INFECTION PREVENTION IN THE SURGICAL INTENSIVE CARE UNIT USING SELECTIVE DECONTAMINATION

Epidemiology, Bacteriology and Clinical practice

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INFECTION PREVENTION IN THE SURGICAL INTENSIVE CARE UNIT USING SELECTIVE DECONTAMINATION

Epidemiology, Bacteriology and Clinical practice

INFECTIE PREVENTIE IN DE CHIRURGISCHE INTENSIVE CARE UNIT DOOR MIDDEL VAN SELECTIEVE DECONTAMINATIE

Epidemiologie, Bacteriologie en Klinische praktijk

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No amount of antibiotic, however potent, can compensate for clumsy operation and hypoxic conditions.

Pollock AV, Lancet 1:225,1988

Aan Lies en Bart,
Aan mijn moeder

Ter nagedachtenis aan mijn vader

CONTENTS

CONTENTS (Continued)

PART A

INTRODUCTION

Chapter 1
INFECTION-PREVENTION IN THE ICU

1.1 Introduction

Lifesupporting techniques in the intensive care unit (ICU) are responsable for the growing number of technically difficult procedures in increasingly older patients but can be detrimental to general defences in these critically ill patients. Major surgical procedures necessitating postoperative intensive care including haemodynamic support, monitoring and mechanical ventilation are therefore frequently complicated by nosocomial infections, which are defined as infections acquired in the hospital environment and predominantly caused by gram-negative hospital bacilli. Therapy of these gram-negative infections is difficult and shows a substantial failure-rate which contributes to the associated morbidity and mortality. Critical care and infection-prevention must be inseparable and intertwined for these reasons.

Until only one decade ago nosocomial infections were thought to originate mostly from exogenous sources such as hands of personnel, invasive procedures and the inanimate environment. Much effort was taken to prevent these infections by rigorous isolation- and barrier nursing techniques, strict hygienic- and handwashing protocols next to the restrictive use of antibiotics generally advocated in order to prevent an increase in resistant micro-organisms. Handwashing discipline is however poor[1-2], and isolation has little effect[3], is time-consuming and labour-intensive[4]. Even when these preventive guidelines were followed vigorously and adequate, infections continued to be a major threat to those critically ill patients[5], illustrated by infection-rates up to 70%[6-7]. This made Haley[8] conclude that only approximately 32% of nosocomial infections were potentially preventable by infection-prevention programmes, and Maki[9] that apparently the inanimate environment had no major contribution to nosocomial infection. Already in the sixties Ravin et al.[10] described the gut as an origin of bacteria and endotoxins causing illness, but it was not until the seventies that more attention was focused to the patients own microflora as an important endogenous reservoir of infection. This reservoir of micro-organisms is however closely interrelated with the environment since "patients are bacteriologic chameleons who assume the flora of their surroundings"[11]. Several

ambitious prophylactic regimes emerged to eliminate this pool of micro-organisms, but many failed because resistance and superinfections resulted.

Selective decontamination (SD) is presented by van der Waay as a novel way of antibiotic prophylaxis which restores or enhances colonization resistance, thereby preventing the more serious gram-negative infections without endangering the hospital environment. For that purpose enteric non-absorbable antibiotics are used in such doses that high intraluminal concentrations in the gut are reached. Consequently, these concentrations are well above the minimal inhibitory concentration (MIC) of most aerobic gram-negative micro-organisms, which minimizes the risk on the emergence of resistance within this bacterial reservoir. Another advantage in this respect is that those non-absorbable antibiotics used in this regime do not reach tissue levels adequate to treat deep organ infections, so they are not in general use in the hospital which again minimizes the danger of developing resistance.

On first sight, this concept looks promising because the more serious gram-negative infections are prevented without causing an increase in resistance. One of the problems in proving the efficacy of selective decontamination is however the use of systemic antibiotics during the first days in the originally described regimen[12]. The reduction in the number of lower respiratory tract infections only reached statistical significance when systemic antibiotics were added to the original enteral regime, which is in fact in contradiction to the concept of selective decontamination. In view of this finding, it is important to know that many infections in the ICU will evolve early during the patients admittance[13-16], so using systemic antibiotics in this period could be therapeutic in occult infections, and could give a distorted view of the "prophylactic" effects of selective decontamination[16-17]. In addition, especially the diagnosis of pneumonia is difficult to assess in critically ill patients. These factors together make the contribution of systemic antibiotics unclear and the results of selective decontamination difficult to interpret.

It also seems likely that infections will lead to excess mortality, prolonged hospitalisation and increase in cost of care. As a result of decreased infection

rates by implementing a prophylactic regime, one would therefore expect to see a decrease in the infection-related mortality. Still, it will be very difficult to detect such a difference, reminding that the infection-related mortality is not easy to disentangle from overall mortality in heterogeneous groups of critically ill patients with several potential causes of death. In agreement with this, Gross et al.[18] and Bryan and colleagues[19] thought that only patients admitted with curable diseases would truly benefit from infection-prevention and -control programmes. Consequently, it will be unreasonable to address the absence of an anticipated mortality-effect to the failure of any intervention in studies using mixed patient-groups. The best study-population would be the one with high risk to develop infections but with low intrinsic risk of dying due to underlying disease.

Until recent years, no randomised studies to the effects of selective decontamination on colonization- or infection-rates were available. The lack of concurrent controls, the heterogeneous mixture of patients and intensive care units, and the absence of consensus in the diagnosis and definitions of infections furthermore precluded a valuable evaluation. To solve this issue we identified the group of patients admitted for oesophageal resection because of carcinoma as a homogeneous group eligible for the purposes of this study. This would restrict conclusions to that patient-group only, but should have increased validity and power concerning effects of selective decontamination on gram-negative colonization- and infection-rates. The elective setting in these patients raised the possibility to restrict the use of systemic antibiotics only to the pre-operative days during which selective decontamination is installed. This would be advantageous both in study-design (no influence of systemic antibiotics on post-operative nosocomial infections) and in decreasing antibiotic pressure in the ICU (and concern for the hospital epidemiology).

In the successive cohort-study the efficacy of selective decontamination was studied with respect to morbidity and mortality, knowing that the relation between infections and death is an intimate one. We recognised a considerable amount of failures of decontamination within the group of ICU-patients receiving SD-medication, and thought these failures (with ineffective infection prevention)

could be responsible for excess (infection related) mortality within the total group of patients receiving this prophylaxis. We thought this group could be responsible for possible unmeasured effects of selective decontamination on mortality. In addition, possible adverse effects of SD on the hospital-flora and the process of rebound colonization after the transfer of patients to the ward were evaluated.

1.2 Patient population

Patients admitted to have an oesophageal resection because of carcinoma belong to a group of high risk patients who easily develop pulmonary tract infections. This is partly due to the operation itself, as a result of which the normal anatomy is disturbed and regurgitation and aspiration of gastro-intestinal contents can easily occur. The upper abdominal and thoracic incisions can furthermore result in insufficient respiration and coughing during the first postoperative days, causing atelectasis and possible pulmonary infiltration. This in combination with the infection-risk on the surgical ICU in general[6] accounts for the 20% pulmonary tract infections in the 60 patients operated yearly. Bearing this in mind, it seemed logical to try to see whether the concept of selective decontamination would be of value in this homogeneous group of patients with serious disturbances of their colonization resistance. Moreover, these patients undergo a standardised trauma and are all postoperatively transferred to the surgical ICU for mechanical ventilation.

The descriptive cohort study evaluates the process and efficacy of selective decontamination in all patients receiving this prophylaxis. Based on the results of the preceding prospective randomised study, selective decontamination was institutionalised in all patients with high risk on pulmonary tract infections undergoing any major surgical procedure. Moreover, existing literature at that time suggested that patients with multiple trauma might also benefit from this prophylaxis. These two groups constituted the majority of patients in the successive study.

1.3 Objectives of investigation

The studies described in this thesis aim to answer the following questions:

does selective decontamination cause

1. a reduction of the number of respiratory tract infections in patients after oesophageal resection?
2. a reduction or disappearance of potentially pathogenic micro-organisms?
3. a reduction of mortality?
4. increased resistance to antibiotics?
5. any adverse effects when discontinuated?

1.4 Outline of the thesis

In **Part A** the extent of the problems in infection-prevention is described in **Chapter 1** and nosocomial infections are defined in **Chapter 2**, in which also the difficulties of infection diagnosis in critically ill patients are reviewed. **Chapter 3** describes the history of antibiotic prophylaxis in surgery, the development and theory of selective decontamination and a review of published trials.

In the second part (**Part B**), original studies to the clinical effect of selective decontamination on gram-negative infections (**Chapter 4**) and colonization (**Chapter 5**) are presented. An analysis of the mortality-effects is given in **Chapter 6**, while **Chapter 7** deals with the consequences of recolonization and possible resistance after withdrawal of this prophylaxis. Results are integrated in the general discussion in **Chapter 8**. References to the literature are given at the end of each chapter.

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Chapter 2

PATHOGENESIS AND DIAGNOSIS OF NOSOCOMIAL INFECTIONS

Magnitude of the problem

2.1 Introduction

Nosocomial infections are those infections acquired within the hospital and mostly caused by aerobic gram-negative micro-organisms, although the increasingly multiresistant *Staphylococcus aureus* and *Enterococcus* sp are becoming more important as etiologic agents in present-day medicine[1-2]. For diagnostic purposes most studies arbitrarily define these infections as emerging after 48 hours of admission, whereas the Centers for Disease Control[3] (CDC) demands "no evidence of infection present or incubating upon hospitalisation", thereby deliberately opposing to time-determinations. According to these CDC-guidelines, the diagnosis of infection can be made on clinical grounds, but almost always needs supportive evidence from subsequent diagnostic procedures. When these data are absent, "the empirical initiation of appropriate antibiotic therapy" is crucial to accept the present symptoms to be the consequence of an infection.

Nosocomial infections occur in 5-10% of all hospital admissions, and are at least contributory in approximately 59% of hospital deaths; while most deaths occur on the medical ward, 25% of deaths on the medical and 50% on the surgical service are associated with infection[4]. The incidence is dependent on the hospital, ward or patient-population studied, and several studies indicated that the surgical ward and intensive care unit harbour the greatest risk to acquire nosocomial infections[5-6]. Surgical patients represent 41% of the admissions but experience 71% of all nosocomial infections distributed through the various sites shown in Table 2.1; they have a 14% risk to develop a pneumonia compared to a 3% risk in all admissions[5]. Particularly the intensive care unit (ICU) which comprises only 8% of all hospital beds knows a five- to tenfold incidence compared to normal wards[7-8] and harbours 33 to 45% of nosocomial infections (Table 2.1). This is probably due to the high number of extremely vulnerable, critically ill patients, and the widespread use of invasive devices[9]. Again, surgical patients are at high risk[4,10] since the surgical ICU shows 35 infections per 100 admissions compared to 14 on the medical ICU[11]. Up to 70% of the patients in a surgical ICU have gram-negative infections after 7 days of admission[12], increasing the mortality to 60%[10,13]. Because of the high antibiotic pressure in the surgical ICU[14], a relatively high

contribution of "epidemic" infection due to (more and more intrinsically) antibiotic-resistant micro-organisms[10,15] is increasingly encountered.

Table 2.1 **Site of nosocomial infection in surgical patients and ICU**

Site	Frequency of involvement (%)	
	Surgical patients[6]	ICU[16]
Urinary tract	42	24
Wound	40	8
Respiratory tract	14	31
Blood (Septicemia)	4	16

After Haley[5] and Weinstein[16]

The impact on socio-economic resources is enormously; nosocomial infections prolong the hospital stay with 3 to 4,5 days per infection and increase the costs with approximately 590 (1976) US-dollars[17]. In order to prevent these nosocomial infections, it is crucial to understand the pathogenesis and to detect risk-factors which predispose to these infections out of the huge amount of epidemiological information. For nosocomial infections in general, Craven and colleagues[10] identified days in the ICU, shock on admission, admission to the surgical ICU, renal failure and the use of chemotherapeuticals or steroids as risk-factors, Pories et al.[18] furthermore identified age above 50 and higher scores in the "Injury Severity Score" (ISS) to be correlated with higher infection-rates. The factors strongly associated with fatality were renal failure and the use of chemotherapeuticals or steroids, but also the acute physiology score, respiratory failure, coma, infection on admission, neurological illness and nosocomial intra-abdominal infection.

The following paragraphs will deal with the description of diagnostic procedures and pitfalls for each category of infection.

2.2 Pneumonia

Epidemiology and etiology

The incidence of nosocomial pneumonia is an overall 0,5 to 5% when all hospital admissions are regarded[19-20] which matches 8,6 episodes per 1000 admissions[21] ranging from 3,6 in non-teaching hospitals to 10,6 on surgical wards of teaching hospitals[22]. The incidence again depends on the population studied; ICU-admitted patients have a 4 to 21 fold incidence compared to those on the ward[6,20], which is the reason why 41% of all pneumonia's occur in the ICU[8]. Within this group of ICU-patients the risk to develop a pneumonia increases from 12 % in those in the medical ICU[23] to 22% in a mixed medico-surgical ICU[24] and 31% in patients in the surgical ICU[6,10-11]. Compared to patients without respiratory support, intubated patients have a 6 to 20 fold increase in pneumonia-rates which can rise up to 70%[25-26], while each extra day on the ventilator increases the risk to develop a pneumonia with an additional 1%[27]. Respiratory tract infections are responsible for an excess stay of 5 to 7 days[5,21] in all patients, or more than 9 days in survivors as seen in a case-matched study[28].

The mortality-rate in ICU-patients with a pneumonia is 42% compared to 12% in those without one[29]. Nosocomial pneumonia accounts for at least 15% of all hospital deaths[19] and is therefore the principal cause for infection-related mortality in the hospital. Fatality rates range from 30% in mechanically ventilated patients[30] to 60% in patients who are admitted with respiratory failure due to a pneumonia[24]. These fatality rates are related to the causative micro-organisms (Table 2.2); high risk microbes are *Pseudomonas* sp, *S.aureus* and *Enterobacteriaceae*[23,25] but most pneumonia's are polymicrobial[22-23,31] with a mortality rate of 67%[25]. Of interest in this regard is that Craig and co-workers[29] identified *Pseudomonas* sp, when causing a pneumonia, as an independent risk-factor for mortality.

Risk-factors

Risk-factors for pneumonia, determined by multivariate analysis or stepwise logistic regression techniques include the presence of general conditions as chronic

Table 2.2 Frequency of isolated pathogens in nosocomial pneumonia.

Pseudomonas sp	17
Staphylococcus aureus	13
Klebsiella sp	12
Enterobacter sp	9
Escherichia coli	6
Serratia sp	6
Proteus sp	4

Modified from Scheld[22]

obstructive pulmonary disease (COPD)[30], age above 70[25,31] and smoking[6]. Surgically induced risk factors are thoracic or upper abdominal incisions[6,25] and whether an emergency-operation was performed[29]. Diminished consciousness and high volumina aspiration are additional factors, whereas the presence of ventilation or intubation alone[25,31] or ventilation for more than either 24[29] or 72 hours[30] represent an independent risk. Respiratory therapy would result in a 4 to 66 fold risk[32], but according to Langer[26] this would only be contributory. Emergency intubation[32] or reintubation[30], frequent ventilator change as well as the presence of an intracranial pressure monitoring device[31] are other risk factors. The use of positive end expiratory pressure ventilation (PEEP) was found to be nearly significant as a risk factor[30]. Additional risk factors for staphylococcal pneumonia are the presence of coma and COPD[33].

Pneumonia is an independent risk factor for fatality when occurring in critically ill patients such as those with abdominal sepsis[34], although this could not be confirmed in another study[35]. When pneumonia is already acquired, the following risk factors are correlated with fatality: age above 60, underlying condition, ICU-admittance and ventilation[10], inappropriate antibiotic therapy, respiratory failure[30], bilateral pneumonia on plain chest film[25], longer time period to develop the pneumonia[21,26], preceding ventilation-period, rapidly or ultimately fatal disease[21] and septic shock[30]. A high risk micro-organism causing the pneumonia was identified as an independent risk factor for fatality[26], but this could not be confirmed by another study[30].

Pathogenesis

Micro-organisms causing pneumonia can be acquired by aspiration, by air or haematogenous spread. While the latter two seem to be far less common[14,32], the one important factor in sequelae preceding pneumonia seems to be oropharyngeal colonization[23,36] and the aspiration of these contaminated secretions. Oropharyngeal colonization is enhanced by illness or immunosuppression[36-37], endotracheal intubation, coma, hypotension, acidosis[23], length of admission[38-39], advanced age[40], number of invasive procedures[13,39-40], and the use of immunosuppressive agents or antibiotics[23,41]. The microbial property to adhere to epithelial cells is amongst others related to the function of fibronectin, an epithelial glycoprotein covering epithelial receptor sites, which is also reduced with illness and after operations[42]. Micro-organisms could even show preference to tracheal cells and can thus cause pneumonia without showing significant colonization of the oropharynx[43].

Acquisition of oropharyngeal micro-organisms by retrograde colonization from the stomach (endogenous colonization) has been described to be enhanced by the presence of nasogastric tubes and the supine position through an increase in gastric reflux[31,44-45]. The influence of gastric pH and subsequent colonization of stomach contents on oropharyngeal or tracheal colonization is repeatedly described[46-47] but the role of stress-ulcer prophylaxis in the pathogenesis of pneumonia is under much debate. Several authors reported the detrimental effect of H_2-antagonists and antacids on the rate of pneumonia by increasing pH[48-50]. Eddlestone and co-workers[51] found a positive effect of sucralfate on pneumonia rates, but whether this effect occurs as a direct antibacterial effect or as a pH effect is still unanswered despite several meta-analyses[20,52]. Cook et al. could not confirm an effect of H_2-blockers or antacids on the incidence of pneumonia in their meta-analysis[52]. Others denied the relation between gastric colonization and pneumonia[53] or could not confirm it[20,54]. Moreover, in the Apte study[50] only 56% of ranitidine treated patients versus 44% of controls showed isolation of the same micro-organism in gastric contents and specimen obtained during the subsequent pneumonia. Finally, Fiddian-Green[54] thought translocation of micro-organisms through the stomach wall could be causally more important since intramucosal pH was a better predictor for pneumonia in their study.

Table 2.3 Definitions of nosocomial pneumonia

Garibaldi,1981[6]

Class 1 : Microbiologically proven pneumonia
Class 2 : Clinically apparent, no bacteriological evidence
Class 3 : Fever, purulent sputum, suggestive radiographic findings

Driks,1987[49]

New infiltrate on plain chest film, and at least three of the following criteria in ventilated patients:

1: Purulent sputum
2: Important nosocomial pathogen in culture of tracheal aspirate
3: Leucocytosis > 10.000/mm^3
4: Temperature > 38°C

Garner (CDC),1988[3]

One of the following criteria:

1: Pneumonia on physical examination and any of:
   a: New purulent or change in sputum
   b: Positive blood culture
   c: Pathogen in tracheal aspirate, bronchial brush or biopsy
2: Pneumonia on plain chest film and any of:
   a: In combination with 1.a-c as above
   b: Virus or viral antigen detected
   c: Serologic evidence of infection
   d: Histologic evidence of infection

Celis,1988[25]

New infiltrate on plain chest film, not otherwise explained, and combination of the following:

1: Temperature > 38°C
2: Leucocytosis > 10.000/mm^3
3: Cough and purulent sputum, bacteria on gram-stain with > 25 polymorphonuclear leucocytes and < 10 epithelial cells per high power field.

Modified from Goldman[63]

Diagnosis

There is no gold standard for the diagnosis of pneumonia, which is mostly defined according to various combinations of clinical, radiological and laboratory findings. It is often suspected, but also easily missed as appeared from post-mortem analyses in the adult respiratory distress syndrome (ARDS)[55]. CDC-definitions

involve typical findings on physical examination and/or chest X-ray and the new onset of purulent sputum, an organism isolated from specimen obtained by transtracheal aspirate, bronchial brushing or biopsy as well as in blood-cultures. Without clinical or radiological evidence of pneumonia, these signs are considered to be the consequence of (tracheo-)bronchitis[3].

Interpretation of clinical and radiological findings is however difficult[22] and often not reproducible, resulting in a wide range of definitions (Table 2.3), incidence rates and much debate. Even the positive response to antibiotic treatment as a clinical indicator of pneumonia is not conclusive for the diagnosis, because both patients with and without a pneumonia showed improvement in a (postmortem) study[56]. Since only 6% of all patients with a pneumonia have positive blood-cultures[22], most authors feel that the use of these in the diagnosis of pneumonia (as proposed by the CDC) is less valid. Transpleural biopsy or needle-aspiration especially in mechanically ventilated patients is too dangerous to be in widespread use[57]. This resulted in the increased weight given to bacteriological isolation of micro-organisms in sputum, but these specimen are difficult to obtain in non-intubated patients and otherwise often contaminated with flora from the more proximal airways as appeared in baboons[58]. The isolation of a given micro-organism is furthermore not solely indicative for a pneumonia but can also mean colonization without an infection being present, although the absence of growth is a strong argument against pneumonia[22]. Attempts to improve the predictive value of sputum-samples include transtracheal aspiration, protected brush specimen (PBS) and broncho-alveolar lavage (BAL). Tracheal aspirates have acceptable sensitivity but show false-positive results in 21% and even up to 85% of patients with COPD[58], although others found results comparable to PBS[59]. Specimen obtained by bronchoscopy often show contaminants but by using a protected wedge catheter or brush the specificity is improved to 80 and 100%[31] and close to that of BAL[30], unless prior antibiotic therapy has been given. Although BAL is easier than PBS and samples a wider area, both diagnostic procedures (with sensitivities between 60 and 90%[20,31]) are difficult to perform in the ICU.

The use of quantitative cultures in the diagnosis of pneumonia is under much debate, because a threshold of 10^3 or 10^5 CFU/ml in specimen obtained by PBS or

BAL is not unanimously accepted[57], and will implicate that the pneumonia is already full-blown[60] and therefore difficult to treat. On the other hand, some patients with proven pneumonia can show only low bacterial counts and will therefore not be treated, whereas others without one can have higher counts and as a result be treated as having a pneumonia[61]. Finally, residual quantities of antimicrobials can remain in the bronchial tree[62] and can therefore prevent growth in samples ("carry-over" effect), reason why some advocate diluting these effects by washing of samples.

Irrespective of the difficulties, one should not only rely on clinical symptoms but search for further confirmation in the need for quick and accurate diagnosis of pneumonia.

2.3 Wound-infection

Epidemiology and etiology

The main problem in establishing the incidence of wound infections is that up to 75% of the wound problems become evident after the discharge of patients[63-64]. Nevertheless, rates from 5 to 20% are reported with 17% of these infections occurring in the ICU[8]. Haley[65] found a frequency of 29%, but also thought them responsible for 57% of excess costs and 42% of the excess stay related to nosocomial infections; Nichols[66] thought these infections responsible for doubling the duration of stay.

A worthwhile evaluation of wound infections must include the different subgroups of wound-classes (Table 2.4)[67] because percentages rise from 1.5% in class 1 to 40% in class 4. Class 1 wounds are said to reflect "surgical care" because all infections in this group are the result of exogenous factors by the absence of endogenous contamination[68]. Any wound infection rate exceeding 2% in this group of wounds is therefore reason for self-reflection although many studies report higher rates. Next to the nosocomial gram-negative bacteria, an increasing number of gram-positive micro-organisms are recognised as etiologic agents[66].

Table 2.4 Wound-class

1. Clean:

   Gastro-intestinal tract is not opened, no inflammation and no break in aseptic technique is encountered (including cholecystectomy, appendectomy and hysterectomy without inflammation).

2. Clean contaminated:

   Clean operation, with opening of the gastro-intestinal tract but without spillage.

3. Contaminated:

   Acute inflammation without pus, or spillage of contents from the gastro-intestinal tract is encountered. "Fresh" traumatic wounds and procedures with a major break in asepsis are included.

4. Dirty:

   Procedures in which pus or a perforated viscus is found, including also "old" traumatic wounds.

From Howard[67]

Pathogenesis and risk factors

Risk factors for wound infections are reducible to host factors, exogenous and endogenous contamination. They include increasing age, obesity, nutritional status and local wound factors, length of pre-operative admission (each extra week doubles the incidence), pre-operative shaving of the operation site, length of operation (each extra hour doubles the percentage whereas the effect of antibiotics is reduced), operation-technique, "breaks" in this technique and wound-class (Table 2.4)[66,69]. Another infection present is also a risk factor for wound infection, but the effect is reduced when therapy for this infection is installed at least 24 hours before surgery[66]. The prophylactic administration of systemic antibiotics is probably most effective when given between 0 and 2 hours before surgery[70] and must be chosen according to the nature of the procedure and micro-organisms expected. However, patients who received peri-operative antibiotics and who developed postoperative wound infections were likely to have infections with bacteria

resistant against the prophylactic agent[71], indicating that prophylactic antibiotics should not indiscriminately been given therapeutically in the postoperative period. To increase the quality of care, a risk-predictor consisting of wound-class, the length of operation and ASA-score (American Society of Anesthesiology) was developed by means of multivariate technique and appeared adequate in predicting the rate of wound infection[69]. Such an index could be very useful in the surveillance of wound infections and in comparing results from different surgeons and hospitals in attempting to lower incidences[65].

Diagnosis

The CDC-guidelines[3] distinguish incisional and deep wound-infections. An infection is incisional when it is present at the incision site, within 30 days of surgery and above the fascial layer, and any of the following:

1. Purulent drainage from wound or drain (above fascia)
2. Positive culture from fluid out of primarily closed wound
3. Surgeon deliberately opening the wound (unless culture is negative)

A deep infection is present at the operative site within 30 days of surgery without an implant or within 1 year when an implant is placed, is located beneath the fascial layer and when drainage of pus from beneath the fascia is encountered, the wound is deliberately opened because of fever or localised pain, or an abscess is spontaneously draining.

2.4 Urinary tract infection

Epidemiology and etiology

Urinary tract infections are responsible for approximately 40% of nosocomial infections[72-73], they occur in 2 patients per 100 admissions and 16% of these infections are encountered in the ICU . These infections are usual benign but 2 to 4% of the patients experience a bacteraemia which then results in a case-fatality of 13 to 30%[74]. There seems to be a slow decrease in the incidence during the last decades, maybe as a result of better infection-control and less extensive

admissions[73]. Especially women are prone to get a urinary tract infection caused by rectal flora.

Pathogenesis and risk factors

Approximately 75 to 80% of nosocomial bacteriuria is caused by instrumentation and catheterisation[72-73]. Bacteria are invading mostly intraluminal in men (often as a result from cross-infection) and periurethral in women, reason why they are susceptible for rectal strains. Bacteria in the urine are found as planktonic growth or growing in the biofilm on the catheter. These bacteria form encrustations and a biofilm around and on the catheter, thereby protecting themselves against antibiotics and rendering urine-samples taken from the catheter not fully reliable. Removing a catheter in treating bacteriuria is consequently more realistic than giving antibiotics.

Risk factors are female gender, the duration of catheterisation, absence of systemic antibiotics and catheter care violations[73].

Diagnosis

The diagnosis is mostly made on clinical grounds (symptomatic bacteriuria) in combination with more than 10^5 CFU/ml. in a urine sample. When no clinical signs are apparent the bacteriuria is called asymptomatic. In addition, the CDC[3] demands no more than 2 species in the cultures.

2.5 Septicemia

Epidemiology and pathogenesis

Catheter-associated (primary) septicemia occurs in 3 to 7 percent of catheters[75], and is mainly related to the percutaneous insertion procedure, insertion in the jugular vein[76] and micro-organisms colonising the skin around the insertion site[75]. Most septicemias (41%) occur in the ICU, which has a rate of bloodstream infection 24 times that of the general ward[8]. Up to 73 % occurs in the surgical ICU, where 5 to 17 % of all patients with multiple devices develop a septicemia,

which is therefore regarded as a marker for infection[6].The infection rate can also be influenced by the dressing, with more infections likely to appear in the group with "op-site" opposed to those with just a dry gauze. A drawback of this study was however that the groups were heterogeneous, different catheters were used and that the "op-site" group included more surgical patients and more subclavian catheters[77]. New investigations are aimed on increasing the barrier function of the skin around the catheter by incorporating cuffs[75] or impregnating the catheters with silver or antibiotics.

Overall mortality in gram-negative (secondary) septicemia which is mostly caused by *Enterobacteriaceae* and *Pseudomonas* sp is 36% while 19% is directly attributable to the septicemia. Mortality is dependent on the severity of the underlying disease, age and the site of infection[78]. When shock is also present, mortality rises to 64% (overall) resp. 50% (infection-related). Most of these septicemia's are the consequence of urinary tract infections which have a lower related mortality opposed to the pneumonia-associated septicemia with a mortality up to 72%[79].

Diagnosis

CDC-guidelines for primary septicemia include the isolation of the same pathogen not related to an infection at another site from at least two bloodcultures in a patient with intravascular access devices. Clinical sepsis additionally includes fever, hypotension or oliguria with no other plausible cause. With the inability to culture micro-organisms "appropriate antibiotic therapy" must be instituted to meet the diagnosis[3].

2.6 Definitions used in the study

Colonization was defined as the isolation of the same micro-organism in two consecutive cultures taken from one locus, without clinical signs of infection. *Recolonization* is colonization during the administration of selective decontamination, *rebound colonization* as colonization after the withdrawal of SD-medication. *Successful decontamination* was reached when no PPM were cultured in oropharynx or rectum, *unsuccessful decontamination* was the inability to reach decontamination within 3 days or was defined when recolonization with PPM occurred.

Infection was defined as the presence of the following clinical signs: temperature above 38° C and characteristic findings at physical examination. When clinically suspected, infections were confirmed by radiological, laboratory and bacteriological findings: a white cell count of less than 4000 or more than 10.000 /mm^3, and positive cultures from the infected area.

Primary infections develop within 48 hours of admission and are mostly caused by community-acquired gram-positive micro-organisms. *Secondary infections*, arising after 48 hours of hospital admission, are presumed nosocomial and are mostly caused by gram-negative micro-organisms. Infections preceded by colonization of the infected organ-system with the same causative micro-organism are defined as *endogenous*.

A *lower respiratory tract infection* is defined when the new onset of purulent sputum was present with rales or dulness to percussion. A new infiltrate on a chest radiograph had to be seen by an independent radiologist, and cultures from bronchoscopic lobular aspirations had to show growth of micro-organisms. A *urinary tract infection* is present when more than 10^6 bacteria per ml in catheter-urine are cultured. *Septicemia* is defined as significant haemodynamic disturbances (hypotension, oliguria or anuria) not explained by other causes and positive blood cultures; primary septicemia is catheter-associated while secondary septicemia is related to other infections in the patient. Every purulent discharge from wounds, with a presence of micro-organisms in gram-stains or cultures is considered a *wound-infection*.

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Chapter 3

ANTIBIOTIC PROPHYLAXIS IN GENERAL SURGERY, ROLE OF SELECTIVE DECONTAMINATION

Review of the literature and theoretical background

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3.1 Introduction

The prophylactic use of antibiotics in surgery is mainly concerned with the prevention of postoperative wound- and deep infections; it is generally accepted as being effective when the proper antibiotic is given in the right dosage for a short period around[1-3] or immediately before[4] the operation, thereby providing effective tissue levels of the drug at the time of surgery. Even patients undergoing clean procedures such as herniorrhaphy and breast surgery may benefit from antibiotic prophylaxis, as indicated in a large multicenter trial (48% fewer infections compared with a placebo-group)[5]. Not surprisingly, 40% of surgical patients receive prophylactic antibiotics, accounting for 30% of all in-hospital antibiotic use[6]. Approximately 20 to 30% of all hospital-admitted patients receive antibiotics during their stay, but in an inappropriate dose or for an inappropriate duration in 31 to 52%, and even up to 62% on surgical wards[2,7-8]. Transfer of resistance among micro-organisms occurs especially on mucosal surfaces in the digestive tract or on the skin[9-10], and the inappropriate use of antibiotics can be one of the causes of the increasing drug-resistance seen in hospital-flora. For that reason each novel prophylactic regimen should be adopted only reluctantly in clinical practice, with maximal surveillance of the possible development of resistance.

3.2 Normal flora in the digestive tract

Colonization of the digestive tract by micro-organisms starts immediately after birth and results within weeks in a flora which is almost similar to the flora in adults[11]; the composition of the normal flora is predominantly influenced by diet and drugs. The stomach and small intestine are normally sterile or have very low bacterial counts while the oropharynx and colon show a huge variety of bacteria. Each micro-organism belonging to the indigenous flora can be advantageous or harmful to the host, depending on the circumstances. The former by preventing colonization mostly synergistic with other members of the indigenous flora, the latter when involved in opportunistic infections or delayed-type graft-versus-host disease, or

when enhancing virulence of other micro-organisms[11-12]. The majority of the indigenous flora is however constituted by anaerobic micro-organisms which have a low pathogenic potential, they occur in concentrations of 10^7-10^9 per milliliter saliva, and 10^9-10^{12} per gram faeces. Furthermore, in the normal population *Staphylococcus epidermidis* harbours the skin and *Enterococci* the gut[11,13].

Table 3.1 Potentially pathogenic micro-organisms (PPM)

Gram-negative species:

- Escherichia Coli
- Klebsiella
- Serratia
- Proteus
- Enterobacter
- Citrobacter
- Pseudomonas
- Haemophilus influenzae
- Acinetobacter
- Branhamella catarrhalis
- Neisseria

Gram-positive species:

- Staphylococcus aureus
- Streptococcus pneumoniae
- Enterococci

Yeasts:

- Candida albicans

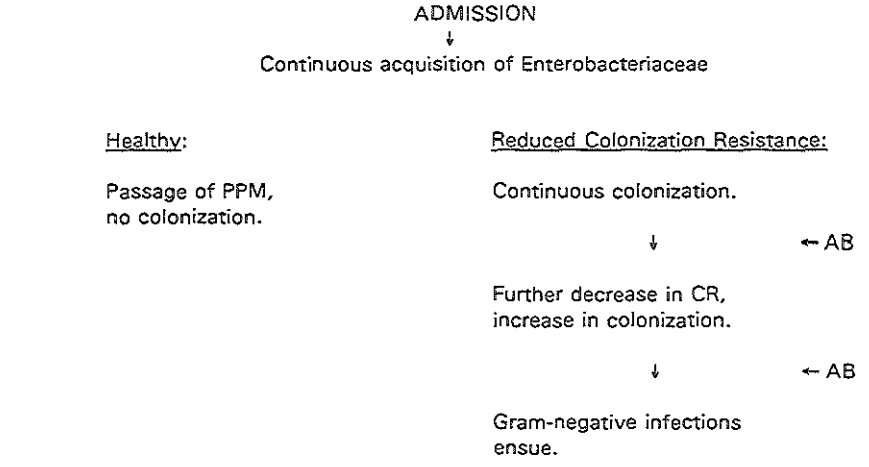
Potentially pathogenic micro-organisms (PPM, Table I) are micro-organisms which can cause infections when the proper conditions are set, especially when infection resistance is impaired. Some persons are oropharyngeal carriers of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Candida albicans*, some carry *Staphylococcus aureus* on the skin, in the oropharynx and gastro-intestinal tract. More than 90% of all healthy individuals carry *Escherichia coli* in the gut. All of the above mentioned (community acquired) micro-organisms can cause infections but these have low morbidity and mortality[13].

A very small fraction of healthy persons can carry aerobic gram-negative micro-organisms (mostly *Enterobacteriaceae*), but in such low numbers that concentrations do not exceed the detection limit (10^2 micro-organisms/g faeces) in cultures. These *Enterobacteriaceae* are ubiquitous in the hospital environment, and frequently colonizing seriously ill patients. Infections caused by these hospital acquired micro-organisms, called nosocomial infections, are serious infections with high morbidity and mortality; therapy knows a high failure rate.

3.3 Colonization and infections; colonization resistance

Despite progress in modern (ICU)-medicine and surgical technique, efforts to prevent nosocomial infections have been disappointing. Control of these life-threatening complications proves to be complex because on admission more than 50% of the patients are already colonised with the micro-organisms that subsequently cause their infection[14], and especially the relation between oropharyngeal colonization and respiratory tract infections is an intimate one[15-16], important evidence for the endogenous etiology of nosocomial infection[17]. In this respect, H_2-blockers can be detrimental to the host by enhancing microbial overgrowth and retrograde oropharyngeal colonization as a result of increased pH (chapter 2).

Figure 3.1 Interaction between PPM and the host, influence of antibiotics



CR: Colonization resistance
AB: Broad-spectrum antibiotics

When admitted to the hospital, the patient's normal microbial flora may be quickly replaced by hospital acquired, aerobic, gram-negative bacilli (colonization), which are increasingly antibiotic-multiresistant[6,15,18]. These potentially pathogenic

micro-organisms (PPM) are listed in Table 3.1. Critically ill and immunocompromised patients will be colonized within a short time of admission[15,19], while healthy individuals are hardly ever colonized with aerobic, gram-negative PPM (Fig. 3.1). Colonization is augmented by disturbances of host flora[20] and is because of the above mentioned frequently encountered in ICU-admitted patients, in whom several risk-factors, described in chapter 2 (pp 27), can be recognised.

Table 3.2 Factors contributing to colonization resistance

Integrity of epithelial and mucosal lining
Desquamation of epithelial and mucosal cells
Saliva and mucus
Secretory immunoglobulin A
Normal swallow and cough reflexes
Chewing and peristalsis, normal defecation
Presence of anaerobic (?) flora in the gut

After experiments in mice, v.d.Waay et al.[21] introduced the concept of colonization resistance. They described the elimination of *Enterobacteriaceae* from the gut and a prolonged prevention of recolonization by these micro-organisms using selective oral antibiotics. They considered colonization resistance as the first host-defence against colonization with potentially pathogenic micro-organisms, consisting of a physiological part (Table 3.2) and a microbiological part, the latter thought to be predominantly constituted by the anaerobic flora which oppose aerobic micro-organisms. This bacterial antagonism occurs mainly by competition for food, but also by producing toxic products, lowering oxygen tension and masking of receptor sites. The importance of normal indigenous flora was illustrated by Bowden[22] and Schwann[23] in patients with pseudomembranous enterocolitis, in whom they saw a rapid cure after the enteral administration of fresh faecal suspension. Others confirmed the pivoting role of the anaerobes in colonization resistance, but thought a polymicrobial flora could maximize it[24,25]. Barza et al.[26] studied colonization resistance in human volunteers, and while they were able to confirm the

devastating effect of broad-spectrum antibiotics on it, they could not prove that anaerobic microbes had a role to play in such resistance. Nevertheless, the microbial equilibrium is a dynamic ecosystem which can effectively prevent colonization with exogenous strains[27]. Patients with reduced defense-mechanisms (Table 3.3) may benefit from an optimal microbiological part of colonization resistance which is unharmed by colonization resistance indifferent antibiotics i.e. antibiotics that leave the anaerobic flora thought to be responsible for colonization resistance undisturbed (Table 3.4). However, there are indications that even when indifferent antibiotics are used, some impairment of colonization resistance can occur[27].

Table 3.3 Factors adversely affecting colonization resistance

Irradiation
Chemotherapy, immunosuppressive agents
Stasis of food and mucus, bacterial overgrowth
Intubation and mechanical ventilation
Aspiration, regurgitation
Bowel dysfunction or retention

3.4 Prevention of colonization by antibiotic prophylaxis

Efforts to prevent colonization using inadequate antibiotic regimens are disappointing[28] and result in colonization with resistant strains[29-30] causing persistent infections with high mortality rates. These infections, occurring during antibiotic therapy and caused by PPM resistant to the antibiotics used, are known as superinfections. As early as 1947 Weinstein[31] had ascribed superinfections with resistant gram-negative PPM to the disturbance of the microbial equilibrium resulting from the use of antibiotics, and in 1970 Price and Sleigh[32] were able to end an epidemic of infections with multiresistant *Klebsiella aerogenes* by the withdrawal of ampicillin and cloxacilline, drugs in use in their ICU for a period of 2 years. They thought the previously sensitive microbial flora was quickly replaced by nosocomial gram-negative bacilli resistant to the antibiotics in use, resulting in

superinfections. By discontinuing all antibiotics the normal flora could be restored and colonization again be prevented by the restoration of colonization resistance.

Attempts to eradicate PPM by total decontamination of the gut and skin in combination with complete isolation seemed worthwhile in granulocytopenic patients, but needed strict patient compliance, were expensive, and only 30 to 40% of all cases proved successful[33-35]. Again the danger of acquisition, colonization and overgrowth of resistant micro-organisms was increased in the unsuccessful cases. The concept of colonization resistance made it possible to introduce a novel method of infection prevention, named selective decontamination by van der Waay[9,21].

Table 3.4 **Antibiotics indifferent to colonization resistance**

Oral:	Intravenous:
Polymyxin E	Cefotaxime
Doxycycline	Ceftazidime
Tobramycin	Cefuroxime
Quinolones	Aminoglycosides
Co-trimoxazole	Quinolones
Trimethoprim	Co-trimoxazole
	Trimethoprim

3.5 Selective decontamination

Selective decontamination has been in use since the early 1980's in patients with granulocytopenia, with promising results[36-37]. Subsequently, its use in patients in the ICU has become the subject of interest. Stoutenbeek et al.[38] were the first to study selective decontamination using a modified regimen in patients with trauma in the ICU and who had been intubated for more than 5 days. They used a combination of non-absorbable antibiotics to reach high topical levels in the oropharynx (paste) and gut (suspension), thus minimising the risk of resistance. Nevertheless, a considerable number of infections still occurred, mainly because the patients suffered from primary respiratory tract infections, caused by

community-acquired micro-organisms which occurred within 48 hours of admission. With the addition of systemic cefotaxime in the first days the rate of respiratory tract infections declined from 59 to 8% and the overall infection rate dropped from 81 to 16%[39]. The use of cefotaxime can be discontinued when adequate decontamination has occurred, as indicated by surveillance cultures (no PPM grown); this systemic antibiotic serves as a protection against early (primary) infections during the first days when selective decontamination has not yet been fully established. Others have changed antibiotic components in the originally described regimen[38] (Table 3.5), with similar effects on the reduction of infection (Table 3.6). Most studies aimed at lowering the number of pulmonary tract infections but some additionally reported a significant decrease in the number of abdominal abscesses[41], urinary tract infections[38,42,47], septicemia[38,41-42,50] and wound infections[38,45]. There are however several studies which could not detect a beneficial effect of selective decontamination on infection rates (Table 3.6), these studies predominantly evaluated medical patients and offer fertile ground for discussion.

3.6 Practical use of selective decontamination

There is much debate concerning the use of stress ulcer prophylaxis (sucralfate or H_2-blockers) causing bacterial overgrowth and enhancing retrograde (endogenous) colonization of the oropharynx (chapter 2, pp 27). Since both selective decontamination and H_2-blockers or antacida influences colonization, controversy exists about the efficacy of either regimen in preventing colonization and pulmonary tract infection. Until now, two studies compared the use of selective decontamination and H_2-blockers with either sucralfate alone[62] or sucralfate with selective decontamination in contrast to H_2-blockers in a third group[51]. The former resulted in less infected patients in the group with selective decontamination and H_2-blockers (12 vs. 27%,p = 0.04) compared with sucralfate but showed no effect on mortality. The latter study showed less pulmonary tract infections in the group with selective decontamination and H_2-blockers compared to H_2-blockers

Table 3.5 Selective decontamination regimens[38,40-62]

Regimen	Reference	Enteral (mg) P	T	N	A	Systemic (mg) C	Tr
Enteral, Oropharyngeal and Systemic Antibiotics[a]:							
PTAC	38,40,44, 47,54,61[b]	100	80	--	500	500	
	48,55[c]	100	80	--	500	1000 x 3	
	57	100	80	--	500	1000 x 6	
	41[b]	200	80	--	500	500	
	45[d]	200	80	--	500	500	
PNAC	43	200	--	50	500	500 x 3	
PNATr	42	200	--	50	500	---	500
PNBTA	51[e]	---	80	--	500	?	
Enteral and oropharyngeal antibiotics:							
PTA	60	100	80		100	No	
Only oropharyngeal antibiotics:							
PTA	49						
Only enteral antibiotics:							
PTA	46[f],50	100	80	--	500	No information	

		P	G	Ne	N	A	V	Na	Ny
PGA	52[g]	50	80	--		(300)			
PNeV	53[i] (x 6)	35		250			250		
PGNy	56,62	100	80						10^6 x 2
PNeNa	59[f]	50		1000				1000	
NNy	58				500 x 3				10.000 x 4

P= Polymyxin E, T= Tobramycin, G= Gentamycin, A= Amphotericin B,
N= Norfloxacin, C= Cefotaxime, Tr= Trimethoprim, Ne= Neomycin,
Na= Nalidixic acid, Ny= Nystatin, V= Vancomycin

a. All regimens except 53 given four times a day, and except for study 45 starting on admission-day; systemic prophylaxis was given for 4 days, except for study 41 and 61. All studies except 46 and 59 achieved oropharyngeal decontamination by a 2% mixture of the enteral antibiotics in orabase.
b. Cefotaxime in both groups for 72 hours (study 61) or for 5-7 days (study 41).
c. Systemic antibiotics were cefotaxime and ampicillin (4 x 1000) or ciprofloxacin (2 x 200), control patients received nystatin 4 times daily.
d. Regimen starting 3 days prior to operation.
e. Oropharyngeal decontamination by a spray containing polymyxin B, neomycine and bacitracin.
f. 2% povidone-iodine lozenge instead of oropharyngeal paste. Amphotericin B in study as well as control groups in study 46.
g. Amphotericin B only oropharyngeal.
i. Oral lozenge, after 1 minute swallowed.

Table 3.6 Selective decontamination trials and results: all infections and the subgroup of pneumonia[38,40-62].

			Infection rate (%)			Mortality rate (%)			
Ref	Des	Inf.	Control group	Study group		Control group	Study group		Subgroup
38	H	All	81	16	**	not mentioned			
		Pn	59	8	**				
40	H	All	24	10	*	24	24		
						3	0	*	Polytrauma
41	R	All	81	39	**	32	28		
						17	4	*	Inf.related
42	R	All	77	52	*	54	31	*	
						15	0	*	Septicemia
		Pn	44	6	**				
43	R	Pn	62	6	**	10	12		
44	H	Pn	42	6	*	not mentioned			
45	R	All	55	21	**	3	5		
		Pn	14	2	*				
46	DPI	Pn	8	0	*	18	12		
						20	4	*	≥ 7 days
47	DPI	Pn	45	10	**	47	38		
						74	36	?	Cardiac Surgery
48	H	All	83	33	*	42	40		
		Pn	42	7	*				
49	DPI	Pn	73	0	**	30	33		
50	R	Pn	43	2	**	92	62	**	
						80	69	?	Abdom.Surgery
						81	50	?	Polytrauma
51	H	Pn	47	10	*	52	24	*	
52	R	Pn	45	5	*	30	26		
53	DPI	Pn	78	16	**	26	28		
54	R	All	31	17	*	19	15		
						21	11		Apache 10-19
		Pn	82	48	*				
55	R	All	50	14	?				
56	R	All	25	13	*	21	15		
57	DPI	All	63	26	**	44	21	*	
		Pn	46	15	**	20	2	*	Inf.related
58	DPI	All	71	48		48	52		
59	R	All	34	33		not mentioned			
61	RD	Pn	4	2		38	34		
62[a]	DPI	All	34	26		17	18		
		All	46	24	*				Apache 17-23

Ref = References, Des = Design; Historical (H) or Randomised (R) controls, Double-blind (D), Placebo controlled (Pl), Inf. = Infections; All or Pneumonia (Pn), Abdom. = Abdominal.

a : Only mid-range APACHE II had significantly lower infection rates
* : $p < .05$
** : $p < .001$
? : p not mentioned.

alone (14 vs. 49%, $p < 0.05$), mortality was not significantly lower (35 vs. 54%). The use of sucralfate with selective decontamination resulted in a further decrease of pulmonary tract infections (7%) but additionally in a significant decrease in mortality in contrast to H_2-blockers (18 vs. 54%, $p < 0.01$).

Patients with cystic fibrosis does not seem to benefit from selective decontamination[63], but the regimen in this study consisted of oropharyngeal application of an antibiotic gel in combination with long-term systemic antibiotics. The possibility of eradicating an epidemic of infection with multiresistant PPM's has been raised[59,64], but with the use of only enteral drug administration no effect on infection rates could be demonstrated in one of these studies[59]. The effect of selective decontamination on mortality is also subject of discussion; either no effect has so far been demonstrated, or the only positive effect is found in subgroups such as patients with trauma[40] or following cardiothoracic surgery[47], or in those with long-term ICU admission[46] (Table 3.6). Only few randomised studies showed a significant decrease in the overall mortality, but in one study a very high mortality rate in the control group was reported[50]. Kerver et al.[41] have shown an effect on infection-related mortality, but the results of Ulrich et al.[42] in this regard have been disputed because they 'treated' colonized patients in the test-group before infections could arise. As described earlier, overall mortality in a study using historical controls was decreased, but results were obscured by the use of stress ulcer prophylaxis[51].

Adverse effects have been described, but are until now of minor relevance. Many clinicians have observed the (expected) shift from Gram-negative to Gram-positive micro-organisms (*S.epidermidis*, *S.aureus*, *Enterococci*) as causes of infection, but these infections are not difficult to treat[35,40,45,65]. McClelland et al.[66] described failure of recognition of a perforation peritonitis due to *S.epidermidis* in a patient receiving selective decontamination, the latter preventing culture of "typical" Gram-negative organisms.

The possible emergence of resistance will remain to be a cause for attention and justifies the use of surveillance cultures. However, no increase in resistance has been reported so far, presumably because the combination of antibiotics in high enteric dosages makes resistance improbable. The non-absorbable antibiotics

suitable for selective decontamination do not reach tissue levels adequate to treat deep organ infection and are therefore not in general use; this minimises the danger of developing resistance[67].

In choosing antibiotics for their use in selective decontamination, faecal adsorption as described for polymyxin[68] and the quinolones[69] has to be considered because this influences free drug concentration on the colonic mucosa and therefore the microbiological part of colonization resistance. The parenteral administration of metronidazole, in general use in gastro-intestinal surgery for prophylaxis of wound infection, is in this regard permitted because the intraluminal drug concentration is too low to affect colonization resistance[70].

The use of selective decontamination has shown to be an effective method of retaining or enhancing colonization resistance in critically ill patients and has led to a reduction of the offensive load of gram-negative nosocomial PPM, thereby reducing life-threatening infections in most studies.

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PART B

ORIGINAL STUDIES

Chapter 4

SELECTIVE DECONTAMINATION TO REDUCE GRAM-NEGATIVE INFECTIONS

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4.1 Introduction

Hospital-acquired infections cause substantial morbidity and mortality, especially on surgical wards and intensive care units (ICU)[1-10]. Most of these infections are endogenous, since they are preceded by colonization of the gastrointestinal tract and oropharynx by increasingly multiresistant gram-negative bacilli (GNB)[2-5,11-14]. Selective decontamination (SD) is a procedure to eliminate these organisms from the digestive tract leaving the anaerobic flora unaffected. The anaerobes are part of the first-line of defence in the gut (colonization resistance[15]), and they play an important part in the prevention of overgrowth of GNB[16]. Results of earlier trials (in which non-absorbed antibiotics were used) in granulocytopenic patients were promising and use of selective decontamination in these patients has been accepted[17,18]. However, the benefit of modified regimens of selective decontamination in intensive care patients remains controversial. A reduction in infection-rate from 81 % to 16 % was reported by Stoutenbeek et al[19] who used selective decontamination with systemic cefotaxime in 122 multiple trauma patients with a moderately long ICU-stay (≥ 5 days). Ledingham et al[20] advocate the use of this antibiotic regimen for unselected groups of patients in non-specialised ICU's; they found a 24 to 10% reduction in acquired infections in patients on a general ICU. A criticism of previous trials is that historical controls and heterogeneous patient-populations were studied[9].

We report a prospective, randomized study on the effects of selective decontamination in a homogeneous group of patients undergoing elective oesophageal resection for carcinoma; we chose this group because there is a high frequency of lower respiratory tract infections with GNB due to lower colonization resistance in such patients.

4.2 Patients and methods

Previous infection rate

To estimate the infection rate for oesophageal resection in our hospital before the trial, we assessed data from 75 patients (54 men, 21 women; mean age 59,5

years, range 39-78) who had had surgery for oesophageal carcinoma in 1985; they had been examined by endoscopy, computed tomography, and ultrasonography. Only patients who had no local ingrowth and no distant metastatic disease were judged to be operable. Since 1983, cefamandole and metronidazole (4 times 1 g respectively 3 times 500 mg a day, 24 hours perioperatively, that is ≤ 1 h before until about 24 h after surgery) were used as prophylaxis in this type of operation. Mean length of time in hospital and ICU was 34 days (range 21-105) and 6,5 days (1-48), respectively. Pneumonia developed in 16 patients (21%), urinary tract infection in 4 (5%), and septicemia in 5 (7%); 5 patients (7%) died. The infection rate and mortality for the 5 years before the study were similar to those for 1985 (20% and 5%, respectively).

Patients and controls

Between March 1986 and December 1988, 181 patients who were going to have surgery for oesophageal carcinoma were included in the study. On admission to hospital the patients were randomised (fixed block size, n=8) and allocated either to a control group (standard antibiotic prophylaxis) or to a test group (SD-medication combined with systemic cefotaxime during the first 4 days). For all patients the bowel was cleared (laxatives and enemas) during the 3 days before surgery. Until November 1986 a combined right-sided thoracotomy and median upper laparotomy was done on the 4th day. Thereafter the operative technique was changed to mobilising the oesophagus and tumour by blunt dissection through a laparotomy, and using a second incision in the neck to complete the oesophagectomy. The upper digestive tract was reconstructed with a tube made from the remaining stomach, or by colonic interposition in 4 patients in each group (Table 4.1). The actual oesophageal resection was an important inclusion-criterium for analysis.

67 patients were excluded from the trial because oesophageal resection was not done (tumour not resectable in 42 patients, tumour of cardia not involving the oesophagus in 12); SD-medication was discontinued (non-compliance because of taste in 2, vomiting and nausea in 4, allergy in 1); or other antibiotics had been used preoperatively (6 patients). Thus, 114 patients (56 test group, 58 control

group) were studied. The trial was approved by the hospital ethical committee and written informed consent was given by the patients.

Table 4.1 Patient-characteristics

	Test (n=56)		Control (n=58)	
Sex (M/F)	35/21		42/16	
Age (mean)	40-77	(60)	42-78	(60.6)
Cardiac history	4		10	
Pulmonary disease	8		7	
Preoperative irradiation	30		33	
Surgical technique (n°)				
Thoracotomy	18	(32%)	18	(31%)
Stomach-tube	50		51	
Colonic interposition	4		4	
Jejunal interposition	2		3	
N° of reinterventions	7	(12%)	7	(12%)
Admission (n° of days)				
ICU-stay/patient (mean)	1-99	(5.5)	0-35	(4.9)
ICU-stay/group	310		286	
Hospital-stay/patient	14-103	(25.6)	11-91	(27.7)
Hospital-stay/group	1434		1608	
Mortality	3		2	

Specific medication

SD-medication consisted of a sticky ointment (Orabase^{R}, Squibb), containing a mixture of 2% polymyxin E, 2% tobramycin and 2% amphotericin B, applied four times a day on buccal mucosa; a suspension of the same drugs (200, 80, 500 mg,respectively) was given at 6 h intervals by mouth, nasogastric tube, or needle jejunostomy. This regimen was started on the day of admission, and continued until the 10th postoperative day (or longer if infection had not resolved); specific antibiotics were also given. We chose this 10-day period because the high risk for aspiration and other respiratory disorders in these patients lessens quickly after 10 days, as we had previously experienced. Systemic cefotaxime (1 g, four times a day) was added as supplementary prophylaxis for the first 3 days before surgery, during which selective decontamination is not yet fully established, and was discontinued after surgery (day 0). On the day of operation, systemic metronidazole (500 mg, 3 times a day) is added as part of the usual (24 hour) prophylaxis

in bowel surgery. Antibiotic prophylaxis in the control-group consisted of systemic cefamandole and metronidazole (4 times 1 g respectively 3 times 500 mg a day), for 24 hours peri-operatively, as is generally accepted for routine bowel surgery and in use since 1983. It was therefore continued in control patients for better comparability.

Bacteriology

Cultures from nose, throat, sputum (when present), urine and faeces (or rectal swab) were taken on admission, and thereafter three times a week. Drains, gastric contents and feeding fistulae were also cultured. Identification of pathogenic micro-organisms and antibiotic sensitivity tests were done according to internationally accepted laboratory practice. Definitions are given in chapter 2, pp 35.

Follow-up

All patients were examined daily for clinical signs of infection during their admission; diagnosis of infection was confirmed by culture. Chest radiographs were taken daily during the first 3 postoperative days and thereafter if clinically indicated. Radiographs were judged by the same radiologist and chest-physician each time, both of whom were unaware of the group the patients had been allocated to. When a lower respiratory tract infection was suspected cultures from lobular aspirations were taken by bronchoscopy. In both groups treatment was only started when there was clinical and microbiological evidence of an infection, although antibiotics were sometimes empirically started when needed. Antibiotics were chosen according to hospital guidelines based on the sensitivity patterns of the isolated micro-organisms. In the test patients, antibiotics that would not affect colonization resistance were given. None of the patients was given H_2-blockers.

Statistical analysis

To detect a significant reduction in postoperative infections, 56 patients were needed in each group, with α and ß at 0,05 (based on the infection rate for oesophageal resection before the study). The chi-square test (with Yates-correction) and two-sided Fisher's exact test were used to compare frequencies.

To compare the number of infections and non-infectious complications, we used the Mann-Whitney test. A p value of 0,05 or less was regarded as significant.

4.3 Results

Table 4.1 shows that the two groups were broadly similar. To exclude any influence of the change in surgical technique on infection rates, we analyzed all infections in patients who had had a thoracotomy (n=36) and in those who had not had one (n=78). Infections developed in 13 (36%) and 33 (42%) patients; lower respiratory tract infections in 5 and 8 patients, respectively. These differences were not significant.

Table 4.2 Acquired infections in the first 10 postoperative days

	Test patients (n=56)			Control patients (n=58)			
Infection	Gram+	Gram-	Total	Gram+	Gram-	Mixed	Total
Pulmonary	1	0	1 (2%)	2	4	2	8 (14%) *
Urinary tract	3	2 @	5 (9%)	4	7	2	13 (22%)
Wound	6	0	6 (11%)	9	5	6	20 (35%) +
Septicemia	1	0	1 (2%)	1	0	0	1 (2%)
Other	5	0	5 (9%)	3	2	4	9 (15%)
Total	16	2	18	19	18	14	51
%	89	11 #		37	35 #	27	

*<0.05, +<0.01, #<0.001 for controls vs.test patients.
@= not preceded by colonization; 4 causative organisms.

Infection rates

During the first 10 postoperative days, 32 controls had 51 infections whereas 12 test patients acquired 18 infections (p< 0,001); there were significantly fewer respiratory tract infections and minor wound infections in the test patients (Table 4.2). All infections were secondary, except for 2 urinary tract infections on admission, which were not included in this analysis. Most infections were

endogenous (test group 83%, controls 73%). In the control group 54% (46/85) of the causative microorganisms were GNB (*Pseudomonas* sp, *Proteus* sp, *Klebsiella* sp, *Enterobacter* sp, *Acinetobacter* sp, *Citrobacter* sp, and *Escherichia coli*), 41% (35/85) were gram-positive cocci (*Staphylococcus epidermidis, S.aureus* and *Enterococcus* sp) and 5% (4/85) were gram-negative diplococci (*Neisseria* sp and *Branhamella* sp). By contrast, in test patients GNB (*Pseudomonas* sp, *Acinetobacter* sp, and *E coli*) accounted for 15% (4/27) of infections and gram-positive cocci for 85% ($p < 0{,}001$, Table 4.3). 12 new infections arose in 4 test patients after SD-medication had been stopped at 10 days: 3 were respiratory tract infections (Table 4.4). 2 patients had not had a previous infection, but were heavily colonised with GNB after discontinuation of SD-medication. Half the infections were gram-negative or mixed (Table 4.3). In contrast, 1 pulmonary tract infection, caused by GNB developed in a control patient.

Table 4.3 **Micro-organisms causing infections**

	First 10 days		After 10 days	
	SD	Control	SD	Control
Gram-negative species *:				
Pseudomonas	1	11	4	1
Acinetobacter	2	7		
Escherichia Coli	1	11		
Proteus		6	3	1
Klebsiella		7		
Enterobacter		3	2	1
Citrobacter		1		
Neisseria		3		
Branhamella		1		
Gram-positive species:				
S.epidermidis	14	17	7	
S.aureus	1	3	5	
Enterococcus	8	15	2	

S. = Staphylococcus

* Number of gram-negative micro-organisms, infections in the first 10 postoperative days: $p < 0.001$, Fisher's exact test.

In a small subgroup of patients (n=26), who stayed for more than 4 days on the ICU, the reduction in infectious complications and the number of respiratory tract infections seen using selective decontamination, is not significant. 5 controls got respiratory tract infections compared with 1 test patient. The therapeutic use of antibiotics in the postoperative period was significantly different in the two groups; 25 controls and 11 test patients needed specific antibiotics (p=0,013, Chi-square test). 3 test patients died (5%); in 2, infections were contributory factors. In the control group 2 patients (3%) died of non-infectious causes.

Table 4.4 Acquired infections after 10 days

	SD	Control
Pulmonary tract *	3	1
Urinary tract	1	
Wound	3	
Other	5	
Total #	12 +	

*: p=0.487, Fisher's exact test.
#: p=0.171, Mann-Whitney test.

4.4 Discussion

We have shown that selective decontamination reduces postoperative infections caused by GNB after elective oesophageal resection and one-stage reconstruction. Factors that may have influenced infection rates, such as a thoracotomy or colon interposition were equally distributed among both groups; moreover, there were no significant differences in postoperative infectious complications for the two surgical procedures.

Between 1983 and the beginning of the present study the systemic prophylaxis, indicated in this kind of operation[21] was cefamandole and metronidazole, 24 hours perioperatively. We decided to give the same systemic prophylaxis to the control group to detect any influences on infection rates, even though a different medication strategy was given to test patients- namely, cefotaxime and metronidazole. We did not expect the results to be influenced by this difference because cefotaxime was only used pre-operatively and during the day of operation, and cefamandole was given to control patients also for 24 h perioperatively. Mandelli and colleagues[22] did not find an effect of systemic prophylaxis on the occurrence of early onset pneumonia in patients in the ICU. Moreover, since the half-life of cefotaxime does not exceed 1 hour[23], we believe that the influence of this drug on the outcome was negligible. For better comparability, metronidazole was given systematically to both groups: the anaerobic gut flora is not affected because intraluminal concentrations are too low[24].

We did not do a double-blind study, because knowledge of culture results is essential to the physicians in charge of the patients, as surveillance cultures are an essential part of selective decontamination. The number of gram-positive infections in the test group was striking, and indicates how important such surveillance cultures are, since gram-positive organisms are not eliminated by this prophylaxis. Cultures are also necessary to detect the development of resistance during the use of antibiotics. The reason why the number of urinary tract infections was non-significantly reduced with SD prophylaxis was probably because most nosocomial urinary tract infections are associated with instrumentation[25] and all of our patients had indwelling urinary catheters.

That patients were rapidly colonised by GNB after discontinuation of SD medication points to a protective influence of selective decontamination, and suggests that SD prophylaxis in these patients should be continued. We cannot comment about a possible effect of selective decontamination on mortality because of the low mortality rate in this group of patients.

Although the reduction in infection rate led to a significant reduction in the number of patients needing therapeutical systemic antibiotics in the test group, this reduction did not influence the length of admission as noted by others[5,9]. In this

group of patients however, the hospital stay depends in our view on surgical complications, which were equally distributed in both groups. Although we could not show a beneficial influence of selective decontamination in patients staying for more than 4 days in the ICU, there was a substantial reduction in the number of respiratory tract infections in this small group who are highly susceptible to gram-negative bacterial infections[2-4,6,8,19]. With more patients to study, a possible beneficial effect would probably also been found in this group with long stay.

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Chapter 5

EFFECTS OF SELECTIVE DECONTAMINATION ON GRAM-NEGATIVE COLONIZATION

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5.1 Introduction

One third of all patients on an intensive care unit (ICU) experience complications resulting in an estimated mortality of 40 %[1]. Among these complications, nosocomial infections are life-threatening, increasing the infection-related mortality to as much as 50%[2-6]. The incidence of nosocomial infections on the ICU is 5 to 10 times as high in comparison to the ward[1]. In addition, 25% of the nosocomial infections emerge in ICU-admitted patients, including 41% of all hospital septicemia's and respiratory tract infections[2,6]. After 2 weeks, 80% of these patients have infections[7-11], of which more than 60% are caused by gram-negative micro-organisms[12].

A relatively constant event, preceding infections in hospital-admitted patients is the colonization of the oropharynx and gastro-intestinal tract with gram-negative bacilli (GNB)[13-19]. Especially oropharyngeal colonization with GNB is strongly associated with the subsequent development of respiratory tract infections , while more than 75% is preceded by oropharyngeal colonization with the same micro-organism[4,11,13,20]. Wound-, and urinary tract infections are related to preceding gastro-intestinal colonization[18,21] and the presence of indwelling catheters or instrumentation[21]. More than 50% of all ICU-admitted patients is already colonized with the pathogen that subsequently causes their nosocomial infection[22], so measures to reduce or prevent infections in these patients must include ways to reduce the acquisition and colonization of GNB.

Selective decontamination (SD) aims to eradicate these GNB from the oropharynx and digestive tract while leaving the anaerobic flora undisturbed. Selective decontamination maintains the colonization resistance (CR) thereby preventing the colonization with GNB and reducing the number of gram-negative infections[23-25].

A prospective, randomised study to the effects of selective decontamination was conducted in a homogeneous group of patients with oesophageal carcinoma, admitted to have a one-stage resection and reconstruction of the alimentary tract. These patients develop postoperative pulmonary tract infections mostly caused by gram-negative micro-organisms with a frequency of 20%, due to the disturbed

colonization resistance. Clinical results on infection rates were presented in chapter 4, in this chapter we describe the effects on gram-negative microbial colonization.

Since each new antimicrobial regimen can promote the overgrowth or acquisition of resistant strains by producing profound changes in the intestinal microflora[1,26-27], surveillance of bacterial resistance will be continuously needed. One third of all gram-negative micro-organisms resistant to aminoglycosides are isolated on the ICU[6], and most resistant strains in hospitals are thought to originate from colonized or infected patients, acting as a reservoir[28]. Therefore we additionally evaluated the effects of selective decontamination on the development of bacterial resistance.

5.2 Patients and methods

Patients

On admission, patients analyzed and found eligible for oesophageal resection were randomised by means of fixed block size (n = 8) randomisation and allocated to a control-group receiving the standard antibiotic prophylaxis used since 1983 in this kind of operation, or a test-group receiving SD-medication with systemic cefotaxime during the first 4 days. During the first 3 pre-operative days of admission, a mechanical bowel-preparation was achieved in all patients and selective decontamination was established in test-group patients, after written informed consent was obtained. Operation takes place on the fourth day, after which all patients were transferred to the surgical intensive care unit and mechanically ventilated. This study was approved by the hospital ethical committee.

Specific medication

Patients in the test-group received SD-medication, as described in chapter 4 (pp 65), consisting of polymyxin E, tobramycin and amphotericin B. A 2% mixture of these drugs in orabase® was applied four times daily on the buccal mucosa, and a suspension of the same drugs, (respective doses 200, 80 and 500 mg) was given in the digestive tract at 6 h intervals (Table 5.1).

Table 5.1 Medication

SD-medication (test-group):	Oropharynx[1]	Digestive tract[1]
Polymyxin E	2%	200 mg.
Tobramycin	2% in orabase	80 mg. suspension
Amphotericin B	2%	500 mg.
Systemic prophylaxis		
test group	: Cefotaxime[2]	4 x 1 g.
	Metronidazole[3]	4 x 500 mg.
control group	: Cefamandole[3]	4 x 1 g.
	Metronidazole[3]	4 x 500 mg.

SD: Selective decontamination

1. Starting on admission-day, every 6 hours, until 10 days post-operatively. In case of an infection, continued until clinically stable and mobilised.
2. Starting on admission-day, discontinued after the operation.
3. Only 24 hours, on the day of operation.

Bacteriology

Bacteriological cultures from nose, throat, sputum, urine and faeces (or rectal swab) were taken at admission and thereafter three times weekly. On indication cultures from wounds, drains and feeding fistulae were taken. Identification of pathogenic micro-organisms and testing on antibiotic sensitivity was done according to internationally accepted laboratory practice. Definitions are given in chapter 2, pp 35.

Epidemiology and Resistance

All strains resistant to the antibiotics used were recorded in both groups. Also, weekly rectal swabs were taken from patients on 4 fixed beds on the surgical ward and ICU. Isolated micro-organisms were tested on their sensitivity to aminoglycosides, and third generation cephalosporins. These data were compared with data from years preceding this study, also considering the antibiotic usage on the ICU and ward.

Statistical analysis

To detect a significant reduction in postoperative infections, 56 patients were needed in each group, when fixing α and ß on 0,05 and considering the 20% infection-rate in the years preceding this study. To compare frequencies we used the Chi-square test (with Yates-correction) and two-sided Fisher's exact test. To compare the number of infections and non-infectious complications, we used the Mann-Whitney test. A p-value of 0.05 or less was considered significant.

5.3 Results

From march 1986 until december 1988 there were 181 patients eligible for the study, but 67 patients were excluded from further evaluation as has been described in chapter 4. Despite thorough analysis 42 patients proved to have metastasis at laparotomy so no oesophageal resection was performed, 12 patients had no oesophageal resection because the tumour of the cardia did not extend into the oesophagus, and another 13 patients showed adverse effects or used other antibiotics pre-operative. From the remaining 114 patients, 56 received SD-medication and 58 patients got the conventional antibiotic prophylaxis. Both groups were highly comparable regarding the most important parameters.

Colonization

On admission, baseline-cultures revealed that 68 patients (60%) were carrier of gram-negative micro-organisms in the oropharynx (mostly *Neisseria* sp) and 88 (77%) carried GNB (predominantly *Escherichia coli*) in the gastro-intestinal tract. When disregarding *E.coli*, 21 patients (18%) carried GNB in the digestive tract (Table 5.2). Gram-positive micro-organisms (Difteroids, Streptococci, *Staphylococcus epidermidis*) were present in the oropharynx in 94 patients (82%) and in 84% of the patients in the gut (Table 5.3).

At operation-day, 93% of SD-medicated patients were free of gram-negative micro-organisms in the oropharynx, with none of the patients having gram-negative bacilli in the respiratory tract. Furthermore, 95% of the patients were free of GNB

Table 5.2 Colonization with gram-negative micro-organisms

		Admission	Day 0	Day 1-10 *	After 10 days
oropharynx					
SD	:	26 (46%)	4 (7%)	2 (4%)	10 (18%)
Control	:	42 (73%)	27 (46%)	24 (42%)	
Respiratory tract					
SD	:	7 (13%)			6 (11%)
Control	:	11 (19%)	11 (19%)	33 (54%)	
Alimentary tract					
SD	:	43 (77%)	3 (5%)		19 (34%)
Control	:	45 (77%)	21 (36%)	20 (35%)	
Urinary tract					
SD	:	11 (20%)		5 (9%)	2 (4%)
Control	:	7 (12%)	13 (22%)	34 (58%)	

SD: Selective decontamination

*. $p < 10^{-6}$, Chi-square test

in the rectum, and none showed GNB in the urinary tract (Table 5.2). During the first 10 postoperative days gram-negative colonization could be prevented in all but 7 patients receiving SD-medication while most control-patients were colonised with new GNB ($p < 10^{-6}$, Chi-square test). With discontinuation of selective decontamination after 10 postoperative days colonization with GNB occurred within 3 to 4 days in 10 patients (18%) in the oropharynx and in 19 patients (34%) in the alimentary tract. 6 patients (11%) showed colonization with gram-negative bacilli in the respiratory tract, 4 (7%) in the urinary tract (Table 5.2). With respect to the gram-positive bacilli, up to 52% of SD-medicated patients and 85% of the control patients showed colonization with these micro-organisms during this period (Table 5.3).

Bacterial resistance

One (1,8%) SD-medicated patient was colonised during the study with a resistant *Acinetobacter*. Two (3,3%) control patients were colonised with *Pseudomonas* strains. Epidemiological data on resistant aerobic gram-negative bacilli are summarized in Table 5.4: as can be seen no significant differences were found, in

spite of the increased amounts of aminoglycosides and cephalosporins used on the ward and ICU (Table 5.5).

Table 5.3 Colonization with gram-positive micro-organisms

		Admission	Day 0	Day 1-10	After 10 days
Oropharynx					
SD	:	45 (80%)	4 (7%)	29 (52%)	13 (23%)
Control	:	49 (85%)	38 (65%)	9 (15%)	
Respiratory tract					
SD	:	17 (30%)	5 (9%)	21 (37%)	8 (14%)
Control	:	20 (35%)	18 (31%)	18 (31%)	
Alimentary tract					
SD	:	51 (91%)	3 (6%)	22 (40%)	9 (16%)
Control	:	45 (77%)	22 (44%)	29 (50%)	
Urinary tract					
SD	:	13 (33%)	1 (2%)	29 (52%)	19 (34%)
Control	:	24 (42%)	2 (4%)	46 (85%)	

SD: Selective decontamination

5.4 Discussion

Patients undergoing one-stage oesophageal resection and reconstruction are susceptible to get respiratory tract infections. Already pre-operative the colonization-resistance is diminished because of the primary disease, mucosal damage following irradiation and disturbed physiological cleaning mechanisms. Post-operative coughing and sighing is impaired because of the pain originating in the thoracic and upper abdominal wounds, in addition to the altered peristalsis and regurgitation.

Selective decontamination is established in most of these patients within 3 to 4 days, in contrary to the longer periods (7-12 days) in other studies[8]. This is probably due to the functional gut in the pre-operative days during which a bowel preparation is performed and selective decontamination is established. Furthermore colonization with GNB could be prevented in almost all SD-medicated patients,

Table 5.4 Resistant (R)* aerobic gram-negative bacilli, epidemiological study

	Before SD (1985)	After SD (1987)	
Department	Sampled / R	Sampled / R	Chi-square
ICU	88 / 12 (13.6%)	83 / 15 (18.1%)	n.s.
	AG: 6 3C: 6	AG: 10 3C: 5	
Ward	77 / 3 (3.9%)	162 / 3 (1.8%)	n.s.
	AG: 3 3C: 0	AG: 2 3C: 1	

SD: Selective decontamination

*. Resistant to one or more aminoglycosides (AG) and / or third generation cephalosporins (3C).

except for 2 patients having oropharyngeal colonization without colonization of the respiratory tract and 5 patients showing colonization in the urinary tract, probably as a result of indwelling catheters (Table 5.2).

The rebound colonization after discontinuation of SD-medication resulted in 3 gram-negative pulmonary tract infections in 2 patients (chapter 4, pp 68). This illustrates the importance of gram-negative oropharyngeal colonization in the pathogenesis of these infections, because these 2 patients were heavily colonized with the causative micro-organisms before the infections occurred. On the other hand, 10 patients (18%) showed oropharyngeal and 6 (11%) showed respiratory tract colonization with gram-negative bacilli in this period, indicating a more complex relationship between colonization, host-factors and infections. The 4 patients having late infections all suffered from surgical complications such as suture leakage which necessitated reinterventions and longer admissions on the ICU, and perhaps these patients will benefit from longer continuation of SD-prophylaxis.

In this study, we saw no increase in resistant strains, despite the growing amounts of antibiotics used (Table 5.4 and 5.5). The possibility of resistance

developing under antibiotic pressure must however be recognised, and therefore a close surveillance remains mandatory.

Table 5.5 **Use of aminoglycosides and third generation cephalosporins in surgical wards and ICU**

	1985		1986		1987	
	gram/ratio		gram/ratio		gram/ratio	
Gentamycin and Tobramycin						
ICU	157	0.06	155	0.07	173	0.06
Ward	43	0.003	144	0.01	143	0.01
Cefotaxime and Ceftazidime						
ICU	271	0.10	587	0.26	866	0.33
Ward	70	0.005	472	0.04	338	0.03

Ratio = grams used/number of patient-days in department.

5.5 Conclusions

Selective decontamination of the oropharynx and digestive tract can reduce gram-negative colonization and subsequent infections after major elective surgery. Selective decontamination is therefore an effective way of prophylaxis without an increase in resistance to the used antibiotics until now, but a careful surveillance is necessary to detect a possible emergence of resistance in the future. Patients having late complications are likely to benefit from prolonged administration of SD-medication to prevent renewed colonization and the development of infections. Selective decontamination must not be discontinued until the condition of the patient makes pulmonary infection improbable.

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Chapter 6

EFFICACY OF SELECTIVE DECONTAMINATION

Effects on mortality and length of admission

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6.1 Introduction

Several studies have shown that selective decontamination as an antimicrobial prophylaxis to prevent gram-negative colonization and infections in haemato-oncological and critically ill patients on the Intensive Care Unit (ICU) leads to a 50 to 80% reduction of infections, especially those of the lower respiratory tract[1-15]. High-risk patient-groups such as multiple trauma[3] or liver-transplant patients[16,17], patients with mid-range APACHE-scores[14], and those undergoing cardiac[10,18] or oesophageal surgery[9] have been shown to possibly benefit from selective decontamination.

The very high mortality-rate up to 70% in patients with a lower respiratory tract infection [19-23] has established a close relation between mortality and infections on the ICU. It is surprising therefore that no study has so far been able to demonstrate a significantly lower mortality or hospital-stay even though highly significant decreases of infection-rates were found using selective decontamination[24,25]. Possible explanations include that these differences are present but not apparent, and that patients may die with infections and not because of them. This would suggest that host-factors may be as important as prophylaxis[26]. The reason for the unclarity could also lie in the fact that until now, no study has investigated the relation between the efficacy of decontamination and the outcome for the individual patient. Instead total rates of infection and subsequent events in groups of patients receiving selective decontamination have been compared to those of controls. Most of these studies have used the APACHE II or SAP-score to match patient-groups in terms of "severity of illness". These scoring-systems are however inaccurate when heterogeneous patients from different intensive care units (ICU's) are studied, because diagnostic categories and the possible acute character of the admission are not weighed in these scores[27]. Furthermore when patients are transferred from other hospitals or wards they introduce an underestimation of illness when scored by APACHE or SAP. Physiological variables, used for these scores, will have responded to therapy while the underlying disease is the cause for non-responsiveness of the patient, necessitating transferral (selection- and lead-time bias[28]).Differences in diagnostic groups could then easily result in unmeasured

differences in mortality between patients with selective decontamination and control-patients. To determine the efficacy and possible benefit of new prophylactic or therapeutic interventions it is therefore better to analyze only primary admissions and to compare actual death-rates with predicted hospital-death rates as described by Knaus[27]. These predicted rates are calculated by a logistic regression formula, in which each diagnostic category, the fact whether operative therapy took place or not, and the possibility of emergency surgery are scored. A beneficial effect will result in a lower actual death rate compared to the predicted rate in the patient group receiving a successful new regimen, whereas groups without this regimen or unsuccessful use of it have an actual rate not different from the predicted rate. On the other hand, when predicted death rates are comparable between groups, they have a comparable "severity of illness" and can thus be compared in terms of survival and length of stay. In this report we present a prospective follow-up study of patients admitted to our surgical intensive care unit and receiving selective decontamination, with special attention for expected and actual death-rates. Since we expected the efficacy of decontamination to be of influence on infection- and mortality-rates we evaluated these rates in terms of successful decontamination or not.

6.2 Patients and methods

Patients

Patients entered into this study were electively admitted to the ICU after a one-stage oesophageal resection and reconstruction for carcinoma as described earlier[9], or were to have a thoraco-abdominal vascular aneurysm repair. They were given selective decontamination electively in combination with a mechanical bowel preparation starting three days prior to the operation. Furthermore, all primary emergency admissions with acute pancreatitis, those with complications after previous surgery and all trauma-patients who were expected to be ventilated for more than 4 days received selective decontamination and were included in this study.

Between November 1989 and May 1991, 135 patients admitted to our ICU received selective decontamination. After excluding 38 patients transferred from other hospitals, we classified the remaining 97 patients with primary admissions to our department according to their admission diagnosis (Table 6.1). Oesophageal resections were done by blunt transhiatal dissection via an upper median laparotomy, reconstruction was performed by a stomach-tube with a cervical anastomosis. Patients with an acute pancreatitis were operated only on demand to remove infected necrosis. All patients were scored according to the APACHE II system on admission and thereafter daily, predicted death rates were calculated on admission. We calculated the expected death rate for groups by adding the individual risks computed according to Knaus[27] and dividing this by the number of patients.

Medication

Selective decontamination consisted of oropharyngeal application of Orabase^{R} containing 2% of polymyxin E, amphotericin B and norfloxacine 4 times daily on the buccal mucosa and tracheostomy-sites. An enteral suspension of the same antimicrobial agents (200, 500, 50 mg respectively) was given by mouth, nasogastric tube or needle-jejunostomy also 4 times daily. With pancreatitis and blind enteric (mostly rectal) segments an enema containing resp. 800, 2000 and 200 mg of the drugs was administered. This regimen was started electively preoperative when possible, or on admission to the ICU (acute patients) and continued until the patients were mobile, transferred to the ward and expected to have a low risk of developing pulmonary infections (estimated at 5 days after detubation).

Parenteral medication was only used as direct 24 hours perioperative infection-prophylaxis, or during the first 5 days when selective decontamination was not yet fully established in patients with acute pancreatitis, and consisted of 750 mg cefuroxime administered iv. three times daily. When infections necessitated administration of systemic antibiotics, preference was given to antibiotics indifferent to the colonization resistance in conformation with hospital guidelines and based on sensitivity patterns.

Table 6.1 Patient characteristics and success of decontamination

	Successful SD	Unsuccessful SD	
Number of patients	72	25	
Gender (M/F)	54/18	18/ 7	
Age	16- 86 (61)	23- 81	(61)
Cardiac history	6	3	
Pulmonary history	8	2	
H_2-Blockers	10	7	
Corticosteroids	12	2	
Tracheostomies	13	8	
Acute admissions	29	19 *	
Diagnostic categories			
Oesophageal resection	39	4	
Trauma	12	6	
Aneurysm repair	9	6	
Septicaemia	5	4	
Pancreatitis	2		
Pneumonia	2		
Neurological	1	1	
Miscellaneous	2	4	
Infections on ICU-admission	10	7	
Apache II day 0	12- 42 (23)	19- 34 +	(25)
day 1	12- 35 (23)	20- 35	(25)
SD-medication, days	2- 88 (16)	3- 76	(20)
N° of patients starting SD,			
before ICU-admission #,	28	1	
on ICU-admission,	28	7	
after ICU-admission @,	16	17	

SD : Selective decontamination
ICU : Intensive Care Unit
Mean values between brackets.

* : Chi-square test, p = 0.004
\+ : Unpaired T-test, p = 0.042
\# : Chi-square test, p = 0.003
@ : Chi-square test, p = 0.001

Bacteriology and definitions

On admission, inventory cultures were taken from the nose, throat, sputum, urine and rectum, and repeated weekly, while other cultures were taken on indication. Identification of pathogenic micro-organisms and testing for antibiotic sensitivity was done according to standard laboratory techniques. Definitions are given in chapter 2, pp 35. Resistance to the antibiotics used in the regimen was recorded

during the study and related to the number of patients colonized with resistant micro-organisms.

Statistics

Comparison of data between two study-groups was done by application of the Chi-square test (with Yates correction) and Fisher's exact test for small numbers. Mean values with close-to-normal distributions were compared by the unpaired t-test, not-normal or skewed distributions (range and median value given) by the Mann-Whitney U-Wilcoxon rank sum W test. Differences were considered significant when p-values were less then 0.05 (t-test, Mann-Whitney, Chi-square and two-sided Fisher's test).

6.3 Results

Of the 135 patients receiving selective decontamination, 38 (28%) came from other hospitals. Because of possible "lead-time bias"[28] these transferred patients were excluded from this study. 48 of the remaining 97 patients were acutely admitted to the ICU whereas 49 underwent elective surgery.

Medication and rate of decontamination

Of the 97 patients with selective decontamination, 90 had no aerobic pathogenic micro-organisms in the oropharynx or rectum upon admission to the ICU, 5 patients were decontaminated within 3 days after ICU-admission. Of the 97 patients receiving selective decontamination, 72 remained successfully decontaminated during their admission whereas decontamination failed in 25 patients (26%). Bacteriology is given in Table 6.2. The success of decontamination was related to the moment of commencement of selective decontamination, 28 of the successfully decontaminated patients received the medication already preoperatively against 1 of the unsuccessfully decontaminated patients (39 vs. 4%, $p = 0.003$). A postoperative start of selective decontamination was seen in 16 successfully and 17 unsuccessfully decontaminated patients (22 vs. 68%, $p = 0.001$, Table 6.1).

Table 6.2 Colonization in oropharynx and rectum

						Failed decontamination			
		Admission		Elimination		Persistance		Acquired	
		O	R	O	R	O	R	O	R
Total	:	48	32	40	24	8	8	32	18
Gram-negative species									
Escherichia Coli	:	17	7	15	5	2	2	4	1
Klebsiella	:	9	2	8	2	1		1	1
Enterobacter	:	3	4	2	4	1		5	2
Serratia	:		1				1	2	1
Proteus	:	5		4		1		4	1
Pseudomonas	:	4	4	3	1	1	3	4	5
Citrobacter	:	2	2	2	2			1	
Acinetobacter	:	1	1	1	1			3	1
Branhamella	:		1		1				
Gram-positive species									
S.aureus	:		4		3		1		3
MRSA	:							2	1
MRSE	:							1	1
Enterococcus	:							3	1
Str.pneumoniae	:		1		1				
C. albicans	:	7	4	5	3	2	1	2	

O : Oropharyngeal colonization
R : Rectal colonization
Acquired: Micro-organisms acquired during selective decontamination
MRSA : Methicillin resistant Staph.aureus
MRSE : Methicillin resistant Staph.epidermidis.

Prophylactic systemic antibiotics were given for 24 hours peri-operatively in 86 patients and in 11 patients as a treatment regimen already pre-operatively because of suspected infections. There were no significant differences in this aspect between groups with successful or unsuccessful decontamination (7 vs. 4 patients).

Table 6.1 shows the relevant parameters of the 72 successfully and 25 unsuccessfully decontaminated patients. Although the group not achieving successful decontamination had higher APACHE II scores and more acute

admissions their predicted mortality-rates were similar to the group with successful decontamination (40 resp.44%), indicating a comparable "severity-of-illness".

Table 6.3 **Infection sites related to the success of selective decontamination**

	Successful SD (72)	Unsuccessful SD (25)
Infected patients	28 (39%)	25 * (100%)
Pneumonia	6	13 *
Pleural empyema	1	2
Mediastinitis	1	
Abdominal abscess	4	6 +
Urinary tract	6	11 #
Septicemia	15	16 #
Pancreatic necrosis	2	
Wounds	10	4
Miscellaneous	1	2

SD : Selective decontamination
Chi-square test : *: $p < 10^{-5}$, +: $p = 0.017$, #: $p < 0.000$

Infection-rates and antibiotic days

Of the 97 patients 53 (55%) developed 105 infections of which 71 (68%) were gram-negative or mixed in origin. It is important to note that all infections were nosocomial although 17 patients had 19 infections on admission to the ICU. Of these patients, 9 had deep abdominal or soft tissue abscesses on ICU-admission and in 5 of them selective decontamination successfully prevented colonization of the oropharynx and gut by the gram-negative micro-organisms already present in the abscesses. All 25 patients with unsuccessful decontamination (100%) and 28 of the 72 successfully decontaminated patients (39%) suffered from nosocomial infections (Table 6.3). In the successfully decontaminated group not only a significant decrease was observed in the number of lower respiratory tract infections, but also in the number of urinary tract infections, abdominal abscesses and septicemia. All these infections were less frequently gram-negative in origin in the adequately decontaminated group compared to failed selective decontamination (53 vs. 80%, $p = 0.006$, Chi-square). The bacteriology is given in Table 6.4.

Table 6.4 Bacteriology of infections

	Successful SD					Unsuccessful SD				
	P	U	W	S	A	P	U	W	S	A
Gram-negative species										
Escherichia Coli	3	3	3		3	1	1	3	2	5
Klebsiella			2		1	2	1	2		1
Enterobacter	2		1	1		2		1	2	2
Serratia						2	1	1	1	
Proteus	1							2	1	3
Morganella									1	
Pseudomonas	1		3			5	1	1		4
Citrobacter			1			1				
Acinetobacter		2				2	1		2	1
Branhamella						1				
Gram-positive species										
S.aureus	1		1	1	1				4	
S.epiderm.			4	1	2		2		1	2
MRSA						1				
MRSE			1	3	1				7	4
Enterococcus		2	2	1	2		3	2	3	6
Str.pneumoniae	1		2							
Anaerobes			4	2	1					3

SD: Selective decontamination, P: Pneumonia, U: Urinary tract infection, W: Wound infection, S: Septicemia, A: Abscess

Str. : Streptococcus
S. : Staphylococcus
MRSA : Methicillin resistant S.aureus
MRSE : Methicillin resistant S.epidermidis.

The use of systemic antimicrobial agents, therapeutic as well as those used in the prophylactic regimen, was significantly lower in the group with successful decontamination, as expressed by the number of antibiotic days (Table 6.5). During this study 2828 of 6680 sampled cultures showed growth of which 42% proved to be gram-negative. 5 primary admitted patients (5%) were colonized with 5 resistant gram-negative strains, 1 multiresistant *Acinetobacter* and 4 *Pseudomonaceae* resistant to norfloxacine(3), tobramycin(3) and co-clavulanic acid/ticarcillin(2).

Table 6.5 **Mortality, duration of stay, ventilation and antibiotic days**

	Successful SD (72)			Unsuccessful SD (25)		
	Range	Median	Me ± St	Range	Median	Me ± St
Duration of stay						
Total	7-195	24	34 ± 31	7-130 *	44	52 ± 35
ICU	1- 94	7	9 ± 13	3- 65 +	18	23 ± 16
Ventilation						
Total	1- 87	3	7 ± 12	1- 40 +	12	17 ± 13
Tracheostomy	1- 87	16	21 ± 23	3- 39	31	25 ± 14
Antibiotic days	0- 85	4	12 ± 18	0-106 +	20	25 ± 24

Infectious mortality	5	(7%)		6 #	(24%)
Actual mortality	13	(18%)	**	11 @	(44%)
Predicted mortality	30	(40%)	**	11	(44%)

SD : Selective decontamination
Me ± St : Mean ± Standard Deviation

* : Mann-Whitney test, $p = 0.002$
\+ : Mann-Whitney test, $p < 0.000$
\# : Fisher's exact test, $p = 0.030$
@ : Chi-square test; successful vs. unsuccessful SD, $p = 0.020$
** : Chi-square test; predicted vs. actual death-rate, successful SD, $p = 0.006$

Ventilation, duration of stay and mortality

The mortality observed in the total group of patients was 25% (24 of 97 patients), 7 due to septicemia and 4 to multiple organ failure (11% infection-related mortality). Actual mortality was significantly correlated to the success of selective decontamination; 18% in the group with successful decontamination and 44% in the unsuccessfully decontaminated patients ($p = 0.02$, Table 6.5), non-infectious mortality was 11% resp. 20% whereas the infection-related mortality was 7 resp. 24% ($p = 0.03$). Predicted death-rates were similar in both groups (40 vs. 44%), the actual death-rate was accurately predicted (calculated) in the unsuccessfully decontaminated group (44%) but significantly lower compared to the predicted mortality-rate in the group with successful decontamination (18% actual vs 40% predicted, $p = 0.006$, Table 6.5).

In the successfully decontaminated group significantly less days of ICU- and

hospital-admission and ventilation days were recorded (Table 6.5). This group however included more elective patients, who have significantly shorter ventilator-periods compared to acutely admitted patients (4 vs 16 days, p = 0.000).

6.4 Discussion

This study reports a significant decrease in mortality and the length of ICU- and total hospital-stay in surgical patients receiving selective decontamination but only when successful decontamination has been reached. This significant decrease was seen in the actual mortality rates but more importantly by comparing actual with predicted death rates in the successfully decontaminated group in contrary to those unsuccessfully decontaminated, indicating a beneficial effect of successful decontamination. Predicted rates were furthermore comparable between both groups despite the difference in APACHE II or the number of acute patients, indicating the comparability in terms of "severity of illness". Predicted mortality-rates calculated this way are superior to APACHE or SAP scores in predicting outcome because these rates account for different diagnostic categories and acute admissions, factors which are not incorporated in the Apache II- or SAP score. However, there can be an important influence of the APACHE II scores used to calculate predicted rates when these scores are determined directly postoperative. Possible hypothermia with hyperglycaemia, low potassium levels, elective ventilation and reduced base excess will greatly influence the total score, which will stabilise on lower values when the direct postoperative stress has subsided. Analysis of the APACHE scores determined on ICU-admission and the next day revealed however no differences between these two values (Table 6.1). We therefore think the observed decrease in (infection-related and total) mortality is the result of a beneficial effect of selective decontamination.

Recently, Gastinne et al.[25] reported in a study of 445 patients on multiple intensive care units that selective decontamination had no significant effect on mortality or the length of stay in the ICU. Their study however concerned the general effect of selective decontamination in predominantly medical patients.

Considering the influence of "diagnostic categories" their conclusions are confined to medical patients only. In the present study, the recognition of a group of surgical patients receiving selective decontamination but not achieving successful decontamination (almost one-quarter of all patients) proved to have important consequences for the outcome of these patients. Whether the failed decontamination in this subgroup of patients is a reflection of their altered peristalsis and subsequently of their altered colonization resistance remains unanswered and may be an epiphenomena leading us to those very ill patients not responding to any therapy. This finding of inadequate decontamination might also explain why earlier studies failed to demonstrate a beneficial effect of this prophylaxis on mortality and admission.

As we have shown previously the success of selective decontamination is high when administered elective and pre-operatively[9]. Accordingly, electively admitted patients appear to benefit most. SD-medication started after ICU-admission is less effective in achieving decontamination and consequently does not reduce the risk of developing a lower respiratory tract infection. A possible correlation between unsuccessful selective decontamination and an acute admission remains to be determined, and future study of these subgroups can possibly predict risk-factors associated with unsuccessful decontamination, so that efforts can be made to eliminate these factors and prevent failure.In contrast to the previous study, we used norfloxacine instead of tobramycin in the antibiotic regimen, merely because it appeared equally effective in selective decontamination[6], but at a much lower expense.

In conclusion, the present study has shown that patients in whom selective decontamination is successful greatly benefit from its administration as is expressed by the reduction of actual mortality in comparison to calculated mortality. However if selective decontamination fails to eliminate all gram-negative micro-organisms from the alimentary tract, patients have a high risk to develop infections and to subsequent death. This group of patients is prone to have prolonged use of antibiotics and longer ICU- and hospital-stay. Studies to identify the cause of failure to decontaminate these patients successfully need to be undertaken.

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Chapter 7

BACTERIOLOGY OF SELECTIVE DECONTAMINATION

Efficacy and rebound colonisation

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7.1 Introduction

Selective decontamination (SD) is a method to prevent infections based on the concept of enhancing colonization resistance (CR), as one of the most important defence-mechanisms of the host against colonization and infection[1-2]. CR consists of a physiological and a microbiological part[3-4], in which the anaerobic flora exerts an important role. The non-absorbable antibiotics used in selective decontamination try to preserve this endogenous flora, and thereby the valuable ecological equilibrium. The effects of selective decontamination on gram-negative colonization and infections have been studied extensively[5-12] and have been communicated in recent reviews[13-14]. The principal conclusion presented in most studies is that gram-negative colonization and infections are prevented but effects on mortality are inconclusive.

We recently described the successful prevention of gram-negative colonization and infections using selective decontamination perioperatively in 56 patients in the surgical intensive care unit (ICU). After discontinuation of the SD-regime on the tenth day we observed a worrisome rebound colonization with gram-negative micro-organisms in 23 patients (41%), of which 4 (7%) developed 12 infections[15]. No infection was caused by antibiotic-resistant micro-organisms (chapter 4).

Apart from one observation in mice[16] this rebound colonization has not been reported in clinical applications. Moreover, besides this direct effect on endogenous infections, the risk of these colonized patients being a source of resistance and infection is a realistic danger[17-18] and has important epidemiological consequences. Especially the ICU has the conditions to enhance the acquisition and spread of epidemic multiresistant strains[19] and since these possibly resistant micro-organisms colonizing the host can persist as "resident flora" for years following hospitalisation[20] they can endanger the ICU- and hospital environment in subsequent admissions. Illustrative in this respect is that as many as 44% of all patients colonized with *Pseudomonaceae* and 81% of those with *Staphylococcus aureus* show these micro-organisms already on admission to the ICU and are therefore apparently previously acquired; these patients also experience more infections

caused by these bacteria than patients not colonized (50 vs 20%, resp. 13 vs 8%)[21]. Because of these hazardous clinical implications it is important to protect patients from getting colonized, whether during or after SD-medication.

We decided to conduct a prospective cohort-study to evaluate the microbiological consequences in patients during and following the use of SD-medication to detect (un-)successful decontamination, possible rebound colonization with persistent, previously eliminated and/or newly acquired strains, infectious complications and resistance. We also tried to determine the period after which SD-medication can be safely withdrawn. In addition we studied the possible epidemiological effects of the transfer of SD-medicated patients from the ICU to the ward.

7.2 Patients and methods

Patients

Patient-populations with the greatest benefit from receiving SD-medication were identified according to earlier experience[15], and based on existing literature[7,12-13] which seems to restrict the indication to surgical patients. All surgical patients undergoing elective operations with an increased risk of pulmonary infection, with subsequent ICU admission were therefore given SD-medication in combination with a mechanical bowel preparation three days prior to the operation, and included in the study. Patients acutely admitted to the ICU with multiple trauma who were expected to be intubated and ventilated for more than 4 days, those with complications after previous surgery and all patients with acute necrotising pancreatitis also received SD-medication and were likewise included. No permission from the Ethical Committee was needed since this application of selective decontamination is institutionalised in our hospital as a result of the previous study[15].

Between November 1989 and May 1991, 135 patients in our surgical ICU received SD-medication during 154 ICU-admissions (there were 19 re-admissions). For this

cohort-study, we evaluated each definite episode in which a given patient (either primarily admitted or transferred) received SD-medication because we were principally interested in epidemiological processes and not in differences between patients. Accordingly, despite the selection-and lead-time bias[22] we included all transferred patients because we thought them to be interesting patients to evaluate in comparison to primarily admitted cases. All patients were scored according to the Apache II system when admitted to the ICU[23].

Oesophageal resections were done by blunt transhiatal dissection via an upper median laparotomy, reconstruction followed by a stomach-tube with a cervical anastomosis. Thoraco-abdominal resections of aneurysms were done via a left-sided thoraco-abdominal incision including the left diaphragm; patients with an acute pancreatitis were operated only when a clinical deterioration appeared from infected necrosis.

Medication and bacteriology

SD-medication consisted of Orabase^{R} containing 2% of polymyxin E, amphotericine B and norfloxacine applied 4 times daily on the buccal mucosa and tracheostomy-sites and an enteral suspension of the same antimicrobial agents (200, 500, 50 mg respectively) given by mouth, nasogastric tube or needle-jejunostomy also 4 times a day (chapter 6, pp 91).

On admission to the ICU (acutely admitted patients) or ward (elective patients), inventory cultures were taken from the nose, throat, sputum, urine and rectum; thereafter once a week while other cultures were taken on indication. On operation-day new cultures were obtained from patients undergoing elective procedures. Again inventory cultures were taken 5 days after discontinuation of SD-medication. Identification of pathogenic micro-organisms and testing for antibiotic sensitivity was done according to standard laboratory techniques. Definitions were as described in chapter 2, pp 35. Resistance to the antibiotics in the regimen was recorded during the study in all cultures including the first inventory- and surveillance-cultures; for epidemiological purposes additional cultures were taken and especially those strains responsible for a rebound colonization were tested on their antimicrobial sensitivity especially versus the SD-antibiotics.

Statistics

Whenever applicable, differences between groups of patients were compared by the Chi-square test (with Yates-correction) and the two-sided Fisher's exact test for small numbers. Mean values with close-to-normal distributions were compared by the unpaired t-test, not-normal distributions by the Mann-Whitney U-Wilcoxon rank sum test. Differences were considered significant when p-values were less than 0.05.

7.3 Results

During this study 135 patients were evaluated in 154 episodes of selective decontamination, their characteristics and admission-diagnoses are given in Table 7.1 and 7.2.

Table 7.1 Patient characteristics

Gender(M/F)	:	103/ 32	
Age	:	16- 86	(61)
Apache II	:	12- 42	(24)
Admission			
Total	:	6-236	(46)
ICU	:	1- 99	(18)
Ventilation	:	1- 87	(14)
SD	:	2- 98	(20)
Successful	:	92	(68%)
Antibiotic days (syst)	:	0-119	(22)
Mortality	:	35	(26%)

Mean values between brackets.
SD : Selective decontamination
Syst : Systemic use of antibiotics

Considering the introduction of selection-bias and the "degree of illness"[22-23] there was an anticipated influence of transferred and re-admitted patients on overall figures; compared to primary admitted patients they were significantly more often unsuccessfully decontaminated (47 vs 26%, $p = 0.02$) and had higher APACHE II-

scores (mean 26 vs 24, $p = 0.02$); they also had longer ventilator-periods, total- and ICU-admissions and more antibiotic days (all $p < 0.000$, Mann-Whitney).

Table 7.2 Diagnoses on admission

Elective:		
Oesophageal resection	:	44
Vascular surgery	:	19
Acute:		
Trauma	:	23
Peritonitis	:	19
Pancreatitis	:	10
Mediastinitis	:	7
R.I.	:	4
M.O.F.	:	5
Mesenterial thrombosis	:	4
Total	:	135

R.I. : Respiratory Insufficiency
M.O.F. : Multiple Organ Failure

In 78 of the 154 episodes with SD-medication 173 strains of potentially pathogenic micro-organisms (PPM) were cultured upon admission, 99 of these strains were obtained from transferred patients in 28 periods. In 19 of the 78 episodes, patients had distinct, localised foci of infection such as abdominal abscesses or pleural empyema which harboured 30 strains, 19 of these were gram-negative. The remaining 76 of 154 episodes revealed non-pathogenic flora in cultures from oropharynx and rectum.

Efficacy of selective decontamination

Selective decontamination could not be achieved in 19 episodes and failed to protect against colonization during this prophylaxis in 30, thus resulting in 49 unsuccessfully decontaminated episodes, a failure-rate of 32%.

The bacteriology is captured in Table 7.3 and 7.4; 64 resp. 79% of the gram-negative pathogenic micro-organisms could be eliminated from the

Table 7.3 Oropharyngeal colonization

	During SD		After SD				
	Admi	Elim	Pers	Acqu	Reap	New	Not
Total :	59	39	20	23	2	16	15
Gram-negative species :	39	25	14	17	2	10	12
Escherichia Coli :	11	8	3	-	1	-	1
Klebsiella :	2	2	-	2	-	3	2
Enterobacter :	5	5	-	3	-	3	2
Serratia :	2	-	2	2	-	-	1
Proteus :	1	-	1	-	-	1	-
Pseudomonas :	12	4	8	8	1	2	5
Citrobacter :	2	2	-	-	-	1	-
Acinetobacter :	1	1	-	2	-	-	1
Branhamella :	2	2	-	-	-	-	-
Haemoph.influenzae :	1	1	-	-	-	-	-
Gram-positive species :	12	8	4	5	-	3	2
S.aureus :	7	4	3	1	-	2	-
S.epidermidis :	1	1	-	-	-	1	-
MRSA :	1	-	1	2	-	-	-
MRSE :	-	-	-	1	-	-	1
Enterococcus :	1	1	-	1	-	-	1
Str.pneumoniae :	2	2	-	-	-	-	-
C.albicans :	8	6	2	1	-	3	1

Admi = Admission, Elim = Elimination, Pers = persistance, Acqu = Acquisition, Reap = Reappearance, New = Newly cultured, Not = Not cultured

Haemoph.: Haemophilus, S.: Staphylococcus, Str.: Streptococcus, C.: Candida

oropharynx (Table 7.3) and rectum or stool (Table 7.4). The persistence of 8 *Pseudomonaceae* and the methicillin resistant *S.aureus* (MRSA) in the oropharynx is an important observation, because 6 of these strains were cultured from transferred patients. During the 30 unsuccessful episodes 5 fungi, 56 gram-negative and 13 gram-positive strains were acquired including multiresistant strains of *S.aureus* (5) and *S.epidermidis* (2). In 14 of the 19 episodes in patients with infectious foci selective decontamination prevented further spread of these micro-organisms to oropharynx or gut.

Table 7.4 Rectal colonization

	During SD				After SD		
	Admi	Elim	Pers	Acqu	Reap	New	Not
Total :	84	64	20	51	12	44	20
Gram-negative species :	70	55	15	39	9	28	15
Escherichia Coli :	27	22	5	8	4	10	2
Klebsiella :	11	10	1	2	3	7	1
Enterobacter :	8	6	2	7	-	4	4
Serratia :	-	-	-	3	-	-	-
Proteus :	9	7	2	5	-	-	3
Pseudomonas :	11	7	4	9	1	3	3
Citrobacter :	2	2	-	1	-	4	-
Acinetobacter :	2	1	1	4	1	-	2
Gram-positive species :	2	1	1	8	2	16	4
S.epidermidis :	-	-	-	-	-	6	1
MRSA :	-	-	-	3	-	-	1
MRSE :	-	-	-	1	-	-	1
Enterococcus :	2	1	1	4	1	10	1
C.albicans :	12	8	4	4	1	-	1

Admi = Admission, Elim = Elimination, Pers = persistance, Acqu = Acquisition, Reap = Reappearance, New = Newly cultured, Not = Not cultured

S.: Staphylococcus, C.: Candida

A possible reason for unsuccessful decontamination was the inadequate use of SD-medication in 20 episodes, in which amongst others the oropharyngeal paste was omitted in 2 and not applied around the tracheostomy in 3 episodes. Selective decontamination was inadvertently ceased for a short time in another 2 episodes but with the renewed start PPM could again be eliminated in both patients. In 11 episodes SD-medication was initiated too late, in 2 it was applied too short. Other failures occurred in episodes where patients suffered from primary respiratory insufficiency (5), were unconscious or had other neurological injuries (10), had a bronchopleural (1) or oesophagotracheal (1) fistula or had to be reintubated (3). In 9 episodes no possible interrelated conditions could be recovered. SD-medication

was discontinued because of these failures in 7 episodes (5%), including 4 because of colonization with resistant micro-organisms. In 3 other episodes colonization with a MRSA followed after the introduction and spread of this strain by a transferred patient, SD-medication was however not discontinued to protect these patients from further gram-negative colonization.

Rebound colonization

Inventory cultures following the withdrawal of SD-medication could be obtained in 90 of the 105 successful episodes and in 33 of the 49 unsuccessful episodes, the remaining 31 were not available because of mortality during the period that selective decontamination was administrated (24 patients) or premature discharge before cultures could be done. Of these cultures, 20 out of 90 successfully decontaminated episodes (22%) showed rebound colonization with pathogenic micro-organisms. Out of the 33 unsuccessfully episodes 19 showed the same micro-organism that was responsible for the colonization during the period of administration of SD-medication while 14 (42%) revealed no growth of PPM. Thus, in 84 of the 123 episodes (68%) a complete colonization with pre-admission strains was encountered.

The microbiological features are shown in Table 7.3 and 7.4; noteworthy is that 2 (8%) of all gram-negative bacilli eliminated from the oropharynx and 9 (16%) of those from the gut reappeared in these cultures. Furthermore, 16 oropharyngeal and 44 rectal strains were newly cultured. On the contrary, 12 of 31 gram-negative strains persisting or acquired in the oropharynx (39%) and 15 of 54 rectal strains (28%) were no longer cultured. There were no infections due to rebound colonization.

Resistance

On admission 4 transferred patients had 7 resistant micro-organisms in their inventory cultures, of which 6 persisted. During the use of selective decontamination, colonization with 25 resistant strains was encountered in 13 episodes (10%). These strains included 4 originally sensitive *Pseudomonas* and 1 *Klebsiella* sp. which developed resistance to norfloxacine (3), tobramycin (2) and co-clavulanic

acid/ticarcillin (3). 7 periods failed solely because of this resistance, in 4 the SD-medication was discontinued. Resistant micro-organisms were the cause for 10 superinfections. In 11 of these 13 episodes no resistant strain could be recovered in the epidemiological cultures after selective decontamination, in 2 they continued to be present.

Epidemiological evaluation of 119 positive cultures from 82 patients revealed 8 patients (9,8%) with 10 strains resistant to aminoglycosides (7), third generation cephalosporins and aminoglycosides (2) and quinolones (3), as well as 3 MRSE and 2 MRSA strains. 6 of these 8 patients showed newly cultured resistant bacteria while 2 were patients from the 13 who already acquired resistance during SD, showing the same resistant micro-organism.

7.4 Discussion

In the present study rebound gram-negative colonization following discontinuation of SD-medication was encountered in 22% of the successfully decontaminated patients without serious infections, while a 10% resistance-rate was found. Rebound colonization with gram-negative micro-organisms can be potentially hazardous in granulocytopenic patients who are totally decontaminated, as described in the haemato-oncological literature[3,24-25]. These immunocompromised patients lack an adequate (microbiological) colonization resistance, so unopposed bacterial acquisition after discontinuing all antibiotics will easily result in life-threatening colonization and infection. Theoretically, this should be a minor problem in selective decontamination, because the indigenous anaerobic gut-flora thought responsible for colonization resistance is unaffected and therefore prevents an overgrowth with aerobic gram-negative bacilli. However, rebound colonization after discontinuation of SD-medication has been described in mice by Speekenbrink and colleagues[16], who reintroduced mice after discontinuation of SD-medication in an untreated population. They saw a substantial increase in total aerobic counts in treated but also in untreated mice. Previously, we found a substantial gram-

negative colonization (41% of patients) following the withdrawal of SD-medication in patients with late complications after oesophageal resection and reconstruction[15], resulting in 3 gram-negative respiratory tract infections. Probably the discontinuation of SD-medication indiscriminately 10 days after surgery irrespective of the patients condition and thereby ignoring the important detrimental effect of trauma and illness on the defence-mechanisms[26-31] promoted these infectious complications. We extended the period of SD-medication arbitrarily to 5 days after extubation when the normal defences against colonization (normal swallowing and coughing reflexes, ability to have oral intake with normal peristalsis and adequate mobilisation) were presumed to be restored, with the described improved results: most patients regained their "normal" flora (recolonization) while even micro-organisms persisting during selective decontamination have disappeared. Consequently, the danger of these patients being reservoirs of nosocomial pathogens for years after hospitalisation seems to be less dangerous than described by others[18-20]. In contrast to the increase in resistance to cefotaxime found by Eastaway[32] our resistance-rate of 10% in cultures after SD-medication is in accordance with the 8% found in control-patients during the previous study[15]. This resistance should however be subject of constant surveillance since it was still the cause for 7 failures.

An interesting aspect is the reappearance of several micro-organisms after the discontinuation of SD-medication indicating only a suppression of micro-organisms (no elimination) and that oropharyngeal decontamination seems to be difficult. This is perhaps due to the presence of foreign material (endotracheal and nasogastric tubes) or to the possible difficulties to bring the active antimicrobials to their place of action; the mucosa. Also the problem of possibly resistant micro-organisms persisting in transferred patients is actual, and stresses the importance of infection-control practice also after surveillance-cultures are known.

In conclusion, rebound colonization after withdrawal of SD-medication seems to offer no problem when the medication is continued until 5 days after extubation in patients with adequate decontamination. This indicates an intact and functional colonization resistance after cessation of SD-medication which prevents the patient

from persistence or new acquisition of resistant strains: the pre-antibiotic endogenous flora is restored in most patients. We advice to stop SD-medication 5 days after extubation when the normal defence-mechanisms are presumed to be restored.

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PART C

GENERAL DISCUSSION AND SUMMARY

Chapter 8

GENERAL DISCUSSION AND SUMMARY

8.1 Introduction

Selective decontamination, at first applied to reduce the number of fever periods in patients with granulocytopenia[1], has been in the centre of interest in intensive care medicine since the application of this prophylactic regimen in trauma patients by Stoutenbeek and colleagues[2]. They described promising results, however in a study using historical, consecutive controls. This base-line study raised several questions, amongst others what influence was present from the systemic antimicrobials in this regimen[3], an item still the cause for continuing debate. To solve this, as well as questions concerning the efficacy of selective decontamination in reducing infectious complications in certain patient groups, several studies were conducted in the mid-80's. The main problem in these studies was the heterogeneity in patient groups, a problem particularly true for patient populations in the intensive care unit.

We identified the group of patients with oesophageal carcinoma, admitted to have a one-stage resection and reconstruction as such a homogeneous group of patients and decided to enrol them in a prospective, randomised study[4] since they have high risk to develop postoperative pulmonary tract infections (chapter 1). The selection of this patient group rendered several additional advantages when compared to other studies using mixed patient groups. Firstly we were able to install selective decontamination already pre-operatively because of the elective procedure, thus resulting in an effective decontamination on the day of operation in 93% of the patients (chapter 5). As a consequence we could discontinue all systemic prophylactic antibiotics directly upon admission to the ICU, knowing that this part of the prophylaxis was intended to treat possible incubating "community acquired" infections and to prevent colonization during the first days in which selective decontamination is not yet installed[2]. This has important epidemiological consequences because antibiotic pressure on the ward with the highest risk on the transfer of resistance[5-7] is consequently diminished. Results showed a highly significant decrease in antibiotic days in patients with successful selective decontamination, including both prophylactically and therapeutically used antibiotics (chapter 6). Moreover a 50% reduction was found in the number of

patients receiving therapeutic antibiotics (chapter 4). Accordingly, no increase in resistance was encountered during the last 6 years of experience with selective decontamination (chapter 5 and 7).

8.2 Selective decontamination and morbidity

The first prospective, randomised study published was that of Kerver and colleagues[8]. They studied mechanically ventilated surgical patients, predominantly those admitted after multiple trauma, and reported a significant decrease in the number of pulmonary tract infections and intra-abdominal abscesses, as well as in the number of septicemias. We found beneficial effects in major elective surgery (chapter 4), and until now at least 14 randomised studies[4,8-20] of which 5 have been conducted in a double blind, placebo controlled design[11-13,16,20] have reported a statistically significant decrease in gram-negative colonization and infection rates in the group with selective decontamination (chapter 3). On the contrary, 4 other randomised studies[21-24] (3 were double blind, placebo controlled[21,23-24]) could not find such a beneficial effect of this prophylaxis, although both Hammond and Gastinne[23-24] did find a significant decrease in the number of gram-negative infections in their study group. The absence of an overall effect is probably at least partly due to the population studied, since most of the studies which reported benefit showed a majority of surgical patients in both groups, while 3 of these 4 inconclusive studies included predominantly medical patients. The fourth study[21] did show a decrease in the number of (gram-negative and gram-positive) infections as well as in the number of infected patients using norfloxacine and nystatin enterally, but this could not reach significance possibly because their surgical patient group was small and very heterogeneous. Although this heterogeneity applies for almost every study being conducted in the ICU, the influence of diagnostic categories on outcome[25] has probably more implications for the comparability between groups in studies with a variety of medical or neurological admissions, such as the studies of Gastinne et al.[23] and Hammond and colleagues[24]. The study of Gastinne[23] was furthermore a multicentre one and included

44 resp. 45% transferrals in both groups, which is an extra factor compromising comparability. Patients in both groups in the study of Hammond et al.[24] additionally received parenteral cefotaxime for 72 hours, which can possibly dilute an effect of selective decontamination. This illustrates that not only the patient population but also the used regimen should always be taken into account when studies are to be designed. Nevertheless, despite the shortcomings in design of several studies there may be an existent difference between surgical and medical patients which is responsible for the different effects on infection rates.

The increase in gram-positive colonization using selective decontamination has until now not been followed by an increase in gram-positive infections, except for the studies of Gastinne[23] and Hammond[24]. When apparent, these infections are however easily treated with current antimicrobials.

8.3 Selective decontamination and mortality

Effects of selective decontamination on survival are not nearly as pronounced as effects on morbidity (chapter 3). One known study with mortality as an endpoint was that of Gastinne et al.[22] which could not detect any effect of selective decontamination but had several drawbacks in design (paragraph 8.2), and another study[20] showed a significant decrease in overall and infection related mortality. They however encountered a considerable increase in resistance against cefotaxime and tobramycin. Blair[17] applied pre-randomised stratification to APACHE II scores, and saw a decrease in mortality in the SD-medicated group with scores between 10 and 19 which was nearly significant ($p = 0.07$). One historical[26] and two randomised[9,14] studies showed a significant decrease in overall mortality although the results in the former[26] were obscured by the simultaneous use of H_2-blockers and sucralfate in different subgroups, and in the Ulrich study[9] antibiotics were given already when colonization was encountered in SD-receiving patients only. Other studies did find beneficial effects on survival, but only in subgroups such as polytrauma[27], surgical patients with infections[8] or septicemia[9], with long term ICU-admission[11], or undergoing cardiac surgery[12]. It is however striking that

most studies reporting an effect on survival regard surgical patients. Effects in medical patients are until now not evident, possibly because of the influence of their underlying illness on mortality[28].

Why should mortality be unchanged when effects on morbidity are so profound, remembering the close relationship between infections and mortality? Since mortality in our group of oesophageal resections was only 5%, no conclusion on mortality effects could be drawn from our first study (chapter 4). To clarify this problem, we conducted a follow up study in which we identified a group of patients receiving selective decontamination without success, experiencing more infections, higher mortality and longer admissions compared to successfully decontaminated patients (chapter 6). We thought that this could be a possible explanation for the obscurity in mortality effects of selective decontamination. We also recognised that no study until then could include enough ICU admitted patients with homogeneous disease to detect possible effects of selective decontamination on survival in a randomised study. At the first international consensus conference in Paris[29], it was calculated that at least 2000 patients were needed in each treatment arm to detect such a difference, given a baseline infection related mortality of 30-35% and a 10-20% effect of selective decontamination. Interestingly, such a difference was indeed measured in a meta-analysis including approximately 4000 patients from 22 controlled randomised studies[30]. To bypass the problems of heterogeneity and numbers of patients, we thought the best way to study the effects on mortality was to characterise all eligible, primary admitted patients by calculating their predicted death rate. Until now, this is the best known method to characterise patients in terms of "severity of illness" (chapter 6) and it can be valuable in determining possible beneficial effects of new therapeutic or prophylactic regimen by comparing actual death rates with these calculated ones; patients serve as their own controls.

In both ways, effects of successful selective decontamination on mortality were highly significant, and this is therefore a strong indication for the beneficial effects of (successful) selective decontamination (chapter 6). The subgroup of

patients experiencing unsuccessful selective decontamination on the other hand might be responsible for the obscurity in effects on mortality in studies until now because they could have diluted effects on overall mortality in the total group of patients receiving SD-medication.

8.4 Selective decontamination; where, how and who

There is much debate concerning the necessity of the different components in the regimen, because different combinations of antibiotics rendered sometimes contradicting results. Early studies have used systemic antibiotics to protect patients against primary infection[3], while others have reported a significant decrease in the frequency of pneumonia with oropharyngeal[13] or enteral application alone [11,14]. However, there is often no clear information about[13], or no difference in[11] the total number of infected patients, or information is incomplete about the therapeutic use of systemic antibiotics in the first days[11].

Parenteral antibiotics

We think that parenteral antibiotics other than those used in the routine surgical wound prophylaxis on the day of operation are superfluous in our elective surgery patients. Selective decontamination in itself can lower the rate of wound infections, but is insufficient to abolish them because this prophylaxis can lower endogenous gram-negative contamination, influencing the exogenous contamination only by reducing the number of colonised patients thereby reducing the load of PPM. To prevent wound infections, additional measures must be included such as systemic antibiotics peri-operative or antibiotics suitable for selective decontamination but also reaching efficient tissue-levels such as quinolones[31]. Systemic antibiotics as an additive in selective decontamination are needed in acutely admitted patients only when infections are suspected during the time that SD is not yet established. Konrad et al.[32] proposed a throat swab to determine whether systemic antibiotics were needed; these were given when PPM's were cultured.

Oropharyngeal and enteral antibiotics

The oropharyngeal part seems necessary to interrupt the sequence of oropharyngeal colonization and subsequent pulmonary tract infections, the enteral component is in our opinion needed to prevent the development of resistance in the reservoir of micro-organisms in the digestive tract. We oppose to the prophylactic use of vancomycin as reported by Pugin[16] because any resistance developing against this antimicrobial agent will leave us empty-handed, and gram-positive infections are until now of minor concern in our population.

Selective decontamination, when

As has been discussed in chapter 4 and 6 it is desirable to start SD-medication as early as possible to achieve successful decontamination since these successfully decontaminated patients seem to benefit most. This is in accordance with Langer et al[33] who thought only measures taken in the first days would reduce the incidence of ICU acquired pneumonia. SD-medication can be discontinued when defences to counteract colonization have been restored (chapter 7) or when selective decontamination has failed.

Surveillance cultures

Surveillance cultures are in our opinion an essential part of selective decontamination, not only to detect possible resistance, but even more importantly to see whether patients become successfully decontaminated and to guide possible therapeutic interventions in the future.

Selective decontamination, to whom

Which patients in the ICU will benefit from selective decontamination and should therefore receive this prophylaxis. In the literature, differences seem to be more pronounced when surgical patients are studied; in a cross-over study the surgical ICU showed better results than the medical ICU[12], and when mortality is used as a criterium for effectivity only surgical patients seem to have better survival until now[8-9,12,14,17,27]. Patients after trauma and those with long stays in the ICU may benefit[8,11,14,27], as well as surgical patients undergoing major procedures in which

the normal anatomy is altered (e.g. oesophageal resection[4]) or in whom defence mechanisms are minimal (e.g. after liver or bone marrow transplantation) so complications are apt to occur[18,34,35]. These patients can have optimal advantage by installing selective decontamination already preoperatively. The use of selective decontamination in patients who have acute necrotising pancreatitis is currently under investigation in a national multicentre trial.

Can we identify those ICU admitted patients who will be at risk to develop infections and will therefore benefit from selective decontamination? This should be no problem in patients with known risk factors (**chapter 2**) but it can be very difficult in acutely admitted patients in whom the further clinical course is unclear. Moreover, can we identify patients who will fail to become selectively decontaminated beforehand? This would offer us the possibility to determine whether a given patient will benefit from selective decontamination and, if not, whether these apparently very ill patients will respond to any other therapy. Further analysis will possibly identify risk factors for unsuccessful selective decontamination and give us either manageable features for the prevention of failure, or perhaps provide us with a sensitive predictor of survival.

8.5 Conclusions

Selective decontamination is a safe method to reduce gram-negative colonization and infections in critically ill patients undergoing major elective surgical procedures. It is desirable to start SD-medication pre-operative in well-defined patient-groups, at risk to develop gram-negative infections because of preëxistent risk-factors, or as a result of the planned operation. SD-medication can be discontinued 5 days after extubation when colonization resistance has normalised, and seems useless when selective decontamination has failed. The period of 5 days is chosen on clinical grounds and has proven to be satisfactory. When successful selective decontamination has been established it is beneficial for the patient in terms of morbidity and survival, for the hospital in terms of epidemiology since the overall use of systemic antimicrobial agents is significantly decreased, and for the community since admission is shorter and costs can be expected to diminish.

8.6 References

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Hoofdstuk 9

ALGEMENE DISCUSSIE EN SAMENVATTING

9.1 Introductie

Levensondersteunende technieken op de Intensive Care Unit (ICU) zijn verantwoordelijk voor het toenemend aantal technisch moeilijke procedures bij steeds oudere patienten, maar kunnen voor diezelfde patient een ernstige bedreiging vormen door de aantasting van de afweer. Grote chirurgische ingrepen worden daarom veelvuldig gecompliceerd door nosocomiale infecties (infecties veroorzaakt door voornamelijk gram-negatieve ziekenhuisbacterien), die moeilijk te bestrijden zijn en een hoge mortaliteit veroorzaken (**hoofdstuk 2**). Om die reden hoort infectieprevention volledig verweven te zijn met de intensive care geneeskunde.

Tot op heden hebben alle maatregelen ter voorkoming van exogene besmetting zoals isolatie en infectie preventie protocollen niet geresulteerd in een volledige preventie van infecties. De bevinding dat veel infecties ontstaan na endogene besmetting met bacterien uit de eigen tractus digestivus maakte de weg vrij voor preventie-programma's met behulp van antibiotica om dit endogene reservoir te elimineren, maar deze resulteerden vaak in het ontstaan van resistente micro-organismen (**hoofdstuk 3**).

Selectieve decontaminatie (SD) is een combinatie van enteraal in hoge doseringen gegeven, niet absorbeerbare antibiotica die werkzaam zijn tegen aerobe, gram-negatieve micro-organismen terwijl de anaerobe microflora zoveel mogelijk onaangetast blijft (**hoofdstuk 3**). In de oncologie is dit al lange tijd een geaccepteerde vorm van antibiotische profylaxe om het aantal koortsperioden in patienten met granulocytopenie te verminderen[1]. Het gebruik van deze profylaxe bij ernstig zieke patienten op de ICU kwam door de studie van Stoutenbeek en collega's in het middelpunt van de belangstelling te staan, omdat zij een sterke vermindering zagen van het aantal infecties in een groep polytrauma patienten[2]. Aangezien zij historische controles gebruikten, en met name het aantal luchtweginfecties pas verminderde na toevoeging van parenterale antibiotica[3] werden in de tachtiger jaren andere studies opgezet om het effect van selectieve decontaminatie te onderzoeken. Het grootste probleem was daarbij om goed vergelijkbare patientengroepen te vinden zodat een statistisch verantwoorde, gerandomiseerde studie kon worden opgezet, een probleem wat vooral groot is bij patienten in de intensive care unit.

De groep patienten met een slokdarmcarcinoom die op onze afdeling worden opgenomen om een resectie van de oesophagus met buismaagreconstructie te ondergaan hebben een groot risico om een luchtweginfectie te ontwikkelen (**hoofdstuk 1**). Omdat deze groep patienten zeer homogeen is, de patienten eenzelfde basisaandoening hebben en een gestandaardiseerd trauma ondergaan is deze groep bij uitstek geschikt om gerandomiseerd te bestuderen ten aanzien van de effecten van selectieve decontaminatie[4]. Een bijkomend voordeel van de electieve ingreep is dat selectieve decontaminatie al pre-operatief kan worden geinstalleerd met als resultaat dat 93% van de patienten effectief gedecontamineerd bleek op de operatiedag (**hoofdstuk 5**). Als gevolg daarvan kunnen alle profylactische, parenterale antibiotica in deze patienten na de operatie gestaakt worden en dat is een gunstige ontwikkeling gezien het feit dat de ICU de afdeling is waar de meeste kans bestaat op ontstaan en verspreiding van resistentie tegen de gangbare antibiotica[5-7]. Zelfs inclusief de profylactisch gebruikte antibiotica vertoonde de groep met effectieve decontaminatie een significante daling in het aantal dagen dat parenterale antibiotica gebruikt werden (**hoofdstuk 6**), en werd een 50% reductie gevonden van het aantal patienten die parenterale antibiotica therapeutisch nodig hadden (**hoofdstuk 4**), waardoor duidelijk is geïllustreerd dat de antibiotische druk is verminderd. Er werd geen toename gevonden van resistente micro-organismen gedurende de 6 jaren van ervaring met deze profylaxe (**hoofdstuk 5 en 7**).

9.2 Selectieve decontaminatie en morbiditeit

De groep van Kerver[8] was de eerste die een gerandomiseerde studie publiceerde over het gebruik van SD-medicatie in voornamelijk multitrauma patienten, en daarin een significante daling van luchtweginfecties, intra-abdominale abcessen en septische perioden meldde. Wij vonden eveneens positieve effecten van selectieve decontaminatie bij patienten die grote, electief chirurgische procedures ondergaan (**hoofdstuk 4**) en tot op heden zijn ons 14 gerandomiseerde studies bekend[4,8-20] die

een significante daling van infecties in de studiegroep vinden; 5 daarvan waren dubbelblind, placebo gecontroleerd[11-13,16,20] (**hoofdstuk 3**). Aan de andere kant zijn er ook 4 studies die geen effect op infectiepercentages konden aantonen[21-24], alhoewel Hammond en Gastinne beiden een daling van het aantal gram-negatieve infecties lieten zien[23-24]. De afwezigheid van een effect is waarschijnlijk deels te wijten aan de bestudeerde populatie, omdat 3 van deze 4 studies met name niet-chirurgische patienten met interne aandoeningen als studiegroep gebruikten, terwijl de meeste studies met aantoonbaar effect van selectieve decontaminatie voornamelijk chirurgische patienten bestudeerden. De vierde studie[21] liet wel een daling van het aantal (gram-negatieve én -positieve) infecties en het aantal geinfecteerde patienten zien. Deze daling was echter niet significant, wat mogelijk te wijten was aan hun kleine, heterogene groep chirurgische patienten. Deze heterogeniteit van patienten is met name van belang voor de vergelijkbaarheid van groepen wanneer patienten uit meerdere diagnostische categorieën samengevoegd worden, zoals in de studies van Hammond[24] en Gastinne[23]. Daarnaast was de studie van Gastinne[23] een multicentrische studie met alle nadelen van dien en was meer dan 40% van de patienten overgeplaatst uit andere centra, waardoor de vergelijkbaarheid van beide groepen nog extra in gevaar komt. Tot slot kregen beide groepen in de studie van Hammond[24] voor niet minder dan 72 uur systemisch cefotaxime toegediend, wat mogelijke gevolgen heeft gehad voor de gemeten infectie percentages. Dit illustreert tevens dat het gebruikte schema altijd kritisch moet worden bekeken wanneer een nieuwe studie wordt gepresenteerd. Ondanks de tekortkomingen in de studie opzet van enkele studies, kán er een verschil bestaan tussen chirurgische en niet-chirurgische patienten waardoor de verschillende effecten op infectie percentages ontstaan.

De toename in gram-positieve colonisatie tijdens het gebruik van selectieve decontaminatie is tot op heden nog niet gevolgd door een toename in gram-positieve infecties, behalve die gemeld in de studies van Gastinne en Hammond[23-24]. Wanneer gram-positieve infecties ontstaan zijn deze echter makkelijk met de gangbare antibiotica te behandelen.

9.3 Selectieve decontaminatie en mortaliteit

De effecten van selectieve decontaminatie op de mortaliteit komen nog niet zo overtuigend over als die op de morbiditeit (**hoofdstuk 3**). De enige studie die mortaliteit als eindpunt definieerde[23] zag geen enkel effect van SD-medicatie maar had zoals vermeld in paragraaf 9.2 vele tekortkomingen. Rocha et al.[20] rapporteerden een significante daling van de totale zowel als van de infectie gerelateerde mortaliteit maar meldden ook een toename van resistentie tegen cefotaxime en tobramycine. Blair[17] stratificeerde zijn patientengroep vooraf naar APACHE II score, en zag een bijna significante daling van de mortaliteit in de groep met APACHE scores tussen de 10 en 19 ($p = 0.07$). Slechts één studie met historische controles[25] en twee gerandomiseerde studies[9,14] vermeldden een significante daling van de mortaliteit. De resultaten in de eerste studie werden echter verstoord door het simultane gebruik van H_2-blokkeerders en sucralfaat in verschillende subgroepen[25], en in de studie van Ulrich[9] werd colonisatie alleen in de studiegroep "behandeld" met antibiotica. Een aantal andere studies vonden een significante daling van de sterfte in subgroepen zoals chirurgische patienten met multitrauma[26], infecties[8] of sepsis[9], langdurig op de intensive care opgenomen patienten[11] of patienten na cardiovasculaire chirurgie[12]. Het is echter wel opvallend dat wanneer een gunstig effect wordt gerapporteerd, dit altijd in een chirurgische groep patienten blijkt op te treden. Effecten bij niet-chirurgische patienten zijn tot op heden nog niet aangetoond, mogelijk ten gevolge van hun onderliggend lijden en de invloed daarvan op de mortaliteit. Een effect van infectie preventie op de mortaliteit kan immers pas meetbaar worden (en dus van nut zijn) als de mortaliteit ten gevolge van het basislijden niet al te hoog is, zoals beschreven door Gross[27].

Waarom is het verschil in mortaliteit zo moeilijk aantoonbaar, terwijl, -de sterke relatie tussen infecties en mortaliteit inachtgenomen-, de effecten op infecties zo duidelijk zijn ? Om deze vraag op te lossen werd een vervolg studie gestart waarin alle patienten met SD-medicatie werden bestudeerd. In deze studie werd een groep patienten herkend die wel SD-medicatie kreeg toegediend, maar niet adequaat gedecontamineerd kon worden. Deze patienten hadden meer infecties, een hogere

mortaliteit en een langere opnameduur ten opzichte van patienten die wél effectief gedecontamineerd konden worden (**hoofdstuk 6**). Wij denken dat deze subgroep waarbij effectieve decontaminatie niet kon worden verkregen verantwoordelijk kan zijn voor de onduidelijke effecten van selectieve decontaminatie op de sterfte binnen de gehele groep patienten.

We realiseerden ons vooraf dat het moeilijk zou zijn voldoende grote aantallen intensive care patienten met vergelijkbare aandoeningen te verzamelen om in een gerandomiseerde studie een uitspraak te kunnen doen omtrent een effect van selectieve decontaminatie op de sterfte. Op de Internationale Consensus Conferentie te Parijs[28] werd berekend dat minstens 2000 patienten per studie-arm nodig zouden zijn voordat een effect zou kunnen worden aangetoond, gegeven een basis mortaliteit van 30 tot 35% en een SD-effect van 10 tot 20%. Het is daarom interessant dat dit effect inderdaad werd aangetroffen in een meta-analyse van 4000 patienten uit 22 gerandomiseerde studies[29]. Om dit probleem van aantal en verscheidenheid van patienten te omzeilen besloten we alle patienten met SD-medicatie te bestuderen, en te karakteriseren via de berekening van hun voorspelde sterftekans door middel van de logistieke regressie formule van Knaus[30] (**hoofdstuk 6**). Voor zover ons bekend is dit de beste formule om patienten te definieren voor wat betreft hun "ernst van ziekte", en kan deze gebruikt worden om effecten van nieuwe prophylactische of therapeutische programma's te bestuderen door de voorspelde percentages te vergelijken met de actuele.

Het effect van selectieve decontaminatie op infectie- en sterfte cijfers was hoog significant in de groep patienten die goed gedecontamineerd kon worden (**hoofdstuk 6**). De subgroep van patienten die niet effectief gedecontamineerd kunnen worden (om wat voor reden dan ook), zijn mogelijk verantwoordelijk voor de tot op vandaag moeilijk te meten effecten van SD-prophylaxe op de sterfte.

9.4 Selectieve decontaminatie, waar, hoe en voor wie

Er is veel discussie omtrent het ideale schema van selectieve decontaminatie omdat veel studies verschillende antibiotica en verschillende componenten gebruikten, met

wisselend resultaat. De eerste studies gebruikten parenterale antibiotica om de patienten tegen vroege infecties te beschermen gedurende de tijd dat selectieve decontaminatie nog niet effectief was[3]. Anderen meldden een significante daling van het aantal luchtweginfecties met oropharyngeale[13] of enterale[11,14] antibiotica alleen, echter zonder duidelijke informatie over het aantal geïnfecteerde patienten[13] of het gebruik van parenterale antibiotica in de eerste dagen[11].

Parenterale antibiotica

Wij denken dat parenterale antibiotica anders dan de routine chirurgische profylaxe op de operatiedag overbodig is voor patienten die electieve chirurgie ondergaan. Selectieve decontaminatie kan op zichzelf het aantal wondinfecties verlagen door vermindering van endogene colonisatie en daardoor van het aantal micro-organismen en "besmettingsbronnen", maar kan nooit alle wondinfecties voorkomen doordat de exogene route door deze profylaxe niet beïnvloed kan worden. Tegen wondinfecties zijn peri-operatief gegeven antibiotica nodig die een adequate weefselspiegel geven ten tijde van de operatie; ofwel parenterale ofwel voor selectieve decontaminatie geschikte antibiotica die ook deels geresorbeerd worden zoals de quinolonen[31]. Bij selectieve decontaminatie zijn parenterale antibiotica ons inziens alleen nodig in acuut opgenomen patienten die verdacht worden van een infectie gedurende de eerste dagen waarin SD nog niet effectief is. Konrad[32] opperde dat bij kweken van PPM van een keelwat afgenomen bij opname systemische antibiotica gegeven zouden kunnen worden.

Oropharyngeale en Enterale antibiotica

Het oropharyngeale deel van selectieve decontaminatie lijkt nodig om de opeenvolging van oropharyngeale colonisatie en luchtweginfecties te kunnen voorkomen, de enterale component tegen wond- en urineweg infecties en mogelijk sepsis; tevens om de ontwikkeling van resistentie binnen het reservoir van micro-organismen in de tractus digestivus te beperken. Ons inziens is het standaard gebruik van vancomycine zoals beschreven door Pugin[16] niet alleen onwenselijk omdat gram-positieve infecties tot op heden goed te behandelen zijn, maar ook

gevaarlijk omdat resistentie ontwikkeling tegen dit middel een probleem op zou leveren bij de behandeling van de methicilline resistente *Staphylococcus* sp.

Selectieve decontaminatie, wanneer

Zoals bediscussieerd in **hoofdstuk 4** en **6** is het wenselijk om SD-medicatie zo vroeg mogelijk te starten om een effectieve selectieve decontaminatie te bereiken, omdat succesvol gedecontamineerde patienten het meeste voordeel hebben. Dit is in overeenstemming met Langer[33] die stelde dat alleen maatregelen genomen in de eerste dagen van opname de incidentie van nosocomiale luchtweginfecties op de ICU zou reduceren. SD-medicatie kan gestopt worden wanneer de afweermechanismen tegen colonisatie en infectie weer zijn genormaliseerd (**hoofdstuk 7**), of wanneer de decontaminatie niet effectief blijkt.

Surveillance kweken

Surveillance kweken zijn een essentieel deel van selectieve decontaminatie, niet alleen om het ontstaan van eventuele resistentie tegen de gangbare antibiotica te onderkennen, maar tevens om te zien of patienten effectief gedecontamineerd zijn en om eventuele therapeutische interventies in de toekomst te bepalen.

Selectieve decontaminatie, bij wie

Welke patienten zullen voordeel hebben bij selectieve decontaminatie en moeten het daarom toegediend krijgen ? De positieve resultaten in de literatuur zijn meer uitgesproken bij chirurgische patienten; in een cross-over studie waren de resultaten binnen de chirurgische ICU beter dan die in de algemene ICU[12] en wanneer de sterfte als effectiviteits criterium wordt gebruikt lijken alleen chirurgische patienten een betere overleving te hebben[8-9,12,14,17,26]. Multitrauma patienten en patienten met een langdurige ICU opname lijken voordeel te hebben[8,11,14,26], zowel als patienten na grote electieve chirurgie waarin de normale anatomie is veranderd (patienten met slokdarmcarcinoom[4]) of die een verminderde afweer hebben door medicatie (levertransplantaties[18,34] en beenmergtransplantaties[35]) zodat gemakkelijk complicaties kunnen ontstaan. Het effect van selectieve

decontaminatie bij patienten met acuut necrotiserende pancreatitis wordt in een nationale multicentrische trial onderzocht.

Kunnen we op de ICU opgenomen patienten die een verhoogd risico hebben op het ontwikkelen van infecties en daarom voordeel kunnen hebben van selectieve decontaminatie vooraf identificeren? Bij patienten met bekende risicofactoren **(hoofdstuk 2)** kan dit positief beantwoord worden, maar bij acuut opgenomen patienten is dat welhaast onmogelijk omdat het verdere klinische beloop onvoorspelbaar is. Zouden we tevens vooraf kunnen bepalen wie succesvol gedecontamineerd zou kunnen worden, dan zou dat een mogelijkheid bieden om vooraf te bepalen wie voordeel heeft van deze profylaxe en wie niet. Dat laatste zou een aanwijzing kunnen zijn dat de betreffende patient zo ernstig ziek is dat hij of zij op geen enkele therapie meer zal reageren. Een verdere analyse zal mogelijke risicofactoren voor onsuccesvolle decontaminatie aan kunnen geven en ons dus een handvat geven voor de preventie van falende selectieve decontaminatie, of ons een predictor van overleving aan de hand doen.

9.5 Conclusie

Selectieve decontaminatie is een veilige methode om gram-negatieve colonisatie en infecties te voorkomen bij ernstig zieke patienten die grote, electief chirurgische procedures ondergaan. Het is wenselijk SD-medicatie zo vroeg mogelijk te starten in goed gedefinieerde patienten groepen die een groot risico hebben op het ontwikkelen van gram-negatieve infecties op basis van preexistente risicofactoren of als gevolg van de geplande operatie. SD-medicatie kan 5 dagen na extubatie gestaakt worden wanneer de colonisatie resistentie zich heeft genormaliseerd, en lijkt van geen nut wanneer een poging tot effectieve decontaminatie geen succes heeft gehad. De periode van 5 dagen is op klinische gronden gekozen en lijkt te voldoen. Wanneer succesvolle selectieve decontaminatie kan worden bereikt is dat van groot voordeel voor de patient gezien de effecten op morbiditeit en overleving, voor het ziekenhuis omdat het gebruik van parenterale antibiotica significant lager is en voor de gemeenschap omdat de opnameduur korter is en de kosten verwacht kunnen worden te dalen.

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