MANAGEMENT OF ACUTE PANCREATITIS IN THE ICU AT UF HEALTH FLAGLER HOSPITAL

OBJECTIVE:

To optimize the diagnosis and management of acute pancreatitis in the Intensive Care Unit (ICU) at Flagler Hospital.

Current literature was reviewed including more recent published guidelines from the American College of Gastroenterology (ACG) (1), the International Association of Pancreatology/American Pancreatic Association (IAP/APA) (2), the Italian Association for the Study of the Pancreas (AISP) (3), the acute Pancreatitis Classification Working Group (4), the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) (5); as well as recent reviews and RCTs studies from major medical journals (6-14), and UpToDate (15, 16).

BACKGROUND:

ETIOLOGY,DEFINITIONS AND CLASSIFIACTION OF ACUTE PANCREATITIS:

Alcohol and gallstone pancreatitis are the two more common etiology. Other etiologies includes medications, post-ERCP, hypertriglyceridemia, trauma, hereditary, and trauma.

In accordance with the revised Atlanta definition and classification (4), **acute pancreatitis will be defined** if at least 2 of the 3 following criteria are present:

1. Abdominal pain consistent with the disease (acute onset of persistent and severe epigastric pain, often radiating to the back).
2. Serum amylase and or lipase greater than three times the upper limit of normal.
3. Characteristic findings from abdominal imaging on contrast-enhanced CT (CECT) or MRI.

Acute pancreatitis will be classified as mild, moderate or severe depending on the presence and duration of organ dysfunction and local or systemic complications:

> **Mild:** No organ failure and no local or systemic complications
> **Moderate:** Transient single or multiple organ failure lasting <48 h and/or local or systemic complications.
> **Severe:** Persistent organ failure lasting >48 h.

Three organ systems should be assessed to define organ failure related to acute pancreatitis: respiratory, cardiovascular and renal. Organ failure is defined as a score of 2 or more for one of these three organ systems using the modified Marshall scoring system (see Table 1) or the SOFA score.

Systemic complications are defined as exacerbations of pre-existing comorbidities, including congestive heart failure, chronic liver disease, and chronic lung disease.

In addition, acute cholangitis is a clinical syndrome characterized by fever, jaundice and abdominal pain (Charcot's triad) which develops as the result of a partial or complete obstruction and infection in the biliary tract. For the diagnosis of cholangitis, clinical and laboratory signs of cholestasis associated with systemic inflammation and imaging findings of biliary obstruction must be present.

Local complications include:
Peripancreatic fluid collections and pancreatic pseudocysts associated with *interstitial pancreatitis.*
Acute necrotic collections, walled-off necrosis and vascular complications associated with *necrotizing pancreatitis.*

Interstitial pancreatitis: Acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognizable tissue necrosis.

CECT criteria (9):

- Pancreatic parenchyma enhancement by intravenous contrast agent.
- No peripancreatic necrosis.

Necrotizing pancreatitis: Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis.

CECT criteria:

- Lack of pancreatic parenchymal enhancement by intravenous contrast agent.
- Presence of findings of peripancreatic necrosis.

Acute pancreatitis fluid collections:

Acute fluid collection associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis. Applies only to areas of peripancreatic fluid seen within the first 4 weeks after onset of interstitial edematous pancreatitis and without the features of a pseudocyst.

CECT criteria:

- Occurs in the setting of interstitial edematous pancreatitis.
- Homogeneous collection with fluid density.
- Confined by normal peripancreatic fascial planes.
- No definable wall encapsulating the collection.
- Adjacent to pancreas (no intrapancreatic extension).

Pancreatic pseudocyst: An encapsulated collection of fluid with a well-defined inflammation wall, usually outside the pancreas, with little or no necrosis. Usually occurs more than 4 weeks after onset of interstitial edematous pancreatitis.

CECT criteria

- Well circumscribed; usually round or oval.
- Homogeneous fluid density.
- No non-liquid component.
- Well defined wall that is wholly encapsulated.
- Maturation usually needs >4 weeks after onset of acute pancreatitis; occurs after interstitial edematous pancreatitis.

Acute necrotic collection: A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can include the pancreatic parenchyma and / or the peripancreatic tissue.

CECT criteria

- Occurs only in the setting of acute necrotizing pancreatitis.
- Heterogeneous and non-liquid density of varying degrees in different locations (some seem homogeneous early in their course).
- No definable wall encapsulating the collection
- Intrapancreatic and / or extrapancreatic.

Walled-off necrosis: A mature, encapsulated collection of pancreatic and / or peripancreatic necrosis that has developed a well-defined inflammatory wall. Usually occurs >4 weeks after onset of necrotizing pancreatitis.

CECT criteria

- Heterogeneous with liquid and non-liquid density, with varying locations (some can seem homogeneous)
- Well-defined wall that is wholly encapsulated.
- Intrapancreatic and/or extrapancreatic.
- Maturation usually needs 4 weeks after onset of acute necrotizing pancreatitis.

Vascular complications: Include thrombosis of the splenic vein (with possible left-sided portal hypertension) or, more rarely, the porto-mesenteric vein and damage of the peri-pancreatic arteries leading to pseudoaneurysm or vascular erosion.

Three clinical features suggest the possibility of a pseudoaneurysm (15):

- Unexplained GI bleed
- Sudden expansion of a pancreatic fluid collection
- Unexplained drop in Hb

SCREENING:

All patients admitted to the ICU with confirmed or suspected diagnosis of acute pancreatitis will be eligible to be included.

Protocols cannot always account for individual variation among patients. They are not intended to supplant physician judgement with respect to particular patients or special clinical situation.

As with any protocol, this protocol serves to provide evidence-based, comprehensive recommendations to guide our multidisciplinary team in patient care, with the expectation that expert practitioners will modify and customize as necessary the present protocol and order set to meet individual patient needs.

MONITORING AND INTERVENTIONS

DIAGNOSIS

A. On admission, risk assessment (mild, moderate or severe), should be performed to assist management and triage. Patients with organ failure should be admitted to ICU or ICCU whenever possible.

B. The etiology of acute pancreatitis should be determined using detailed personal (i.e. previous acute pancreatitis, known gallstone disease, alcohol intake, medication and drug intake, known hyperlipidemia, trauma, recent invasive procedures such as ERCP) and family history of pancreatic disease, physical examination, laboratory serum tests, and imaging studies

Laboratory serum tests

C. In addition to serum amylase and lipase, the following variables should be established on admission: CBC, electrolytes, BUN, creatinine, AST, ALT, alkaline phosphatase, serum glucose, PT/INR, PTT, serum triglyceride, EKG and CXR. Arterial blood gas analysis is generally indicated whenever oxygen saturation is less than 94% or the patient is tachypneic or when metabolic acidosis is suspected. The frequency of repeat determinations depends on the clinical course.

Importantly, pancreatic enzyme concentrations on admission are not associated with disease severity. The disease can be serious, even fatal, although the enzymes are only slightly increased (<three-times normal).

Imaging studies

D. Abdominal ultrasound should be performed in all patients.

Patients with mild acute pancreatitis (no organ failure or systemic or local complications) usually do not need pancreatic imaging except for *abdominal ultrasound* (1).

E. CECT and / or magnetic resonance imaging (MRI) of the pancreas should be reserved for patients in whom the diagnosis is unclear, fail to improve clinically, confirmation of severity based on clinical predictors is needed or to evaluate suspected complications. *Optimal timing for initial CT assessment is at least 72 hours after onset of symptoms* (1-3).

Diagnostic imaging is essential in patients with a slight enzyme elevation. *Computed tomography (CT) and MRI are comparable in the early assessment of acute pancreatitis*. MRI, by employing magnetic resonance cholangiopancreatography (MRCP), has the advantage of detecting choledocholithiasis down to 3 mm diameter and pancreatic duct disruption while providing high-quality imaging for diagnostic and / or severity purposes. MRI is helpful in patients with a contrast allergy and renal insufficiency where T2-weighted images without gadolinium contrast can diagnose pancreatic necrosis.

CECT is the best imaging study for evaluating vascular complications.

F. Follow up CT or MR in acute pancreatitis is indicated when there is clinical deterioration or lack of clinical improvement, or especially when invasive intervention is considered.

G. In the absence of cholangitis and / or jaundice, MRCP or endoscopic ultrasound (EUS) rather than diagnostic ERCP should be used to screen for choledocholithiasis if highly suspected.

EUS is superior to MRCP in excluding the presence of small (<5mm) gallstones but MRCP is less invasive and more available.

H. In patients considered to have *idiopathic acute pancreatitis*, after negative routine work-up for biliary etiology, EUS is recommended as the first step to assess for occult microlithiasis, neoplasms and chronic pancreatitis. If EUS is negative, (secretin-stimulated) MRCP is advised as a second step to identify rare morphologic abnormalities.

MANAGEMENT OF ACUTE PANCREATITIS

Fluid therapy

I. 10 ml/Kg over 30 minutes in patients with hypovolemia or tissue hypoperfusion followed by 1.5 ml/Kg/h of isotonic crystalloid solution (LR or normosol) should be provided to all patients, unless cardiovascular and / or renal comorbidites exist. Early aggressive intravenous hydration is most beneficial the first 12 – 24 h, and may have little benefit beyond.

Antibiotics

J. *Prophylaxis with antibiotic therapy is not recommended for any type of acute pancreatitis unless infection is suspected or has been confirmed.*

RCTs do not support the routine use of antibiotics for avoiding pancreatic necrosis infection, reduction in mortality or incidence of non-pancreatic infections (10). This position is shared by all society guidelines and reviews (1-3, 6-8, 15).

K. Infected necrosis should be considered in patients with pancreatic or extrapancreatic necrosis who deteriorate or fail to improve after 7 - 10 days of hospitalization. In these patients, empiric use of antibiotics should be given.

However, if blood and other cultures are found to be negative, markers such as procalcitonin are unremarkable and no source of infection is identified, antibiotics should be discontinued. The use of CT FNA to guide the appropriate antibiotics is usually not necessary (1-3, 6-8, 15).

Antibiotics shown to penetrate necrotic tissue and inflammatory ascites, in addition to activity against suspected pathogens should be considered first-line. These include: e carbapenems, quinolones or 3rd and 4th generation cephalosporins plus metronidazole, as well as piperacillin/tazobactam. The antimicrobial regimen should be tailored to the patient once culture and sensitivity results are obtained.

L. Extra-pancreatic infections such as cholangitis, sepsis, urinary tract infection and pneumonia, should receive appropriate antibiotic accordingly.

M. Routine administration of antifungal agents along with prophylactic or therapeutic antibiotics is not recommended either.

Nutrition

The timing and route for starting feeding depends on the severity of acute pancreatitis and clinical improvement (1-3,5).

N. In patients with mild acute pancreatitis who do not have organ failure or necrosis, *oral feeding* will be started once abdominal pain, nausea and vomiting, and inflammatory markers are improving. A low-fat solid diet appears as safe as a clear liquid diet.

O. *In patients with moderate to severe acute pancreatitis enteral nutrition is the recommended nutritional support.* Enteral nutrition will be started, unless contraindicated, at a trophic rate and advanced to goal as fluid volume resuscitation is completed within 24–48 hours from admission, after obtaining hemodynamic control.

P. On a case to case basis, in patients with moderate to severe AP, oral feeding might be initiated when symptoms improve, with an interval of 3 to 5 days before tube feeding is considered.

Q. *Parenteral nutrition will be considered only when enteral nutrition fails or if the requested nutritional goal is not reached.*

RCTs conducted in patients with moderate to severe acute pancreatitis and subsequent meta-analyses have demonstrated that enteral nutrition, when compared to parenteral nutrition, is able to reduce pancreatic and extra-pancreatic infective complications, multi-organ failure, surgical intervention, and mortality (11-13).
This position is shared by the Gastroenterology and Pancreatology Societies (ACG and IAP/APA) (1, 2) as well as the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN) (5).

In moderate to severe acute pancreatitis*, oral feeding* is often not tolerated due to pain, nausea and vomiting related to ileus or extrinsic compression from fluid collections impairing gastric emptying or cannot be provided in the occasions when patients require intubation.

Current guidelines recommend that enteral nutrition should be started within 24–48 hours from admission, after obtaining hemodynamic control. It is usually indicated for at least 7–10 days (1,2,5).

The SCCM and ASPEN guidelines specifically suggest that patients with moderate to severe acute pancreatitis should have a naso-oroenteric tube placed and enteral nutrition started at a trophic rate and advanced to goal as fluid volume resuscitation is completed within 24–48 hours of admission (5).

Nevertheless, recent RCT study (14) suggested that an oral diet might be tried early in patients with severe acute pancreatitis, as two thirds of them would tolerate it, without a worse outcome. This trial did not show the superiority of early nasoenteric tube feeding, as compared with an oral diet started after 72 hours of presentation, in reducing the rate of infection or death in patients with acute pancreatitis at high risk for complications.

Therefore, in patients with moderate to severe AP oral feeding might be initiated when symptoms improve, with an interval of 3 to 5 days before tube feeding is considered. In patients who cannot tolerate oral feeding after this time, tube feeding can be initiated with the use of a standard nasoduodenal feeding (Dobhoff) tube and a standard polymeric formula.

Nasogastric and nasojejunal delivery of enteral feeding appear comparable in terms of efficacy and safety. Either elemental or polymeric enteral nutrition formulations can be used. There is no indication for performing standard routine nasogastric suction unless gastric retention resulting in dilatation of the stomach, obstruction or a paralytic ileus, is diagnosed.

The role of ERCP

R. Patients with acute pancreatitis and concurrent acute cholangitis should undergo *ERCP and sphincterotomy* within 24 h of admission.

S. *ERCP and sphincterotomy* should be performed within the first 72 hours from the onset of pain when an impacted biliary stone has been demonstrated.

T. Nonsteroidal anti-inflammatory drug (NSAID) suppositories will be considered, unless contraindicated, to prevent severe post-ERCP pancreatitis in high-risk patients.

Currently, there is no conclusive evidence regarding the optimal timing of *ERCP* in patients with biliary pancreatitis without cholangitis. However, it is recommended that *ERCP and sphincterotomy* should be performed within the first 72 hours from the onset of pain when an impacted biliary stone has been demonstrated.

The role of surgery in necrotizing pancreatitis

U. The decision to proceed with an invasive intervention will be the result of a consensus approach by the different specialties involved including gastroenterology, interventional radiologist, general surgeon, primary care physician and the intensivist group.

The indications for invasive interventions are the presence of infection, obstructive symptoms or vascular complications.

Common indications for intervention (either radiological, endoscopical or surgical) in necrotizing pancreatitis are:

- Clinical suspicion of, or documented infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled-off.
- In the absence of documented infected necrotizing pancreatitis, ongoing organ failure for several weeks after the onset of acute pancreatitis, preferably when the necrosis has become walled-off.
- Ongoing gastric outlet, intestinal, or biliary obstruction due to mass effect of walled-off necrosis.
- Persistent symptoms (e.g. pain, 'persistent unwellness') in patients with walled-off necrosis without signs of infection (i.e. arbitrarily >8 weeks after onset of acute pancreatitis.
- Disconnected duct syndrome (i.e. full transection of the pancreatic duct) with persisting symptomatic (e.g. pain, obstruction) collection(s) with necrosis without signs of infections (i.e. arbitrarily >8 weeks after onset of acute pancreatitis).
- Persistent pancreatic fistula despite medical treatment including pancreatic ascites, pancreatico-pleural fistula or a high output external fistula.
- Vascular complications including damage of the peri-pancreatic arteries leading to pseudoaneurysm or active bleeding from vascular erosion.

For patients in whom infected necrosis develops, the optimal interventional strategy is the minimally invasive step-up approach with a delay in definitive treatment preferably for more

than 4 weeks to allow liquefication of the contents and the development of a fibrous wall around the necrosis (walled-off necrosis) is now standard.

The step-up approach consists of antibiotic administration, percutaneous drainage including image-guided retroperitoneal catheter drainage or endoscopic transluminal drainage, as needed, and after a delay of several weeks, surgical video-assisted retroperitoneal or laparoscopic necrosectomy, if required. This approach is superior to traditional open necrosectomy with respect to the risk of major complications or death, and approximately one third of patients treated with this approach will not require debridement (1-3,6-8, 16).

Routine percutaneous fine needle aspiration (FNA) of peripancreatic collections to detect bacteria is not usually indicated, because clinical signs (i.e. persistent fever, increasing inflammatory markers) and imaging signs (i.e. gas in peripancreatic collections) are accurate predictors of infected necrosis in the majority of patients. There is also a risk of FNA false-negative results.

Invasive decompression in patients with abdominal compartment syndrome (ACS) is indicated when a sustained intra-abdominal pressure >20 mmHg is associated with a new onset organ failure refractory to medical therapy and nasogastric/rectal decompression.

In case of surgical decompression for ACS, the retroperitoneal cavity and the omental bursa should be left intact to reduce the risk of infecting peripancreatic and pancreatic necrosis. The standard surgical treatment is a decompressive midline laparotomy. To avoid an open abdomen and its negative effects of evisceration of the intestines, fluid losses and contamination, primary closure with mesh-grafts can be considered after an open laparotomy.

For vascular complications, endovascular procedure is the first choice and consists of superselective catheterization of the artery involved with distal and proximal embolization of the lesion and the endoluminal sac of the pseudoaneurysm. Surgery is indicated in patients with hemodynamic instability, after failure of endovascular procedures or with venous bleeding.

Unless arterial embolization is performed first, pseudoaneurysm is considered to be an absolute contraindication to endoscopic drainage because severe and even fatal hemorrhage has occurred following endoscopic drainage in patients with an unsuspected pseudoaneurysm (16).

Treatment of splanchnic vein thrombosis (splenic, portal, and/or superior mesenteric veins) should focus on the underlying pancreatitis as effective treatment may result in spontaneous resolution of the thrombosis. Despite the theoretical possibility of hemorrhage into pancreatic necrosis or fluid collections, anticoagulation should be initiated if there is extension of the clot into the portal or superior mesenteric vein resulting in hepatic decompensation or compromise of bowel perfusion (16).

The presence of asymptomatic pseudocysts and pancreatic and / or extrapancreatic necrosis do not warrant intervention, regardless of size, location, and / or extension.

In patients with mild acute pancreatitis and cholelithiasis, a cholecystectomy should be performed before discharge to prevent a recurrence of acute pancreatitis.

In a patient with necrotizing biliary acute pancreatitis, in order to prevent infection, cholecystectomy should be delayed until active inflammation subsides and fluid collections resolve or stabilize.

In patients with biliary pancreatitis who have undergone sphincterotomy and are fit for surgery, cholecystectomy is advised, because ERCP and sphincterotomy prevent recurrence of biliary pancreatitis but not gallstone related gallbladder disease, i.e. biliary colic and cholecystitis.

Pain Management

Opioids are safe and effective at providing pain control in patients with acute pancreatitis. Hydromorphone or fentanyl are considered the drugs of choice, usually in the form of a patient-controlled analgesia pump. Fentanyl is generally preferred due to its better safety profile, especially in renal impairment. Patients on patient-controlled analgesia should be carefully monitored for opiate-induced sedation and respiratory depression.

V. Fentanyl 25 micrograms IV bolus through analgesia pump with a 10-minute lock-out period will be recommended.

VTE and GI ulcer prophylaxis

W. Intermittent compression devices and pharmacologic prophylaxis with SC low molecular weight (LMW) heparin will be performed unless contraindicated following present Flagler VTE Prophylaxis Protocol.
For patients with renal failure (creatinine clearance <30 mL/min), unfractionated heparin (UFH) will be used.
For patients with heparin-induced thrombocytopenia, fondaparinux will be used.
For patients at high risk of bleeding, intermittent pneumatic compression will be used

X. Routine use of *proton pump inhibitors or H2 blockers* are not recommended in patients with acute pancreatitis.

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Table 1 Modified Marshall scoring system for organ dysfunction

	Score				
Organ system	0	1	2	3	4
Respiratory (PaO2/FiO2)	>400	301–400	201–300	101–200	≤101
Renal* (sCr, mg/dl)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (SBP†)	>90	<90, FR	<90, not FR	<90, pH<7.3	<90, pH<7.2

For non-ventilated patients, the FiO2 can be estimated from below:
Supplemental oxygen (l/min) FiO2 (%)
Room air 21%
2L 25%
4L 30%
6 - 8L 40%
9 - 10L 50%

A score of 2 or more in any system defines the presence of organ failure.

*A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine (sCr) ≥1.4 mg/dl.

†Off vasopressor support.

FR: fluid responsiveness