Selective decontamination of the digestive tract in elective gastrointestinal surgery
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Introduction and outline of the thesis
INTRODUCTION

Colorectal surgery is associated with a high risk of postoperative infection due to contamination by bacteria in the large intestine. These postoperative infectious complications increase hospital stay and costs of treatment.\(^1\) Despite the use of perioperative antibiotic prophylaxis, improvements in surgical techniques and peri-operative care, the complication rate and surgical site infections (SSI) after abdominal surgery and especially colorectal procedures, remains high (30-51 %).\(^2-5\)

The most common infectious complications after surgery are urinary tract, wound and pulmonary infections. These hospital acquired infections or nosocomial infections occur in 4-7% of patients and are defined as infections who arise after 48 hours after hospital admission. In 90% this infection is caused by bacteria, mostly aerobe Gram-negative micro-organisms,\(^6,7\) only in 10% by virusses, fungi and parasites. If an infection occurs within the first 48 hours of admission, it is called a community acquired infection and is highly influenced by the carrier state of the patient and its department (e.g. oncology or dermatology). These Gram-negative infections generally originate from the patient’s digestive tract.

The gut micro flora forms a diverse and complex ecological community of more than 100 trillion microorganisms. There are about 500-1000 different species. They play a role in collecting energy from the fermentation of undigested carbohydrates and absorption of short chain fatty acids but also in producing vitamins (B and K) and hormones,\(^8,9\) influence the gut and systemic immune systems and preventing growth of potentially pathogenic bacteria.\(^10\) Gut micro flora is mainly composed by three enterotypes: *Prevotella, Bacteroides* and *Ruminococcus*.\(^11\) There are functional differences between these enterotypes, for instance in producing vitamins and nutrients.

<table>
<thead>
<tr>
<th>Oropharyngeal cavity</th>
<th>Concentration per ml saliva</th>
<th>Gastro-intestinal tract</th>
<th>Concentration per gram faeces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaerobic bacteria</td>
<td>(10^7)</td>
<td>Anaerobic bacteria</td>
<td>(10^{11})</td>
</tr>
<tr>
<td>Aerobic bacteria</td>
<td></td>
<td>Aerobic bacteria</td>
<td></td>
</tr>
<tr>
<td>-Streptococcus viridans</td>
<td>(10^{3-7})</td>
<td>-Streptococcus faecalis</td>
<td>(10^{5-7})</td>
</tr>
<tr>
<td>-Staphylococcus aureus</td>
<td>(10^3)</td>
<td>-Staphylococcus aureus</td>
<td>(10^3)</td>
</tr>
<tr>
<td>-Streptococcus pneumoniae</td>
<td>(10^3)</td>
<td>-Enterobacteriaceae</td>
<td></td>
</tr>
<tr>
<td>-Haemophilus influenza</td>
<td>(10^3)</td>
<td>Escherichia Coli</td>
<td>(10^{5-7})</td>
</tr>
<tr>
<td>-Enterobacteriaceae</td>
<td>(\leq 10^3)</td>
<td>Klebsiella species</td>
<td>(\leq 10^3)</td>
</tr>
<tr>
<td>-Pseudomonads</td>
<td>(\leq 10^3)</td>
<td>Enterobacter species</td>
<td>(\leq 10^3)</td>
</tr>
<tr>
<td>-Candida albicans</td>
<td>(10^3)</td>
<td>-Pseudomonads</td>
<td>(\leq 10^3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Candida albicans</td>
<td>(10^3)</td>
</tr>
</tbody>
</table>
In the upper gastro-intestinal (GI) tract of adult humans, the esophagus contains only the bacteria swallowed with saliva and food. The esophagus and stomach are not normally colonized by indigenous flora, but from time to time a limited number of transient organisms may be present. Because of the high acidity of the gastric juice, very few bacteria (mainly acid-tolerant lactobacilli, or *Helicobacter pylori*) can be cultured from the normal stomach. The proximal small intestine has little Gram-positive flora, consisting mainly of lactobacilli and Enterococcus faecalis, and can be considered as sterile. Type of bacteria of the digestive tract are mentioned in table 1.

A small percentage (10-40%) of “healthy” individuals carry *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenza* and *Candida albicans* in their oropharynx. The normal intestinal flora contains anaerobe bacteria, *Streptococcus faecalis* and *Escherichia coli*. A small percentage (<20%) is intestinal carrier of *Staphylococcus aureus* and *Candida albicans*. *Klebsiella species, Proteus species* and *Enterobacter species* can also be found in healthy individuals. *Pseudomonadeae* do not belong to the indigenous flora of the digestive tract. The composition of the flora of the gastrointestinal tract varies along the tract (at longitudinal levels) and across the tract (at horizontal levels) where certain bacteria attach to the gastrointestinal epithelium and others occur in the lumen.

In healthy individuals the intestinal microbes form a symbiosis, but when acquired (aerobic) potentially pathogenic micro-organisms (PPMs) colonise the digestive tract, they can cause postoperative infections. When a patient has acquired a PPM, passage or colonisation can occur. Passage is defined as a situation in which the PPM, mainly Gram-negative microorganisms, does not reach a high concentration and is removed of the digestive tract within 6 days.

Colonisation is the development of the pathogen at the appropriate portal of entry, including the urogenital tract, the digestive tract, the respiratory tract and the conjunctiva. If the amount of PPM is high and the colonisation resistance low, an infection can occur. Colonisation resistance is a part of the anti-microbial defense of the host in all tracti coated with epithelium and it is lowered by host associated factors (old age, trauma, surgery) and iatrogenic factors (antibiotics, cytostaticum, drains, intubation), which can cause shifts in population, damage of intestinal mucosa or immunosupression. Especially the anaerobic flora are responsible for the colonisation resistance.

Bacterial translocation is defined as the passage of viable micro-organisms through intact gastro-intestinal mucosa. Particles of bacteria, like endotoxins, can also penetrate (absorption). Type of bacteria, concentration of bacteria, malnutrition and parenteral feeding increase the chance of translocation. Intact anatomy and function of the respiratory, urinary and gastrointestinal tract, helps to prevent adherence of bacteria to epithelium and mucosal cells. A functional gut barrier, coated with mucus, is the first line of defence against enemies who enter the gastrointestinal tract. Furthermore, permeation of endotoxins from the gut into the systemic circulation can cause sepsis if the gut barrier function fails, for example during surgery. This disturbance in digestive flora can lead to bacterial overgrowth (>10⁶ aerobic PPMs).

Microbial pathogenicity has been defined as the structural and biochemical mechanisms whereby microorganisms cause disease. Some microorganisms cause more serious clinical
disease than others. (table 2) Bacteria with low pathogenicity Index (IPI) will seldom be followed by an infection. In total, there are 15 potentially pathogenic micro-organisms that play a role in the concept of carriage.\textsuperscript{13} If the colonisation resistance is intact, there are no Gram-negative bacteria in the oropharynx. However, microbiota of the oropharyngeal cavity, can cause infections of the respiratory tract as the intestinal microbiota are responsible for infections in the urogenital tract. Bacteria from both systems can cause wound infections, depending on the distance of the wound to mouth or anus. In conclusion, the digestive tract is the largest and most important reservoir of (multi resistant) PPMs, mainly Gram- negative strains, and the source of most infections. Colonisation resistance of the digestive tract plays a central part in the development of (endogenous) infections, because if colonisation resistance is sufficient, colonisation of PPMs will not occur.

<table>
<thead>
<tr>
<th>Highly pathogenic IPI = 0.9-1.0</th>
<th>Potentially pathogenic IPI = 0.3-0.6</th>
<th>low to (a) pathogenic IPI = 0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neisseria Meningitidis</td>
<td>S.pneumoniae</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>Salmonella Spp</td>
<td>H.influenza</td>
<td>Proteus</td>
</tr>
<tr>
<td>Moraxella Catarrhalis</td>
<td>Morganella</td>
<td>Enterobacter</td>
</tr>
<tr>
<td>Escherichia Coli</td>
<td>S.aureus</td>
<td>Citrobacter</td>
</tr>
<tr>
<td>Candida Albicans</td>
<td>Serratia</td>
<td>Pseudomonas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acinetobacter Spp</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mrsa</td>
</tr>
</tbody>
</table>

**Table 2** | Pathogenicity of microorganisms.

IPI = intrinsic pathogenicity index  
MRSA = Methicillin-resistant S. aureus

**ANTIBIOTICS**

Prophylactic perioperative intravenous antibiotics are standard use in gastro-intestinal surgery because of the high risk of SSI.\textsuperscript{14} The prophylaxis must cover both aerobic and anaerobic bacteria with minimal toxicity and costs. A recent Cochrane analysis showed a significant reduction in surgical wound infections when prophylactic systemic antibiotics with aerobic and anaerobic coverage were used compared to placebo, with a statistically significant benefit in favor of antibiotic prophylaxis with a variety of antibiotics (RR 0.30, 95% CI 0.22 to 0.41 (P < 0.00001)), reducing the overall SWI rate from 39% to 10%. No statistically significant differences were found when comparing short- and long term duration of prophylaxis or single dose versus multiple dose antibiotics. Combined oral and intravenous antibiotic prophylaxis showed statistically significant improvements in SWI.
rates when compared to intravenous alone (RR 0.55, 95% CI 0.41 to 0.74) in 13 trials with 2362 patients. In conclusion, when oral antibiotics were combined with intravenous antibiotic prophylaxis, the risk of surgical site infections (SSI) was 75% lower than with intravenous antibiotics alone.\textsuperscript{15}

Schardey \textit{et al.} demonstrated that the addition of oral antibiotics in upper GI surgery to standard perioperative intravenous antibiotics, reduced postoperative infectious complications (from 44.7% in the placebo group to 30.4% in the SDD group) as well as anastomotic leakage (10.6% to 2.9% ($p = 0.0492$)).\textsuperscript{16}

\textbf{The principle of Selective decontamination of the digestive tract}

The use of oral antibiotics on top of systemic antibiotic treatment, was introduced into intensive care medicine by Chris Stoutenbeek in 1984 as an infection-prophylaxis regimen to reduce or even eradicate aerobic PPMs, from oro-pharynx to rectum, while leaving the normal anaerobic flora, who are responsible for maintaining a sufficient colonisation resistance, largely undisturbed.\textsuperscript{17,18}

It was called selective decontamination of the digestive tract (SDD) and consisted of a topical, non-absorbable, antibiotic combination of Polymixin E (Colistin\textsuperscript{®}), Tobramycin and Amphotericin B (Fungizone), which was taken orally, four times daily. Polymixin eradicates Gram-negative rods, for instance \textit{Pseudomonas aeruginosa}. Tobramycin is an aminoglycoside against aerobic Gram-negative bacteria (Proteus, \textit{Pseudomonas}, \textit{Salmonella}, \textit{Shigella}, \textit{Klebsiella}, \textit{Serratia}, \textit{Enterobacter} and \textit{Escherichia coli}) and some staphylococcus species (\textit{Staphylococcus aureus}). Amphotericin B is a polyene antibiotic (obtained from a strain of \textit{Streptomyces nodosus}) which kills fungi and yeasts and works especially against \textit{Candida albicans}, \textit{Cryptococcus neoformans}, \textit{Histoplasma capsulatum} and \textit{Coccidioides immitis}, but not against bacteria or viruses. All components have hardly any uptake into the systemic circulation. Decontamination of the oropharynx was accomplished by using a sticky paste called Orabase\textsuperscript{®}, which contained polymyxin E 2%, Tobramycin 2% and Amphotericin B 2% with sodium carboxymethylcellulose base. It is used in critically ill patients, admitted to the intensive care unit (ICU) because generally in those patients there is a connection between the airway and the environment by intubation and/or the impossibility to swallow and therefore the absence of normal barrier function of both respiratory and digestive tract. On the ICU, the classical SDD strategy consists of four components, including systemic antibiotics to control primary endogenous infections, high level of hygiene to control exogenous infections, surveillance samples to monitor efficacy of treatment and of course the SDD to prevent secondary carriage and subsequent endogenous infections.\textsuperscript{19,20}

The use of SDD for the critically ill patients on an ICU has been extensively assessed in literature. A systematic review with over 8000 patients, showed that SDD significantly reduced overall bloodstream infections (OR, 0.73; 95% CI 0.59 - 0.90; $P = 0.0036$), Gram-negative bloodstream infections (OR, 0.39; 95% CI, 0.24 - 0.63; $P < 0.001$) and overall mortality (OR, 0.80; 95% CI, 0.69 - 0.94; $P = 0.0064$) in critically ill patients admitted to the ICU.\textsuperscript{21} The positive effect of SDD was reconfirmed by Liberati \textit{et al} in 2009. They conducted a Cochrane analysis of trials on patients admitted to the ICU, comparing a combination of
topical and systemic antibiotics. There was a significant reduction in both respiratory tract infections (number of studies = 16, OR 0.28, 95% CI 0.20 to 0.38) and total mortality (number of studies = 17, OR 0.75, 95% CI 0.65 to 0.87) in the treated group. In 15 years and over 5000 patients, no resistance has been seen against the antibiotics used in SDD.23,24

In 1990, Stoutenbeek advocated the use of SDD as a peri-operative infection prophylaxis in elective surgery25,26 including oesophagectomy27 and gastrectomy16. A randomized controlled trial comparing one gift of oral ciprofloxacin 500 mg on the day before surgery versus no oral therapy in elective colorectal surgery, demonstrated fewer postoperative complications. Postoperative wound infections occurred in 18 (11.3%) patients in the oral group versus 39 (23.2%) patients in the control group (p = 0.007).28 Encouraged by the good results in our ICU patients population29,30, peri-operative SDD was successfully introduced in the Onze Lieve Vrouwe Gasthuis (OLVG) in Amsterdam in 1999 in elective oesophageal and colorectal surgery on our surgical ward.

From the current literature, one might conclude that SDD decreases infectious complications in critically ill patients, admitted to the ICU. While SDD eliminates the most important source of infections, namely pathogenic bacteria of our own intestinal tract, it could be also indicated when the gut barrier function fails, for example during surgery. In that case, perioperative SDD could prevent postoperative infectious complications caused by translocation of intestinal Gram-negative rods and yeasts. Another possible effect of SDD is the reduction of perioperative endotoxaemia caused by permeation of bacterial compounds through a diminished gut-blood barrier during surgery This may translate into less systemic inflammatory response.31 However, perioperative endotoxemia is specifically studied during cardiac surgery and may be less prevalent during GI surgery, although sometimes reported.12,32

It also has been suggested that the lower rate of anastomotic leakage with SDD is explained by the fact that overgrowth of Gram-negative bacteria may induce mucosal inflammation, abscess formation and necrosis at the suture, and therefore a higher change of anastomotic dehiscence.33

But although SDD seems to decrease respiratory tract infections, bloodstream infections and mortality in the critically ill patients on the ICU34, it is not yet clear if it has the same advantages in “healthy” individuals, who need to undergo elective gastrointestinal surgery. A considerable disadvantage of SDD for instance, is the bitter taste and consequently possible nausea. Patients admitted to the ICU are not fully aware of this bad taste, while they are critically ill and/or intubated and sedated, but elective patients are not and could therefore reject intake. Furthermore, it is not clear how many days before and after surgery a patient must take SDD to achieve optimal decontamination.

The great advantage of SDD however, is that the costs to produce it are low and every hospital can make their own SDD. Therefore SDD seems to be a simple, useful, inexpensive method to prevent postoperative infectious complications, but clinical trials in elective gastro-intestinal surgery are needed to support results and outcome of already published studies on SDD.
OUTLINE OF THE THESIS

Up till now, there is still a need to improve perioperative protocols in patients who need to undergo elective gastro-intestinal surgery, to prevent postoperative infectious complications, while these complications will result in a prolonged hospital stay and high costs. Selective decontamination of the digestive tract is an infection prophylaxis regimen to reduce or even eradicate aerobe PPMs from oro-pharynx to rectum, while leaving the normal anaerobic flora largely undisturbed, thereby reducing the incidence of organ site infections. SDD reduces respiratory tract infections, bloodstream infections and mortality in patients admitted to the ICU. The aim of this thesis was to analyse the effect of perioperative SDD combined with systemic perioperative antibiotics in elective gastrointestinal surgery, on postoperative infectious complications and anastomotic leakage. Furthermore, we hope to give an overview of the clinical applicability of SDD in surgery.

In 1999, SDD was introduced on the surgical ward of the Onze Lieve Vrouwe Gasthuis in Amsterdam. It was given to patients who underwent left sided colorectal surgery. In chapter 2, we performed a retrospective analysis of prospectively collected data. The control group consisted of a historical cohort of patients who were not treated with SDD. We analysed postoperative complications, hospital stay and mortality and tried to identify independent predictors of postoperative complications.

To confirm the results of our retrospective analysis, we performed a randomized, double blinded, placebo controlled clinical trial. In chapter 3 we describe the results of this RCT of patients undergoing elective gastro-intestinal surgery. Patients were classified into 4 groups (A,B,C or D). Group A included patients undergoing esophageal and gastric surgery, group B Hepato-Pancreato-Biliary (HPB) surgery, group C colectomies, and group D rectal resections. Most patients underwent a (partial) colectomy. Endpoints were postoperative infectious complications and anastomotic leakage. Secondary endpoints were mortality and hospital stay.

Although the use of SDD in the ICU is widespread, the use of SDD on the surgical ward is not, according to the literature. In chapter 4 a point prevalence survey was carried out and an online questionnaire was sent to GI surgeons of 86 different hospitals in the Netherlands. The aim of this study was to objectify current application of SDD as well as the use of mechanical bowel preparation and perioperative antibiotics. The cost-effectiveness of SDD on the ICU has been described in literature with lower costs in patients who received SDD. This could be the result of the effect of lower morbidity on hospital stay and the use of systemic antibiotics, combined with the higher amount of survivors. In chapter 5 we describe the costs of patients of our previously mentioned RCT. We compared the costs of patients who received SDD with those who were randomized to placebo treatment. The aim was to analyse if the reduction in postoperative infectious complications lead to lower costs.

To find more evidence to support the conclusions of our randomized trial, we performed a systematic review to determine the effect of SDD in elective gastro-intestinal surgery. The results of our search are presented in chapter 6.
Finally, the aim of the study presented in chapter 7 was to analyze the results of preoperative cultures, peroperative rectal swabs and cultures of postoperative infections after gastrointestinal surgery, in patients who received perioperative SDD and patients with placebo.
REFERENCES


INTRODUCTION AND OUTLINE OF THE THESIS


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