Nutrition in patients with acute pancreatitis
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Acute pancreatitis is a disease with varying severity. Patients with the mild form do not require nutritional support because oral intake is resumed rapidly. Studies on nutritional support in acute pancreatitis have included patients with both mild and severe disease. In this heterogeneous group, total parenteral nutrition did not improve outcome compared with no nutrition at all. This is caused in part by an increase in septic complications during total parenteral nutrition. Likewise, no benefit from enteral nutrition was observed compared with no nutrition, probably because the group was heterogeneous or because nutritional goals were not achieved. Patients with severe acute pancreatitis become profoundly catabolic. This group undoubtedly requires nutritional support to treat undernutrition. The limited available data indicate that enteral nutrition, if well tolerated, is superior to parenteral nutrition for patients with severe acute pancreatitis. Based on current knowledge, a combination of early total parenteral nutrition and enteral nutrition is advisable as soon as enteral nutrition is tolerated. Monitoring of gut function is crucial in this situation.

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Abbreviations
SIRS systemic inflammatory response syndrome
TPN total parenteral nutrition

Acute pancreatitis accounts for approximately 3% of all acute admissions for abdominal pain. Usually, the course of disease is relatively benign, and spontaneous recovery with conservative treatment is to be expected in most patients [1••]. However, approximately 20% of patients develop severe acute pancreatitis, and these patients account for approximately 80% of the mortality caused by this unpredictable disease [2•]. Mortality has a characteristic biphasic distribution [3], with early deaths occurring during the first days of admission and delayed mortality occurring after 2 to 3 weeks. Therefore, it is important to predict which patient will develop severe acute pancreatitis and which patient will suffer from mild disease. Various scoring systems have been used to make that prediction, most commonly the Ranson, Imrie, and APACHE II scores [2•,4–7]. Although these scoring systems are valuable for comparison of patient groups, their value in everyday clinical practice is limited because of the multiple factors rooted in the etiology, pathophysiology, and treatment of acute pancreatitis.

Many authors have attempted to influence the outcome of severe acute pancreatitis by focusing on factors of supposed etiologic or pathophysiologic importance. In this context, the issue of nutrition is under debate. This article discusses the pros and cons and the current and future role of nutrition in acute pancreatitis, with a brief discussion of the etiology and pathophysiology of acute pancreatitis.

Pathophysiology of acute pancreatitis
The two main etiologic factors in acute pancreatitis are alcohol and gallstone disease, although a variety of rarer causes have been reported [8•]. The disease is characterized by autodigestion of the gland [8•] caused by inappropriate proteolytic enzyme release with a resulting local and systemic activation of the inflammatory cascade [1••], which appears to be unstoppable. Activation of the inflammatory cascade contributes to the occurrence of systemic inflammatory response syndrome (SIRS) accompanied by acute phase protein secretion [9]. Progressive autodigestion contributes to pancreatic necrosis, which may become infected [10]. Infected necrosis can give rise in turn to septicemia, often progressing to overwhelming sepsis and multiple organ failure.

Multiple organ failure results in deficient renal clearance of toxic substances and cytokines, reduced hepatic clearance of endotoxin, and increased gut permeability [11–13]. Increased gut permeability facilitates translocation...
of microorganisms from gut lumen into blood [14], increasing the risk of secondary infection of pancreatic necrosis. This vicious circle is detrimental to the patient.

**Implications of pathophysiology for treatment**

Treatment currently focuses on three factors of supposed pathophysiologic significance. First, it is generally accepted that secondary infection of pancreatic necrosis constitutes one of the crucial factors in the progression from SIRS to sepsis in patients with severe acute pancreatitis. Thus, the issue of selective decontamination of the gut has been explored [15]. Based on a number of clinical studies, it is beneficial to administer broad-spectrum antibiotics in an early stage to prevent pancreatic infection [2,16••,17]. Second, recent data suggest that it is possible to diminish the systemic inflammatory response syndrome in critically ill patients by giving specific antiinflammatory components like platelet activating factor antagonists [18,19]. However, in a large multicenter trial, this result could not be confirmed for patients with severe acute pancreatitis [20••]. Third, it has been suggested that renal replacement therapy may clear cytokines from the body in patients with sepsis, although no firm evidence exists [13].

The mainstay of treatment of acute pancreatitis in the past decades has been avoidance of food intake, thus “resting the pancreas” [21]. The assumption is that avoiding further activation of pancreatic enzyme secretion is of prime importance. However, administration of somatostatin, which reduces pancreatic secretions, does not affect outcome [22].

**Implications of treatment for pathophysiology**

Although a “nil by mouth” approach may be beneficial to the pancreas, it deprives an already catabolic patient of crucial nutrients. Also, this classic treatment results in intestinal rest, which may have profound adverse effects for the patient with acute pancreatitis. The absence of enteral nutrition induces intestinal villus atrophy and adversely affects intestinal barrier function [1••,23], which facilitates bacterial translocation. It would therefore seem logical to feed patients with acute pancreatitis to meet caloric and protein requirements and to protect intestinal barrier function. The crucial questions are whether there are sufficient data to support this view and what the optimal route of administration would be.

**Should nutrition be given?**

Recently, several authors have addressed whether any form of nutrition is better than no nutrition at all. Administration of nutrition to patients admitted with severe acute pancreatitis may be beneficial because it prevents undernutrition [1••]. However, Powell *et al.* [24••] showed that early enteral nutrition compared with no nutrition did not affect overall outcome, had no effect on markers of SIRS, and presumably had an adverse effect on intestinal barrier function.

Interpretation of studies on nutrition in acute pancreatitis is rendered difficult by many variables. Patients included in studies on severe acute pancreatitis based on admission Ranson or Imrie criteria often progress to only mild pancreatitis. Impaired gastric emptying, ileus, and abdominal compartment syndrome [25] often impair oral feeding. Enteral feeding tubes sometimes are difficult to position, and dislodgement is common.

**Should parenteral nutrition support be given?**

Patients with severe acute pancreatitis are catabolic and have increased energy expenditure [1••]. They need appropriate administration of calories and nitrogen. Because such administration is not feasible by the oral route if one adheres to a “nil-by-mouth” regimen, many studies have explored the feasibility and benefits of total parenteral nutrition (TPN) in pancreatitis. It has been shown that TPN is feasible and safe in many institutions. TPN does not significantly stimulate pancreatic secretion in humans [26], and there is no adverse effect of TPN on pancreatic function [21,27]. TPN makes it possible to administer the required amount of nutrition irrespective of bowel function [21]. However, in the only randomized, controlled trial of TPN versus no nutrition at all, TPN did not improve outcome for patients with mild to moderate pancreatitis [28••].

**Arguments against total parenteral nutrition support**

Administration of TPN requires insertion of an intravenous line. This insertion introduces the potential of line sepsis, which may lead to secondary infection of pancreatic necrosis. Sitges-Serra *et al.* [29] have suggested that parenteral feeding leads to expansion of the extracellular fluid compartment, rapid weight gain, and a decrease in plasma albumin and hemoglobin. These changes are associated with an increase in postoperative complications for depleted surgical patients [29]. However, these effects of TPN on extracellular fluid may represent merely the effect of rehydrating a moderately dehydrated patient group. The beneficial effects of administering nutrition counteract the effects on serum albumin [30].

Critical illness is associated with intracellular dehydration, which might be causally related to accelerated proteolysis [31]. However, it is unclear whether proteolysis is cause or consequence, and how these changes ultimately affect protein breakdown during acute and chronic disease. TPN carries the risk of patient overfeeding, which may adversely affect outcome [32]; this problem has been addressed by many authors. Hyperlipidemia and hepatic dysfunction may lead to discontinuation of TPN. Administration of carbohydrates in this
situation may aggravate hepatic steatosis because these patients have some degree of insulin resistance [1••]. Finally, deprivation of luminal nutrients during TPN is associated with mucosal atrophy in animals and humans [23,33,34], leading to increased intestinal permeability [33,34] and translocation of microorganisms and endotoxin.

**Should enteral support be given?**

A growing body of evidence suggests that enteral nutrition, even if administered in small quantities, prevents intestinal mucosal atrophy, thereby improving intestinal barrier function [35]. Improvement of intestinal barrier function is beneficial because it prevents bacteria and their products from gaining access to the circulation [36]. This may reduce the risk of secondary infection of pancreatic necrosis, thus interrupting the vicious circle that is so important in the pathophysiology of acute pancreatitis. Also, enteral nutrition makes intravenous access unnecessary, which reduces the risk of systemic bacteremia caused by line colonization and infection. Enteral nutrition has been shown to reduce septic complications compared with TPN in both rats and humans with severe acute pancreatitis [37•,38]. However, in the only randomized, controlled trial of enteral nutrition versus no nutrition for patients with moderate to severe acute pancreatitis, no significant beneficial effect was observed [24••].

The optimal timing of the start of nutrition and the appropriate quantities are still under discussion. For years, the belief that the pancreas and hence the bowel should be rested was a major impediment to the introduction of early enteral nutrition. However, enteral nutrition beyond Treitz ligament induces hardly any activation of pancreatic enzyme secretion, is relatively simple to achieve, and carries a limited risk of complications [36,37•,39]. Eatock et al. [40] showed that even early nasogastric feeding (< 48 hours of admission) was feasible and safe for patients with severe acute pancreatitis. Furthermore, enteral nutrition is considerably less expensive than TPN [1••,37•,41•].

Three randomized, controlled trials comparing early enteral nutrition with TPN have been conducted [37•,41•,42••]. For patients with severe acute pancreatitis, Kalfarentzos et al. [37•] demonstrated a significant reduction in septic complications in the enteral nutrition group. For patients with mild to moderate pancreatitis, Windsor et al. [42••] failed to achieve a significant reduction in SIRS, sepsis, organ failure, or intensive care unit stay in the enteral nutrition group, although a tendency toward improved outcome in this group was observed. In a third study during mild acute pancreatitis, only a significant cost-benefit was demonstrated for enteral nutrition compared with TPN [41•].

**Arguments against enteral support**

It is well known that oral nutrition stimulates pancreatic secretion; therefore, it has long been argued that the pancreas should be rested [1••]. However, several authors have disputed this assumption, and there is convincing evidence that the rigid concept of pancreatic rest is not tenable, because fasting and nasogastric suction are not beneficial [43]. Oral, intragastric, intraduodenal, and even colonic infusion of nutrients does significantly stimulate pancreatic secretion [1••,44,45]. Conversely, enteral nutrition into the proximal jejunum by a nasojunal tube does not have significant effects on enzyme secretion by the pancreas [1••,39,46]. Also, enteral nutrition by a jejunostomy feeding tube during acute pancreatitis prevents bacterial translocation in rats [38]. Clearly, delayed gastric emptying, abdominal compartment syndrome [25], diarrhea, aspiration of gut contents, inability to place a jejunal feeding tube, tube dislodgement, and ileus secondary to pancreatitis may affect the feasibility of full enteral nutrition. The implementation of early enteral nutrition makes adequate clinical monitoring of intestinal function compulsory.

In this context, it is not surprising that several authors [24••,41•] were able to achieve administration of only 20 to 70% of targeted caloric requirements by the enteral route. However, this is not an argument against enteral nutrition. Because of the benefits of using the natural route of nutrition, enteral nutrition by a nasojejunal tube or a jejunostomy feeding tube should be aimed for whenever possible [41•].

**Specific nutrients**

Recently, several nutrients with beneficial effects in critically ill patients have been suggested. Of these, glutamine, arginine, and several immune-enhancing formulas are of particular interest.

Glutamine is the most abundant free amino acid in the body pools [47,48]. Most is produced and stored in skeletal muscle, from which it is released under many physiologic and pathophysiologic conditions. Glutamine is a fuel for the gut and the immune system [49–53] and is important in nitrogen and acid-base homeostasis [48,50]. Currently, it is considered a conditionally essential amino acid [50]. This paradigm indicates that under physiologic circumstances, the body can produce sufficient amounts of glutamine—meaning that it is nonessential—but this is not the case during critical illness and nutritional depletion when glutamine requirements are increased [54]. Depletion in itself may lead to decreased plasma glutamine concentrations [55], but this may also be an effect of the inflammatory state associated with chronic disease or malignancy. Because glutamine uptake by the intestines appears to be concentration dependent, these reduced plasma glutamine concentrations are reflected in diminished mucosal glutamine content [55]. The functional significance of these alterations is underpinned by the observation of gut mucosal atrophy in patients and animals receiving glutamine-free...
TPN and its reversal by glutamine-enriched formulas [33,56]. Glutamine-enriched TPN thus prevents mucosal atrophy and improves intestinal barrier function [33,34,54,57–60]. Enteral administration of glutamine-enriched nutrition to multiple trauma patients reduces septic complications compared with glutamine-free enteral nutrition [61]. Studies on glutamine supplementation during pancreatitis are scarce, although glutamine levels in plasma and muscle are known to decrease in severe acute pancreatitis [62,63]. In the only study comparing standard and glutamine-enriched TPN in patients with acute pancreatitis, the glutamine-fed group had a diminished cytokine interleukin-8 release from peripheral blood mononuclear cells and improved lymphocyte proliferation [64••]. This finding is compatible with observations by others that glutamine-enriched enteral nutrition lowers the systemic inflammatory response in multiple-trauma victims [61].

Arginine has immunotrophic effects [65] that may explain the benefits of arginine supplementation to critically ill patients. Arginine plays a role in intestinal mucosal regeneration in severely injured animals [66–68]. Some of the benefits of glutamine supplementation have been attributed to arginine [69]. The intestines convert glutamine to citrulline, which is released in the portal vein and passes the liver without uptake. Citrulline is then converted by the kidneys to arginine, which possibly explains the increased arginine levels during glutamine supplementation [61,69,70]. No trials have been conducted on arginine supplementation as such to patients with acute pancreatitis. This may be a fruitful area of future research. Immune-enhancing feeds containing arginine, nucleotides, and ω-3 fatty acids may improve outcome in the critically ill [35], but no reports are available on their use in patients with pancreatitis [1••].

Conclusions
The interpretation of available data from studies on nutrition in pancreatitis is difficult because the patient group is nonhomogeneous. Patients with mild acute pancreatitis do not need nutritional support because normal oral intake is usually resumed within 4 to 7 days. There are no data to suggest that nutritional support affects the underlying disease process [1••]. It appears that nutritional support is beneficial to patients with severe acute pancreatitis because it may prevent underlying malnutrition and starvation. Thus, nutritional support should be considered for any patient with severe acute pancreatitis [1••]. There is no convincing evidence that either enteral nutrition or TPN is superior, although there are data to suggest that early enteral nutrition is beneficial [37•]. Surprisingly, the United Kingdom guidelines for the management of acute pancreatitis do not mention nutrition at all [5]. The guidelines from the American College of Gastroenterologists recommend administration of TPN to patients with severe disease who will not receive oral nutrition for 7 to 10 days [7]. From a theoretical standpoint, enteral nutrition seems preferable. The route of nutrition should be decided by clinical monitoring of intestinal tolerance and the need to achieve adequate nutritional intake [32]. A combination of early parenteral and enteral nutrition as soon as tolerated appears the most realistic option. If a patient with severe acute pancreatitis undergoes surgery for treatment of intraabdominal complications, it is wise to insert a jejunostomy feeding tube [1•••]. The potential benefits of specific nutrients in severe acute pancreatitis require further study.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as: • Of special interest •• Of outstanding interest


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21 Adelmore, multicenter, double-blind, randomized, placebo-controlled study of the effects of the platelet activating factor antagonist lexipafant on organ failure in severe acute pancreatitis.


The surgical patient

The only randomized trial on glutamine supplementation in 14 patients with severe acute pancreatitis.