Nutritional Support in Acute Pancreatitis

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Importance of Pancreatic Rest

That pancreatic rest and a reduction in exocrine secretion may allow a more expedient resolution of pancreatic inflammation is an important clinical precept in the management of patients with acute pancreatitis. Fortunately, the most common deleterious effect of early advancement to oral diet is an uncomplicated exacerbation of symptoms, which in one multi-center trial occurred in 21% of patients recovering from acute pancreatitis [1]. Of greater concern is a true exacerbation of pancreatitis, which occurs in less than one fifth of those patients who demonstrate an exacerbation of symptoms (or in 4.3% of patients overall) [1]. Relapse in response to early advancement to oral diet does impact patient outcome with regard to length of hospitalization. Length of hospitalization after advancement to oral diet was prolonged from 7 days in those patients who advanced successfully, to 18 days in those patients who suffered relapse [1]. Total length of hospitalization was nearly doubled from 18 to 33 days (p < 0.002), when relapse occurred in response to early advancement to oral diet [1]. The development of late complications of major peripancreatic infection in response to early dietary advancement described in early retrospective studies [2] has not been demonstrated in more recent prospective studies.

The understanding of what constitutes pancreatic rest has improved over the past decade. A reduction in the enzymatic protein portion of pancreatic exocrine secretion appears to be the most important factor in resolving the inflammatory response. While fluid volume and bicarbonate output from the pancreas are often simultaneously stimulated with increases in protein
enzyme output, the three aspects of pancreatic secretion are not necessarily
linked through the same stimulatory factors. Management strategies which
reduce protein enzyme output with a continued output of volume and
bicarbonate may be sufficient to rest the pancreas and allow resolution of
inflammation [3]. A reduction in protein enzyme output to basal unstimulated
levels may not be required to rest the pancreas, as a reduction to subclinical
levels may be sufficient to promote convalescence. This strategy may be
guided by resolution of symptoms. Very little secretion in the pancreas may
occur at the height of acute inflammation. But most importantly, pancreatic
rest may be achieved by early enteral feeding infused low in the
gastrointestinal (GI) tract at the level of the jejunum with formulas comprised
of components that minimize pancreatic stimulation.

Reduced Pancreatic Stimulation with Jejunal Feeding

The safety of early enteral feeding and the ability to reduce pancreatic
stimulation with jejunal infusion of nutrients was clearly demonstrated in the
first prospective randomized trial of enteral versus parenteral feeding in acute
pancreatitis [4]. Patients placed on early jejunal feeding within 48 h of
admission for acute pancreatitis demonstrated that there was no prolongation
of the time to normalization of amylase, advancement to oral diet, length of
time spent in the intensive care unit, or overall length of hospital stay [4]. Use
of the enteral route did not increase nosocomial infections or affect overall
mortality [4].

The ability of early enteral feedings to rest the pancreas relates to the fact
that there are various levels of stimulation throughout the GI tract [5]. These
levels of pancreatic stimulation include the cephalic, gastric, and intestinal
phases [5]. The lower these nutrients are infused in the GI tract, the less likely
they are to stimulate pancreatic secretion. Feeding low enough into the GI
tract (i.e., the jejunum) may not only bypass the stimulatory factors, but
ironically may stimulate a number of inhibitory polypeptides. Pancreatic
inhibitory polypeptide, polypeptide YY, somatostatin, luminal proteases, and
even bile acids all inhibit or reduce pancreatic secretion and may be released
in response to jejunal feeding.

Specific characteristics and the degree of digestive complexity of
individual nutrients have a differential effect on pancreatic secretion [5, 6]. Of
the three major macronutrients, fat is the most potent stimulus of the
pancreas and intraluminal carbohydrate is the least. Long-chain fatty acids
appear to stimulate the pancreas more than medium-chain triglycerides [5, 6].
Intact protein stimulates the pancreas more than individual amino acids, and
small peptides may be the form of protein which has the least stimulatory
effect. Agents with high osmolarity may stimulate the pancreas more than
agents with low osmolarity [6].
With a basic understanding of these concepts, the clinician may envision a scale over which the degree of pancreatic stimulation is determined by the inherent nature and method of delivery in which nutrients are administered. At one end of the scale is oral feeding, which invokes the greatest degree of pancreatic secretion. Delivery of nutrients to progressively lower levels of the GI tract (from the stomach to the duodenum to jejunum), is associated with a diminishing degree of stimulation. At the other end of the scale, parenteral infusion, in the absence of hypercalcemia or hypertriglyceridemia, has the least stimulatory effect and the lowest likelihood for relapse [5]. Similarly, with regard to components of the individual nutrients, fat would be at the end of the scale causing the greatest stimulation of the pancreas. Protein, and then carbohydrate, would be at the opposite end of the scale leading to lesser degrees of stimulation. The degree of disease severity (as determined by the presence or absence as well as the degree of pancreatic necrosis) [7] determines the maximal number of stimulatory factors that may be tolerated without relapse.

**Importance of Maintaining Gut Integrity**

While the tenant of pancreatic rest is of central importance in managing patients with acute pancreatitis, maintaining gut integrity is equally important. The GI tract is the largest immune organ in the body, containing 65% of immune tissue overall and up to 80% of the immunoglobulin-producing tissue of the body [8, 9]. As a result, utilization of the GI tract modulates the overall systemic immunity and leads to a dramatically favorable impact on patient outcome.

In the fed state, the normal villi, rich blood supply, and intercellular tight junctions contribute to the overall integrity of the GI tract. Propulsive contractions keep the concentration of bacteria at normal levels, and the secretion of bile salts and secretory IgA in response to luminal nutrients coat the bacteria and prevent adherence to the gut wall and subsequent translocation [10, 11]. The healthy gut acts as an important antigen-processing organ, in which bacterial antigen is presented across the M cells, stimulating the release and maturation of a population of pluripotential stem cells [12, 13]. These cells will migrate out from the Peyer's patches, through the mesenteric lymph nodes and thoracic duct, into the systemic circulation as a mature line of B- and T-cell lymphocytes. A portion of these cells returns to the GI tract as gut-associated lymphoid tissue (GALT) [11–13]. Lymphoid follicles are comprised mostly of helper T cells, which induce the production of secretory IgA by the plasma cells. Diffuse lymphoid tissue contained within the intestinal villi have a wider variety of cells, including helper T cells, cytotoxic T cells, B cells, and plasma cells [11–13]. A separate population of cells generated in the maturation of the pluripotential stem cells migrate out as mucosal-associated
lymphoid tissue (MALT) to distant sites such as the lungs, genitourinary, breast and lachrymal glands [10–13].

In a situation of even brief disuse, gut integrity may deteriorate. In contrast to the fed state, fasting leads to villous atrophy, diminished blood flow, and loss of interepithelial tight junctions. This opens paracellular channels, allowing translocation of bacteria [13]. Reduced contractility promotes bacterial overgrowth [10]. Without nutrient-induced stimulation of secretory IgA and bile salts, bacteria are able to adhere to the luminal wall, promoting even greater translocation of bacteria and their secretory products (i.e., endotoxin) [10]. The mass of GALT may diminish, as does the antigen processing and buildup of MALT at distant sites.

The most important aspect of gut disuse may be the diminished blood supply to the gut, which leads to ischemia/reperfusion injury [14]. The generation of superoxide radicals in response to ischemia/reperfusion may promote the gut as a priming bed for macrophages [14, 15]. Macrophages, primed and activated at the level of the gut, may migrate out to distant sites such as the liver, lung, and kidney. There, they may diapedese into these tissues, introducing oxidative species [15]. Activated macrophages are the key step linking issues of gut deterioration with more systemic factors which adversely affect patient outcome [15, 16]. Activated macrophages initiate the arachidonic acid cascade.

Although simplified, the concepts presented point to the pivotal importance enteral nutrition plays in determining whether the gut promotes inflammation or enhances appropriate immune function in the setting of pancreatitis. Gut disuse, with or without parenteral feeding, leads to a process in which there is macrophage/neutrophil activation and a nonspecific pattern of exaggerated systemic inflammatory response with multiple organ failure [14–17]. On the other hand, utilizing the gut and infusing luminal nutrients instead leads to a different process characterized by the orderly generation of GALT/MALT, and the incidence of nosocomial infection and organ failure is reduced [11–13].

With loss of integrity, there is evidence in pancreatitis patients that the gut becomes ‘leaky’. In a prospective randomized trial, Windsor et al. [18] showed that patients with pancreatitis maintained on enteral tube feeding had no change in IgM antibodies to endotoxin over a week of enteral feeding. In contrast, controls placed on total parenteral nutrition (TPN) and gut disuse demonstrated a statistically significant increase in IgM antibodies to endotoxin of 24.8% in response to a week of parenteral feeding (p < 0.05) [18]. Evidence that loss of integrity and a leaky gut lead to an increased generation of superoxide radicals was shown in the same study by the fact that total antioxidant capacity (as measured by an enhancement chemiluminescence assay) was shown to be reduced by 27.7% in the group placed on TPN [18]. In contrast, study patients on enteral feeding showed a statistically significant increase in antioxidant capacity by 32.6% over a similar week of enteral feeding (p < 0.05) [18].
The more important contribution from the leaky gut with compromised integrity relates to its effect on the overall stress response and disease severity caused by pancreatitis. In pancreatitis patients, significant increases in stress-induced hyperglycemia were seen in a control group placed on TPN and gut disuse [4]. No such increases in serum glucose levels were seen in the study group placed on enteral feeding [4]. In a separate study, C-reactive protein levels in a group of pancreatitis patients randomized to TPN did not change over a week of parenteral feeding [18]. In contrast, C-reactive protein levels decreased significantly from 156 to 84 g/dl in a study group placed on enteral feeding (p \(\leq 0.05\)) [18]. In the same study, APACHE II scores decreased significantly over a week of feeding within the enteral group, with no significant change in the group placed on TPN and gut disuse [18]. At the end of 1 week of nutritional therapy, 9 of 11 patients in the enteral group had resolved the systemic inflammatory response syndrome, contrasted with the group placed on TPN and gut disuse in which only 2 out of 12 patients resolved the systemic inflammatory response syndrome over their 1st week of therapy (p \(\leq 0.05\)) [18].

Most importantly, the issues of enteral access and maintenance of gut integrity in acute pancreatitis ultimately impact patient outcome. In a prospective randomized trial, patients with severe acute pancreatitis and necrosis on computerized tomography scans placed on enteral feeding developed significantly fewer septic complications compared to a similar group of patients placed on TPN and gut disuse (incidence of septic complications 28 vs. 50%, respectively, p \(\leq 0.03\)) [19]. Additionally, the number of infections in those patients who developed septic complications was reduced significantly as well from 1.35 in the group randomized to TPN/gut disuse, to 0.56 in the group on enteral feeding (p \(\leq 0.03\)) [19]. In fact, overall complications were reduced significantly from 75% in the group placed on TPN/gut disuse to 44% in the early enteral group (p \(\leq 0.05\)) [19].

**Identifying Patients in Need of Aggressive Enteral Nutritional Support**

Determining which patients need aggressive nutritional enteral support can be difficult for the clinician. Surprisingly, clinical assessment and physical examination on admission have been shown to be inferior to APACHE II scores in differentiating patients with severe pancreatitis with a higher likelihood of morbidity and mortality [20, 21] from those with mild to moderate pancreatitis and a low likelihood of complications. In two studies, the sensitivity of clinical assessment in identifying patients with severe pancreatitis was only 34–44%, whereas the sensitivity for an APACHE II score of \(>9\) was 63–82% [20, 21]. While the APACHE II score was superior to clinical assessment in predicting severe attacks on admission, the overall accuracy for clinical assessment was higher on admission because most mild attacks were
correctly predicted [20, 21]. At 48 h, the sensitivity of both the APACHE II score of >9 and the Ranson criteria of >2 was greater (75–82%) in identifying patients with severe pancreatitis than clinical assessment (44–66%) [21]. The overall accuracy for clinical assessment at 48 h was 87–89%, which was slightly higher than the two scoring systems at 69–88% [20, 21]. Those patients with APACHE II scores of >9 and Ranson criteria of >2 account for 20% of hospital admissions, tend to have pancreatic necrosis on CT scan, have a 19% mortality rate, 38% incidence of complications, and are unlikely to achieve an oral intake successfully within 7 days of admission [7, 21–23]. In contrast, those patients with APACHE II scores of ≤9 and Ranson criteria of ≤2 account for 80% of hospital admissions, tend not to have necrosis on CT scan, have a 0% mortality rate, 6% complication rate, and a 81% incidence of reaching an oral diet successfully within 7 days of admission [7, 21–23]. Using these parameters, the clinician can predict the patients likely to develop severe pancreatitis who need aggressive enteral nutritional support and placement of early enteral access.

Is There a Role for TPN in Severe Acute Pancreatitis?

In the only prospective randomized trial of TPN versus no nutritional therapy, patients with predominantly mild acute pancreatitis (mean Ranson criteria of 1.1) placed on early TPN actually did worse than controls that received only intravenous fluid resuscitation without nutritional support [23]. TPN patients were hospitalized for 16 versus 10 days in the control group (p < 0.04), and the catheter-related sepsis in the TPN group was 10.5 versus 1.5% in historical controls (p = 0.003) [23]. Patients with mild to moderate disease do not require nutritional support. TPN is not a consideration in these patients unless a late complication develops. TPN should only be considered in those patients with severe pancreatitis who are intolerant for enteral feedings or in whom enteral access cannot be obtained. Extrapolation of data from other patient populations (such as burns, trauma and critical care) suggests that it may be pertinent to withhold TPN in these patients for the first 5 days until the peak inflammatory response passes [23, 24].

Do Complications or the Need for Surgery Contraindicate Enteral Feeding?

Complications such as pancreatic ascites, fistulas, or pseudocysts are part of the natural disease course of acute pancreatitis. Information from mostly retrospective case series indicates that use of the enteral route is safe and allows resolution of these complications in most circumstances [6, 25, 26]. Experience from the literature involves patients with chronic pseudocysts,
fistulas, or ascites who tend to be past the peak of inflammation. These patients continue to require hospitalization, but are fed successfully by nasoenteric tube or by elemental or semi-elemental diet ingested orally. Resolution of the complication usually occurs over several weeks, with a few episodes of diarrhea as the only problem [6, 25, 26].

The need for surgery to treat hemorrhagic or infectious complications from pancreatitis gives the opportunity to obtain a more definitive enteral access [27, 28]. In two studies from Europe in which patients operated on for acute pancreatitis were randomized to enteral feeding or TPN postoperatively, no differences in outcome between the two groups were seen [29, 30]. Responses in pancreatic secretory output postoperatively were similar as well [29, 30]. These studies demonstrate that enteral feeding via jejunostomy in these patients following major pancreatic surgery is safe and well tolerated.

**Initiation of Feeds**

In a patient determined to be a candidate for enteral feeding for severe acute pancreatitis, a nasoenteric tube should be placed endoscopically or fluoroscopically at or below the ligament of Treitz. The tube may be secured at the nose using a nasal bridle. Feeds may be started at 25 cm³/h and advanced to goal levels (25 cal/kg/day) over the first 24–48 h.

If the tube is low enough in the GI tract, almost any formula may be successful in putting the pancreas to rest. To obtain a maximal reduction in enzyme output, however, two groups of formulas may be selected. Earlier elemental formulas that are nearly fat-free and comprised of individual amino acids may result in the least stimulation of the pancreas. Small peptide formulas in which 70% of the fat is in the form of medium-chain triglycerides may cause slightly greater stimulation of the pancreas, but this is offset by greater, more efficient absorption.

Usually partial ileus is a minimal problem, occasionally requiring a decrease in rate, but not necessarily cessation of feeds. The timing and advancement to oral diet is somewhat difficult, but in general should be considered once the patient has been pain free for 24–48 h, with levels of amylase and lipase decreasing toward normal. Criteria which may help in indicating readiness for advancement to oral diet include a total duration of painful period <6 days, serum lipase on the day prior to advancement of <3 times normal, and a CT score on pancreatic necrosis of C or better [1].

**References**


**Discussion**

**Dr. Berger:** To your knowledge are there any data showing that early antioxidant therapy will bring any changes, because there are groups [1] saying that they include them in their management. There are poor quality studies using selenium saying the same [2]. Are you aware of any developments in this area?

**Dr. McClave:** I was at ESPEN 2 and there were some papers on selenium, but I can't remember if they were on pancreatitis patients or not, but the effects you see from total parenteral nutrition (TPN) were improved. That is why I think it will be a huge step in improving the efficacy from TPN by including those very early on.

**Dr. Nitenberg:** I think you did not mention the type of enteral nutrition you propose for your patients. Do you think that in this type of patient with acute pancreatitis you can use polymeric diets or do you think that you have to use an oligopeptide diet or elemental diet?

**Dr. McClave:** A good question and a couple of different reactions. I think if the tube is down low enough the type of formula does not matter, but to ensure that there is tolerance then I think there are two categories of formulas that will work. One would be the old elemental nearly fat-free formulas, and this is the one disease process where I think that makes sense, in which the content of fat is the greatest stimulant of exocrine secretion. The other formula would be small peptide formulas in which the fat is in the form of medium chain triglycerides (MCT) and in the small peptides. There have been two studies, one in rabbits where the pancreatic duct was ligated, and individual amino acids were not absorbed as well as if they took the individual amino acids and made a dipeptide out of them, so that would suggest that peptides are better. And then there was a study in humans with cystic fibrosis in chronic pancreatitis and their small peptide absorption was better than elemental formulas. But I think if the tube is down low enough it is not a critical issue. Once 10 years ago we had the tube 10 or 12 cm below the ligament of Treitz and every time we started feeding we had an exacerbation of pain, and these were patients in whom I would use the fat-free elemental formula.

**Dr. Moore:** There is the concept that arginine via nitric oxide could hurt the gut. At our trauma research center we tried to implicate nitric oxide in different injury models, and it turns out that when we create sepsis with lipopolysaccharide (LPS), nitric oxide synthetase is expressed in the ileum. If we look at shock or gut ischemia reperfusion we don't get that same induction of nitric oxide synthetase. To implicate it into reperfusion injury of the gut we have to go to very severe ischemic insult. I think that hemorrhagic shock is different from sepsis when it comes to nitric oxide synthetase. The second point I would like to make is, you are saying that you are going to assess the severity of pancreatitis by the degree of pancreatic necrosis. That would mean you get a CT scan on everybody. The third comment I have is when Dr. Kudsk and I started promoting enteral nutrition in trauma patients in the late 1980's it took a decade before it became a standard of care. So I wonder now how you are going to promote this concept.
Dr. McClave: First on the issue of sepsis versus ischemia reperfusion versus pancreatitis, I think we are all nervous with circulating LPS and endotoxin to be pounded on with arginine, but the point I was trying to make was that pure stress alone without endotoxin might be different. I am not an immunologist, but this feeding alone produces that tolerance factor and a downregulatory response, is that going to help protect us in that situation? The second issue about whether or not we need a CT scan, they are going to get it anyway. This is controversial but I think it is almost a standard of care as if pancreatic necrosis is present on CT scan that antibiotics are standard of care. I agree with that. If the scores are really low, if you have 0 Ranson criteria to an alcoholic pancreatitis and alcohol ideology tends to have milder pancreatitis than the gold standard of some other ideology, and you have 5 Apache points, it would be tough to justify a CT scan there. I wish our residents and doctors would check these scoring systems before they get the CT scan, but it is close to being a standard of care I think. The last question is how do we promote this to other doctors. We had some conversation earlier this week that is it still the gold standard to give TPN, and I would make the point that there is a difference between the gold standard and common practice. I think the evidence would suggest that the gold standard should be enteral feeding but common practice is still TPN or providing nothing, and there we just have to educate our doctors and show them the data.

Dr. Rosenfeld: Just a short comment about a study in 1991 showing that TPN that was not started until 72 h reduced morbidity and complications. Could you comment on these results, does this reduce complications and morbidity?

Dr. McClave: Was that an earlier study where the timing of TPN was looked at?

Dr. Rosenfeld: Yes, not starting TPN until 72 h reduces complications and mortality.

Dr. McClave: All right, early versus late. I think it is tough without a control group that got no TPN and without a control group that got oral feeding. I don't know what to do with those data. I just suggest the opposite that we wait later and that is because we don't have a control group from that study. I can't extrapolate from that study.

Dr. Schulz: I think we have to focus a little bit on feeding the gut in different immune system settings. We should distinguish between the small bowel and the colon. The small bowel does not usually have relevant bacterial concentrations like the colon. Looking at the immune system there is also a big difference because we find no Peyer's patches in the colon but we have millions of lymphocytes and intraepithelial lymphocytes in the colon. T-cell subtypes differ in their homing location in the intestine. From an immunological standpoint and the different physiological functions, the colon and the small bowel look like different organs. This has to be considered when we talk about feeding the gut and using fiber for the colon mucosa or immune-enhancing diets for the small bowel mucosa. My question is, do you have any data about the bacterial setting in necrotic pancreatitis? We have tried to find some, but have failed so far.

Dr. McClave: First about your comment, I would almost put the question back to you. I guess we are interested in permeability at the level of the colon because that is where all the bacteria are, pus is the setting, is the environment, is permeability determined by what is going on higher up in the small bowel where this immune tissue is, and I would think it could be the situation where what is going on in the small bowel sets the tone for the colon. You might comment on that. As far as evidence of what is in the pancreatic abscess and where they came from: usually these are multiorganisms and they tend to be enterocoliforms. There are all kinds of anecdotal data that bacteria from the gut are getting through lymphatics or micropools in the colon and then are setting the pancreas from the gut, but they are anecdotal data. But certainly those data on endotoxin exposure would suggest that you may infect the pancreas from coliforms in the gut.
**Dr. Cynober:** I would like further comment on the question of nitric oxide. Just to summarize the result of very simple experiments we performed in our laboratory with rats (unpublished data). We had control rats and of course no mortality occurred. We had healthy rats receiving \(L\)-nitro-arginine methyl ester (\(L\)-NAME) or a thiourea which are inhibitors of the constitutive nitric oxide isoform and inducible enzyme, respectively, there was no mortality with the two inhibitors. Then in another group we administered LPS from *Escherichia coli* at 10 mg/kg and there was also, no mortality. The 4th group was rats receiving both LPS and L-NAME, and we had 40% mortality. In my opinion we have to carefully discuss this issue because obviously in a certain number of situations the effect is not the same whether you are inhibiting nitric oxide synthetase in the endothelium or in immune cells. There are data which indicate that the nitric oxide-increased production by endothelial cells in the splanchnic area is absolutely mandatory to maintain regional blood flow, and blocking this enzyme will kill the animals. Finally from the data you presented I have not noticed any positive effect with an immune-enhancing diet, but I have also not noticed deleterious effects.

**Dr. McClave:** You are right, there is a dichotomy here that inhibiting nitric oxide is not, it is a double edge sort, they are good things that come from generating nitric oxide-like bacterial killing and the other thing is blood flow, but maybe that is one of the issues that maintains blood flow into the gut. I don't know what the right answer is. The bigger concern for me is do we behave differently if there is ongoing sepsis at the outset and noncirculating endotoxin versus they are just inflamed with the pancreatitis. We start our immune formula and then the patients become septic: are we obligated to stop or can we just feed through the sepsis; I don't know the answer to those questions.

**Dr. Martindale:** My question is on the timing of the CT – back to Dr. Moore’s question. As you know if you do it at 72 h you have a 90% accuracy of picking up pancreatic necrosis, if you do it at 24 h it is only about a 50% accuracy. So I wonder if there should be a time when we resuscitate the patients, watch them, and then CT them to look for the necrosis?

**Dr. McClave:** I think we have to be careful. I believe in this window of opportunity and I don't know how long it is. The best thing I can do is look at the studies where the patients get enteral feeding versus they don't. When the patients don't get enteral feeding, usually by around day 5 or 6 they are starting some feeding. So you can almost look at feeding within 48 h to 5 or 6 days, and I think we are going to see benefits from the early feeding. If we wait until the 72-hour marker to let the CT scan decide for us, we may be missing opportunities, so I would go back to the scores on admission and at 48 h to determine whether we feed or not, and the time of the CT scan is usually somewhere in there. It is a great point, you can miss necrosis if the CT scan is done too early.

**Dr. Carlson:** One of the things that we see in surgical practice is the establishment of infected pancreatic necrosis if only for the reason that we don't know that we are into a cycle of complex high-risk surgical treatment. It is clear that there are groups of people who develop sterile necrosis who you can often treat conservatively and it takes a long time until they settle, and there is another group of patients who develop infective necrosis who very rapidly deteriorate and have a prohibitive mortality if you don't operate on them. The question I want to ask is, what are the factors in relation to intestinal microbiology which determine which people get sterile and which people get infected necrosis? Bengmark (unpublished) for example has recently done some work on synbiotics. Is this an area we should be looking at, in which we are not just talking about manipulating gut nutrition but manipulating gut microbiology simultaneously.
Dr. McClave: It is a good question and I don’t know whether feeding or not changes the bacterial flora in the gastrointestinal tract. But I think an important concept is that pancreatic necrosis is not a contraindication to feeding. It is actually the feeding, if anything, that is going to protect the patient from getting that necrosis infected, and I think that is the most important part. Whether it changes the flora or not I don’t know.

Dr. Déchelotte: I would like to come back to a point of pathophysiology which perhaps addresses the time of early ischemia of the pancreas itself. It is well known that in these patients there may be some splanchnic ischemia including the gut and pancreas. I can remember an experimental study in rats some years ago with chemically induced pancreatitis that was aggravated with simultaneous ischemia, the pancreas itself with an increase in the IL-8 level. We know that IL-8 is a good predictor of severity in the pancreas. There was a study by Debaux in glutamine-supplemented parenteral nutrition that nicely showed a declined the IL-8 level, and on the other hand Roth has shown negative results in pancreatitis. So my suggestion would be to think of an earlier supply of some specific nutrients to the gut and to the pancreas, at the same time protecting from this ischemic and oxidative stress injury quite early, because we generally discuss nutritional support in acute pancreatitis patients after 2 or 3 days at the best, and by then we have probably missed half of our ability to do something.

Dr. McClave: Great point and I am fascinated by the concept that enteral feeding would help promote blood flow to the pancreas and prevent ischemic damage. The second issue that this evokes is the concept of adequate resuscitation, and we have talked about the danger of overloading with salt water, but in pancreatitis they really talk about being overly aggressive to the point that your end point of adequate resuscitation is a drop in hematocrit by 10%. So I think apart from getting feeding started, there is also adequate resuscitation. These patients are obviously losing water and volume and it is a very important part, maybe just as important as feeding.

Dr. Déchelotte: Do you think it would be possible to have minimal enteral feeding in these patients, very minimal caloric supply in the very early hours, but maximal supply of the specific nutrients such as glutamine and antioxidants?

Dr. McClave: I made a comment yesterday about how much enteral feeding it takes to get the job done. I don’t think trophic feeding is enough. What we are talking about is the functional opening up of those channels and I think it takes closer to 50–60% of calories to get that achieved so I think you have to get the feeding high enough or you won’t get the end point you want.

Dr. Labadarios: One would accept that the enteral route is becoming increasingly the route of choice in pancreatitis. The data you presented seemed to show that there is a group or a subgroup within a population of patients with mild to moderate pancreatitis, who actually don’t tolerate enteral feeding. What reasons do you think may be involved in those patients who actually do not tolerate enteral feeding?

Dr. McClave: I am not sure I understand what you are getting at there, but you may be referring to the Schneider study where they didn’t know how severe the pancreatitis was and yet they tried to enterally feed the patients, which means that they tried to enterally feed patients with mild and moderate pancreatitis. Tolerance is a slippery slope and there is a tremendous variation in the local expertise and their ability to do it right, and so I think that is why we see differences in tolerance. Does that answer your question?

Dr. Labadarios: Partly yes. Perhaps I should make my question a little bit clearer. The concept that is emerging is that all patients with mild to moderate pancreatitis will tolerate enteral feeding provided you don’t lose the window of opportunity, but clinical experience may actually be a little bit different.
**Dr. McClave:** You might be misinterpreting it. I don’t think they need nutritional support unless a complication develops or they deteriorate. But if our assessment priorities are correct on admission, the mild or moderate patients will do well, the chances are they will be on an oral diet within 7 days, and the risk of complications is very low. So really you don’t need to challenge them with enteral feeding. That does not mean they won’t exacerbate on day 5 when you give them clear liquids, there is no guarantee, but the point is that you don’t need to have aggressive artificial nutritional support in those patients.

**Dr. Fusco:** How can you avoid pancreatic stimulation just feeding by the intragastric route? In our experience the only way to reduce the pancreatic enzyme flow is to infuse enteral feeding after the ligament of Treitz.

**Dr. McClave:** I had a talk with Dr. Imrie 2 weeks ago. We had a very sick patient, who we described in our lecture, a 72-year-old man with 5 Ranson criteria, which means a 40% mortality rate, diabetic, on the ventilator with chronic renal insufficiency, BUN and creatinine of 50 and 5 on a good day, and he got into the study. We randomized the jejunal feeding and he did well for 6 days. Then on the 7th day he became very ill and his temperature went from 37.8 to 40°C, his white count, which had decreased from 20 down to 15, shot up to 30, and he looked septic. But all our cultures were negative, the chest X-ray which already showed inflammatory respiratory distress syndrome did not change, none of the cultures were positive. I remember at 4 o’clock in the afternoon I got a call from one of my colleagues who just told me that the tube was back in the stomach. We put the tube back down into the jejunum, no other management occurred other than that, and the fever went back down and the patient did well, but it scared us to death. And that is why I comment on the Imrie study. If your institution is still trying to decide how they stand on this issue, I do not encourage intragastric feeding because a patient like this will scare everybody. But Imrie’s experience tells us that we can be surprised at how many patients with severe pancreatitis will tolerate that.

**Dr. Fusco:** This is not our experience because usually when we put the feeding tube into the stomach, we have many problems, particularly abdominal pain and bleeding, and so on. Maybe in the intensive care unit the patients are sicker and they won’t tolerate this.

**Dr. McClave:** Another point I would like to make is that the tube needs to be down at or below the ligament of Treitz, and it is difficult for a radiologist to do this, and certainly bedside techniques can do that. They are secured with the bridle to the nose because if we are going to spend 30 min putting it in the right place we don’t want it to come out 12 h later, that is important.

**Dr. Ribeiro:** If the gut is the main source of infection in severe acute pancreatitis is there a place for early selective decontamination of gastrointestinal tract?

**Dr. McClave:** The whole concept of decontamination is a huge controversial topic and there are tons of studies. My understanding is that it does eradicate short-term infection but that concepts of factorial resistance because of huge issue. We certainly don’t have any data on pancreatitis. I think we can accomplish our end points without doing that.

**Dr. Maiorova:** I want to attract your attention to extremely severe acute pancreatitis in children. The reason for the development of acute pancreatitis in children is usually different from adults and, on the other hand, children are not always small adults. So could you comment. Would you suggest some differences in nutritional support of small patients or children with acute pancreatitis compared with the adults?

**Dr. McClave:** I am an adult gastroenterologist, I just don’t have any experience, I am sorry.
Dr. Martindale: Are you using immune-enhancing diets in your pancreatitis patients now?

Dr. McClave: No but I really want to bring it up because Nestlé has agreed to support a trial. We are doing a multicenter trial right now and we are going to have 3 arms in the study, TPN done correctly, extreme enteral feeding with immune formulas, and then a group that gets nothing for 5–7 days and then goes to TPN or enteral feeding. I think using immune formulas is the right way to go, but it needs to be looked at.

Dr. Déchelotte: Don't you think you should have a 4th arm with standard enteral nutrition?

Dr. McClave: Yes, that would be the ideal, to have a group that gets a standard enteral formula and a group that gets an immune-enhancing formula. But the problem is patient recruitment is tough, even with the 7 centers that we have identified.

Dr. Bouletreau: I have a question going back to gastric feeding, because from a clinical point of view it is so much easier. Do you think it would be harmless to begin with gastric feeding and test tolerance, and then switch to jejunal feeding in a second round?

Dr. McClave: I don't think it is a good idea because the patient would get sick instead of better, and if you go and put the tube down their nose and their stomach and they get worse, can you imagine what it is going to be like to say to them now we want to go back and use a bigger tube, an endoscope that goes further down. I think it would be problematic. But it is a great point and I think there is a percentage of patients that would tolerate it, but I don't think it is the best way to go.

Dr. Bouletreau: So what is your recommendation?

Dr. McClave: You get the tube in, you do your markers on admission. In our institution these patients are in the emergency room for 20–24 h, so by the time we are called they are well into the 2nd day. If we react immediately and get them on schedule that day, we are still barely getting the tube in within 48 h from the time they came to the hospital. So you really have to mobilize forces quickly and get the tube in.

Dr. Rosenfeld: How do you follow up tube position?

Dr. McClave: We don't have to be getting the KUB every day, we can be guided by patients’ symptoms. You check amylase and lipase but you can't have a tight think about it. If the patient is on TPN and the amylase goes from 250 to 270 nobody worries because he is on TPN. If it goes from 250 to 256 he is on enteral feeding. So you use it with clinical judgment. The patient’s symptoms of abdominal pain, nausea, are valid and can guide your judgment. Another thing you should pay attention to is the residual volume. If the tube is in the small bowel and everything is going well, the residual volume should be <10 cm³, it should be very low. In a patient where the tube flips back from the small bowel to the stomach the residual volume about 12 h before goes to 50 and then 80 and then 120. So patients’ symptoms can guide you and if they are questionable, if there is slow resolution of the symptoms, you might check those tube positions, and certainly after you have placed the tube check it one time as your start.

Dr. Martindale: Another controversial area that I hear many questions on is the amount of fat in the diet. As you know cholecystokinin is stimulated by fat in the diet. Does a high-fat diet make this worse? The second question on this, should we withhold intravenous lipids from people that we are unable to treat enterally?

Dr. McClave: I will start with the fat content diet first. Dr. Friedman is a gastroenterologist at Harvard who has done some studies on this. His patients have chronic alcoholic pancreatitis and are in and out of the hospital. They drink a small peptide formula with medium chain triglyceride oil orally. He can keep his patients out of hospital and has better pain management just by that dietary manipulation, drinking it. The data on fat in TPN in pancreatitis is on the case report level and there are two papers. One was a horrible case report: the patient got abdominal pain, went to
surgery and had complications. It turned out to be pancreatitis. He had been getting TPN, and they did not check the triglyceride levels, they just said that it could be the fat in the TPN. But in the second study by Lashner and Henauer, the patient was on 10% fat and tolerating it well. This patient had inflammatory bowel disease. They went to 20% fat and the patient got pancreatitis. He had pancreatitis, and when the fat went to 20% he flared, but when it went back down to 10% it was well tolerated. I think if your triglyceride levels are below 400 you are fine.

Dr. Déchelotte: I would like to come back to the point of gastric feeding and nasojejunal feeding. It seems to me that until now we don’t have the evidence that gastric feeding would be really worse than nasojejunal feeding. We have studies in healthy volunteers showing that intragastric feeding stimulates pancreatic secretion in comparison to nasojejunal feeding which inhibits pancreatic secretion. But in these settings with rather low amounts of nutrition in the first days I think we like the evidence, and it is a very important practical point because it is time-consuming as you know to put in nasojejunal tubes. The nasogastric tube moves every time, and it has a great impact on the medical facilities and medical time in our units. We have some data from groups such as our colleagues in Budapest who reported 2 or 3 years ago in ASPEN or the European Gastroenterology Congress that they always put gastric tubes in their pancreatitis patients, even severe patients, just because they do not have nasojejunal tubes available, and they have had very good experience with tolerance. It was not a randomized trial actually, but I think this rough experience on over 300 patients fed intragastrically is quite astonishing.

Dr. McClave: It is a great point and it hits on the issue of local expertise and can we find cost-effective ways of getting the tube into the small bowel and how can we get either our radiologist or endoscopist to get this tube down the small bowel, how can we do it cost-effectively and more easily. We are working on this. We are working on things like a portable camera that has a battery-operated light source so the whole cord is not dragged down, you just work with it in your arms and slime it down quickly, a small caliber tube that goes to the nose so you have to sedate the patient. Those are some moves in the right direction. But you have a good point about intragastric feeding, that a lot of patients are going to tolerate it, but I think you are playing with fire. Physiologically all that stimulation is right there, there are three levels but the big one is right there in the proximal duodenum. So I would rather work on expeditious low-cost ways to get into the small bowel.

Dr. Schultz: When you talk about enteral nutrition do you mean enteral nutrition with or without fiber? Are there any arguments against increased fiber contents?

Dr. McClave: I would be interested to see that but I have no data and I am not even sure what results I would expect. But it is very important and it should be investigated. That is why I said we have a lot of questions still to be answered in this area.

References