Experimental studies on surgical treatment of peritonitis
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Chapter 1

Introduction
Morbidity and mortality in patients with severe forms of generalized peritonitis are high. Therefore, early control of infection is of utmost importance.

Initially, bacteria and small particles encounter three categories of host defense mechanisms in the peritoneal cavity: (i) removal via diaphragmatic lymphatics, (ii) killing of bacteria by phagocytic cells, and (iii) sequestration by fibrin formation. However, overwhelming inflammation may result in persisting fibrin formation which occludes the lymphatic stomata in the diaphragm. Furthermore, fibrin entraps bacteria which renders them unreachable for phagocytic cells. Moreover, bacteria entrapped in fibrin, as well as shortage of oxygen in the peritoneal fluid and activation of neutrophils, causes extracellular release of neutrophil enzymes which results in continued stimulation of inflammation. Thus, a self-perpetuating inflammatory process in the peritoneal cavity will establish. Absorption of inflammatory mediators into the systemic circulation, causes sepsis, shock, and multiple organ failure which, in turn, augment the severity of the intra-abdominal inflammatory process by decreased visceral blood flow, hypoxia, and translocation of bacteria and endotoxin from the gastro-intestinal tract.

The ideal strategy to be followed in the surgical treatment of generalized fecal peritonitis consists of three stages. First, removal of the source of peritonitis, which is quite obvious. Second, debridement of the peritoneal cavity with the elimination of all microorganisms and adjuvant substances. However, morbidity associated with radical debridement is high, and improved survival is not obvious. Remarkably, no experimental studies concerning the effect of debridement on intra-abdominal bacterial growth or mortality are reported. Despite the widespread use of intra-operative lavage with saline, the experimental results concerning the efficacy are contradictory. Intra-operative lavage with antibiotics has also obtained contradictory support from studies of both experimental and clinical peritonitis. Antiseptics like noxythioline and povidone-iodine have an almost universal bactericidal spectrum, but since they have a short duration of action and since they are toxic, these agents are not commonly used for intra-operative lavage in clinical
are toxic, these agents are not commonly used for intra-operative lavage in clinical practice. Taurolidine, a chemotherapeutic agent, has profound anti-bacterial activity and anti-endotoxic properties, while it suppresses the production of TNF in vitro. In animal studies, however, intra-operative lavage with taurolidine shows no unequivocal bactericidal or anti-endotoxic effect. The third stage in the treatment of generalized peritonitis comprises the prevention of secondary infection of the abdominal cavity. Only limited information about the phenomenon of bacterial translocation, the role of a regimen to selectively decontaminate the digestive tract, and the efficacy of intra-abdominal anti-inflammatory agents, are present. This thesis aims to give more insight in the effect of debridement and intra-operative lavage with saline or taurolidine, and intra-abdominal instillation of taurolidine or imipenem/cilastatin after debridement and lavage with saline, in rats with fecal peritonitis. Furthermore, it tries to answer the question if a regimen of selective decontamination of the digestive tract prevents secondary infection of the abdominal cavity and/or endotoxemia, in rats with sterile peritonitis. It also addresses the question if the phenomenon of bacterial translocation and endotoxin absorption, besides in rats, also occurs in severely ill patients. Finally, it determines the effect of fish oil given intra-peritoneally on the intra-abdominal inflammatory process, and the incidence of MOF in rats with sterile peritonitis.

Chapter 2

Lavage with Tauroline or Saline
To determine the effect of intra-operative lavage with saline solution on survival and on plasma endotoxin level, and to determine if taurolidine has beneficial properties as compared to saline solution, we performed an experimental study in rats with faecal peritonitis. Eighty-nine Wistar rats were injected intra-peritoneally with a faecal suspension, containing B. fragilis $10^4$ cfu and E. coli $10^4$ cfu. They were divided into two treatment and two control groups. The abdominal cavity of the animals in the treatment group were debrided and rinsed by either saline solution or taurolidine. Rats in the control group were either not operated or operated with only debridement of the abdominal cavity. We concluded that intra-operative lavage with saline solution prolongs survival and diminishes plasma endotoxin level as compared to the control groups. We found no additional advantages of taurolidine over saline solution.

Chapter 3

Intra-peritoneal Antimicrobials
We determined the effect of intra-peritoneal instillation of taurolidine or
imipenem/cilastatin on mortality, and on the concentration of bacteria, endotoxin, and tumour necrosis factor (TNF) in rats with intra-peritoneally injected bacteria. Thirty rats were inoculated intra-peritoneally with two enteric bacterial strains, followed by either taurolidine, saline, or imipenem/cilastatin. Abdominal fluid and blood were analysed at different time intervals. The survival rate was highest in the imipenem group. The bacterial concentration in abdominal fluid in the taurolidine and imipenem group was lower than in the saline group, but the concentration in the imipenem group was lowest. The endotoxin concentration in abdominal fluid and plasma in the taurolidine group was lower than in the other two groups. The TNF concentration in abdominal fluid and plasma in the taurolidine group was lower than in the saline group, whereas the concentration in the imipenem group was higher.

We concluded that topically applied taurolidine in rats with intra-peritoneally injected bacteria may have a weak antibacterial effect, and lowers concentrations of endotoxin and TNF. Topically applied imipenem/cilastatin has profound bactericidal activity but induces endotoxin and TNF release.

Chapter 4

Debridement, Lavage, and Intra-peritoneal Antimicrobials

In rats with fecal peritonitis, we studied the effect of intra-abdominal debridement, lavage with saline, and additional intra-abdominal instillation of taurolidine or imipenem/cilastatin on: intra-abdominal bacterial growth, intra-abdominal endotoxin concentration, bacteremia, plasma endotoxin concentration, abscess formation, and mortality. Debridement temporarily diminished bacterial growth and endotoxin level in the abdominal cavity, and delayed mortality. Lavage with saline further diminished bacterial growth and endotoxin level. It also diminished plasma endotoxin level, and mortality. Additional instillation of taurolidine did not lower the bacterial concentration. The abdominal endotoxin level was diminished initially. The plasma endotoxin level was significantly diminished. Instillation of imipenem/cilastatin, after debridement and lavage, significantly lowered all parameters measured.

We concluded that debridement, lavage with saline, and additional instillation of imipenem/cilastatin, all have an accumulatively diminishing effect on bacterial growth, endotoxin levels, abscess formation and mortality in rats with fecal peritonitis. Instillation of taurolidine only diminishes endotoxin levels.

Chapter 5

Prevention of Bacterial Translocation
This study was undertaken to find out whether translocation of bacteria to the abdominal cavity and endotoxemia in rats with sterile peritonitis could be prevented by selective decontamination of the digestive tract. Sterile peritonitis was caused by the intra-peritoneal injection of either 100, 150, 200 or 300 mg of zymosan suspended in paraffin. The frequency of infection of the abdominal cavity depended on the dose of zymosan given, ranging from 20% in rats receiving 100 mg to 89% in rats receiving 300 mg of zymosan. In rats not receiving antibiotics for selective decontamination of the digestive tract (the control group), Gram-negative bacilli were isolated from the digestive tract in all rats, and Gram-negative bacilli were isolated from the abdominal cavity in 10 of 19 rats. In rats receiving antibiotics for selective decontamination of the digestive tract, Gram-negative bacilli were isolated from the digestive tract in none of the 14 rats, and similarly, Gram-negative bacilli were isolated from the abdominal cavity in none of the 14 rats (p<0.005). Moreover, in rats receiving antibiotics for selective decontamination of the digestive tract, endotoxin level in feces and plasma and mortality, were significantly lower as compared to rats not receiving antibiotics for selective decontamination of the digestive tract.

We concluded that selective decontamination of the digestive tract prevents translocation of Gram-negative bacilli to the abdominal cavity, and endotoxemia and early mortality in rats with sterile peritonitis.

Chapter 6

Translocation of Bacteria and Endotoxin in Organ Donors

We determined if bacterial translocation and endotoxin absorption occurs in twenty-one (multiple) organ donors with an anatomically intact GI-tract. The occurrence of factors that may promote bacterial translocation and/or endotoxin absorption were measured. Bacterial concentration in the mesenteric lymph nodes, abdominal exudate, blood, liver, lung, and spleen was determined. Endotoxin level in abdominal fluid, peripheral- and portal blood was determined. The anatomical integrity of the bowel wall was verified. Factors that may promote bacterial translocation and/or endotoxin absorption were present in all donors. Cultures revealed bacteria in 14 (66%) donors. In 81% of these cultures the bacteria isolated were identical to those isolated from the bowel content, demonstrating bacterial translocation. Endotoxin was found in 53% of the abdominal fluid samples and in 19% of the peripheral- and 10% of the portal blood samples. Light- and electronmicroscopical examination of the bowel wall showed no anatomical abnormalities.

We concluded that bacterial translocation and endotoxin absorption occurs frequently among organ donors and probably other critically ill patients.
Chapter 7

Fish Oil in Experimental, Sterile Peritonitis

We determined if fish oil given intraperitoneally would cause a reduction in the release of tumour necrosis factor and interleukin-6 in abdominal exudate and blood (experiment A), and if it reduces the incidence of organ failure in rats with sterile peritonitis (experiment B). Thirty six selectively decontaminated rats were used in each experiment. All rats were pretreated with 2 mL fish oil, lecithin, or saline, intraperitoneally for one or six weeks before intraperitoneal injection of zymosan. Experiment A: Samples of abdominal exudate and plasma were taken regularly for 24 hrs after the zymosan had been given. Experiment B: Clinical, biochemical, and histological variables were measured over a 12-day period after the zymosan had been given. Concentrations of tumour necrosis factor and interleukin-6 in abdominal exudate and plasma were significantly higher in rats pretreated with fish oil, compared with control rats in Experiment A. This effect was more pronounced after six weeks of pretreatment. There were no significant differences between the groups for any variable as measured in Experiment B.

We concluded that fish oil given intraperitoneally increased rather than reduced local and systemic release of tumour necrosis factor and interleukin-6, and that it did not reduce the incidence of organ failure in rats with sterile peritonitis.

Chapter 8

General Discussion

We mainly concentrated on the following issues.

(i) Debridement and intra-operative lavage of the abdominal cavity. These treatment modalities are the cornerstones of the treatment of generalised peritonitis, since they are effective methods to diminish the concentration of bacteria and toxins and adjuvant substances in the abdominal cavity. However, they cannot prevent the formation of residual abscesses, even if systemic antibiotics are given. Therefore, optimizing local therapy is mandatory.

(ii) Topical application of antimicrobials. Improving intra-abdominal bacterial killing may be accomplished by intra-abdominal application of antimicrobials. Imipenem/cilastatin proved to be effective to diminish the bacterial concentration, but induced a (small) endotoxin and TNF release. Intra-abdominal application of a single dose of taurolidine had no bactericidal properties, but did provide an endotoxin-inactivating and TNF down-regulating effect. Therefore, a combination of these agents may result in better local control of the intra-abdominal infectious process.

(iii) Modulation and control of translocation of bacteria and endotoxin. The phenomenon of bacterial translocation and endotoxin absorption in rats with sterile
peritonitis, and in severely ill patients, is discussed. Prevention of secondary infection of the abdominal cavity by gut derived microorganisms may be performed by a regimen of selective decontamination of the digestive tract.

(iv) *Prevention/reduction of the intra-abdominal inflammatory response.* Intra-abdominal application of fish oil did not diminish inflammation.

(v) *Future studies.* Several issues addressing the improvement of surgical treatment of generalised peritonitis are discussed briefly.