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CE Acute Pancreatitis: Exploring Nutrition Implications

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Abstract

Diseases of the pancreas vary by type, etiology, pathophysiology, and outcomes. One of the principle therapeutic considerations in all types of pancreatic diseases is nutrition. This review will consider acute pancreatitis (AP). Choice of patient, type and composition of nutrition, and timing of initiation will be discussed as components for achieving the maximum benefits of nutrition therapy in AP. The paradigm of nutrition therapy in AP has shifted to early enteral and/or oral nutrition based on disease severity to help mitigate the underlying inflammatory cascade of events leading to AP, beginning with anatomic and functional intestinal changes. Additionally, newer research investigating the inflammatory changes that instigate, maintain, and propagate AP will be discussed in terms of the nutrition effects on systemic inflammation. Nutrition therapy can mitigate the inflammatory changes in the intestinal tract and help with intestinal motility, bacterial overgrowth and translocation. It can help maintain intestinal bacterial composition and abundance similar to predisease levels. This review will also discuss the changes in the intestinal microbiome and effects of probiotics in AP. (*Nutr Clin Pract.* 2020;35:807–817)

Keywords

acute pancreatitis; enteral nutrition; inflammation; nutrition support; nutrition therapy; pancreatitis

Introduction to Acute Pancreatitis

Prevalence

Annually in the US, gastrointestinal (GI) disease affects 60–70 million citizens, resulting in 4.6 million hospitalizations.[1] Acute pancreatitis (AP) was the most common single GI diagnosis in hospitalized patients, with ≈275,000 admissions and an estimated $2.6 billion per year.[1,2] AP is the fifth leading cause of hospital deaths.[3] The reported incidence ranges from 13 to 45 cases per 100,000 worldwide and is increasing.[3,4] AP hospitalizations and costs have risen by 20%–30% in the last 10 years.[2,3] The use of tests to measure serum pancreatic enzymes in the emergency department has increased by ≈60% over 10 years, causing an increased rate of AP diagnoses.[4] Another explanation of increased incidence is the increase in obesity and subsequent gallstone formation. Recurrent AP is not well defined but has been estimated to have an incidence of ≤15%.[5]

Symptoms

AP is a potentially fatal condition often associated with nausea or vomiting and abdominal pain with or without eating.[5] There are 2 major types of pancreatic pain: (1) type A and (2) type B. Type A is characterized by a short (<10 days) interval of pain separated by longer pain-free periods. Type B is characterized by a long (1–2 months) interval of severe, unremitting pain.[5] Pain can be epigastric, in the right upper quadrant, or even radiate to the back.[5] Other clinical features include fever and ileus.

Etiology

Cholelithiasis is the most common cause of AP.[2,3] Pancreatitis developed in 0.05%–0.2% of patients per year among those with known gallstones.[5] Small gallstones were associated with increased annual risk of AP.[5] There is a 95% chance of biliary etiology for AP when serum aspartate transaminase (AST) is >3 times the upper limit of normal, even if imaging does not confirm gallstones.[6] Pancreatitis in women is more likely related to gallstones.[4]

Alcohol misuse is the second most common cause. Prolonged alcohol use (4–5 drinks daily for >5 years) is most commonly required to cause pancreatitis.[2,3] Overall lifetime risk of AP among heavy drinkers is 2%–5%.[2,5] Smoking has been shown to accelerate the progression of alcoholic pancreatitis.[3] Risk of nongallstone AP is more than double

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in smokers with ≥20 pack-year smoking history compared with those who have never smoked.[3] Interestingly, binge drinking has not been shown to significantly increase the risk of AP.[4] Pancreatitis in men is more likely related to alcohol use.[4]

Combined, gallstones and alcohol misuse cause 80% of AP. Other causes are endoscopic retrograde cholangiopancreatography (ERCP)-associated AP (3.5% of all ERCPs), hyperlipidemia, hypercalcemia, type II diabetes (relative risk [RR], 1.86–2.89), increased abdominal adiposity (waist circumference > 105 cm infers a 2-fold increased risk), and less common conditions (such as cationic trypsinogen; familial pancreatitis; cystic fibrosis transmembrane conductance regulator gene, *CFTR*; and serine peptidase inhibitor Kazal type 1 gene, *SPINK1*, mutations).[3,4,6] Pancreas divisum was not shown to be an independent risk factor for AP.[3] Of note, the risk of pancreatitis is 2–3 times more common in African American populations than in white populations.[4]

Pathophysiology

The pathophysiology of gallstone and alcoholic pancreatitis is not similar.[3] The mechanism of gallstone-mediated AP is likely obstructive. Once the obstruction occurs, there is backup of bile into the pancreas, as well as stagnation of bile in the biliary tract. Acinar cells of the pancreas take up bile acids via bile acid transporters.[3] Once within the cell, bile acids increase intra-acinar calcium concentrations and activate proinflammatory mediators signaling pathways causing pancreatic parenchymal damage.[3] Pancreatic duct obstruction also impedes exocytosis of zymogen granules from acinar cells.[3] Accumulation of trypsin within pancreatic vacuoles leads to digestive enzymes autodigesting the pancreas.[3] Acinar injury due to autodigestion stimulates inflammation of the pancreatic parenchyma, leading to AP.[3] Early phases of AP cause mitochondrial damage and adenosine triphosphate depletion in pancreatic ductal cells driving the cell death, ultimately leading to pancreatic necrosis.[5,7]

Alcohol, however, exerts localized toxic effects on pancreatic stellate cells. This causes inflammation of the pancreas during AP.[3] Alcohol also increases the propensity of pancreatic secretions to form protein plugs, which eventually calcify. These calculi cause ulceration of adjacent ductal epithelium, scarring, further obstruction, and acinar atrophy and fibrosis.[3]

Diagnosing Acute Pancreatitis

Diagnosis of AP requires the presence of 2 of the 3 following criteria: (1) characteristic abdominal pain, (2) pancreatic enzyme levels 3 times the upper limit of normal (amylase/lipase), and (3) characteristic findings on imaging (computed tomography [CT]/magnetic resonance imaging) (Table 1).[3,5] Elevated serum lipase is more specific than amylase.[6] To rule out gallstone etiology, abdominal ultrasound is commonly performed, but endoscopic ultrasound (EUS) is the most accurate method to identify cholelithiasis or choledocholithiasis.[6]

Table 1. Diagnosis of Acute Panceatitis.

Diagnosis of acute pancreatitis	
Abdominal pain	Characteristic abdominal pain (epigastric or upper abdominal pain usually constant with possible radiation to back or flank)
Lab values	Serum amylase and/or lipase >3 times upper limit of normal
Imaging	Characteristic findings from abdominal imaging

Table 2. Revised Atlanta Criteria—Classification of Acute Pancreatitis.

Classification	Definition
Mild	No organ failure. No local complications (fluid collections/effusions)
Moderate	Transient organ failure <48 hours (respiratory/cardiac/renal/hepatic/hematologic/neurologic) +/− Local complications (fluid collections/effusions)
Severe	Persistent organ failure >48 hours (respiratory/cardiac/renal/hepatic/hematologic/neurologic)

If a patient has characteristic abdominal pain and pancreatic enzyme elevation, the recommendation is to wait 2–3 days after the onset of attack to determine the severity of the disease, because initially, 15%–30% of patients have a normal CT scan.[6] Clinical severity of AP is stratified into 3 categories (Table 2). Mild AP has no organ failure and no local or systemic complications and is often associated with discharge within 3–7 days of onset. Moderately severe AP has ≥1 transient organ failure (<48 hours) and/or systemic or local complications. Severe AP has persistent organ failure or multiorgan failure (>48 hours), which most commonly is associated with necrosis and higher mortality.[3]

Acute peripancreatic fluid collections occur within the first several days of onset.[3] Acute necrotic collections can include only peripancreatic tissue and can be sterile or infected.[3] Pancreatic necrosis on imaging is the absence of enhancement on imaging and may not be apparent until 3 days after disease onset.[6] Diagnosis of infected pancreatitis is usually based on gram stain and culture of infected

Table 3. Definitions of Pancreatic Fluid Collections.

Type of collection	Time, wk	Location	Imaging
Interstitial edematous pancreas			
Acute peripancreatic fluid collection	<4	Adjacent to pancreas, only extrapancreatic	Homogeneous fluid that is not encapsulated
Pseudocyst	>4	Adjacent to pancreas	Homogeneous fluid that is encapsulated
Necrotizing pancreatitis			
Acute necrotic collection	<4	Intraparenchymal and/or extrapancreatic	Heterogeneous fluid collection with possible loculations that is not encapsulated
Walled-off necrosis	>4	Intraparenchymal and/or extrapancreatic	Heterogeneous fluid with nonliquefied material and possible loculations that is encapsulated

pancreatic material from fine needle aspiration (FNA).[6] A high index of suspicion should be present when there is air within the pancreatic necrosis on imaging and/or if the patient has worsening pain and leukocytosis 1–2 weeks after disease onset.[6] The revised Atlanta Classification clearly delineates these definitions of pancreatic fluid collections.[8] (Table 3)

Mortality of AP

Studies evaluating mortality of all GI diseases have shown that AP was the 14th leading cause of death from any GI disease, including hepatic/biliary causes.[1] Overall mortality for all causes of AP is ≈2%.[2,5-9] Age >60, multiple comorbid conditions, obesity, and long-term heavy alcohol use all predict higher mortality.[2] Admission laboratory results are also associated with a higher likelihood of mortality (eg, hemoconcentration, azotemia, C-reactive protein (CRP) >150, and acute fluctuations of blood glucose).[2,11] Importantly, the serum levels of amylase/lipase are not prognostic factors for AP.[2] Pain is also insensitive for diagnosis and prognosis.

Many clinical complications can increase the likelihood of mortality. A systemic inflammatory response syndrome (SIRS) lasting >48 hours was associated with higher mortality and a worse prognosis.[2] The literature reports mortality with early extended (>30%) pancreatic necrosis or infected necrosis with organ failure to be as high as 42%.[6,12] This is much greater than patients who have sterile necrosis and organ failure.[6,12] Multisystem organ failure within the first week is associated with 50% mortality.[6] Infected pancreatic necrosis is predominant, along with multisystem organ failure, later on during hospitalization.[6]

Risk Stratification

The goal of risk stratification tools in AP is to identify patients at risk for developing major negative outcomes, including persistent organ failure, infected pancreatic necrosis, and death. An AP severity prediction tool within 48–72 hours of presentation enables triage of patients to the appropriate level of care to decrease morbidity and mortality. A diverse array of severity prediction tools exist, categorized as clinical scoring systems, single laboratory values, and other variables. Some examples of commonly used clinical scoring systems are Ranson criteria, Acute Physiology And Chronic Health Evaluation II (APACHE II), bedside index in AP (BISAP), early warning system, Glasgow-Imrie score, CT severity index, and Japanese severity score (Table 4).

Determining disease severity is difficult. Clinically, APACHE II and Ranson criteria have poor sensitivity, especially on admission (39%–63%).[13] These improve (but not significantly) from the initial admission screen to 48 hours into the disease.[13] Investigators have concluded that available predictive tools have limited clinical utility by having only moderate predictive value for persistent organ failure and mortality.[14] Additionally, delays in management may occur while waiting for the 48–72-hour screening.[6,15] Some studies have demonstrated that the best screening tool to predict organ failure was the Glasgow-Imrie score on admission and the Japanese severity score at 48 hours.[14] Most often, clinicians use a combination of APACHE II score and Ranson criteria, as well as imaging details, to determine the treatment of patients.

BISAP is a validated clinical scoring system that predicts in-hospital mortality based on 5 variables: (1) blood urea nitrogen (BUN) > 25 mg/dL, (2) impaired mental status, (3) SIRS, (4) age >60, or (5) presence of pleural effusion.[9,10] If patients have a BISAP score of <2 points, their likelihood for mortality is <1%; 2 points, 2%; and if ≥3 points, 5%–20% mortality risk.[9,10] The BISAP score is helpful because it stratifies patients within the first 24 hours of admission.[9,10]

Admission hematocrit of >44% and failure to decrease at 24 hours were good indicators of pancratitc necrosis and predictors of organ failure because of persistent under resuscitation and fluid sequestration.[6] Other clinical factors used to assess severity include age, comorbidities, low urine output, rebound abdominal pain, altered mental status, and abdominal and flank bruising.[6] The presence of systemic inflammation is diagnosed by 2 of the following criteria: (1) temperature < 96.8°F or 100.4°F, (2) heart

Table 4. Risk Stratification Tools for AP.

Risk stratification tools for AP	Components of stratification tools
Ranson criteria	Five variables (age, glucose, WBC, LDH, and AST) calculated on admission and 6 variables (HCT, BUN, Ca, P_aO_2, base deficit, and fluid deficit) at 48 hours after admission to risk stratify and predict mortality.
APACHE II	Mortality prediction tool using multiple clinical and laboratory variables in its calculation (history of organ failure, age, temperature, MAP, pH, pulse, Na, K, Cr, acute renal failure, HCT, WBC, GCS, F_iO_2, respiratory rate, etc)
BISAP	Score allowing for early identification of increased risk of in-hospital mortality secondary to AP. (BUN, impaired mental status, SIRS, age >60, and pleural effusion)
EWS	Guideline to quickly determine degree of illness of a patient using vital signs (respiratory rate, oxygen saturation, temperature, blood pressure, heart rate, and level of consciousness)
Glasgow-Imrie score	A score for patients with AP to determine severity of pancreatitis based on 8 values within 48 hours of admission (P_aO_2, age, PMNs, Ca, renal function, AST, serum albumin level, and blood sugar)
CT severity index	A grading system based off CT findings to define severity of inflammation and necrosis of the pancreas
Japanese severity score	A score to predict in-hospital mortality based on 9 prognostic factors (base deficit, P_aO_2, BUN, LDH, platelet count, Ca, SIRS, and age)

AP; acute pancreatitis; APACHE II; Acute Physiology And Chronic Health Evaluation II; AST, aspartate transaminase; BISAP, bedside index in acute pancreatitis; BUN, blood urea nitrogen; Ca, Calcium; Cr, Creatinine; CT, computed tomography; EWS, early warning system; F_iO_2, fraction of inspired oxygen; GCS, glasgow coma scale; HCT, hematocrit; K, Potassium; LDH, lactate dehydrogenase; MAP, mean arterial pressure; Na, Sodium; P_aO_2, partial pressure of oxygen; PMNs, neutrophils; SIRS, systemic inflammatory response syndrome; WBC, white blood cell count.

rate >90 beats per minute, (3) respiratory rate >20 breaths per minute, and (4) white blood-cell count < 4000 or > 12,000 or 10% bands.[16] Although SIRS criteria is no longer utilized to diagnose sepsis, these clinical values have been shown to be associated with increased organ system failure and 25% mortality rate with persistent SIRS during hospitalization.[6]

Metabolic Response to Acute Pancreatitis

Inflammation

AP is a spectrum of diseases, ranging from mild inflammation to severe pancreatic necrosis. Regardless of severity, inflammation underlies the pathophysiology of AP. The sentinel AP event (SAPE model) identifies a sentinel point in time at which various risk factors (eg, alcohol consumption) become causative and initiate the progression to pancreatitis.[17]

The production of immunoglobulin A (IgA) by the intestinal epithelial barrier is the first line of defense in AP. AP causes weakening of this defense system because of increased capillary leakage and decreased ability of tight junctions to maintain a barrier secondary to inflammatory mediators. When the intestinal barrier is compromised, intestinal bacteria can penetrate the bloodstream. Invading microorganisms are recognized in minutes by multiple components of innate immunity.[18] Peak inflammatory cytokine production occurs 24–36 hours after onset of pain, with subsequent systemic manifestations and distant organ failure 2–4 days later.[19] This dysregulation of the immune system leads to overwhelming systemic inflammation and immune paralysis, thus worsening AP.[18]

Inflammation is fueled by tumor necrosis factor (TNF) secretion secondary to endotoxin, hypoxemia, hypotension, ischemia, and reperfusion. Nitric oxide synthesis is increased activating the arachidonic acid pathway and inducing cyclooxygenase (COX) activation.[18] TNF and interleukin (IL) 1 are synergistic, leading to increased permeability and neutrophil activation.[18] IL-1 also induces fever, T-cell and macrophage activation, and COX and nitric oxide synthase.[18] IL-8 is an endogenous chemoattractant, which is present for a longer duration and is proinflammatory.[18] IL-6 has been used as a marker of severity of the inflammatory response.[18] It has both proinflammatory and anti-inflammatory roles.[18]

Metabolic Changes

Similar to patients with sepsis and shock, patients with AP exhibit a typical metabolic pattern of systemic inflammation, elevated protein catabolism, and deranged glucose metabolism as a result of elevated insulin secondary to reduced glucose uptake and accelerated neoglucogenesis.[11,20] Net nitrogen loss can be up to 20–40 g/d.[20] Negative nitrogen balance is associated with increased mortality.[21] Premature intra-acinar activation of trypsinogen resulting in acinar injury upregulates proinflammatory mediators, release of cytokines, systemic inflammation, and microcirculatory injury.[12] This ultimately leads to hypoperfusion of gut mucosa, resulting in a loss of gut barrier integrity and translocation of gut flora.[12]

In both sepsis and the SAPE model of AP, the gut plays a key role in modulating inflammation in several important ways. In the healthy state, a single-cell layer of mucosal epithelium allows absorption of nutrients while maintaining an effective barrier against luminal bacteria.[19] In times of illness, this balance is disrupted. Failure of the gut barrier through loss of intestinal integrity creates a portal for bacterial translocation and endotoxin entry, loss of villus height, and disrupted CD4:CD8 ratios in mesenteric lymph nodes, the spleen, and peripheral blood.[19] This increased propensity for bacterial translocation across the gut lumen into the circulation is one described mechanism underlying sepsis.[3] In summary, the gut plays a key role in modulating the overall stress response. [22]

Changes in Gut Barrier

The mucosa-associated lymphatic tissue constitutes 50% total body immunity acccounting for 70% of all antibody production.[18,19] The maturation of mucosa-associated lymphatic tissue (MALT) tissue occurs via introduciton of physiologic amounts of intraluminal antigen and subsequent immune tolerance. The 2-hit hypothesis of multiorgan failure in AP describes the first hit as injury from hypoxia and hypotension.[18] The second hit occurs as a result of ischemia and reperfusion and/or bacterial infection, increasing severity and organ failure.[18] This leads to injury to MALT, decreased immunity, and uncontrolled systemic events causing increased endotheial permeability and endotheilal damage, accumulation of leukocytes, bacterial and endotoxin translocation, increased susceptibility of microbiological infection, and dysfunction leading to disseminated intravascular coagulation and multiorgan dysfunction.[18] Ultimately, the patient stops eating because of pain and critical illness, and IgA-producing cells decrease within a few hours of stopping oral intake, worsening the likelihood of organ failure and severe AP.

Treatment of Acute Pancreatitis

Medical Treatment

No single set of guidelines can be applied to the diverse pathophysiology seen in AP.[6] There are, however, guidelines to medically optimize patients on admission. Early fluid resuscitation is important. Fluid resuscitation by american college of gastroenterology (ACG) guidelines is recommended to begin at 250–500 mL/hr.[3,5] Urine output goals should be ≈0.5 mL/kg/hr if not in renal failure.[6] Supplemental oxygen, especially in elderly patients, also improves outcomes.[6] Adequate analgesia is another important aspect of treating early AP.[3,5] Physiologic stress hyperglycemia, especially in patients who are not diabetic, is a predictor of mortality.[11] A blood sugar level > 180 mg/dL (10 mmol/L) at admission in a patient who does not have diabetes is associated with increased mortality.[11] The presence of hypoxia, tachypnea, delirium, and SIRS should merit consideration for intensive care unit (ICU) admission.[6]

Traditional management of AP did not include nutrition therapy, based on the erroneous premise of allowing the "pancreas to rest" in the early phases of disease. Additionally, some thought that stimulating the exocrine function of the pancreas via enteral feeding would have negative consequences on prognosis by favoring the autolytic processes of the pancreas, thus injuring the surrounding soft tissues. Starvation within this old paradigm has been shown to contribute to further alteration of the gut mucosa, its microenvironment, immune function, and permeability, promoting the risk of bacterial translocation. Ralls et al demonstrated the detrimental decreases in the intestinal barrier function with starvation in humans.[23] Further evidence shows that starvation leads to loss of gut barrier function, production of cytokines (eg, toll-like receptor 4, TNF-α), decreased transepithelial resistance, and atrophy of gut-associated lymphoid tissue in conjunction with systemic inflammation.[23,24]

Schmid-Schonbein developed a modern theory of "autodigestion," combining the role of pancreatic enzymes and systemic inflammation.[25,26] In the healthy intestine, pancreatic enzymes are confined to remain within the intestinal lumen. In starvation, the gut mucosal barrier is breached, and pancreatic digestive enzymes escape into the intestinal wall and the systemic circulation. Within the intestinal wall, these enzymes generate tissue-degradation products, among which cytotoxic "unbound free fatty acids" and other inflammatory mediators flow into the systemic circulation, compromising cell function and leading to peripheral organ failure.

A meta-analysis of 7 trials analyzing prophylactic antibiotic use demonstrated no benefit in preventing infected necrosis or mortality.[5,6] The ACG does not recommend prophylactic antibiotics for patients with pancreatic necrosis or any type of AP. The American Gastroenterological Association recommends propylactic antibiotics only for patients with >30% of pancreatic necrosis because of the higher incidence of infection.[5]

Prevention is important. Patients with hyperlipidemia, hypertrigliceridemia, or hypercalcemia require treatment and monitoring. Post-ERCP pancreatitis is reported in 3%–5% of cases. Minimizing manipulation of the pancreatic duct, prophylactic nonsteroidal anti-inflammatory–drug use, and periprocedural hydration may help to decrease this incidence.[6]

A feared complication of AP is splenic vein thrombosis (20%) and bleeding (<5%).[3] Splenectomy is not recommended.[3] Unexplained GI bleeds in patients with AP need emergent CT to rule out visceral pseudoaneurysm (ie, splenic artery, branches from celiac and superior mesenteric artery, gastroduodenal artery, inferior pancreaticoduodenal

artery, etc), and if it is identified, rapid angiographic intervention is necessary.[6]

Endoscopic Treatment

Patients with AP may present with or develop indications for endoscopy. Initially, if the cause is biliary in nature, EUS and ERCP need to be considered. Evidence shows early ERCP decreased complications of acute biliary pancreatitis by 50%.[6] Others have shown that there is no difference in organ failure, local complications, and overall morbidity and mortality. Ultimately, ERCP should be reserved for patients with acute cholangitis complicated by acute biliary pancreatitis (10%), patients with dilated common bile duct, or patients with choledocholithiasis.[6] There is no evidence for routine ERCP without the listed indications to decrease complications, cost, or length of stay.[6]

In 5%–15% of patients with AP, peripancreatic fluid collections form and are seen on imaging or become symptomatic.[8] Fluid collections are categorized as pseudocysts or necrotic fluid collections (Table 3).[8] Sponaneous resolution of pancreatic pseudocysts occur in 33% of patients, especially if minimally symptomatic and/or <4 cm in diameter.[3] Large fluid collections (>4 cm) and/or symptomatic collections should initially be managed with endoscopic intervention.[3] Evolution of pancreatic fluid collections, which may take weeks to months, tend to develop a wall of granulation tissue surrounding fluid or necrotic material.[6] The presence of walled-off necrosis is not an indication for treatment but may require treament for secondary infection or other symtoms (obstruction).[6] Infection with pancreatic necrosis occurs 33% of the time and requires FNA to direct antimicrobial therapy, as well as percutaneous and/or endoscopic drainage.[27] A multicenter randomized trial demonstrated that endoscopic drainage was not superior to percutaneous drainage for major complications or death.[27] In the surgery group, percutaneous drainage was successful in 51% of patients.[27] In 40% of patients who underwent endoscopic drainage, no further intervention for necrosis was needed.[27] In summary, length of stay, development of pancreatic fistula, and new-onset cardiovascular organ failure were more common in the surgical group, leading authors to recommend endoscopic drainage for infected necrosis before surgery.[27]

Surgical Treatment

Surgical treatment is becoming uncommon with increased observation of small, noninfected, asymptomatic fluid collections that can be treated with conservative, nonprocedural management.[6] The step-up management of infected necrosis with percutaneous catheters and antibiotics with minimal invasive necrosectomy, if needed, has been shown to decrease onset of organ failure by 30% and obviate the need for surgical necrosectomy by 35%–50%.[3,27]

Surgical management of biliary causes of pancreatitis is controversial. Cholecystectomy is indicated as soon as possible, based on resolution of clinical symptoms (ie, resolution of pain or minimization of pain) and normalization of labartory values and should not exceed 2–4 weeks after discharge to prevent recurrence of AP.[6] If the patient improves quickly with type A pain, cholecystectomy during hospital admission is recommended. Empiric cholecystectomy may be considered in patients with an in situ gallbladder and with unexplained relapsing AP, as this could be caused by microcholelithiasis.[6] Patients who are not surgical candidates should be considered for endoscopic sphincterotomy to provide protection from subsequent attacks of AP.[6]

Nutrition Treatment

Overview

With the knowledge that inflammation plays a central role in initiation and progression of AP, the benefits of nutrition therapy in modulating the oxidative stress response and counteracting the catabolic effects during the initial phase of AP are paramount.[28] The major benefit of nutrition therapy is its immunologic effect, including maintenance of normal intestinal motility and IgA production, prevention of bacterial overgrowth, and decreased bacterial translocation and intestinal permeability.[29] Nutrition therapy reduces overall disease severity, measured using CRP and hyperglycemia, and causes faster resolution of the disease process (ie, duration of systemic inflammation, hospital length of stay).[30] Additional unexpected benefits of nutrition include reducing intra-abdominal pressure and improving postoperative closure of pancreatic fistulas. Thirty-day fistula closure rates were reported to be 60% (24 out of 40) with enteral nutrition (EN) compared with 37% (14 out of 38) with parenteral nutrition (PN).[31] Klek et al reported the odds ratio of closure to be 2.57 in the EN vs PN groups.[31]

Oral Nutrition

The PYTHON study, which was a seminal multicenter, randomized, controlled superiority trial in patients with AP, compared early EN within 24 hours to on-demand oral intake >72 hours after presentation to the emergency department.[32,33] Patients with AP who were at high risk for complications (APACHE II score of ≥8, an Imrie or modified Glasgow score of ≥3, or a serum CRP level of >150 mg/L) were randomly assigned to nasoenteric tube feeding within 24 hours after randomization (early group) or to an oral diet initiated 72 hours after presentation (on-demand group), with tube feeding provided if the oral diet was not tolerated.[32,33] The primary end point was a composite of major infection (infected pancreatic necrosis, bacteremia, or pneumonia) or death during 6 months of

follow-up.[32,33] A total of 208 patients were enrolled at 19 Dutch hospitals. The primary end point occurred in 30 of 101 patients (30%) in the early group and in 28 of 104 (27%) in the on-demand group (RR, 1.07; 95% CI, 0.79–1.44; $P = .76$).[32,33] There were no significant differences between the early group and the on-demand group in the rate of major infection (25% and 26%, $P = .87$) or death (11% and 7%, $P = .33$).[32,33] In the on-demand group, 72 patients (69%) tolerated an oral diet and did not require tube feeding.[32,33] The on-demand group also had shorter time to oral intake (6 vs 9 days; $P = .001$).[32,33] In conclusion, this trial did not demonstrate superiority of early nasoenteric tube feeding, when compared with an oral diet after 72 hours, in reducing the rate of infection or death in patients with AP at high risk for complications.[32,33]

What type of oral diet (eg, food consistency) is recommended? Does one have to start with clear liquids? Three studies asked the question of a clear-liquid diet vs either a low-fat solid diet or a soft diet. There was no difference between a clear-liquid diet and a low-fat solid diet.[34] When comparing clear liquids with a soft diet, hospital length of stay was decreased in the group receiving a soft diet in both studies.[35,36]

In summary, satisfying patient wishes for an oral diet without a clear-liquid restriction decreased overall hospital length of stay compared with the current oral intake guidelines, which require absence of pain and a normal chemical profile (eg, lipase).[37] In mild AP, oral feeding can be started if there is no nausea or vomiting and abdominal pain has improved or resolved.[3,22]

Enteral Nutrition

EN is feasible, safe, and beneficial in all types of pancreatitis.[22] If bacterial translocation can be reduced through maintenance of intraluminal nutrition therapy, it is reasonable to attempt it.[7] EN preserves gut barrier integrity and function, reducing colonic bacterial overgrowth and diminishing endotoxin and bacterial translocation.[7,38,39] EN over PN showed decreased levels of TNF, IL-1, IL-6, and IL-8 in the EN group.[38] The 2016 American Society for Parenteral and Enteral Nutrition/society of critical care medicine guidelines recommend EN over PN and show a reduction in infectious morbidity (42.6% vs 16.1%, $P < .0001$) and mortality (16.4% vs 6.1%, $P = .02$).[40] A meta-analysis of 8 randomized clinical trials (RCTs) found that EN significantly decreased mortality, organ failure, and surgical intervention compared with PN.[22] EN vs PN mortality rates showed increased survival with EN (4% vs 15.9%).[22] In patients with complications of AP, including fistulas, ascites, or pseudocysts, tolerance to EN is described.[22]

A systematic review of complications due to EN and PN in patients with predicted severe AP was performed.[42,43] PN was most often associated with hyperglycemia, which increased morbidity and mortality in critically ill patients, including those with severe AP. However, a lower and smaller range for blood glucose goal (81–108 mg/dL) worsened mortality compared with more conventional glucose control (≤180 mg/dL) because of increased hypoglycemic complications.[45] Although the exact mechanism for higher hyperglycemia rates in the PN group remains to be determined, disturbances in carbohydrate metabolism or increased endogenous insulin concentrations are thought to be potential mechanisms. Hyperalimentation due to PN is unlikely to be a major contribution, since no significant difference in nutrient delivery between the EN and PN groups was shown.[43,44,46,47] Mechanical complications with EN and PN consist of central venous access infections and dislodgement of feeding tubes with requirement for replacement.

The issue of EN tolerance can be difficult to define and is controversial in the literature. Tolerance can be divided into 2 broad categories. The first is related to the phases of stimulation of pancreatic enzyme secretion. Pancreatic enzyme stimulation may be influenced by the level at which EN is infused (ie, gastric vs postpyloric), content of EN formula, and individual patient variation. Tolerance is also related to motility and access to the GI tract, including infusion method, duodenal compression, duration of ileus, and institutional experience and expertise. Randomized studies comparing EN by the gastric-vs-jejunal route in severe AP has demonstrated similar outcomes.[48,49] Pain, diarrhea, and energy balance were no different in the gastric-vs-jejunal feeding groups.[50] Although theoretically advantageous, semi-elemental diets containing small peptides and middle-chain fats that do not require pancreatic enzymes for digestion are unnecessary. Both oligomeric and polymeric diets were well tolerated in severe AP.[51]

The timing of EN and its maximum benefits have been investigated. A meta-analysis by Petrov et al included 11 randomized controlled trials.[42,43] The authors demonstrated that the optimal benefits of EN occurred when started within 48 hours of illness.[42,43] Rates of multiorgan failure (RR, 0.44), infectious complications (RR, 0.46), and mortality (RR, 0.46) were significantly reduced.[42,43] However, initiation of EN after the first 48 hours of admission showed no significant difference compared to the PN group.[42,43] Bakker and colleagues demonstrated that in the EN arm of 8 RCTs, composite mortality, organ failure, and infectious necrosis were significantly reduced in patients receiving EN within 24 hours vs after 24 hours of admission (19% vs 45%, $P < .05$).[32,33] Finally, Sun et al reported pancreatic infection, multisystem organ failure, ICU length of stay, and SIRS response to be significantly lower in the early EN vs delayed EN groups in severe AP.[52] The authors concluded early EN moderates excessive immune responses from inflammation (such as reduced oxygen delivery, villus ischemia, enterocyte apoptosis, and tight junction separation) and improves clinical outcome.[19,52]

There is also concern that when patients have severe AP with shock requiring vasopressors, EN could cause gut ischemia. Multiple studies, including the NUTRIREA-2 Trial, have demonstrated that the risk of developing nonocclusive mesenteric ischemia in patients receiving EN was about 2% (20-kcal/kg/d EN delivered to patients receiving an average of 0.56-μg/kg/min norepinephrine).[19] Another study, the TARGET Trial, which gave energy-rich EN to patients in shock requiring vasopressors found a 0.05% incidence of nonocclusive mesenteric ischemia patients.[19] Finally, a study that identified 12,000 patients in septic shock on vasopressors receiving EN found the incidence of nonocclusive mesenteric ischemia to be 0.3%.[19] Ultimately, EN is safe, even in patients in shock from AP.

Parenteral Nutrition

Recent evidence indicates decreased morbidity, particularly infectious complications, and mortality with the use of PN in critical illness, including severe AP patients. Xian-Li et al conducted a prospective randomized control trial in severe AP and showed that the start of PN 24–48 hours after obtaining hemodynamic control reduced complications, hospital stay, and mortality in this population (mortality PN/glutamine 0% vs PN 14.3%, $P < .05$).[53] PN should be initiated at $\geq$5 days to allow the inflammatory response to subside.[16,40,41]

Another trial of PN in high-risk patients was reported by Harvey et al in the CALORIES Trial group.[54] This was a multicenter trial performed in England and included 2400 ICU patients who were randomly assigned to be fed through either the parenteral or the enteral delivery route, with nutrition support initiated within 36 hours after admission and continued for up to 5 days. The primary outcome was all-cause mortality at 30 days.[54] After 30 days, 393 of 1188 patients (33.1%) in the PN group and 409 of 1195 patients (34.2%) in the EN group died (RR in the PN group, 0.97; 95% CI, 0.86–1.08; $P = .57$).[54] The PN group had significantly lower hypoglycemic events (3.7% vs 6.2%; $P = .006$) and vomiting (8.4% vs 16.2%; $P < .001$).[54] There were no differences in the mean number of treated infectious complications (0.22 vs 0.21; $P = .72$) or 90-day mortality (37.3% vs 39.1%; $P = .40$).[54] The authors concluded that there were no significant differences in 30-day mortality between the EN and PN groups.[54] PN can equal EN, although it should be considered only in high-risk critical illness when EN is unavailable.[54]

PN causes profound changes in small-intestinal bacterial communities moving from a gram-positive Firmicutes flora to a gram-negative Proteobacteria-dominated community.[23,55] PN has been shown to abruptly deprive the intestinal microbiome of nutrients and create a state of nutrient withdrawal.[23,55] Consequences of intestinal-bacterial nutrient deficiencies lead to local and systemic infectious complications, multiorgan failure, and mortality.[10,56,57] PN causes increased inflammatory cytokines with decreased regulatory cytokines within the bowel wall, leading to a proinflammatory state in the GI tract.[23,55] Overall, PN is more expensive than EN or oral nutrition and associated with more complications.[6] PN should not be the first line of nutrition therapy for patients with AP.

Challenges of Nutrition Therapy

GI tolerance is a common complication associated with oral and enteral feeding. Most studies that evaluated oral and enteral feedings excluded patients who were having continued nausea or vomiting, or they received less energy via calories than recommended. The recommended algorithm of nutrition therapy based on tolerance is to start with a diet that the patient can take by mouth. If they are unable to tolerate it, attempt administration of enteral via an nasogastric or an nasojejunal tube. Finally, PN should be the last option for nutrition in patients with AP.[6]

A lower incidence of pain was described using jejunal vs oral feeding, presumed to be due to less pancreatic stimulation following gastric feeding.[5] Diarrhea is another common side effect associated with EN. One study demonstrated that PN patients had reduced odds of diarrhea (80%, $P < .001$).[58] The mean difference in diarrhea was 19% ($P < .001$).[58] Diarrhea is a common side effects of many ICU treatments (eg, antibiotics) but still occurs at a relatively low frequency.[58]

Endocrine abnormalities are common in patients with AP. Stress hyperglycemia is not uncommon. Stress hyperglycemia at admission is associated with higher mortality, higher stroke rates, and higher myocardial infarction rates, especially in patients without a prior diabetes diagnosis. Adding enteral or parenteral (less than historical formulations) therapy may worsen control of blood glucose levels and should be treated.[11]

Lastly, pancreatitis causes exocrine dysfunction. It can take 2–3 months for this to recover, thus contributing to enteral feeding intolerance.[3] Pancreatic enzyme replacement may improve tolerance of oral nutrition and/or EN.[3]

Other Modalities

Specific Nutrients

Recent interest in pharmaconutrition diets (otherwise known as immune formulas) in all types of seriously ill patients has grown. There are very few clear recommendations on the prognostic benefits of these diets, specifically for AP patients. Scientifically based evidence and, therefore, recommendations on enteral pharmaconutrition are ambiguous. Some described benefits include improvements in inflammatory markers and suggest outcome benefits (eg, hospital and ICU length of stay, duration of EN, and infections

complications—specifically pneumonia) with the administration of nutrition enriched with pharmaconutrients.[59,60,61] The immune components studied included ω-3 polyunsaturated fatty acids (eg, fish oil), arginine, and glutamine supplementation. A meta-analysis of immune formulas compared to standard nutrition formulas in severe AP showed no benefit.[42,43,44,62]

Glutamine is an important substrate for the unfed enterocyte.[19] Long-term PN can cause a glutamine deficiency, leading to dysfunction of the gut.[38] Glutamine-supplemented PN preserves gastric-associated lymphatic tissue cell mass and antibacterial defenses and has been encouraged in patients with critical illness associated with a catabolic response.[19,22] Parenteral glutamine supplements in patients receiving PN have reported prognostic benefits with shorter hospital stay, reduced infectious complications, reduced need for surgery, better glycemic control, and faster resolution of inflammatory biochemical markers.[40,41,63,64,65] One study demonstrated that overall complications in patients receiving glutamine supplementation was 25% vs 47% in the PN-only group.[66] Patients receiving EN did not benefit significantly from glutamine supplementation.[66]

Somatostatin is another adjunct sometimes used in treating pancreatitis. Somatostatin is a hormone that suppresses the release of pancreatic secretions and is sometimes referred to as the great inhibitor. It is believed that somatostatin may allow the pancreas to rest by inhibiting pancreatic secretions. Clinically, octreotide is used because of its longer half-life compared with somatostatin (72–98 vs 2–3 minutes). One small study demonstrated possible reduction in overall mortality in patients with severe AP; however, the largest single RCT on octreotide in moderate to severe pancreatitis demonstrated no effect on mortality, organ failure, or secondary infections.[6] Neither agent has demonstrated effectiveness in treating AP, and its use is not included in most treatment algorithms.[5,6]

The Microbiome

A "healthy" microbiome depends on many factors, including host genetics, nutrition, age, and environmental stress, to maintain healthy microbial diversity.[71] The human GI tract has a rich microbiota consisting of $>10^{14}$ microorganisms and >5000 genes.[12] Firmicutes and Bacteroidetes are the most prevalent bacteria, constituting 80%–90% of the gut microbiome.[12] The gut microbiome influences the immune system through its effect on systemic metabolism.[12] A healthy gut is a combination of a diverse bacterial community, maintenance of intestinal immunity (eg, IgA), and barrier function, which limits the growth of pathologic flora and maintains homeostasis.[12]

Critical illness increases gut microbial immigration, changes environmental growth conditions of the microbiome, and impairs microbial clearance.[19] There is strong evidence that changes occur in the intestinal microbiome immediately after the index sentinel event in AP and subsequently thereafter. There is known dysbiosis associated with pancreatic disease and even worse with patients with obesity, metabolic syndrome, and diabetes.[12] The ICU environment of gastric acid suppression and reduced oral feeding also creates a microbial imbalance.[19] The gut microbiome may drive the proinflammatory response in AP.[18] To add insult to injury, animal models have shown that enteral starvation alters levels of Firmicutes and Bacteroides to Proteobacteria compared with oral-fed mice.[55] A significant percentage of patients with AP have increased intestinal permeability.[12] Circulating bacterial DNA representative of gut bacteria was found in 68.8% of patients with AP.[12] Patients with gut dysbiosis have been found to have worse outcomes.[23]

Probiotics

Prospective RCTs have demonstrated decreased length of stay in enterally fed patients who also received probiotics.[22] Probiotics are live microorganisms that are safe to be consumed. One study evaluated patients receiving *Lactobacillus plantarum* and demonstrated significantly decreased infection rates but no mortality difference.[22] There is also laboratory evidence that *Saccharomyces boulardii* with concomitant ciprofloxacin administration lowered severity of acute necrotizing pancreatitis.[22]

Ecoimmunonutrition (EIN) is a new term describing the administration of probiotic-containing capsules (*Bacillus subtilis* and *Enterococcus faecium*) with PN or EN. The combination of EN and EIN showed decreased endotoxin, TNF-α, and IL-6 and improved outcomes.[3,17] Another meta-analysis evaluating the role of probiotics favored the probiotic group over the control with respect to infection and hospital length of stay.[67] Administering probiotics to patients with sepsis has been shown beneficial in small studies, but there is no RCT to date. Finally, a multicenter, double-blind, placebo-controlled trial called PROPATRIA studied 298 patients who were randomized to receive fiber plus EN or both of those plus probiotics.[22] The results showed similar infectious rates but higher mortality (6% vs 16%) in the group receiving probiotics.[22] Also, there was more organ failure and multiorgan failure in the probiotic group.[22] Therefore, probiotics cannot be recommended for management of AP based on available data, but there is a need for further investigation.[12,22]

Conclusions

Pancreatitis involves a wide spectrum of illness severity, from mild to severe pancreatitis with infected necrosis. Systemic inflammation is involved in all types of AP, but dysregulation of this inflammation promotes worsening disease severity. All patients with AP should have nutrition as a critical component of their medical therapy. Whether

the patient has mild disease (without pain, nausea or emesis, or systemic inflammation) and can tolerate an oral diet of low-fat solid foods or severe pancreatitis in which enteral feedings should be administered, daily reassessment of tolerance should be conducted. In mild disease, providing an on-demand oral diet, not limited to clear liquids, is safe. This does not need to happen within 24 hours of admission but has been shown to have equivalent outcomes if started at 72 hours after onset of pancreatitis. With AP complications (such as fluid collections, necrosis, and sepsis), nutrition therapy is paramount. Gastric feeding with a standard polymeric formula is recommended. Tolerance should be closely monitored. If there is intolerance (eg, pain, nausea, emesis), postpyloric feeding may be trialed. PN should be used last for continued intolerance. Lastly, at this time, probiotics should not be recommended.

Statement of Authorship

P. A. Codner and A. E. Murphy soley contributed to the conception and design of the research; P. A. Codner and A. E. Murphy contributed to the acquisition, analysis, and interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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