# Bio-ecological control of acute pancreatitis: the role of enteral nutrition, pro and synbiotics

Stig Bengmark

**Purpose of review**

Increasing knowledge, both experimental and clinical, supports the fact that early and aggressive enteral nutrition has the capacity to reduce superinflammation and prevent infections in severe acute pancreatitis. Clearly, the main role of enteral nutrition is to boost the immune system, and not, at least initially, to provide calories. Whereas enteral nutrition improves, parenteral nutrition reduces immune functions.

**Recent findings**

The content of enteral nutrition solutions is more important than the route of administration *per se*. Antioxidants, plant fibres and live lactic acid bacteria are especially important for boosting the immune system. Recent studies support the fact that enteral nutrition and the supply of fibres and live lactic acid bacteria may significantly reduce the rate of infections. So far none of the treatments has been able to reduce the incidence of the systemic inflammatory response syndrome and multiorgan dysfunction syndrome. A recent unpublished study indicates, however, that the systemic inflammatory response syndrome and multiorgan dysfunction syndrome can also be reduced if much higher doses of lactic acid bacteria and a combination of several bioactive lactic acid bacteria are used (synbiotics).

**Summary**

Immunosupporting enteral nutrition with synbiotics is an important tool to control superinflammation and infection, and might also reduce the multiorgan dysfunction syndrome and systemic inflammatory response syndrome. It is essential that it is supplied early, if possible in the emergency room. New autopositioning regurgitation-resistant feeding tubes are available to facilitate such a policy.

**Keywords**

acute pancreatitis, enteral nutrition, fibres, lactobacillus, prebiotics, probiotics, synbiotics

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Institute of Hepatology, University College London Medical School, London, UK

Correspondence to Stig Bengmark, MD, PhD, FRACS (hon), FRCPS (hon), 185 Barrier Point Road, Royal Docks, London E16 2SE, UK
Tel and fax: +44 20 7511 6841; e-mail: s.bengmark@ucl.ac.uk

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**Abbreviations**

**LAB** lactic acid bacteria
**SAP** severe acute pancreatitis
**TEN** total enteral nutrition
**TPN** total parenteral nutrition


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## Introduction

There is no disease on which more effort has been spent to develop and try sophisticated systems to stage the disease, evaluate organ dysfunction and predict outcome as in severe acute pancreatitis (SAP). Almost one third of clinical publications on the disease focus on classification systems, and involve almost all the big names in clinical SAP research. The obvious reason is the unusual and unacceptably high morbidity and mortality rates that are associated with the disease. Such systems are of the greatest importance in that they can help navigate the patient through the difficult early hours, prevent the development of infected pancreatic necrosis, and reduce the incidence of multiple organ failure. So far, success in such attempts has remained elusive. Most of the scoring systems are unfortunately based on assessments made 48 h, sometimes even 60–72 h, from admission, or eventually from the onset of symptoms, timepoints when most of the damaging superinflammation and concomitant cytokine storm has already blown over. It is unfortunate that both early resuscitation and the institution of immunosupportive measures are delayed as patients often arrive in hospital 24–48 h after the onset of disease. Much of the support that exists has a narrow therapeutic window of not much more than 36 h, when determined and aggressive management can be expected to have a pronounced positive impact on outcomes. Aggressive measures, including the institution of enteral nutrition, should be recommended to begin on arrival in the emergency room, and before and in parallel with preliminary diagnostic procedures. It is better to treat a few patients unnecessarily than to lose valuable time.

## Importance of immune condition and resistance to disease

A recent Chinese study compared 27 possible risk factors obvious within 24 h [1], and found early shock, pleural effusion, arterial pH, immediate/early complications and APACHE II scores on single regression analysis and only

arterial pH on multiple regression analysis to be associated with early death (within $< 24$ h of admission). Halonen *et al*. [2] compared previously predictive systems with a novel prediction model based on four variables: age, chronic health status, the need for mechanical ventilation, and the highest serum creatinine value within 60–72 h of admission. The authors concluded that both Ranson and Imrie scores are inadequate indicators of mortality and that their new model is as accurate as APACHE II scores, which are based on no less than 14 variables. Of the four factors suggested, one is retrospective and obviously not useful for the guidance of management during the first 3 days. Two, eventually all three, that remain are factors that mainly reflect on the patient's premorbid condition and ability to resist disease, e.g. the robustness of the innate immune system. Imrie [3] has also recently emphasized patient-associated factors, especially obesity, and suggested a cheap yet untested prognostic system based on body mass index, age, chest X-ray and oxygen saturation. The organ systems most often involved in early (within 24 h) single organ failure are pulmonary (91%, 81%), renal (4.5%, 5%) and coagulation (4.5%, 14%) [4,5]. If the early superinflammation in these systems can be prevented or made transient it will significantly contribute to favourable outcomes.

## Gut-associated superinflammation

Severe attacks of acute pancreatitis are strongly associated with the priming and subsequent overactivation of leukocytes, which contribute to the production of inflammatory mediators and the induction of distant organ failure [6]. Even if it starts as a lesion restricted to the acinar cells of the pancreas, its consequences will, within hours if not minutes, spill over to the gut, the home of approximately 80% of the immune system, and soon also to the rest of the body. Important ingredients in the progress of the disease are stress-released norepinephrine and the increased virulence of gut luminal bacteria [7,8], splanchnic hypoperfusion and endotoxemia [9]. Immune suppression develops early, with signs of the suppression of the expression of monocyte HLA-DR and of hyperinflammation, and is strongly associated with the later development of septic complications and poor outcomes [10,11••,12••]. The early exaggerated release, especially of anti-inflammatory cytokines IL-1-ra, IL-6, IL-10, IL-11 is significantly correlated with the severity and outcome of SAP [11••,13••,14]. The degree of oxidative stress and neutrophil activation are also of great importance for outcomes [14]. Antigens, probably of intestinal origin, will activate T cells, which further fuel the inflammatory response [15]. Crucial to this process are the dendritic cells, which have been suggested to act as the gatekeepers to/conductors of the immune response [16•]. These cells have the unique ability, without disrupting the barrier function, to sample bacterial and other antigens in the gut continuously by sending processes into the gut lumen. On the basis of the information received they develop the expression of MHC class II and co-stimulatory molecules and activate naive T cells (one dendritic cell is said to activate up to 1000 T cells), and determine the active or non-responsive (tolerance) response, and the type of T-cell response: T helper type 1, type 2 or unpolarized. The content in the gut of flora as well as the availability of nutrients are important in this process. When cytokine levels were studied in ascites, thoracic duct lymph and plasma, the highest levels were found in ascites followed by lymph and plasma, and proinflammatory activity dominated in the peritoneal compartment and anti-inflammatory activity in plasma [17]. The high neutrophil activation and the dominance of anti-inflammation in plasma (and distant organs) might explain the high incidence of chest inflammation and infections in SAP patients.

## Importance of flora and supplemented lactic acid bacteria

A significant reduction in the commensal flora occurs early in the disease process, as a result of both disease and pharmaceutical treatment. It has been observed in experimental pancreatitis that anaerobic bacteria and lactobacilli are significantly reduced within 6–12 h after induction both in the distal small bowel and in the colon. These changes are almost instantly followed by significant overgrowth with potentially pathogenic microorganisms, such as *Escherichia coli*, and dramatic increases in mucosal barrier permeability (lumen to blood) and in endothelial permeability (blood to tissue) [18,19], associated with increased microbial translocation and microbial growth in mesenteric lymph nodes and pancreatic tissue [20].

It is increasingly evident that attempts to protect and enforce the body's immune functions and its ability to resist the progress of disease should be given the highest priority. A treatment strategy emphasizing the consideration of patient-associated factors (improvement of resistance to disease) and fewer disease-associated factors (pharmaceutical treatment of disease) favours immunomodulation over antimicrobial treatment. It has long been known that the administration of antibiotics will suppress various immune functions, and especially macrophage activities such as the chemiluminescence response, chemotactic motility, bactericidal and cytostatic ability [21,22]. This is so with standard antibiotic administration and is probably even worse with selective digestive tract decontamination. It is a historic landmark that routine antibiotic prophylaxis has (finally?) been shown to be of no benefit in reducing the risk of developing infected pancreatic necrosis [23].

## Bio-ecological control: a key to favourable outcomes

The primary goal of early treatment is to reduce the two major determinants of a bad prognosis: the severity of multiple organ failure and the extent of necrotic areas, which in a later phase constitute a burden to the immune system and also a culture medium for bacterial superinfection [24,25••]. Many steps are seemingly important: to avoid infusion into the circulation of stored blood, macro and fat molecules, which have been shown to reduce the immune functions; to keep blood glucose levels under strict control; to avoid antibiotics and other pharmaceutical agents as far as possible; and to avoid/reduce the use of lines, tubes and drains, which all provide sources of infection, especially in the immunocompromised patient – see further [26,27]. SAP patients have a documented deficit in antioxidants, flora, and the supply of fibre and nutrients, especially micronutrients, which should be compensated for [26,27]. Patients in intensive care units have in most cases lost their entire *Lactobacillus* flora [28]. The colonic mucosa normally obtains most of its needs of calories and antioxidants from the lumen and most of the absorbed nutritive substances are either produced or released by microbial fermentation of plant fibres. Immediate enteral nutrition should have as a primary goal the provision of antioxidants, fibres and lactic acid bacteria (LAB) in abundance. However, complementary supplementation of fluids and electrolytes must in the early phase often be provided parenterally (take care: glucose!).

## Enteral nutrition over total parenteral nutrition

In most studies so far, enteral nutrition has been introduced too late; early enteral nutrition has often been defined as within 48 h, sometimes even 72 h. Despite that, enteral nutrition, according to a recent meta-analysis based on six randomized controlled trials [29••], when compared with total parenteral nutrition (TPN), was associated with a significantly lower incidence of infections [relative risk (RR) 0.45; 95% confidence interval (CI) 0.26–0.78, $P = 0.004$), reduced surgical interventions (RR 0.48; 95% CI 0.22–1.0, $P = 0.05$) and reduced length of hospital stay (mean reduction 2.9 days, 1.6–4.3 days, $P < 0.001$), but no significant differences were observed in mortality (RR 0.66; 95% CI 0.32–1.37, $P = 0.3$) or non-infectious complications (RR 0.61; 95% CI 0.31–1.22, $P = 0.16$). A recent small, but well performed, study with total enteral nutrition (TEN) [30], which was commenced within 6 h of diagnosis, but regretfully, with no nutrients for the colon (fibre in the supplied nutrition solution) has been reported to give significant improvements in outcome. Three out of nine TPN-treated patients developed respiratory organ failure, and another three out of nine TPN-treated patients developed other single organ failures; no such complications were seen in TEN-treated patients [30]. Hospital stay (7 days, 4–14 versus 10, 7–26, $P = 0.05$), but also time to passing flatus and time to opening bowels (1 day, 0–2 versus 1–5, $P = 0.01$) was shorter in the TEN group. Improvements were also reported for the enteral nutrition-treated patients in C-reactive protein, levels of anti-endotoxin antibodies, and the degree of fatigue, but no differences were observed in plasma glutamine concentrations. In a recent study on 63 patients [31], enteral nutrition, with solutions also containing fibres, was commenced within 12 h after operation for SAP, and significant differences in late (> 3 days) pulmonary complications (15.2 versus 43.3%, $P < 0.05$), late renal insufficiency (0 versus 26.7%, $P < 0.05$), and wound and catheter-related septic complications (9.1 versus 30.0%, $P < 0.05$) were reported. However, no differences were observed in the length of hospital and intensive care unit stay or the rate and development of multiorgan dysfunction syndrome. Two out of 33 enteral nutrition-treated and eight out of 30 control patients died.

## Pro and synbiotics: a new treatment modality

The early supplementation of synbiotics to SAP patients has so far only been reported in one study [32], in which patients were supplemented daily with either 1 billion live or 1 billion heat-killed *Lactobacillus plantarum* 299 plus 10 g oat fibres during the first week. Infected pancreatic necrosis and abscesses were seen in one out of 22 patients (4.5%) supplied live LAB versus seven out of 23 (30%) of those supplied heat-killed LAB ($P = 0.023$). The study was criticized for having several methodological shortcomings, such as including no prestudy power calculation, having no defined primary endpoint, and a lack of analysis by intention to treat, and doubtful data analyses [33,34]. Despite that, the fact that similar observations were made in other groups of patients with other disease entities supports the conclusions drawn [35–37], but more studies are clearly needed. A yet unpublished study supplementing a mixture of four different LAB (Synbiotic 2000), and compared with the previous study, a much larger dose of LAB ($2 \times 40$ billion per day), and four different fibres (20 g per day) reported a significant reduction ($P < 0.05$) in observed combined systemic inflammatory response syndrome plus multiple organ failure, as eight out of 33 treated patients (24%) developed the syndromes compared with 14 out of 29 control patients (48%) (A. Olah, personal communication).

The need for confirmatory studies by other groups is obvious. One such ongoing study involves 15 Dutch university or major hospitals and a total of 200 patients [38]. The administration of a new multistrain probiotic product (Ecologic 641) is instituted within 3 days from the onset of abdominal pain and is given twice a day via nasojejunal tube for 28 days or to discharge. No routine prophylactic antibiotics will be provided.

## Importance of tools for effective tube feeding

Most experience supports the practice of providing enteral nutrition, when the patient cannot eat, via a nasojejunal tube. Some years ago the author developed a special autopositioning, regurgitation-resistant tube (Bengmark Flo-Care tube; Royal Numico-Nutricia Group, Zoetermeer, the Netherlands), with the ability to absorb gastrointestinal motility for placement where intended, without the need for radiology or endoscopy. An early study reported successful intubation in 10 out of 10 patients with acute pancreatitis [39]; the head of the tube reached its optimal position within an average of 5.2 h, and always within 24 h. A recent study [40] obtained successful placement in patients with normal gastric emptying within 24 h in 78% compared with 14% with a standard straight tube ($P = 0.041$), and in patients with impaired gastric emptying (as in most SAP patients) a successful placement within 24 h in 57% compared with 0% with standard tubes ($P = 0.07$). A recent study reported successful insertion in 12 out of 16 acute pancreatitis patients (75%), with the tube reaching the Treitz ligament within a median of 12 h [41].

## Conclusion

It is unfortunate that enteral nutrition continues to be regarded mainly as a tool for the delivery of nutrients and not as an instrument for the immunomodulation/bioecological control of inflammation and infection. This is probably the reason why a change of attitude has taken and continues to take such a long time. Most centres continue to adhere to the principle of awaiting the cessation of nausea and vomiting as well as the return of appetite before initiating oral or enteral feeding [42]. A recent study from China involving 50 acute pancreatitis patients [43] suggested an average of 9.1 days (6–42) on TPN before the institution of tube feeding, which continues for another 9 days before oral feeding is resumed and is followed by approximately another week before release from hospital (24.5 days after admittance).

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