

## **Prophylaxis and treatment with antibiotics or probiotics in acute pancreatitis**

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### **1. Introduction**

Acute pancreatitis is the most common gastrointestinal disease requiring acute hospitalization and its incidence is rising (23). Approximately 20% of patients develop necrotizing pancreatitis (4, 10). Necrotizing pancreatitis is defined by either pancreatic parenchymal necrosis and/or peripancreatic tissue necrosis (3, 4). These patients are at risk for (multiple) organ failure often due to a persisting systemic inflammatory response syndrome. If the (peri)pancreatic collections with necrosis remain sterile the majority of patients will recover with conservative measures without the need of an invasive intervention (10). Secondary infection of necrosis develops in 30% of patients with necrotizing pancreatitis which increases morbidity and mortality substantially (24, 35). Overall mortality of necrotizing pancreatitis (15% to 30%) is much higher as compared to mild pancreatitis (0% to 1%) (13, 18).

Secondary infection of the peripancreatic collections or pancreas necrosis is considered to be caused by bacterial translocation: the phenomenon that enteral bacteria cross the

gastrointestinal mucosal barrier and invade the systemic compartment or by haematogenous spread from other sites in the body (9). Based on experimental and clinical studies it is believed that bacterial translocation is the results of a cascade of events depending on a disturbance of host-bacterial interactions on three levels: 1) the intestinal lumen; the presence of impaired small bowel motility and bacterial overgrowth, 2) the intestinal epithelium; structural mucosal barrier failure leading to increased gut permeability (15) and 3) the immune system; a dysregulation in the balance of the pro- and anti-inflammatory factors (2). Another possible pathway was found in an experimental study in rats suggesting that transmission by mesenteric lymphatics is also involved in the process of bacterial translocation (17).

Early in the disease course of necrotizing pancreatitis two treatment strategies have been suggested to prevent secondary infection of peripancreatic collections and pancreas necrosis:

1. Prophylactic administration of antibiotics
2. Therapeutic administration of probiotics.

These treatment strategies will be consecutively discussed.

## 2. Antibiotics

Multiple studies have studied the prophylactic use of systemic antibiotics in acute pancreatitis over the last decades (11, 37). The rationale for prophylactic treatment is to diminish potential hematogenous spread of pathogens after bacterial translocation has occurred.

In the last decades, 14 randomized controlled trials studied the effect of systemic antibiotic prophylaxis on prevention of infection of pancreatic necrosis (11, 37). In the 1990's enthusiasm for antibiotic prophylaxis was expressed through a number of small case series and editorials (6, 8, 12, 26). As a result, many surgeons, such as in the United Kingdom, started using antibiotic prophylaxis.(25) Overall, the studies at that time were underpowered and generated variable results, but still the meta-analysis at that time suggested a reduction in morbidity and mortality. But there were also concerns about selection of multidrug resistant bacteria and opportunistic fungal infections (25).

A Cochrane review by Villatoro in 2006 suggested a survival benefit and a decrease in pancreatic sepsis associated with the prophylactic use of beta-lactam group antibiotics (36). However, due to two new double-blinded randomized clinical trials the conclusion on prophylactic antibiotics changed (7, 28). The Vilatoro group included those trials in their 2010 Cochrane review which included seven studies with in total 404 randomized patients. They found no statistically significant effect on the reduction of mortality (8.4% vs. 14.4%) and the presence of infected pancreatic necrosis (19.7% versus 24.4%). The rate of other infections (not related to necrosis) were also not significantly reduced by prophylactic antibiotics. A trend, but without statistically significant difference, was shown with beta-lactam antibiotics towards less mortality and infected pancreatic necrosis. Interestingly, this effect was stronger for imipenem which showed no reduction in mortality but a reduction in pancreatic infections (RR 0.34 95% CI 0.13 – 0.84) (37). Overall the

quality of studies remained a major concern throughout the years regarding this subject; all studies were underpowered. It was concluded that there is no evidence for the prophylactic use of antibiotics in acute pancreatitis (37). This was confirmed by a second review, which also suggested that further research is needed to find sub-populations that may benefit from prophylactic antibiotics (11).

Selective digestive tract decontamination (SDD) is used on many intensive care units, particularly in ventilated patients. The goal of decontamination of the upper respiratory and digestive tract attempts to reduce infections by decreasing the microorganisms' colonization at these sites. Both selective decontamination of the oropharyngeal tract (SOD) and digestive tract (SDD) with nonabsorbable antibiotics have shown a modest decrease in mortality and reduced rates of bacteraemia (29). The only trial of SDD in patients with severe acute pancreatitis demonstrated a significant reduction of gram-negative bacterial colonization of the digestive tract, and a significant reduction of morbidity and mortality (14). Due to the moderate methodological quality (a non-blinded, underpowered study with lack of clear definitions) and the overall scarceness of evidence in severe acute pancreatitis, SDD is not considered standard practice in severe acute pancreatitis.

### Conclusion

Current evidence does not support routine antibiotic prophylaxis or SDD in patients with severe acute pancreatitis (10). This, however, does not imply that antibiotic treatment (rather than prophylaxis) is ineffective and should not be started as soon as evidence for the superinfection of (peri) pancreatic necrosis emerges. In most cases infected (peri) pancreatic necrosis can be treated successfully with appropriate antibiotics which often eliminates the need for interventional approaches.

### 3. Probiotics

Probiotics are defined as: 'Living micro-organisms which, when administered in adequate amounts, confer a health benefit on the host' (1). Probiotics can be administered together with prebiotics (synbiotics), non-digestible fibers that, when added to probiotics, enhance their activity. Probiotics have been suggested to reduce bacterial translocation (in acute pancreatitis) through a beneficial effect on three levels of host-bacterial interactions; the intestinal lumen, the intestinal epithelium and the immune system.

Bacterial overgrowth of potential pathogens is prevented in the intestinal lumen by a direct antimicrobial effect and competitive growth (30). At the intestinal epithelium probiotics prevent bacterial adherence to the epithelial surface by competitive exclusion and inhibition of a pathogen-induced increase of epithelial permeability. They also regulate enterocyte gene expression involved in the maintenance of the mucosal barrier and thus may preserve epithelial function (15, 16). Also selected probiotic strains have been found capable of inhibiting local pro-inflammatory reactions in enterocytes after i.e. pathogenic bacterial adhesion or ischemia (16). Finally, in vitro probiotic strains have been shown to induce production of the anti-inflammatory cytokine interleukin-10. A similar effect is thought to have a regulatory effect on the mucosal and systemic immune system in humans (19).

In various experimental studies the prophylactic role of probiotics in acute pancreatitis has been examined. In rats with pancreatitis probiotics reduced overgrowth of potential pathogens in the duodenum resulting in reduced bacterial translocation to extra intestinal sites and a reduction in mortality (34).

In clinical studies the prophylactic use of probiotics was examined in several randomized controlled trials. In patients undergoing major abdominal surgery the administration of pre- and probiotics significantly reduced the incidence of

postoperative infections, although there were some methodological issues in these studies (20, 27, 31).

Initially, two small randomized controlled trials, both from Hungary, studied probiotic prophylaxis in acute pancreatitis. The first trial showed in 45 patients with predicted mild and severe pancreatitis that probiotics reduce pancreatic sepsis and the need for surgical intervention (21). The second trial studied 62 patients with severe pancreatitis and concluded that nasojejunal feeding with synbiotics may prevent organ dysfunction in the late phase of severe acute pancreatitis (22). Because of the lack of stronger evidence, a larger randomized controlled multicenter trial was performed (PROPATRIA) where probiotics were compared with placebo in 298 patients with predicted severe pancreatitis. No probiotic effect was found in reducing infectious complications. There was, however a surprisingly higher rate of bowel ischemia (9 vs. 0) and mortality (16% vs. 6%) in the probiotics group (5). The mechanism explaining this adverse effect remains, unclear even after post hoc research in experimental animals (32, 33).

### Conclusion

There is currently no place for the treatment of acute pancreatitis patients with probiotics. Further research on probiotic prophylaxis in patients with organ failure has been returned to the experimental stage to study the possible mechanism of adverse events such as those observed in the PROPATRIA study.

### 4. Summary

Based on the current literature and in accordance with IAP/APA Acute Pancreatitis Guidelines(10):

1. Intravenous antibiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis. (GRADE 1B, strong agreement)
2. Probiotic prophylaxis is not recommended for the prevention of infectious

complications in acute pancreatitis.  
(GRADE 1B, strong agreement)

3. Intravenous antibiotics should be given in case of suspected infection of necrotising pancreatitis and further intervention considered.

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