Acute Pancreatitis

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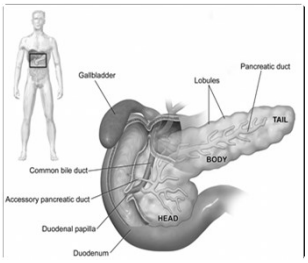
Disclosure

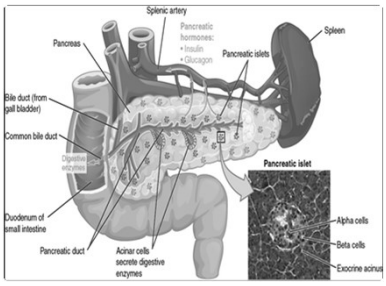
- Tracy Daum DNP, AG-ACNP has no financial relationships with commercial interests to disclose

Objectives

- Discuss etiology of acute pancreatitis.
- Explain local and systemic complications of acute pancreatitis.
- Identify treatments for acute pancreatitis.



Anatomy



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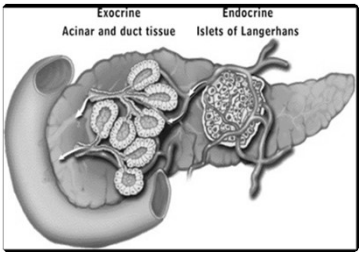


Anatomy

Functions of the Pancreas

Endocrine Function

- 3 million pancreatic islet cells
- 4 types of cells involved in glucose regulation:
  - Alpha Cells
  - Beta Cells
  - Deta Cells
  - Gamma Cells

Exocrine Function

- Secretion of enzymes into the duodenum
  - Assist in the breakdown of carbohydrates, proteins and fats
- Digestive Enzymes
- Proteases:

Exocrine Pancreatic Insufficiency (EPI)

Symptoms

- Steatorrhea
- Weight Loss
- Fatigue
- Flatulence and abdominal distention
- Edema

Consequences of EPI

- Bleeding Disorders
- Metabolic Bone Disease
- Neurological Manifestations
- Anemia
- Hypocalcemia

Acute Pancreatitis

- An acute inflammatory process of the pancreas
  - Accompanied by abdominal pain and elevation of serum pancreatic enzymes
- Classifications of Pancreatitis:
  - Mild, Moderate or Severe
- Further Classification of Pancreatitis:
  - Interstitial, Hemorrhagic or Necrotizing

Acute Pancreatitis: Pathophysiology

- Initial injury: there is an extensive inflammatory response due to pancreatic cells synthesizing and secreting inflammatory mediators: TNF-Alpha and IL-1.
- Hallmark of acute pancreatitis is a manifestation of the inflammatory response: the recruitment of neutrophils to the pancreas. In addition of inflammation: edema, vascular injury and cellular death occur.
- Inflammatory response leads to the secondary manifestations of pancreatitis: hypovolemia from capillary permeability, ARDS, DIC, renal failure, CV failure and GI hemorrhage.

Etiology of Pancreatitis	
Alcohol abuse (50%)	Sphincter of Oddi Dysfunction
Biliary Tract (30%)	Pancreatic Divisum
Idiopathic (10%)	Traumatic Pancreatitis
Tobacco abuse	Infectious (Mumps, CMV)
Metabolic	ERCP
Autoimmune Pancreatitis	Medications
Hereditary Pancreatitis	Scorpion Bite

Acute Biliary Tract Disease

- Cholelihiasis is the most common cause of pancreatitis in the US.
  - Biliary tract disease accounts for 30% of cases
  - Exact mechanism is not completely understood:
    - Most believe that the obstruction of the major papilla by stones causes reflux of bile into the pancreatic duct-this initiates a complex cascade that results in acute pancreatitis.

EtOH and Tobacco Abuse

- Alcohol is the second leading cause of acute pancreatitis.
  - In many patients, chronic pancreatitis is already established.
  - Mechanisms: Abnormal sphincter of Oddi motility, direct toxic and metabolic effects and small duct obstruction by protein plug formation.
- Smoking increases the risk of alcoholic and idiopathic pancreatitis.

Idiopathic Acute Pancreatitis

- Defined as pancreatitis without an etiology established after initial laboratory (including lipid/Ca levels) and imaging tests (US/CT).
- Recommend checking Celiac Panel
- Thought that IAP can be caused by occult biliary microlithiasis and sphincter of oddi dysfunction involving the pancreatic duct.
- Recommend Tobacco cessation

Pancreatic Divisum

- Pancreas Divisum is the most common congenital anomaly of the pancreas-occurs approximately in 10% of the population.
- It is a result of incomplete or absent fusion of the dorsal and ventral ducts during development.
- Thought that AP may result from stenosis of the minor papilla with obstruction to flow from the accessory pancreatic duct.
- Also, CFTR gene is reported to cause some incidences of pancreatitis with patients with Divisum.

Metabolic Disorders

- In patients with hyperlipidemia, triglyceride levels are usually greater than 1,000-2,000mg/dl.
- It is believed that lipase present in the pancreatic capillaries metabolizes the levels of triglyceride generating toxic free fatty acids.
- In some cases, serum amylase is not elevated because of an inhibitor in the serum of the patients with elevated triglyceride levels because it interferes with measuring serum amylase.

Hereditary Pancreatitis

- Hereditary Pancreatitis-an unusual form of acute and chronic pancreatitis that runs in families. **The risk of pancreatic cancer is >50x normal.**
- Responsible for 2-3% of all cases of chronic pancreatitis
- SPINK1/PSTI N34S Mutation
  - Superposition of the porcine SPINK1 structure on the human SPINK1 structure
  - SPINK1/PSTI mutations occur in about 2% of the population.
  - **SPINK1/PSTI are clearly associated with ICP (25%)**
  - **SPINK1/PSTI mutations may lower the threshold for pancreatitis from other genetic or environmental factors but themselves are not disease causing.**
- PRSS1 Mutations: 2 mutations are both common and disease causing: PRSS1 R122H and N291
  - Individuals with either of the two mutations have about 80% chance of developing acute pancreatitis. Of those with AP, about 50% develop CP.
  - **40% with chronic pancreatitis will develop pancreatic cancer by age 70. Tobacco abuse doubles risk**
- Linkage of HP to chromosome 7q35
  - Trypsin inactivation

Medications

CLEARLY LINKED TO PANCREATITIS	WEAK ASSOCIATION	QUESTIONABLE
Azathioprine	Sulfasalazine Valproic acid	Acetaminophen Octeotride
5-Mercaptopurine	Captopril Furosemide	Cyclosporin
Bactrim	Alfa-interferon Thiazide diuretics	Cytarabine
Pentamidine	Estrogens Metronidazole	Erythromycin
2',3' Dideoxyinosine	Aminosalicylic acid Tetracylcine	Roxithromycin
Asparaginase	Corticosteroids Sulindac	Ketoprofen
Methyl-dopa	Corticosteroids Acetaminophen Isotretinocin	Metolazone

Signs and Symptoms

Symptoms:
- Epigastric Abdominal pain
  - May radiate to the back or right/left flank
  - Usually: Abrupt Onset, Steady/Severe, Worsened by walking/lying supine.
  - May be alleviated by: Knee to Chest positioning, Leaning forward, Sitting
- Nausea and Vomiting
- Steatorrhea

Hemodynamics:
- Fever
- Tachycardia, Hypotension
- Tachypnea

Physical Examination:
- Jaundice
- Grey Turner's Sign/Cullen's Sign (Hemorrhagic Pancreatitis)
- Cool/Pale Skin (Decreased Intravascular Volume)
- Decreased breath sounds (Pleural effusion)
- Ascites

Differential Diagnosis

- Gastritis/PUD
- Perforated Viscus
- Acute Cholecystitis
- SBO
- Mesenteric Ischemia/Infarction
- Ruptured AAA
- Biliary Colic
- Inferior MI/Pneumonia

Laboratory Values

- **Serum Amylase and Lipase**
  - Serum lipase remains elevated longer than serum amylase and is more specific.
  - 3x the upper limit of normal
- Leukocytosis (10,000-30,000/mL)
- Hemoglobin: Elevated/Decreased
- Elevated CRP after 48 hours can suggest pancreatic necrosis
- AST/LDH elevation (tissue necrosis); Elevated serum bilirubin (biliary cause); Elevated ALT: more than 150units/L suggestive of biliary pancreatitis
- Elevated BUN/Cr
  - Serum Creatinine >1.8mg/dL at 48 hours is associated with development of pancreatic necrosis
- Electrolyte Derangement:
  - Hyperglycemia; Hypokalemia-associated with vomiting; Hyperkalemia: associated with acidosis
  - Hypocalcemia: less than 7 *with normal Albumin, associated with poorer prognosis. Why: may reflect fat saponification and correlates with severity of disease
- Proteinuria; Granular casts; Glycosuria (10-20% of cases)
- Urinary trypsinogen-2, trypsinogen activation peptide and carboxypeptidase B-are not widely available

X-Ray Imaging

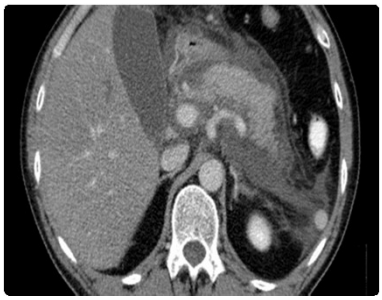
- AXR:
  - gallstones, a sentinel loop, colon cutoff sign.
- CXR:
  - Atelectasis of lower lobe of lungs +/-pleural effusion.

Ultrasonography

- Not a sensitive test for pancreatitis
  - Overlying intestinal gas and fatty tissue may obscure the pancreas in 1/3 of patients.
- US is very sensitive for detection of gallstones, bile duct stones and bile duct dilatation.

CT

- Unenhanced CT vs. Enhanced CT imaging-debatable and dependent on renal function
  - Avoid contrast with Cr >1.5 or AKI
- Unenhanced CT: Useful for demonstrating enlarged pancreas with an uncertain diagnosis and differentiating your diagnosis.
- Enhanced CT: Particularly helpful to identify areas of necrotizing pancreatitis, vasculature and size/involvement of local complications of pancreatitis.
  - Gold standard for diagnosing:
    - Pancreatic necrosis, peripancreatic collections, grading acute pancreatitis



Imaging

MRI/MRCP

- Suitable alternative to enhanced CT imaging when AKI/Renal failure is present
- MRI/MRCP can better evaluate the biliary tract and pancreatic duct
  - Evaluation for choledocholithiasis
  - Evaluation in setting of IAP for pancreatic ductal disruption/pancreatic divisum

According to the American Gastroenterological Association (AGA)

- Establish diagnosis with in 48 hours of admission
  - Clinical features, elevations in amylase/lipase levels
  - Elevation of lipase level is more specific and preferred.
- Confirmation of diagnosis is best achieved with enhanced CT imaging.
  - Early CT imaging (within 72 hours) will underestimate amount of pancreatic necrosis.
- Consider Acute pancreatitis as part of your differentials for patients admitted with unexplained MOSF or SIRS.

Acute Pancreatitis: First 72 hours

- Supportive Management
  - Gold Standard: Fluid Resuscitation
  - Pain Control
  - Correction of Electrolyte Disturbances
  - ICU care when cardiovascular and/or respiratory insufficiency is present
- Gallstone Pancreatitis c/b choledocholithiasis with biliary obstruction or cholangitis
  - ERCP + Supportive care

AGA: Assessment of Disease Severity

- Clinicians should define severe disease by presence of organ failure/local pancreatic complications.
- Multiorgan system failure and persistent/progressive organ failure are most closely predictive of mortality and most reliable markers of severe disease.
- APACHE II system is preferred

A Total Acute Physiology and Chronic Health Evaluation Score (APACHE-II Score)

- Rectal Temperature
- Mean Arterial Pressure
- Heart Rate
- Respiratory Rate
- Oxygen Delivery
- Arterial Ph
- Serum Sodium
- Serum Potassium
- Serum Creatinine
- Hematocrit
- WBC
- History of Severe Organ Insufficiency

Ranson's Criteria

ON ADMISSION: THREE OR MORE OF THE FOLLOWING PREDICT A SEVERE COURSE COMPLICATED BY PANCREATIC NECROSIS WITH SENSITIVITY OF 60-80%	WITHIN 48 HOURS: DEVELOPMENT OF THE FOLLOWING WITHIN THE FIRST 48 HOURS INDICATES A WORSENING PROGNOSIS:
Age over 55 years	Hematocrit drop of more than 10%
WBC >16,000	BUN rise >5mg/dL
Blood glucose >200mg/Dl	Arterial PO2 of <60mmHg
Serum lactic dehydrogenase >350units/L	Serum Calcium of <8mg/dL
Aspartate Aminotransferase >250 units/L	Base deficit >4
	Estimated fluid sequestration of >6 L

Correlating Ranson's Criteria and Mortality Rate

NUMBER OF CRITERIA	MORTALITY RATE
0-2	1%
3-4	16%
5-6	40%
7-8	100%

Severity Index in Acute Pancreatitis Points

- Grade of Acute Pancreatitis
  - Normal pancreas 0
  - Pancreatic enlargement alone 1
  - Inflammation compares with pancreas/peripancreatic fat 2
  - One peripancreatic fluid collection 3
  - Two or more fluid collections 4
- Degree of Pancreatic Necrosis
  - No necrosis 0
  - Necrosis of 1/3 of pancreas 1
  - Necrosis of 1/2 of pancreas 2
  - Necrosis of more than ½ of pancreas 6
  - CT severity index (CTSI) CT grade necrosis score (0-10)

Severity Index for Acute Pancreatitis

CT Grade	Points	Pancreatic Necrosis	Additional Points	Severity Index	Mortality Rate
Normal Pancreas	0	0%	0	0	0%
Pancreatic Enlargement	1	0%	0	1	0%
Pancreatic inflammation and/or peripancreatic fat	2	<30%	2	4	<3%
Single acute peripancreatic fluid collection	3	30-50%	4	7	6%
2 or more acute peripancreatic fluid collections or retroperitoneal air	4	>50%	6	10	>17%

Local vs. Systemic Complications

Local complications

- Fluid collections, Pancreatic pseudocyst, Pancreatic necrosis (sterile vs. infected) and Pancreatic ascites.
  - These complications are twice as frequent in ETOH/Biliary pancreatitis.

Systemic complications are seen in acute/severe pancreatitis.

- Pulmonary edema/ARDS/Renal dysfunction/GI Bleeding/Colitis/Splenic Vein thrombosis.
  - Inflammatory changes from the pancreas may extend to the kidneys, stomach, colon and splenic vein

Fluid collections

- Common in patients with acute pancreatitis; occurs in ~50% of patients with acute pancreatitis.
  - Fluid collections are often ill defined and evolve over time; most are managed conservatively.
  - Simple fluid collections resolve spontaneously in most patients, so therapy is not usually required.
  - The presence of gas within a fluid collection suggests underlying infection and mandates therapy.

Pseudocysts

- The mechanism of pseudocyst is speculative: it is thought to have resulted from the rupture of a pancreatic duct, activation of interstitial pancreatic enzymes, parenchymal necrosis, intraductal leakage and local mesothelial cells reacting to wall-off fluid collection by formation of a fibrous membrane.
- Pseudocysts may be classified as communicating or noncommunicating with the pancreatic duct.
- Signs/Symptoms: Epigastric pain, mass, emesis, mild fever, weight loss, and unresolved pain.
- Diagnostic Findings:
  - US: fluid filled mass
  - CT: Fluid filled mass; will show if there are several cysts and accurately provides detail regarding ductal dilatation.

Pseudocysts

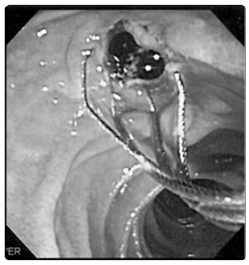
- Complications: Infection, bleeding into a cyst, fistula, pancreatic ascites, GOO, SBO, biliary obstruction
- Treatment: Pseudocysts larger than 6cm rarely spontaneously resolve. Conservative management is recommended but intervention should be taken if symptoms/complications occur.
  - It takes 6 weeks for pseudocyst walls to mature-most will resolve within this period if they are going to resolve spontaneously
  - Bleeding into cyst: Angiogram/Embolization
  - Pseudocyst with infection: Percutaneous drainage and antibiotics. (Persistent leukocytosis, unexplained fever or gas on the CT scan)
  - Endotherapy/Surgical Options: Cyst gastrostomy, Cystduodenostomy, RNY Cystojejunostomy, distal pancreatectomy vs. VARDS.

Pancreatic Necrosis

- Pancreatic necrosis is a significant complication of acute pancreatitis and may result in mortality rates as high as 15%.
- Pancreatic necrosis is a result of an obstruction of the pancreatic microcirculation.
  - Demonstrated by dynamic contrast-enhanced CT-gold standard of detection of pancreatic necrosis with accuracy >90%.
  - Necrosis does not take up IV contrast on imaging (Does not enhance)

Pancreatic Necrosis

- Suspicion for Infected Necrosis:
  - Persistent leukocytosis, unexplained fever or gas on the CT imaging.
  - US or CT guided needle aspiration of suspected infections should be examined and cultured.
    - Send for amylase and culture data
    - Monomicrobial infection is uncommon; polymicrobial infection is more resistant and leads to poorer prognosis
- Treatment:
  - Depends on pattern and anatomic location
  - Percutaneous drainage and or endoscopic or surgical debridement



Endoscopic Intervention vs Surgical Intervention

Systemic Complications

- Shock-Hypovolemic vs. Septic
- Pulmonary Involvement:
  - Pleural effusion with resultant lung compression
  - ARDS
  - Pancreatic-pleural fistula
- Acute Renal Failure
- Hyperglycemia
- Erosion of vascular structures by abscesses or pseudocysts may cause gastrointestinal hemorrhage
- Colonic strictures, fistulas and perforation
- Coagulopathy
- Splenic vein thrombosis or pseudocyst formation in the spleen
  - Splenic vein thrombosis can lead to gastric varices

Management of Mild Acute Pancreatitis

- NPO Status for complete pancreatic "rest"
  - Once pain is improved-may start clear liquid diet.
    - Pain may recur with diet advancement to Low Fat diet
- Aggressive IV Hydration
  - Early Resuscitation: 1/3 of the total 72 hour fluid volume administered within 24 hours of presentation may reduce the frequency of SIRS and organ failure.
  - Lactated Ringers is preferred; overly aggressive fluid resuscitation may lead to morbidity as well.
  - Recommend a rate of 200ml/hr; recommend reassessing fluid requirements at frequent intervals within 6 hours of admission and then for the next 24-48 hours.

Management of Acute Pancreatitis

- Pain relief
  - Demerol or Morphine
    - Morphine was originally thought to cause Sphincter of Oddi spasm but is now acceptive alternative.
- Nutritional Support
- Closely monitoring hemodynamics
- Biliary Pancreatitis
  - Pancreatic Divisum/Pancreatic ductal disruption: ERCP with endotherapy or pancreatic ductal stenting.
  - Cholelithiasis: Laparoscopic Cholecystectomy is performed within the same hospitalization
    - In some cases, ERCP with sphincterotomy alone is effective.

Management of Severe Acute Pancreatitis

- ICU admission
  - Invasive hemodynamic monitoring
  - Intra-abdominal pressure monitoring:
    - In setting of ongoing fluid sequestration which may be pronounced in the abdomen leading to ascites or abdominal compartment syndrome.
- Aggressive volume resuscitation
  - Lactated Ringers-fluid of choice
  - Rate: Intermittent bolus may be required (500ml/hr) if hemodynamically unstable and then rate 250-300ml/hr.
    - Volume resuscitation is necessary in setting of severe pancreatitis: there is leakage of fluids and IVF are warranted to maintain intravascular volume.
    - Resuscitation targeted for adequate UOP, hemodynamic stability and modest decrease in Hemacrit
    - Caution: With colloid therapy: there may be increased risk of developing ARDS
    - If shock continues despite adequate volume replacement: consider pressor therapy
- NPO status for pancreatic rest
  - Nutritional support: TPN vs. Enteral Feedings. Post pyloric feeds are preferred but sometimes not tolerated with an ileus.
- Specialist consultations: GI medicine, Surgery, Interventional Radiology
  - Endotherapy/ERCP vs. surgical intervention vs. percutaneous drainage

Management of Severe Pancreatitis

- Electrolyte Derangement: Can be life threatening
  - At risk for hypokalemia due to prolonged vomiting and loss of K into protein-rich fluid that leaks into peritoneal cavity.
  - Hypocalcemia: Persistently low levels of Ca increase mortality. Signs of low CA: neuromuscular irritability, nausea, vomiting, decreased cardiac output and laryngeal spasm. Closely monitor for tetany: Chvostek's and Trousseau's signs.
- Acute Renal Failure
  - Usually secondary to pre-renal state from fluid loss into the abdomen.
- Pulmonary Dysfunction/Management
  - ALI/ARDS: Characterized by diffuse pulmonary infiltrates on CXR, arterial hypoxemia, pulmonary hypertension and decreased pulmonary compliance.
  - Closely monitor for hypoxic and hyper carbic respiratory failure.
  - Oxygen Delivery to tissues and prevention of visceral ischemia is essential.

Antibiotic Therapy

- Controversial
- ABX should be given for known extra pancreatic infections: cholangitis, catheter-acquired infections, bacteremia, UTI, PNA.
- The AGA recommends: prophylaxis antibiotics should be restricted to patients with substantial pancreatic necrosis (>30%) and should not continue longer than 14 days.
- ACG does not recommend prophylactic antibiotics in severe acute pancreatitis. Use of antibiotics in sterile necrosis is not recommended.
- Infected necrosis should be considered in patients with pancreatic/ extra pancreatic necrosis who clinically deteriorate or fail to improve.
  - Recommend CT to evaluate for signs of infection and collection/pseudocyst/necrosis appearance
  - Recommend FNA sampling to evaluate if sterile vs. contaminated
  - In patients with suspected infected necrosis: Antibiotics known to penetrate pancreatic necrosis are gold standard: Carbapenems, Quinolones and metronidazole

Thank you!