida albicans	5	2	-
Other yeasts	1	3	1
Total*	41	34	6

* Several patients acquired more than one species of microorganisms.

† Overall $p < 0.001$. Difference between Group I & II not significant ($p = 1.00$), between Group I & III $p < 0.0001$, between Group II & III $p < 0.0001$.

biotic therapy. In group II, there was only a small, non-significant, increase in the concentration of Gram-negative bacilli in the stomach following antibiotic therapy (Fig. 5).

Gram-positive cocci

The number of patients exhibiting gastric colonization with Gram-positive cocci rose from 15% on admission to about 30% in both control groups. In group III the rate of gastric colonization with Gram-positive cocci decreased from 18% on admission to zero after ten days of SDD. However, Gram-positive cocci were not persistently eliminated from the stomach in all patients: four patients in group III

STOMACH

Figure 5 The influence of antibiotic therapy on the concentrations of Gram-negative bacilli in the stomach in Group I and Group II. The increase in concentration in Group I is statistically significant ($p=0.029$), in Group II the increase in concentration is not significant ($p=0.17$).

acquired *Enterococcus faecalis*, a microorganism which is only moderately susceptible to norfloxacin.

Yeasts

On admission, yeasts were cultured from the stomach of 33% of the patients in group I, 62% in group II and 47% in group III. In group I and group II, this percentage remained approximately the same throughout the study. In group III the colonization rate was reduced to 7%. Antibiotic therapy did not influence the concentration of yeasts in the stomach.

RECTUM E.COLI

RECTUM OTHER GRAM-NEGATIVE BACILLI

Figure 6 Colonization of the rectum with *E. coli* and other Gram-negative bacilli.

Colonization of the rectum

Gram-negative bacilli

On admission *Escherichia coli* was cultured from the rectum of virtually all patients (Fig.6). In all groups, the incidence of rectal colonization with *E.coli* decreased during admission. In both control groups the decrease was not significant. SDD was very effective in eliminating *E.coli* from the lower digestive tract: in all group III patients, decontamination of the rectum from *E.coli* was achieved after the first defaecation. However, since bowel movements were impaired in many patients, it sometimes took more than ten days for decontamination of the rectum to occur.

Colonization of the rectum with other microorganisms than *E.coli* occurred frequently in groups I and II (Fig.6 and table VIII). In group III, three patients acquired transient colonization with Gram-negative bacilli susceptible to norfloxacin.

Table VIII Intensive care acquired Gram-negative bacillary colonization of the rectum (E. coli not included).

	Group I (n=18)	Group II (n=21)	Group III (n=17)
Number of patients acquiring new Gram-negative bacillary colonization of the rectum†	14 (78%)	14 (67%)	3 (18%)
95% confidence interval	52-94%	43-85%	4-43%
Gram-negative bacilli			
Acinetobacter sp.	3	4	1
Citrobacter sp.	4	3	—
Enterobacter sp.	3	5	—
Klebsiella sp.	5	6	—
Morganella morganii	1	—	—
Proteus sp.	3	2	—
Pseudomonas aeruginosa	4	8	2
Totals*	23	28	3

* Some patients acquired more than one species of Gram-negative bacilli.

† Overall $p < 0.001$. Difference between Group I & II not significant ($p=0.68$), between Group I & III $p < 0.001$, between Group II & III $p < 0.006$.

Gram-positive cocci

Gram-positive microorganisms cultured from the rectum were all *Enterococcus faecalis*, except for a *Staphylococcus epidermidis* cultured from one patient in group III.

Intensive care acquired lower respiratory tract infection

Detailed information about the lower respiratory tract infections that occurred during this study has been provided elsewhere (chapter V). The results can be summarized as follows: in group I, 14 patients (78%) acquired lower respiratory tract infection. Several patients in group I acquired more than one lower respiratory tract infection, and the total number of respiratory tract infections in this group was 25.

In group II, 13 patients (62%) acquired 22 lower respiratory tract infections. Only one patient in group III (6%) acquired a lower respiratory tract infection.

Almost all lower respiratory tract infections in both control groups were endogenous (Fig.7). Of the 25 lower respiratory tract infections in group I, 23 (92%)

Figure 7 Origin of microorganisms causing lower respiratory tract infection in group I and group II.

were endogenous. In five cases the causative microorganism was first cultured from the stomach, in 12 cases the oropharynx was the primary site of colonization. In the remaining six cases, microorganisms were cultured simultaneously from both oropharynx and stomach.

In group II, 20 of the 22 lower respiratory tract infections (91%) were preceded by colonization of the stomach (two patients), the oropharynx (13 patients) or both (five patients).

Three of the four exogenous infections were preceded by colonization of the nose with the causative microorganism.

The only infection in group III was not preceded by colonization at any site and probably resulted from direct cross-contamination.

Antibiotic therapy

Even though, in both control groups, a restrictive antibiotic policy was followed, seventeen patients in group I (94%) and all 21 patients in group II received antibiotic therapy, mostly from an early stage (Table IX). In group III only 11 patients (65%) required antibiotic therapy. The antibiotic use, as expressed as the number of antibiotic days per patient (one antibiotic day is use of one antibiotic during one day) or as the number of antibiotic courses per patient, in group III is less than in both control groups. Even if the five day course of cefotaxime given to all patients in group III is included, the antibiotic use in this group is still lower than in both control groups.

Table IX further specifies the number of patients receiving particular antimicrobial agents. All but one patient in group I received one or more courses of therapy with high dose penicillin ($\geq 10^6$ tid) or with a penicillin derivative (ampicillin, amoxicillin, flucloxacillin), antibiotics that are known to disturb MCR (chapter I). In groups II and III, the use of antibiotics was restricted to those that are known not to disturb MCR.

The application of our regime of SDD and systemic cefotaxime was not accompanied by an increase of the incidence of resistance against the antibiotics used. However, these data should be interpreted with some caution since only 17 patients were treated with the regime (95% confidence interval 0-16%).

Discussion

The use of antibiotics disturbing MCR in group I led to a significant increase in the concentrations of Gram-negative bacilli in oropharynx and stomach, whereas in group II the use of antibiotics not influencing MCR did not have this effect. Aspi-

Table IX Antibiotic therapy per group

	Group I (n=18)	Group II (n=21)	Group III (n=17)
Patients receiving antibiotic therapy	17 (94%)	21 (100%)	11 (65%)*
95% confidence interval	73-100%	84-100%	38-86%
Mean number of antibiotic courses/patient†	5.2	3.2	1.5*
Mean number of antibiotic days/patient††	42	26	13*
Number of patients receiving:			
Antimycotics	3 (17%)	2 (10%)	2 (12%)
Aminoglycosides	16 (89%)	12 (57%)	4 (24%)
Cefotaxime	—	5 (24%)	3 (18%)*
Other cephalosporins	5 (28%)	20(95%)	7 (41%)
Penicillins	17 (94%)	—	—
Metronidazole	3 (17%)	6 (29%)	3 (18%)
Cotrimoxazole	1 (6%)	8 (38%)	3 (18%)
Other antibiotics	12 (67%)	5 (24%)	2 (12%)

* The initial five day course of cefotaxime is not included.

† Overall $p=0.0001$. Difference between Group I & II $p=0.046$, between Group I & III $p=0.0002$, between Group II & III $p=0.0007$.

†† Overall $p=0.001$. Difference between Group I & II n.s. ($p=0.12$), between Group I & III $p=0.0017$, between Group II & III $p=0.0027$.

ration of oropharyngeal and gastric contents plays a pivotal role in the development of lower respiratory tract infection (chapter II). Higher concentrations of microorganisms in oropharynx and stomach will result in higher numbers of bacteria reaching the lower respiratory tract in case of aspiration. In an animal experiment, intratracheal instillation of a bolus of 10^4 microorganisms produced severe infection [Berendt, 1978]. If the concentration of microorganisms in oropharynx or stomach exceeds $10^6/\text{ml}$, this threshold can easily be passed, with a consequent increase of the risk of lower respiratory tract infection. Therefore, the use of antibiotics that do not affect MCR is to be preferred. The great variety of antibiotics currently available makes it possible to effectively treat most infections without disturbing MCR.

In all patients with early lower respiratory tract infection (occurring within five days after admission), this infection was caused by microorganisms that already colonized the oropharynx on admission (chapter V). In half of these patients the

causative microorganism had already colonized the lower respiratory tract on admission. If the spread of microorganisms to the lower respiratory tract has already occurred, SDD alone is not effective. Our regime of SDD in association with short-term cefotaxime eliminated all potentially pathogenic microorganisms from the lower respiratory tract. The effect of norfloxacin and polymyxin E is limited to oropharynx, stomach and lower digestive tract. Therefore, the elimination of microorganisms from the lower respiratory tract and the prevention of early lower respiratory tract infection can be completely attributed to cefotaxime. Cefotaxime 500 mg tid proved adequate in this study.

In the control groups, the acquisition of new Gram-negative bacilli in both oropharynx and stomach was a frequent event. In group III protection against the acquisition of new microorganisms (especially against Gram-negative bacilli) persisted long after cefotaxime prophylaxis was discontinued, and is therefore thought to be achieved by SDD.

To achieve persistent decontamination of the oropharynx, the use of antibiotics in a sticky mouth paste that slowly releases constant amounts of the drugs is essential [Stoutenbeek, 1987]. Other methods of topical administration of antibiotics may result in fluctuating oropharyngeal concentrations of antibiotics that will mostly be too low to be effective.

The administration of antibiotics via the gastric tube is important to prevent gastric colonization. It should be continued even if, like in most of our patients, peristalsis is impaired. If bowel movements are normal, a rapid decontamination of the whole digestive tract from aerobic Gram-negative bacilli will occur. This eliminates a major source of urinary tract infection [Daifuku, 1974], of cross-infections [Penn, 1981], of wound infections [Van Saene, 1979] and of colonization of the patients own oropharynx [Le Frock, 1979]. Moreover, successful elimination of intestinal Gram-negative bacilli is likely to prevent endotoxaemia via reduction of the faecal endotoxin pool.

The possible emergence of antibiotic resistance still remains a concern. Problems may arise both from the selective pressures for resistance imposed by the regime of SDD and, possibly, from the induction of β -lactamases in certain species of Gram-negative bacilli during the initial periods of cefotaxime therapy [Brun-Buisson, 1987; Livermore, 1987]. However, in our study as well as in others [Stoutenbeek, 1984, A; Kerver, 1987; Unertl, 1987], the alternative of traditional management (i.e. administration of antibiotics only on clinical evidence of infection) involved extensive use of a wide range of antibiotics and hence the same potential problems.

Moreover, SDD is specifically designed to prevent colonization or overgrowth with antibiotic-resistant strains, and the extensive microbiological surveillance should allow early detection of problems and prompt institution of control measures [Alcock, 1988].

So far, the results with SDD and systemic antibiotic prophylaxis are encouraging: despite careful monitoring, problems of resistance have not been encountered in our study nor in others [Stoutenbeek, 1984; Kerver, 1988; Ledingham, 1988], even though a regime of SDD and systemic prophylaxis has been used in one center for 30 months [Stoutenbeek, 1987, A].

The regime of SDD described in this study proved to be at least as effective as the PTA-regime, which most other authors used [Stoutenbeek, 1984; Kerver, 1988; Ledingham, 1988]. In our opinion the regime we studied is to be preferred over the PTA-regime. The use of norfloxacin instead of tobramycin is not only less expensive, but also safer on theoretical grounds. In humans the decontaminating range of tobramycin appears to be narrow. MCR may be disturbed at daily doses of 300 mg of orally administered tobramycin, which is the daily dose used for SDD [Mulder, 1984]. This might, in case of contamination with a microorganism resistant to all antimicrobial agents used, facilitate colonization with – and the outgrowth of – this microorganism to high concentrations, with consequent risk of infection and of contamination of other patients. Norfloxacin, in the dose used in this study, does not disturb MCR [De Vries-Hospers, 1985].

Another disadvantage of oral tobramycin is that, although the agent is poorly absorbed, detectable serum levels may occur. It was reported that, in patients with renal failure, the serum tobramycin level may even exceed 2 mg/L with the consequent risk of ototoxicity and nephrotoxicity [Sciara, 1988]. Norfloxacin is absorbed from the digestive tract, but has no serious side-effects [Corrado, 1987].

However, because the administration of norfloxacin resulted in the development of cartilage erosions in juvenile animals of some species [Corrado, 1987], it is recommended not to use norfloxacin in patients whose skeletal growth is incomplete.

Conclusion

In this study in patients requiring prolonged mechanical ventilation, a novel regime of SDD, in combination with short-term systemic cefotaxime, effectively eliminated potentially pathogenic microorganisms from oropharynx and stomach. Moreover, the regime put an end to colonization of the lower respiratory tract with commensal oropharyngeal flora, which was frequently present on admission. SDD prevented the acquisition of new microorganisms in oropharynx and stomach.

The influence of SDD and short-term systemic cefotaxime on the lower respiratory tract infection rate will be discussed in the next chapter.

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CHAPTER V

Selective decontamination and short-term systemic antibiotic prophylaxis in mechanically ventilated patients: clinical results.

Results

Study population

Information about the population studied has been provided in chapter IV.

Colonization of the oropharynx

In both group I and II over 80% of the patients acquired one or more new species of microorganisms in the oropharynx during intensive care stay, predominantly Gram-negative bacilli (Table 1)

Table 1 Intensive care acquired colonization of oropharynx and stomach

	Group I (n=18)	Group II (n=21)	Group III (n=17)
Number of patients acquiring new colonization of the oropharynx†	15 (83%)	19 (90%)	2 (12%)
95% confidence interval	59-96%	70-99%	1-36%
Microorganisms involved*			
Gram-negative bacteria	22 (76%)	24 (67%)	0 (-)
Gram-positive bacteria	3 (10%)	9 (25%)	1 (-)
Yeasts	4 (14%)	3 (8%)	1 (-)
Number of patients acquiring new colonization of the stomach††	17 (94%)	19 (90%)	4 (24%)
95% confidence interval	73-100%	70-99%	7-50%
Microorganisms involved*			
Gram-negative bacteria	27 (66%)	20 (59%)	1 (-)
Gram-positive bacteria	8 (20%)	9 (26%)	4 (-)
Yeasts	6 (15%)	5 (15%)	1 (-)

* Several patients acquired more than one microorganisms (see Fig. 1).

† Overall $p < 0.001$. Difference between Group I & II not significant ($p = 0.85$), between Group I & III $p = 0.0001$, between Group II & III $p < 0.0001$.

†† Overall $p < 0.001$. Difference between Group I & II not significant ($p = 1.00$), between Group I & III $p < 0.0001$, between Group II & III $p < 0.0001$.

Acquisition of more than one new species of microorganisms occurred frequently in both group I and group II (Fig. 1a). Acquisition of Gram-negative bacilli was completely prevented in patients receiving selective decontamination (group III). Two patients in this group acquired new microorganisms in their oropharynx: a α -haemolytic streptococcus (not susceptible to the topically applied antibiotics) and one yeast (susceptible to amphotericin B).

Figure 1 Number of newly acquired species of microorganisms per patient in the oropharynx (fig. 1a) and in the stomach (fig. 1b).

Colonization of the stomach

Acquisition of new microorganisms, mostly Gram-negative bacilli, in the stomach occurred in about 90% of the patients in groups I and II (Table I), frequently with more than one microorganism (Fig. 1b). Colonization of the stomach with Gram-negative bacilli was virtually completely prevented in group III patients. The only

exception was the isolation in one patient of an *Acinetobacter anitratus* susceptible to the trial medication. From the stomach of this patient two other newly acquired microorganisms were isolated, probably due to improper application of the antibiotics (suction was applied to the nasogastric tube immediately after administration of the trial medication). The Gram-positive bacteria isolated from the stomach in the three groups were all enterococci.

More detailed information about colonization of the oropharynx and the stomach was provided in chapter IV.

Lower respiratory tract infection

Fourteen patients in group I (78%) and 13 patients in group II (62%) acquired at least one lower respiratory tract infection (Table II). Several patients in both control groups acquired more than one respiratory tract infection. The 14 patients in group I together acquired 25 infections and for the 13 patients in group II the number of infections was 22. Of the 47 infections in both control groups, 43 (91%) were of endogenous origin. In seven cases the causative organism was first cultured from the stomach and in 25 cases the oropharynx first became colonized. In the remaining 11 cases microorganisms were cultured simultaneously from both oropharynx and stomach. Three of the four exogenous lower respiratory tract infections were preceded by colonization of the nose.

Table II Intensive care acquired lower respiratory tract infection

	Group I (n=18)	Group II (n=21)	Group III (n=17)
Number of patients infected†	14	13	1
Percentage of patients infected	78%	62%	6%
95% confidence intervals	52-94%	38-82%	0-29%
Total number of infections*	25	22	1
Pneumonia	5	5	0
Purulent tracheobronchitis	20	17	1
Gram-positive infections	2	3	0
Gram-negative infections	20	17	1
Mixed infections	2	1	0
Yeast infections	1	1	0
Percentage preceded by colonization	92%	91%	0%

† $p < 0.001$, difference between Group I & II n.s. ($p=0.47$), between Group I & III $p < 0.0001$, between Group II & III $p=0.0007$.

* Several patients acquired more than one lower respiratory tract infection.

In group III, only one patient acquired a respiratory tract infection. This infection occurred on the 21th day of mechanical ventilation and was not preceded by colonization of either oropharynx, stomach or nose.

Figure 2 depicts the cumulative percentage of patients that acquired lower respiratory tract infection. After ten days of mechanical ventilation, about 50% of the patients in both control groups had acquired infection.

ICU-ACQUIRED LOWER RESPIRATORY TRACT INFECTION

Figure 2 Cumulative percentage of patients acquiring lower respiratory tract infection during ICU-stay (Kaplan-Meier method).

Lower respiratory tract infections were predominantly caused by Gram-negative bacilli (table III). However, there was a difference between the etiology of early respiratory tract infection (occurring in the first five days after admission) and late respiratory tract infection. In early infection, Gram-positive cocci and *Haemophilus influenzae* played an important role, whereas in late infection Gram-negative bacilli prevailed, causing 74% of the infections (fig. 3).

Of all cases of lower respiratory tract infection, ten (five in group I and five in group II) were associated with definite radiologic signs of pulmonary infiltration, the others being cases of purulent tracheobronchitis.

Table III Etiology of lower respiratory tract infection

	Group I	Group II	Group III
Gram-negative bacilli	22	14	1
Acinetobacter sp.	2	1	—
Citrobacter sp.	3	—	—
Enterobacter sp.	3	1	—
Escherichia coli	4	1	—
Klebsiella sp.	3	1	—
Morganella morganii	1	2	—
Proteus mirabilis	2	—	—
Pseudomonas aeruginosa	4	6	—
Pseudomonas maltophilia	—	2	—
Serratia marcescens	—	—	1
Gram-positive bacteria	4	6	0
Enterococci	2	2	—
Staphylococcus aureus	1	3	—
Streptococcus pneumoniae	—	1	—
Other Streptococci	1	—	—
Other Gram-negative bacteria			
Haemophilus influenzae	3	5	—
Yeasts			
Candida albicans	1	1	—
Total*	30	26	1

* Several infections in Group I & II were caused by more than one species of microorganisms.

Infections at other sites

The frequency of urinary tract infection in the three groups did not differ significantly (Table IV). Septicaemia and wound infection hardly occurred in group III. Lower respiratory tract infection was the source of septicaemia in four cases (two in group I and two in group II). The infections at other sites included five cases of pleural empyema (three in group I and two in group II) which were all preceded by lower respiratory tract infection with the same microorganism.

Mortality

In group I, four patients (22%) died, in two cases (11%) death could be attributed

Table IV Infections at other sites

	Group I (n=18)	Group II (n=21)	Group III (n=17)
Patients acquiring urinary tract infection†	6 (33%)	8 (38%)	6 (35%)
Number of infections*	8	10	6
Microorganisms involved:			
Gram-positive	3 (38%)	4 (40%)	4 (67%)
Gram-negative	4 (50%)	4 (40%)	2 (33%)
Yeasts	1 (13%)	2 (20%)	—
Patients acquiring septicaemia†	5 (28%)	8 (38%)	1 (6%)
Number of infections*	7	9	1
Microorganisms involved:			
Gram-positive	4 (57%)	6 (67%)	—
Gram-negative	3 (43%)	1 (11%)	1
Mixed Gram-positive/negative	—	1 (11%)	—
Yeasts	—	1 (11%)	—
Patients acquiring wound infection†	2 (11%)	5 (24%)	0
Microorganisms involved:			
Gram-positive	1	1	—
Gram-negative	1	3	—
Yeasts	—	1	—
Patients acquiring other infections†	7 (39%)	7 (33%)	3 (18%)
Microorganisms involved:			
Gram-positive	3	2	3
Gram-negative	4	5	—

† No significant differences.

* Some patients acquired more than one infection at the same site.

to ICU-acquired lower respiratory tract infection. The two deaths (10%) in group II were not infection related. Of the two deaths (12%) in group III, one was related to infection: a Herpes simplex viral pneumonia. The mortality was too low to permit conclusions.

Antibiotic use

The reduction of the respiratory tract infection rate in group III resulted in a reduction of the use of systemic antibiotic therapy in this group. The number of patients requiring antibiotic therapy was 17 (94%) in group I, 21 (100%) in group II, but

EARLY INFECTIONS (n=14)

gram-positive cocci 22%

gram-negative cocci 44%

yeasts 6%

H. Influenzae 28%

LATE INFECTIONS (n=33)

gram-positive cocci 13%

gram-negative cocci 74%

yeasts 5%

H. Influenzae 8%

Figure 3 Microorganisms isolated in early and late lower respiratory tract infection in patients from both control groups.

only 11 (65%) in group III. The mean number of antibiotic days per patient (one antibiotic day is the use of one antibiotic during one day) in group III was 13 (excluding five days of cefotaxime prophylaxis/patient). This is lower than in group I (mean 42 days) or in group II (mean 26 days) ($p=0.001$).

It should be stressed that antibiotic therapy was instituted by the responsible physicians in the ICU. The infection criteria they used were not always strictly the same as those employed in this study. Therefore, the use of antibiotics does not necessarily reflect the incidence of infection. However, it gives an impression of how the different antibiotic policies influenced the prescription of antibiotics by the physicians in the ICU.

For more detailed information on the antibiotic therapy see chapter IV.

Discussion

Although all but one patient in group I were treated with antibiotics lowering MCR, and mostly from an early stage, this did not result in a higher incidence of colonization and infection in group I than in group II in which the patients did not receive therapy affecting MCR. It is probable that, in these critically ill patients,

colonization resistance is already so severely impaired by reduction of the PCR that disturbance of the MCR does not result in a further increase of the colonization and infection rate. However, whereas PCR is quickly restored when the patient is extubated and regains consciousness, disturbance of the MCR by antibiotic therapy persists, leaving the patient prone to an increased risk of superinfection [Van der Waaij, 1982]. Therefore the use of antibiotics that do not affect MCR still is to be preferred.

As in other studies [Kerver, 1987; Stoutenbeek, 1984], lower respiratory tract infections in the control groups were generally preceded by colonization of either oropharynx, stomach or both with the causative microorganism.

We defined early respiratory tract infection as infection occurring within the first five days after admission, because it appeared that all these infections were caused by bacteria that already colonized the upper respiratory tract on admission. Frequently, these bacteria have already gained access to the lower airways soon after the onset of acute disease, either by aspiration of oropharyngeal contents [Langer, 1987] or by intubation [Nair, 1986]. This explains the important role of *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*, which colonize the oropharynx of about 50% of healthy individuals [Wilson, 1983; Sanderson, 1985], in the etiology of early respiratory tract infection. Because early respiratory tract infection is often already incubating on admission, it can not be prevented by SDD alone. Therefore SDD was combined with five days of systemic cefotaxime. At the present time, all authors that have used cefotaxime for this purpose, have administered daily doses of 4 g [Stoutenbeek, 1984; Kerver, 1988; Ledingham, 1988]. However, a lower dose of cefotaxime achieves serum and sputum levels exceeding the minimum inhibitory concentrations for *Streptococcus pneumoniae*, *Haemophilus influenzae* and most Gram-negative bacilli [Carmine, 1983]. We therefore lowered the cefotaxime dose to 500 mg tid which, in combination with selective decontamination of oropharynx and stomach, successfully prevented early lower respiratory tract infection.

After the fifth day of mechanical ventilation, lower respiratory tract infection was frequently caused by ICU-acquired microorganisms. The great majority of these newly acquired microorganisms were Gram-negative bacilli. This has also been found by others [Johanson, 1972; Ruiz-Santana, 1987]. We confirmed the important role of oropharyngeal colonization in the pathogenesis of respiratory tract infection. Our results further underscore the importance of bacterial colonization of the stomach in the pathogenesis of lower respiratory tract infection: the stomach was the primary source of microorganisms in seven cases of lower respiratory tract infection and played a role in eleven other cases.

It should be stressed that not mechanical ventilation but intubation is the principal factor resulting in aspiration of oropharyngeal and gastric contents. The presence

of an endotracheal or tracheostomy tube interferes with the normal clearing mechanisms of the trachea. Furthermore, the tube cuff does not protect against micro-aspiration: small quantities of oropharyngeal secretion frequently pass the cuff, especially if high volume cuffed tubes are used [Pavlin, 1975; Seegobin, 1986].

SDD (group III) virtually eliminated colonization of oropharynx and stomach. In absence of gastric retention, the application of antibiotics in the stomach has the additional advantage of eliminating potentially pathogenic microorganisms from the lower digestive tract, thereby eliminating a major source of oropharyngeal colonization [LeFrock, 1979] and of urinary tract infection [Daifuku, 1984]. Since most of our patients had impaired peristalsis, decontamination of the rectum from Gram-negative bacilli in patients in group III was not always rapidly achieved. This explains why, in contrast to the results of other studies [Stoutenbeek, 1984], SDD did not reduce the incidence of catheter-associated urinary tract infection: frequently, urinary tract infection had already developed before decontamination of the rectum was achieved. In case of impaired peristalsis, decontamination of the rectum – and thereby possibly the prevention of urinary tract infection – might be achieved with enema's containing the same antimicrobial agents as are administered via the nasogastric tube.

It may be difficult to distinguish microbial colonization of the lower respiratory tract of intubated patients from lower respiratory tract infection. "True" diagnosis would require histological confirmation which cannot be obtained during life. Other reliable techniques like bronchoalveolar lavage [Chastre, 1988] or the use of a protected specimen brush [Fagon, 1988] are not yet routinely available. For the diagnosis of lower respiratory tract infection we used criteria commonly applied to intubated patients [Caplan, 1981; Craven, 1986; Unertl, 1987]. However, most authors consider infiltrative changes on the chest X-ray mandatory for the diagnosis lower respiratory tract infection and consequent institution of antibiotic therapy. In our opinion purulent tracheobronchitis should also be treated because it represents a symptomatic infection and because it not infrequently develops into pneumonia [Unertl, 1987]. The high incidence of pneumonia-associated septicaemia and mortality in other studies [Caplan, 1979; Caplan, 1981] can partly be attributed to the postponement of antibiotic treatment until after the development of infiltrations on the chest X-ray.

Mortality in this study is low. This is partly explained by the design of the study: the fact that only patients with a duration of mechanical ventilation exceeding four days were included eliminates early mortality. Even taking this into account, mortality in the control groups still seems low considering the high incidence of lower respiratory tract infection. This might in part be caused by the improved treatment of Gram-negative bacillary lower respiratory tract infection in the last years and by

the prompt institution of antibiotic therapy. Furthermore, the mortality due to ICU-acquired lower respiratory tract infection has probably been overestimated. In a recent study a direct relationship between ICU-acquired pneumonia and increased mortality could not be established [Craven,1986]. Of the 30% mortality related to nosocomial pneumonia in another study, only 7% could really be attributed to pneumonia [Leu,1986]. Mortality following nosocomial pneumonia seems to be caused by underlying disease rather than by pneumonia itself. This explains the low infection related mortality in our two control groups, which makes it difficult to show possible differences in infection related mortality between the groups. Therefore, the assessment of the regime used in this and other studies depends mainly upon bacteriological and morbidity data. These data suggest strongly that the application of SDD in association with a short course of antibiotic prophylaxis represents a substantial advance in the control of ICU-acquired lower respiratory tract infection.

Conclusion

SDD in combination with an initial short course of systemic cefotaxime proved to be safe and effective in the prevention of respiratory tract infection in patients requiring prolonged mechanical ventilation. Our newly developed regime of SDD is as effective as the PTA-regime, but is less expensive and is safer on theoretical grounds. Provided that facilities for detailed microbiological surveillance are available, a regime of SDD, in association with a short course of systemic antibiotic prophylaxis, should be applied from an early stage to all patients expected to require prolonged mechanical ventilation. In patients that are otherwise at risk for developing mechanical ventilation associated lower respiratory tract infection e.g. patients whose oropharynxes are already heavily colonized with Gram-negative bacilli on admission, the use of SDD should also be considered.

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Selective decontamination and short-term systemic antibiotic prophylaxis in mechanically ventilated patients: cost-effectiveness analysis.

Introduction

Intensive care acquired infection is a major problem in critically ill patients [Daschner, 1982; Donowitz, 1982]. Not only are intensive care acquired infections associated with a considerable increase in morbidity and mortality [Thorp, 1979], they also result in increased costs due to prolonged hospital stay and extra diagnostic and therapeutic services [Haley, 1981]. Lower respiratory tract infection is one of the most frequently reported infections in ICU patients [Massarani, 1986], especially in those patients requiring prolonged mechanical ventilation [Cross, 1981]. Respiratory tract infection further is, together with septicaemia and wound infection, one of the infections associated with the greatest increase in cost [Haley, 1981]. The magnitude of the economic consequences of these infections stresses the need for continued preventive efforts.

We studied the efficacy of a novel regime of SDD in the prevention of respiratory tract infection in critically ill patients that were mechanically ventilated for at least five days (chapter V). In a prospective three group study the incidence of lower respiratory tract infection in a group of patients receiving SDD in combination with a short course of systemic cefotaxime (group III) was compared with two groups of patients in which antibiotic therapy was instituted only on clinical evidence of infection. In control group I our previous antibiotic policy was continued: on clinical evidence of infection patients were treated with antibiotics known to affect the anaerobic gastro-intestinal flora. In control group II, the use of antibiotics was restricted to those not influencing the anaerobic gastro-intestinal flora. The reason for the institution of two different control groups is provided elsewhere (chapter III).

The clinical results of this study have been described in chapter V. It may be concluded that SDD, in association with a short course of cefotaxime, is effective in preventing lower respiratory tract infection in mechanically ventilated patients. However, the decision whether or not to introduce this strategy as a routine approach, can only be taken after the medical results have been complemented by an economic appraisal.

The question addressed in this chapter is: which of the three strategies employed to prevent or to treat lower respiratory tract infections is the most efficient? This question will be answered by means of a cost-effectiveness analysis [Drummond, 1980], in which the hospital charges, and the costs of bacteriologic cultures and of antibiotic therapy in the three groups are prospectively compared.

Methods

The study design has been described in chapter III. The costs associated with infection and infection prevention were estimated as follows:

Acquisition costs of antibiotics

The acquisition costs of the usual daily dose of every antibiotic used were quantified. The costs of antibiotic therapy were estimated by multiplying these costs by the amount of days the patient used the antibiotic.

The acquisition costs of antibiotic therapy varied from DFI 8.64 per day (penicillin) to DFI 295.80 per day (vancomycin).*

Costs of bacteriologic cultures

Cultures of tracheal aspirate and urine were performed on admission. Thereafter urine was cultured once weekly and tracheal aspirate thrice weekly. Cultures from both sites were performed more often if necessary. Cultures from other sites (e.g. blood, wounds, drains etc.) were taken if this was indicated on clinical grounds.

To evaluate the effect of SDD, surveillance cultures of oropharynx, stomach and rectum were performed twice weekly.

The cost of each culture was DFI 25.50, to which DFI 13.60 has to be added for each microorganism cultured, this being the cost of susceptibility testing.

Cost of the regime

The cost of the regime used for selective decontamination was DFI 25.64 per day. For the first five days DFI 46.74 per day has to be added, this being the cost of systemic cefotaxime. These are merely acquisition costs, the costs associated with the application of SDD and systemic antibiotic prophylaxis (e.g. nurses fees, disposable gloves etc.) were not taken into account.

Other costs

The costs of lower respiratory tract infection are not limited to those of antibiotics and of bacteriological cultures. Lower respiratory tract infection also results in an increased use of drugs other than antibiotics and in an increased use of disposa-

* One DFI is approximately US \$ 0.50.

bles. Furthermore it might increase the need of laboratory tests, respiratory therapy etc., with consequent increased costs [De Clercq, 1983]. However, the design of our study does not permit the estimation of these costs. All these costs are included in the routine charges for hospitalization at the Intensive Care Unit, which were Dfl 2,250.- per day or per part of a day (September 1987).

Results

Study population

From May 1986 to September 1987, 56 patients (18 in group I, 21 in group II and 17 in group III) were included in the study. The three different groups were comparable with respect to age, sex and the severity of disease as determined by the APACHE II score [Knaus, 1985]. Duration of intubation and of ICU-stay were lowest in group III. However, these differences did not reach significance. For detailed information about the study population see chapter IV.

Table I Intensive care acquired infections

Number of patients acquiring infection (percentage)	Group I (n = 18)	Group II (n = 21)	Group III (n = 17)
Respiratory tract infection†	14 (78%)	13 (62%)	1 (6%)
Number of infections	25	22	1
Urinary tract infection*	6 (33%)	8 (38%)	6 (35%)
Number of infections	8	10	6
Septicaemia*	5 (28%)	8 (38%)	1 (6%)
Number of infections	7	9	1
Wound infection*	2 (11%)	5 (24%)	0
Number of infections	2	5	—
Other infections*	7 (39%)	7 (33%)	3 (18%)
Number of infections	7	7	3
Total patients acquiring infection*/††	16 (89%)	18 (86%)	10 (59%)

† $p < 0.001$, difference between Group I and Group II n.s. ($p = 0.47$), difference between Group I and Group III $p < 0.0001$, difference between Group II and Group III $p = 0.0007$.

* No significant differences.

†† $p = 0.057$.

Infections

The differentiation of antibiotics used in group I and group II did not result in a difference in the infection rate. SDD and short-term systemic cefotaxime in group III decreased the lower respiratory tract infection rate. The urinary tract infection rates in the three groups did not differ. Infections at other sites than the urinary and respiratory tract occurred in only three patients in group III (Table I).

Costs of bacteriological cultures.

The lower incidence of lower respiratory tract infection in group III resulted in a slight reduction of the amount of cultures of tracheal aspirate and in a much lower percentage of positive cultures as compared to both group I and group II. Consequently, the need for susceptibility testing in group III decreased and the costs of routinely performed bacteriological cultures in group III were lower than those in both other groups (Table II).

In group III patients, surveillance cultures of oropharyngeal secretion, gastric contents and rectum were performed twice weekly to monitor the effect of SDD. The mean costs of these cultures were Dfl 857.- per patient. The costs of surveillance cultures in patients in both control groups were not taken into account because the performance of surveillance cultures in these patients only served study purposes.

Table II Bacteriological Cultures

Number of cultures (% of cultures positive)	Group I (n=18)	Group II (n=21)	Group III (n=17)
Tracheal aspirate mean per patient	200 (69%) 11.11	204 (75%) 10.71	154 (38%) 9.06
Urine mean per patient	88 (15%) 4.89	93 (27%) 4.43	62 (19%) 3.65
Wounds mean per patient	21 (100%) 1.17	20 (100%) .95	13 (100%) .77
Mean cost cultures/patient (Dfl)	618.00	575.00	420.00

Acquisition costs of antibiotics

In group I and group II, virtually all patients received antibiotic therapy (Table III). The number of antibiotic courses prescribed was highest in group I and so were the costs of antibiotic therapy. Although there was no significant difference

in the infection rate between group I and II, the number of antibiotic courses per patient prescribed in group II was lower than in group I. The percentage of patients receiving antibiotic therapy and the number of antibiotic courses per patient was lowest in group III. Consequently, the costs of antibiotic therapy in group III were lower than in both other groups. Even if the costs of SDD and systemic cefotaxime in group III are added, the total antibiotic costs per patient in this group are still lower than in both control groups (Table III).

Table III Acquisition costs of antibiotic therapy

	Group I (n=18)	Group II (n=21)	Group III (n=17)
Patients receiving therapeutic antibiotics (percentage)	17 (94%)	21 (100%)	11 (65%)
Antibiotic courses/patient†	5.2	3.2	1.5 (2.5)*
Antibiotic days/patient	42	26	13 (18)*
Costs of antibiotic therapy††	4,022	1,840	901
Costs SDD and systemic cefotaxime	—	—	855
Total antibiotic costs/patient (DFI)	4,022	1,840	1,758

* The numbers in parentheses include systemic cefotaxime prophylaxis.

‡ Overall $p=0.0001$. Difference between Group I & II $p=0.046$, between Group I & III $p=0.0002$, between Group II & III $p=0.0007$.

†† Overall $p=0.0015$. Difference between Group I & II n.s. ($p=0.15$), between Group I & III $p=0.0016$, between Group II & III $p=0.0052$.

Overall costs

Table IV gives an overview of the mean costs of antibiotic therapy and of bacteriologic cultures in patients in each group. For group III, the mean costs of the regime of selective decontamination and systemic cefotaxime are added, as are the costs of surveillance cultures.

The routine hospital charges accounted for the major part of the costs. These charges were lowest in group III, in which the average ICU-stay was shortest. However, the difference in duration of ICU-stay, and consequently the difference in hospital charges, was not significant. In table IV, the hospital charges are, therefore, mentioned separately.

Table IV Mean overall costs per patient

Costs in DFI (range)	Group I	Group II	Group III
Antibiotic therapy	4,022 (0-11,586)	1,840 (170-3,993)	901 (0-3,597)
SDD and systemic cefotaxime	—	—	857 (439-1,772)
All antibiotics	4,022 (0-11,586)	1,840 (170-3,993)	1,758 (439-4,702)
Bacteriological cultures	618 (180-1,224)	575 (153-1,074)	420 (153-859)
Surveillance cultures	—	—	857 (260-2,251)
Total	4641 (265-12,679)	2415 (455-4,703)	3036 (866-7,194)
Hospital charges	70,625 (20,250-180,000)	58,393 (22,500-114,750)	54,662 (18,000-135,000)

Discussion

Selective decontamination (consisting of topically applied polymyxin E, tobramycin, and amphotericin B), in combination with short-term systemic antibiotic (cefotaxime) prophylaxis, prevents colonization of oropharynx and stomach with potentially pathogenic microorganisms and reduces the incidence of lower respiratory tract infection in patients receiving prolonged mechanical ventilation [Stoutenbeek, 1984; Kerver, 1988; Ledingham, 1988]. We prospectively proved that a novel regime -using norfloxacin as the principal agent for SDD- in association with a lower dose of cefotaxime is equally effective (chapter V).

The present chapter offers a comparison of the financial costs of infection and infection prevention, which can easily be measured. However, an economic appraisal should not only take financial aspects into account, but also the fact that the aim of ICU treatment -to change the course of the patients disease for the better so that the patient is able to leave the ICU alive, in the best possible condition and in the shortest amount of time- was best met in group III.

Financial costs

Antibiotic therapy

In group I we more or less adhered to the previous antibiotic policy on our ward. In group II the use of antibiotics was restricted to those antibiotics not disturbing

the anaerobic gastro-intestinal flora. The incidence of infection in both control groups did not differ significantly. However, the number of antibiotic courses prescribed per patient in group I was higher, as were the costs of antibiotic therapy. Although, due to the great spread of the antibiotic costs between patients within the same group, this last difference is not statistically significant, it is in agreement with the results of a recent study, in which the introduction of antibiotic formulary restrictions as such considerably reduced total antibiotic use, as well as the costs of antibiotic therapy [Woodward,1987]. The reduction of the average costs of antibiotic therapy in group III as compared to both other groups can be attributed to the reduction of the respiratory tract infection rate. The reduction of the costs of antibiotic therapy more than outweighed the costs of the antibiotics that were used for SDD and systemic prophylaxis.

Bacteriological cultures

The overall costs of routinely performed bacteriological cultures in group III were lower than in both control groups. The decreased risk of lower respiratory tract infection might enable us to decrease the frequency of cultures of the tracheal aspirate from three times weekly to twice weekly, with consequent further reduction of the costs. This would have saved about two cultures of tracheal aspirate per patient, which, with an average cost of Dfl 40 per culture, would result in a further reduction of the costs of about Dfl 80 per patient.

SDD necessitates the introduction of surveillance cultures of oropharynx, stomach and rectum. These cultures are indispensable to monitor the effect of SDD and the possible development of resistance against the antibiotics used [Schimpff,1981]. Since we did not observe the emergence of resistance against the antibiotics used for SDD, we consider it safe to perform surveillance cultures only once weekly in the future. This would reduce the costs of surveillance cultures to approximately half, estimated savings about Dfl 400 per patient.

Additional costs

One should be aware that the costs of infection are not limited only to those of antibiotics and bacteriological cultures. Infection might also increase the need for other ancillary services such as chest X-rays, laboratory tests, respiratory therapy etc., and increase the use of drugs other than antibiotics and the use of disposable material [De Clercq,1983]. Inversely, a reduction of the infection rate may result in a reduction of these costs. The reduction of the lower respiratory tract infection rate induced by the introduction of SDD might, for example, enable us, after about the fourth day of admission, to reduce the frequency of chest X-rays from once daily (costs Dfl 53/day) to thrice weekly (average costs Dfl 23/day). With a mean duration of stay 23 days, this would have saved Dfl 570 per patient.

The three modifications suggested above, would have reduced the average costs of treatment in group III by Dfl 1050 to Dfl 1986 per patient, the lowest of all groups.

Overall costs

Although the differences in duration of stay and consequent hospital charges fell short of statistical significance, we feel that these differences deserve consideration in the overall analysis: ICU-acquired respiratory tract infection has often been shown to prolong ICU and hospital stay significantly [Haley, 1980; Haley, 1981; De Clercq, 1983; Craig, 1984] and the lack of significance in our study seems to be due to the great spread in the duration of ICU-stay.

Beneficial effects of SDD

Reduction of the lower respiratory tract infection rate has beneficial effects on the health of patients which include the following:

- (1) Decrease of infection-associated mortality.
In our – relatively small – study population infection related mortality was too low to permit any conclusions. However, Ledingham et al reported that the use of the PTA-regime in combination with a short course of systemic cefotaxime was associated with a reduction in mortality in patients staying at the ICU for seven days or more [Ledingham, 1988].
- (2) Reduction in the use of toxic antibiotics.
The use of aminoglycosides, well known for their nephrotoxicity and ototoxicity [Schentag, 1982; Eisenberg, 1987] was required in 16 patients in group I (89%), 12 patients in group II (57%), but only in four of the patients receiving SDD (24%).
- (3) Decrease of the incidence of residual symptoms.
Our knowledge about the harmful long-term effects of lower respiratory tract infection is still unsatisfactory. Lower respiratory tract infection might result in residual symptoms in the form of recurrent respiratory tract infection [Fry, 1960], in the loss of functioning lung tissue, or occasionally even the loss of a complete lung.

Until present, there have been no negative effects reported on the use of SDD in mechanically ventilated patients, even though this technique has now been used for more than two-and-a-half years at one ICU [Stoutenbeek, 1987].

Conclusion

SDD, in combination with initial systemic antibiotic prophylaxis, prevents colonization of oropharynx and stomach with potentially pathogenic microorganisms and reduces the incidence of lower respiratory tract infection in mechanically ventilated patients [Stoutenbeek, 1984; Kerver, 1988; Ledingham, 1988]. However, the PTA-regime, in combination with high dose cefotaxime, is about four

times as expensive as the regime we have described [Vollaard,1984]. A cost-effectiveness analysis of the PTA-regime has never been performed. Although our analysis does not take into account all costs associated with lower respiratory tract infection or with the administration of SDD, we conclude that the regime studied is cost-effective in that it has great clinical benefits over the conventional antibiotic policy for no -or only a few- extra costs [Doubilet,1986].

The use of the regime of SDD consisting of norfloxacin, polymyxin E and amphotericin B in combination with a short course of systemic, low dose, cefotaxime should be considered in every ICU for patients expected to require prolonged mechanical ventilation.

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Summary and general discussion

Introduction

Lower respiratory tract infection is a major problem in mechanically ventilated patients. In patients requiring prolonged mechanical ventilation the incidence of respiratory tract infection may be as high as 60 percent, resulting in a considerable increase of morbidity, of the length and costs of hospitalization and probably also of mortality.

Colonization of the oropharynx and of the stomach with potentially pathogenic microorganisms plays a key role in the development of lower respiratory tract infection (chapter II):

- Early lower respiratory tract infection (occurring in the first five days after admission) is frequently caused by oropharyngeal commensal microorganisms (*Haemophilus influenzae*, *Streptococcus pneumoniae* and *Staphylococcus aureus*), that reach the lower airways by aspiration at the onset of acute disease or at intubation.

- Soon after the onset of disease, colonization of the oropharynx and of the stomach with high concentrations of Gram-negative bacilli occurs in almost all critically ill patients. Aspiration of oropharyngeal and gastric contents around the cuff of the endotracheal tube, which frequently takes place, spreads Gram-negative bacilli into the lower respiratory tract, where infection may result.

Since oropharyngeal and gastric contents are the principal source of microorganisms causing lower respiratory tract infection, a reasonable strategy of infection prevention would be the elimination of potentially pathogenic microorganisms from these sites.

Selective decontamination of the digestive tract is a novel method of infection prevention. It aims at the elimination of potentially pathogenic microorganisms from the digestive tract, at the same time leaving the autochthonous anaerobic flora intact. Parts of this anaerobic flora protect against colonization of the digestive tract with Gram-negative bacilli. This protective effect is called microbial colonization resistance (chapter I).

Selective decontamination has proved to be effective in the prevention of infections in neutropenic patients. The first studies in mechanically ventilated patients also showed a beneficial effect of selective decontamination on the infection rate. However, these first studies were not prospectively controlled; the infection rates were compared with those in historical control groups. Moreover, the regime of selective decontamination used in these studies contained tobramycin, which car-

ries the risk of disturbance of microbial colonization resistance, as well as -especially in patients with impaired renal function- a small risk of toxicity by tobramycin resorption.

Study design

Our study provides a prospective, controlled assessment of the effect of a novel regime of selective decontamination on the lower respiratory tract infection rate in patients receiving prolonged (at least five days) mechanical ventilation.

On admission patients were randomly allocated to one of three groups. Patients in both control groups I (n=18) and II (n=21) did not receive antibiotic prophylaxis, antibiotics were administered only on clinical evidence of infection. In group I infections were treated with antibiotics known to disturb the microbial colonization resistance, whereas in group II the use of antibiotics was restricted to those that are known not to have such effect. The aim of this part of the study was to determine the influence of antibiotics from these different categories on the colonization and infection rate.

Patients in group III (n=17) received a regime of selective decontamination from admission until extubation, in conjunction with a short course of systemic cefotaxime. Selective decontamination consisted of norfloxacin 50 mg, polymyxin E 200 mg and amphotericin B 500 mg, administered four times daily via the gastric tube. A sticky paste containing 2% concentrations of the same agents was applied to the buccal mucosa four times daily. Intravenous cefotaxime (500 mg) was administered to patients in group III eight hourly during the first five days of admission.

Results

On admission the oropharynx was frequently colonized with commensal microorganisms and, less often, with Gram-negative bacilli. In both control groups this colonization persisted and often resulted in early lower respiratory tract infection. In group III all oropharyngeal commensals and Gram-negative bacilli were eradicated from the upper and lower respiratory tract and early lower respiratory tract infection was completely prevented.

Patients in both control groups frequently acquired new microorganisms – predominantly Gram-negative bacilli – in oropharynx and stomach. Eighty-three percent of the patients in group I and 90% of the patients in group II acquired at least one new species of microorganisms in their oropharynx during admission. New colonizations of the stomach occurred in 94% of the patients in group I and in 90% of the patients in group II. In group III selective decontamination virtually prevented the acquisition of new microorganisms at both sites (chapter IV).

The administration of antibiotics that disturb the microbial colonization resistance

(group I) caused a significant increase of the concentration of Gram-negative bacilli in oropharynx and stomach, whereas antibiotic therapy in group II did not affect the oropharyngeal or gastric concentration of Gram-negative bacilli. Although an increase in the oropharyngeal and gastric concentration of microorganisms increases the risk of lower respiratory tract infection, there was no significant difference in the respiratory tract infection rate between group I and group II. In group I, 14 patients (78%) together acquired 25 lower respiratory tract infections, versus 13 patients (62%) who acquired 22 infections in group II ($p=0.47$). In both control groups, colonization of oropharynx and stomach played a pivotal role in the pathogenesis of lower respiratory tract infection: over 90% of the respiratory tract infections in these groups were preceded by colonization of oropharynx, stomach or both with the causative microorganism. In the group of patients receiving selective decontamination and systemic cefotaxime, the incidence of lower respiratory tract infection was significantly lower than in both control groups: only one patient (6%) in group III acquired lower respiratory tract infection ($p<0.001$). This infection was not preceded by oropharyngeal or gastric colonization with the causative microorganism (chapter V).

Most lower respiratory tract infections in both groups were caused by Gram-negative bacilli. However, in the etiology of early respiratory tract infection the commensal flora of the oropharynx (*Streptococcus pneumoniae*, *Staphylococcus aureus* and especially *Haemophilus influenzae*) also played an important role.

The regime of selective decontamination and systemic antimicrobial prophylaxis used in this study decreased the costs of antibiotic therapy to such an extent that it more than outweighed the costs of the regime. Although the costs of routinely performed cultures were lowest in group III, the total costs of bacteriological investigations in this group were higher than in both other groups. This was entirely due to the costs of the surveillance cultures of oropharynx, stomach and rectum, which are necessary to monitor the effect of selective decontamination. Despite this, we found the application of our regime of selective decontamination in mechanically ventilated patients cost-effective in that it provides great benefits without – or with only few – extra costs (chapter VI).

Discussion

The use of antibiotics that disturb the autochthonous anaerobic flora and thus the microbial colonization resistance, increases the concentrations of Gram-negative bacilli in the oropharynx and in the stomach of critically ill patients. This increases the risk of lower respiratory tract infection. However, elimination of this risk (group II) only slightly reduced the incidence of lower respiratory tract infection. This might be explained by the fact that, in these critically ill patients, the physio-

logical colonization resistance (swallowing, salivation, coughing, etc.) also is severely reduced, by disease itself as well as by endotracheal intubation and other medical interventions. In moderately ill patients the restriction of the use of antibiotics to those that do not affect the autochthonous anaerobic flora might be sufficient to prevent colonization and infection with Gram-negative bacilli. In mechanically ventilated patients it certainly is not, which necessitates the addition of other prophylactic measures.

Selective decontamination of the oropharynx and of the lower digestive tract (in combination with short-term systemic cefotaxime) was very effective both in eradicating already existing colonization and in preventing new colonization of the oropharynx and of the stomach of mechanically ventilated patients. Elimination of these major sources of microorganisms causing lower respiratory tract infection resulted in a highly significant decrease of the incidence of unit-acquired respiratory tract infection.

The addition of short-term antibiotic prophylaxis to the regime for the first days after intubation is necessary because, at admission at the ICU, oropharyngeal microorganisms often have already gained access to the lower respiratory tract where they can not be reached by antibiotics that are topically applied to the higher airways.

An additional advantage of selective decontamination is that, if bowel movements are not impaired, the antibiotics applied to the stomach also decontaminate the lower digestive tract and the faeces. This eliminates a major source of endogenous infection, of endotoxaemia and of cross-infection. Furthermore, the elimination of Gram-negative bacilli from oropharynx and lower digestive tract eliminates two major sites of development of resistance to antibiotics.

Conclusions

The use of antibiotics which disturb the autochthonous anaerobic flora of oropharynx and lower digestive tract, gives rise to an increase in concentrations of Gram-negative bacilli in stomach and oropharynx of critically ill patients. The use of these antibiotics in hospitalized patients should be avoided if possible.

Selective decontamination with norfloxacin, polymyxin E and amphotericin B in combination with short-term systemic cefotaxime proved to be an effective, safe and cost-efficient strategy for the prevention of respiratory tract infection in mechanically ventilated patients. A regime of selective decontamination in association with an initial course of systemic antibiotic prophylaxis should be applied from an early stage in all patients requiring prolonged mechanical ventilation.

Samenvatting en discussie

Inleiding

Infecties van de lagere luchtwegen vormen een groot probleem bij kunstmatig beademde patiënten. Bij patiënten die gedurende langere tijd moeten worden beademd, stijgt de incidentie van deze infecties tot boven de 60 procent. Lagere luchtweginfecties resulteren in een stijging van de morbiditeit, van opnameduur en -kosten en waarschijnlijk ook van de mortaliteit.

Kolonisatie van de oropharynx en van de maaginhoud met potentieel pathogene micro-organismen spelen een sleutelrol in de pathogenese van infecties van de lagere luchtwegen (Hoofdstuk II).

Voor zover infecties ontstaan gedurende de eerste dagen na opname, worden zij meestal veroorzaakt door micro-organismen die als commensaal in de oropharynx vóórkomen, te weten: *Haemophilus influenzae*, *Streptococcus pneumoniae* en *Staphylococcus aureus*. Deze micro-organismen bereiken de lagere luchtwegen door aspiratie, optredend tijdens of kort na het ontstaan van ziekte of trauma, of tijdens het intuberen.

Bij ernstig zieke patiënten raken oropharynx en maaginhoud meestal snel gekoloniseerd met Gram-negatieve bacillen, dikwijls in hoge concentraties. Door aspiratie van maag- en keelinhoud langs de manchet van de endotracheale tube -hetgeen frequent voorkomt- bereiken deze Gram-negatieve bacillen de lagere luchtwegen, waar zich vervolgens een infectie kan ontwikkelen.

Oropharynx en maag zijn dus de belangrijkste bronnen van verwekkers van lagere luchtweginfecties bij beademde patiënten. Het ligt voor de hand te veronderstellen dat eliminatie van potentieel pathogene micro-organismen uit oropharynx en maag zal leiden tot een reductie van het aantal infecties van de lagere luchtwegen.

Selectieve decontaminatie van de tractus digestivus is een nieuwe methode van infectiepreventie, waarbij wordt gestreefd naar de eliminatie van (aerobe) potentieel pathogene micro-organismen uit de tractus digestivus. De anaerobe intestinale flora wordt hierbij intact gelaten. Deze anaerobe flora (of althans een deel daarvan) speelt een belangrijke rol bij de bescherming van de tractus digestivus tegen kolonisatie met Gram-negatieve bacillen. Dit beschermend effect wordt microbiële kolonisatieweerstand genoemd (Hoofdstuk II).

Bij neutropenische patiënten bleek de toepassing van selectieve decontaminatie te resulteren in een sterke reductie van het aantal infecties. Ook de eerste onderzoeken naar het effect van selectieve decontaminatie bij kunstmatig beademde patiënten tonen een vermindering van het aantal infecties. Echter, bij deze eerste onderzoeken ontbrak een prospectieve controle. De resultaten werden vergeleken met de incidentie van infecties in historische controlegroepen. Voorts bevatten vrijwel alle tot nu toe onderzochte regimes tobramycine. Dit is duur en kan bovendien – met name bij patiënten met gestoorde nierfunctie – leiden tot toxiciteit ten gevolge van tobramycine resorptie.

Opzet van het onderzoek

Dit proefschrift beschrijft een prospectief gerandomiseerd onderzoek naar het effect van een nieuw regime van selectieve decontaminatie op de incidentie van lagere luchtweginfecties bij patiënten die langdurig (gedurende tenminste vijf dagen) kunstmatig werden beademd.

Bij opname werden de patiënten willekeurig verdeeld over drie groepen. Patiënten in beide controle groepen I (n=18) en II (n=21) ontvingen geen antibiotische profylaxe; antibiotica werden uitsluitend voorgeschreven als er sprake was van een infectie. In groep I werden infecties behandeld met antibiotica die de anaerobe flora van de tractus digestivus (en dus de microbiële kolonisatieweerstand) verstoren, terwijl in groep II uitsluitend middelen werden gebruikt zonder invloed op de microbiële kolonisatieweerstand. Het doel van dit deel van de studie was, de verschillen in de invloed van antibiotica uit deze twee categorieën op de frequentie van kolonisatie en infectie te bepalen.

Bij patiënten in groep III (n=17) werd van opname tot detubatie een regime van selectieve decontaminatie toegepast. Het regime bestond uit norfloxacin 50 mg, polymyxine E 200 mg en amfotericine B 500 mg, vier maal daags toegediend via de maagsonde. Een mondpasta die dezelfde middelen bevatte (elk in een concentratie van 2%) werd vier maal daags in de mond aangebracht. Patiënten in groep III kregen voorts systemische antibiotische profylaxe (cefotaxime 3 dd 500 mg i.v.), maar dit alleen gedurende de eerste vijf dagen.

Resultaten

Bij opname was de oropharynx vaak gekoloniseerd met commensale micro-organismen en, zij het minder frequent, met Gram-negatieve bacillen. In beide controlegroepen bleef deze kolonisatie niet alleen bestaan, zij gaf bovendien frequent aanleiding tot infecties van de lagere luchtwegen (die zich vaak al manifesteerden gedurende de eerste dagen na opname). In groep III werden alle commensale micro-organismen en Gram-negatieve bacillen uit de oropharynx geëlimineerd en werd vroege infectie van de lagere luchtwegen volledig voorkómen.

Patiënten in beide controlegroepen verwierven tijdens opname frequent nieuwe micro-organismen – vooral Gram-negatieve bacillen – in de oropharynx zowel als in de maag. Drieëntachtig procent van de patiënten in groep I en 90% van de patiënten in groep II verwierven tenminste één nieuw micro-organisme in de oropharynx gedurende het verblijf op de intensive care. Nieuwe microbiële kolonisatie van de maaginhoud kwam voor bij 94% van de patiënten in groep I en bij 90% van de patiënten in groep II. In groep III voorkwam selectieve decontaminatie de acquisitie van nieuwe micro-organismen in maag en oropharynx vrijwel volledig (Hoofdstuk IV).

Het toedienen van antibiotica (in groep I) die de microbiële kolonisatieweerstand verstoren, leidde tot een stijging van de concentratie Gram-negatieve bacillen in oropharynx en maag. Het gebruik van middelen zonder invloed op de kolonisatieweerstand in groep II leidde niet tot veranderingen in de concentraties Gram-negatieve bacillen. Desondanks was er geen significant verschil tussen groep I en II voor wat betreft de incidentie van infecties van de lagere luchtwegen: in groep I kregen 14 patiënten (78%) tesamen 25 lagere luchtweginfecties, terwijl 13 patiënten (62%) in groep II in totaal 22 infecties kregen.

De meeste infecties van de lagere luchtwegen in beide controlegroepen werden veroorzaakt door Gram-negatieve bacillen. In de etiologie van de vroege luchtweginfecties (optredend gedurende de eerste dagen van beademing), speelden micro-organismen die als commensaal in de oropharynx voorkomen eveneens een belangrijke rol.

In beide controlegroepen speelde kolonisatie van oropharynx en maaginhoud een sleutelrol in de pathogenese van infecties van de lagere luchtwegen: meer dan 90% van de luchtweginfecties in deze beide groepen werd voorafgegaan door kolonisatie van oropharynx, maaginhoud of beide met hetzelfde micro-organisme. De toepassing van selectieve decontaminatie in combinatie met systemisch cefotaxime leidde tot een significante reductie van de incidentie van lagere luchtweginfecties. Slechts één patiënt (6%) in groep III kreeg een lagere luchtweginfectie tijdens opname. Deze infectie werd niet voorafgegaan door kolonisatie van maaginhoud of oropharynx met het desbetreffende micro-organisme (Hoofdstuk V).

Het in deze studie gebruikte regime van selectieve decontaminatie in combinatie met systemische antibiotische profylaxe leidde tot een daling van de kosten van antibiotische therapie die meer dan opwoog tegen de kosten van het regime.

Hoewel de kosten van het gebruikelijke bacteriologisch onderzoek het laagst waren in groep III, waren de totale kosten van bacteriologisch onderzoek in deze groep hoger dan in beide controlegroepen. Dit werd veroorzaakt door de kosten van de bewakingskweken, die noodzakelijk zijn om het effect van selectieve decontaminatie te vervolgen. Aangezien deze kweken meestal negatief uitvallen, zouden de tarieven aangepast kunnen worden, zodat selectieve decontaminatie

ook in dit opzicht voordeliger zou worden. Bovendien kan de frequentie van de bewakingskweken worden gereduceerd.

Discussie

Het gebruik van antibiotica die de autochtone anaerobe flora van de tractus digestivus – en dus de microbiële kolonisatieweerstand – verstoren, leidt bij ernstig zieke patiënten tot een stijging van de concentraties van Gram-negatieve bacillen in oropharynx en maag. Dit vergroot de kans op lagere luchtweginfecties. Toch leidde eliminatie van dit risico in groep II slechts tot een geringe reductie van de incidentie van lagere luchtweginfecties. De verklaring hiervoor is waarschijnlijk gelegen in het feit dat, bij deze ernstig zieke patiënten, de fysiologische kolonisatieweerstand (slikken, hoesten, speekselvloed etc.) ook verstoord is. Deze verstoring kan worden veroorzaakt door de ziekte, alsook door intubatie en ander medisch handelen.

Bij patiënten die minder ernstig ziek zijn kan verwacht worden dat beperking van het arsenaal antibiotica tot middelen die de kolonisatieweerstand niet verstoren zal leiden tot preventie van kolonisatie en infectie met Gram-negatieve bacillen. Bij de door ons onderzochte categorie patiënten was dit niet het geval, hetgeen verdergaande profylactische maatregelen noodzakelijk maakt.

Selectieve decontaminatie in combinatie met kortdurende systemische toediening van cefotaxime zorgde ervoor dat micro-organismen die de oropharynx en de lagere luchtwegen reeds koloniseerden werden geëlimineerd en voorkwam bovendien acquisitie van nieuwe micro-organismen in oropharynx en maag van beademde patiënten. Hiermede werden de twee belangrijkste bronnen van bacteriën die lagere luchtweginfecties veroorzaken geëlimineerd, hetgeen resulteerde in een significante reductie van de incidentie van op de intensive care verworven lagere luchtweginfecties.

Selectieve decontaminatie elimineert niet alleen Gram-negatieve bacillen uit het bovenste deel van de tractus digestivus, doch – bij intacte peristaltiek – ook uit het onderste deel van de tractus digestivus en de faeces. De voordelen hiervan zijn: de eliminatie van een belangrijke bron van infectie en kruisinfectie, alsook van een bron van endotoxaemie. Verder verdwijnen met de eliminatie van Gram-negatieve bacillen uit oropharynx en het lagere deel van de tractus digestivus twee belangrijke plaatsen waar resistentie tegen antibiotica zich kan ontwikkelen.

Conclusies

Het gebruik van antibiotica die de kolonisatieweerstand verstoren leidt tot een stijging van de concentraties Gram-negatieve bacillen in oropharynx en maag van

ernstig zieke patiënten. Het gebruik van deze antibiotica dient bij gehospitaliseerde patiënten waar mogelijk te worden vermeden.

Selectieve decontaminatie met norfloxacin, polymyxine E en amfotericine B in combinatie met kortdurende systemische cefotaxime profylaxe bleek een veilige, effectieve en kostendekkende manier om lagere luchtweginfecties bij langdurig beademde patienten te voorkomen. Bij patiënten waarvan wordt verwacht dat zij langer dan enkele dagen kunstmatig zullen moeten worden beademd, is vanaf de start van de beademing, de toepassing van selectieve decontaminatie in combinatie met kortdurende systematische profylaxe geïndiceerd.

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