Acute Pancreatitis

Management Strategies: What to do Now?

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Medicine Grand Rounds

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Humanitarian Service Award Delivered by Mother Teresa 1995
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OUTLINE

I. DEFINITIONS

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Acute Pancreatitis is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems. Pathologic findings range from interstitial edema and fat necrosis of the pancreatic parenchyma to pancreatic and peripancreatic necrosis and hemorrhage. These changes represent a continuum. Despite all attempts at objectivity, acute pancreatitis remains a clinical diagnosis. Initial episodes of acute pancreatits for patients later found to have chronic pancreatitis will be classified as acute pancreatitis.

Mild Acute Pancreatitis is associated with minimal organ dysfunction and an uneventful recovery. It lacks the described features of severe acute pancreatitis. Failure to improve within 72 hours should prompt additional investigations for complications of pancreatitis. The predominant macroscopic and histologic feature of mild acute pancreatitis is interstitial edema. Infrequently microscopic area of parenchymal necrosis may be found. Peripancreatic fat necrosis may or may not be present. The majority (75% or greater) of pancreatitis cases will be mild.

Severe Acute Pancreatitis is associated with complications such as organ failure or local complications such as necrosis, abscess, or pseudocyst. Clinical characteristics include 3 or more Ranson's criteria or an Apache II score of at least 8, or organ failure. Organ failure is defined as any of the following: shock (systolic blood pressure of 90mm Hg or less); pulmonary insufficiency (PaO2 60mm or less); renal failure (creatinine 2mg/dl after rehydration; gastrointestinal bleeding (500cc in 24 hours); disseminated intravascular coagulation (platelets 100,000/ mm3 or less, fibrinogen less than 1.0g/l and fibrin split products > 80ug/cc); or severe metabolic disturbances example calcium 7.5mg/dl. The Apache II system may be used to quantify severity at any time during the course of acute pancreatitis, while Ranson and Glasgow criteria have not been validated for periods longer than 48 hours from admission. Additionally Apache II does not require 48 hours to indicate severe disease.

Acute Fluid Collections occur early in the course of acute pancreatitis. They are located in or near the pancreas and always lack a wall of granulation or fibrous tissue. These collections are common in patients with severe pancreatitis occurring in 30-50% of cases. However, more than 50% resolve spontaneously. Imaging techniques do not demonstrate a defined wall surrounding an acute fluid collection. The pathologic finding is the lack of defined wall. Bacteria are variably present.

Acute Pseudocyst is a collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue which arises as a consequence of acute pancreatitis, pancreatic trauma, or chronic pancreatitis. Histologically they are characterized by a well-defined wall of fibrous or granulation tissue. A pseudocyst is often sterile. If pus is present the lesion is more correctly termed pancreatic abscess. The formation of a pseudocyst requires 4 or more weeks from the onset of acute pancreatitis. In contrast, a pseudocyst associated with chronic pancreatitis lacks an antecedent episode of acute pancreatitis.

Pancreatic Abscess is a circumscribed intra-abdominal collection of pus usually in proximity to the pancreas containing little or no pancreatic necrosis, which arises as a consequence of acute pancreatitis or pancreatic trauma. Differentiating a pancreatic or peripancreatic abscess from infected necrosis is the presence or absence of pancreatic necrosis. An abscess is characterized by the presence of pus and a positive culture for bacteria or fungi without necrosis. It is likely that pancreatic abscesses arise as a consequence of limited necrosis with liquefaction and secondary infection. The term pancreatic abscess has been improperly used for all forms of pancreatic infections. The distinction between pancreatic abscess and infected necrosis is critical for two reasons: the mortality risk for infected necrosis is twice the risk for pancreatic abscess and the treatment is markedly different. Abscesses that arise from elective pancreatic surgery are more accurately classified as post-operative abscesses.

Pancreatic Necrosis is a diffuse or focal area of nonviable pancreatic parenchyma typically associated with peripancreatic fat necrosis. Dynamic CT is the current standard for the clinical diagnosis. Nonenhanced pancreatic parenchyma (contrast density < 50 Hounsfield units) larger than 3 centimeters or involving more than 30% of the pancreas are requisite criteria for CT diagnosis. The densities of the pancreas and spleen should be similar. Thus splenic density may be used as a semiquantitative measure of pancreatic density. The accuracy of CT for pancreatic necrosis is over 90% but is not infallible. Usually pancreatic necrosis is confined to the pancreatic periphery and the core of the gland is preserved. Microscopically, there is extensive interstitial fat necrosis with vessel damage and necrosis, which affects acinar cells, islet cells, and pancreatic ductal system. Hemorrhage is variably present.

Confusing terminology

Phlegmon was coined in 1973 to describe a palpable mass composed of sterile edematous inflammatory tissue. The term was subsequently been used to describe pancreatic necrosis associated with secondary infection. Phlegmon may thus be used to describe an edematous or necrotizing pancreatitis either sterile or infected. More precise definitions are available. This ambiguous term should no longer be used.

Infected pseudocyst is unclear and should be discarded.

Hemorrhagic pancreatitis should be restricted to the operative or post-mortem appearances of the gland.

II. BACKGROUND

Background Clinical Impact and Economics

Acute pancreatitis is a disease of increasing incidence. Population based studies from the United States, United Kingdom, and Italy have noted a doubling or tripling of pancreatitis incidence over the past 30 years ranging from 19/100,000 to 38/100,000. The majority of pancreatitis cases (approximately 75%) are self-limiting and associated with interstitial histologic changes. However 25% of cases are severe and life threatening. Severe pancreatitis is associated with the histologic finding of necrotizing pancreatitis. The outcome of death from severe pancreatitis has averaged 30%. Significant causes of death are respiratory failure in the first week and infectious thereafter. A review of patients from 1942 to 1978 noted respiratory

death accounting for 60% of deaths. However, improvements in intensive care units have significantly improved overall mortality rates of 2 to 3 fold since that time. The improvement in respiratory care and decrease in the mortality from respiratory failure has influenced the causes of death. Infections are currently the most common cause of death. Despite these advances no impact on death from severe pancreatitis has occurred over the past decade.

Severe pancreatitis results in a life threatening illness. In an era of cost containment we should ask if our efforts are productive. The treatment generally requires significant health care resources with a mean cost of $29, 505 - $45,000. The median length of stay was 74 days. A cost utility analysis demonstrated a mean benefit of 8.55 quality adjusted life years (QALY) at a cost of $3,451 per year saved. This is similar to the benefit of coronary artery bypass grafting or thrombolytic therapy for acute coronary artery disease at $32,678 dollars ($2,400 per QALY 1988 cost non-adjusted) and significantly better than $9,715 per QALY (1988 costs non-adjusted) for kidney transplantation.

If patients survive, they return to work 90% of the time. Quality of life surveys indicate physical performance is 86-94% of age matched controls on Short Form 36 Health Survey (SF-36). This level of physical performance is significantly better than comparison scores for patients with congestive heart failure or chronic obstructive pulmonary disease. Unfortunately, severe pancreatitis creates a propensity to develop diabetes (54% in alcoholic subgroup).

The treatment of severe pancreatitis results in quality of life superior to illness associated with congestive heart failure or chronic obstructive pulmonary disease. The cost of therapy for severe pancreatitis is equivalent to costs associated with acute coronary syndromes. Therapy for severe pancreatitis results in equivalent adjusted life year survival costs to coronary artery disease bypass grafting.

III. PATHOPHYSIOLOGY

Acute pancreatitis is associated with activation of trypsinogen, which initiates a cascade of inflammation. The injury phase is swift with peak response within 48-72 hours. Research aimed at preventing or aborting the inflammatory cascade may offer new treatment approaches. However, the early activation and peak of the inflammatory cascade will require treatment within 48 hours from onset of pain. This will require education similar to the campaign for thrombolytic treatment of coronary artery disease.

Animal investigations have provided many valuable clues to human disease. The impracticality of obtaining human pancreatic tissue or inducing pancreatitis in humans leads to the reliance on animal models. Unfortunately, advances in animal models have led to many failed clinical trials; whereas, 81% of animal studies noted a positive outcome, compared to only 7.7% in human studies. Reasons for the discrepancy include animal models initiating therapy simultaneously with onset of pancreatitis rather than delayed after induction of pancreatitis, failure to identify subgroups of patients likely to benefit (human trials), and inadequate patient numbers of severe subgroups.

The rat model with cerulein secretagogue induced pancreatitis has led to the following understanding. Trypsinogen is synthesized in the rough endoplasmic reticulum and transported to the Golgi system. The co-synthesis of trypsinogen and pancreatic secretory trypsin inhibitor prevents trypsinogen activation. Proteins are sorted at the Golgi system, and trypsinogen and other digestive enzymes are condensed into vacuoles.

The importance of trypsinogen activation causing pancreatitis in animal models is supported by the prevention of ERCP induced pancreatitis (in humans) through the preprocedure administration of gabexate, a trypsin inhibitor. Trypsinogen activation occurs with the hydrolysis of the N terminal trypsinogen activating peptide. The removal of the 10 amino acids allows a conformational change resulting in active trypsinogen. Subcellular fractionation of acinar cells reveals active trypsinogen, trypsinogen activating peptide (TAP), and cathepsin B (a lysosomal enzyme capable of activating trypsinogen). TAP was identified in the cytoplasmic vacuoles but not in the zymogen granules, endoplasmic reticulum, cytoplasm or acinar lumen. TAP and Cathepsin B colocalized in areas of the acinar cell. The use of electron microscopy and antibodies to TAP and GRAMP-92 (a marker of lysosomes and recycling endosomes) revealed antibodies colocalized to 75% of small vacuoles in 30 minutes but progress to large vacuoles in 60 minutes after induction of pancreatitis.

Mutations in the cationic trypsinogen gene are associated with activation of trypsinogen. Excessive trypsinogen activation within the pancreas normally undergoes hydrolysis at the R 117 position followed by reduction of a disulfide bond and separation of two globular domains. The separation of the two globular domains inactivates trypsin, protecting the pancreas from auto digestion and represents a protective mechanism from premature protease activation. A hereditary form of pancreatitis has been linked with T-cell receptor B chain (TCR*B*) gene locus on chromosome 7q35. An Arg-His substitution was identified at residue 117 in four families (HP1). However, this mutation is not found universally among patients with this syndrome. A second mutation (HP2) arginine to isoleucine at position 21 has been identified. These mutations eliminate the protective mechanism and render patients susceptible to recurrent pancreatitis.

Mutations of the transmembrane conductance regulator gene (CFTR) have recently been linked to idiopathic and chronic pancreatitis. The CFTR gene controls the chloride flow through a cyclic AMP chloride channel. Mutations in the gene have been linked to cystic fibrosis with over 750 mutations identified. The presence of two alleles has been associated with severe pancreatic exocrine dysfunction as compared to mild dysfunction with one allele. Evidence suggests the pancreas is very susceptible to decreased CFTR function. CFTR normally promotes the dilution and alkalization of pancreatic juice. This mutation may lead to ductal obstruction. Other potential mechanisms include damage to the acinar cell with a reduced intracellular pH via loss of bicarbonate producing epithelium. Additionally, CFTR protein is involved in intracellular vesicle targeting, membrane recycling, and ion transport. In 27 patients with idiopathic pancreatitis DNA was tested for 17 CFTR mutations and 5T allele in intron 8 of the CFTR gene. An abnormal CFTR allele was seen in 37%. The allele presence versus the expected prevalence was 11:1 $P<0.001$. None had a diagnosis of cystic fibrosis, although three patients on further testing had abnormal nasal cyclic AMP mediated chloride transport. In a group of 134 patients with chronic pancreatitis DNA mutations of CFTR were evaluated. Mutations present in 95% of cystic fibrosis individuals in northwest England were found in 13.4% of patients with chronic pancreatitis. The prevalence of 13.4% mutations was compared to the expected frequency of 5.3% $P<0.001$. The 5T allele was seen is 10.4% $P=0.008$. It is hoped that this discovery may lead to further understanding of pancreatitis mechanisms. Speculation continues regarding the site of cystic fibrosis mutations effect at the duct or the acinar cell.

In summary, trypsin normally remains inactive until it reaches the duodenum where enterokinase activation initiates the cascade. The body uses a series of protective mechanisms including the separation of lysosomes and zymogen, synthesis of pancreatic trypsin inhibitors, regulation of intracellular calcium and pH, and R-117 fail-safe autolysis site. In pancreatitis trypsinogen is activated at the early stage of secretagogue induced models. Activation of trypsinogen occurs within a cytosolic vacuole containing digestive enzymes and cathepsin B. Trypsinogen activation occurs in a pathway of enzyme secretion (non-zymogen), and after

activation trypsin is released into the cytosol. However, the initiating event remains unclear. Two theories have been proposed to explain these findings. In one theory activation of digestive enzymes is initiated by lysosomal hydrolases acting on trypsinogen after fusion of the zymogen granules and lysosomes. The second theory suggests the activation occurs along a normal secretory pathway. Activation of trypsinogen becomes pathologic with secretory blockage. A unifying feature of both mechanisms is the colocalization of digestive zymogens with lysosomal hydrolases resulting in activation of the zymogens.

The multiorgan system failure (MOF) with pancreatitis is similar to MOF found with other illnesses including sepsis, major burns, and trauma. The development from a local event to systemic complications has been linked with the production of cytokines. Activated pancreatic enzymes are not capable of inducing cytokine production from isolated macrophages nor will they induce pulmonary distress when given intravenously. The discovery of cytokines involvement in adult respiratory distress syndrome in the early 1990's promoted further investigation. Ascitic fluid from pancreatitis given intravenously induces adult respiratory distress syndrome in rats. This mechanism is aborted in knockout mice involving interleukin 1 (IL-1) or tumor necrosis factor (TNF) receptors. Levels of interleukin 1 and TNF mRNA were 30 times elevated versus controls after intravenous administration of pancreatic ascites. Further, up-regulation of interleukin 1 and tumor necrosis factor, occur in the pancreas within an hour after the induction of pancreatitis and is correlated with the degree of pancreatic inflammation.

The mechanism responsible for initiating the cytokine cascade is incompletely understood. Macrophages are believed to be the most important source of cytokines as acute inflammation precedes the recruitment of immune specific T and B cells. A variety of other mediators are released including platelet activating factor, prostanoids, complement, bradykinins, etc.

Interleukin 6 (IL-6) has been independently associated with adult respiratory distress syndrome and severe pancreatitis. IL-6 elevation further correlates with the severity of pancreatitis. IL-6 is produced by immune accessory cells including monocytes, macrophages, lymphocytes, endothelial cells, and non-immune cells including intestinal epithelium, and osteoblasts. Stimulation of the autonomic nervous system results in endogenous interleukin-6. However, this effect can be blocked with B-adrenergic antagonist. These observations suggest a stress-induced release of IL-6 in pancreatitis. Interleukin 8 (IL-8) appears to be the earliest cytokine appearing in human serum following onset of severe acute pancreatitis. The release of IL-8 contributes to the early neutrophil activation and the release of neutrophil elastase. IL-8 presence and neutrophil elastase positively correlate with the severity of acute pancreatitis. IL-8 is produced primarily by monocytes and endothelial cells. The source of IL-8 may be resident macrophages. Histamine and other proteins released into the interstitial space activate the endothelial cells. The endothelial cells once activated would release IL-8 and platelet activating factor (PAF).

PAF is a structural component of membrane lipids and is released upon the action of phospholipase A^2. PAF exerts a range of effects via a cell-surface receptor. Actions include the interaction between endothelial cells and Polymorphonuclear (PMN) cells with resultant migration of activated WBC in tissue. Two pathways of biosynthesis occur: a de novo pathway and a remodeling pathway. The remodeling pathway is the route to mediate inflammation and results in eicosanoid production. Formation of PAF is linked to receptors, which are intracellular and extracellular. The receptors are coupled through guanosine triphosphate protein, which activate protein kinase C to increase intracellular calcium. Increased calcium promotes production of PAF by the remodeling pathway. Degradation of PAF is mediated by a calcium independent acetylhydrolase specific

to PAF. PAF is not degraded for excertion and returns to the lipid pool, which is large, compared to active PAF.

PAF appears to play a role in injury to lung, kidney, gastrointestinal tract, endothelial cell (ischemia/shock), and pancreas. The various organs and the ability of many different cell lines to synthesize and respond to PAF suggest a biological significance. Chinese physicians have been using ginkolids (PAF antagonist derived from the fossil tree ginkgo biloba) for over 5,000 years in treatment of lung disease including asthma. Trials involving PAF antagonist in pancreatitis have recently shown promise. A clinical trial randomized 83 patients with acute pancreatitis to placebo or lexipafant in a double blind placebo controlled study. Lexipafant 60mg was administered intravenously for three days. The disease was classified as severe in 29 patients with an APACHE score of 8 or more. In this subgroup a significant reduction in organ failure (P=0.041) and IL-8 levels (P=0.038). A subsequent report published only in abstract form found a mortality benefit for the subgroup with pancreatitis treated within 48 hours. This study randomized 290 patients with APACHE score of 6 or greater to lexipafant 100mg daily or placebo. Lexipafant resulted in lower organ failure P=0.04 and pseudocyst P=0.02 formation. Mortality was unchanged except for treatment within 48 hours onset: 20/98 (20.4%) controls versus 11/107 (10.3%) lexipant (P=0.04). This work suggests PAF antagonist benefit is maximum within 48 hours of presentation. A multicenter double blind placebo controlled randomized trial with PAF acetylhydrolase is currently underway. This investigational treatment will be available to Parkland patients with an APACHE score of 8 or greater who are randomized within 48 hours.

IV. CLINICAL SCORING SYSTEM

Pancreatitis variable presentations and severity lead to confusion over appropriate care. The early recognition of severe pancreatitis was often subjective in criteria. In an effort to identify patients with severe pancreatitis early in hospital course, 100 consecutive patients who were admitted to Bellevue and New York University Medical Center from January 1971 and October 1972 were evaluated. The etiology of pancreatitis was alcoholism in 74; biliary, 14; postoperative, 5; and other, 7. The diagnosis was histologically proven at autopsy or surgery in 27 patients. In 73 the diagnosis was clinical with pain in the upper abdomen with elevated amylase. Forty-eight objective features during the initial 48 hours of hospitalization were recorded and analyzed including age, hematocrit, white blood cell count, urea nitrogen, glucose, amylase, calcium, potassium, sodium, bicarbonate, lactic dehydrogenase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, arterial $p0_2$, and base deficit. Fluid sequestration was estimated by subtracting measured urinary and nasogastric output from the volume of intravenously administered fluid. Variables at 48 hours including nasogastric volume, intravenous fluid volume, estimated fluid sequestration was recorded. The 48-hour change in hematocrit, urea nitrogen, amylase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, lactic dehydrogenase were noted. The 48-hour high for hematocrit, base deficit, urea nitrogen, glucose, amylase, LDH, SGOT, SGPT, albumin and 48-hour low for hematocrit, white blood cell, glucose, urea nitrogen, amylase, calcium, SGOT, SGPT, LDH were noted. The patients were divided into two groups: non-severe who recovered spontaneously (69) and severe (31) who required more than 7 days in the intensive care unit (16) or died (15). Thirteen variables correlated with morbidity or mortality including: **On admission** age, glucose, white blood cell count, urea nitrogen, LDH, SGOT, SGPT, **48 hours change** hematocrit and urea nitrogen, **48 hour lowest** serum calcium and arterial oxygen tension, **48 hour high** base deficit, **48 hour total** fluid sequestration. These criteria were used as a prognostic scoring system, which are recognized as Ranson's criteria. Three or more positive signs were associated with significant risks of death or complications. There was no correlation with admission amylase and severity of illness.

A disadvantage of the Ranson's criteria is often the time required to fulfill requirements for severe disease. This inherent delay led Imrie et al to propose a simplification of this scoring system, which gained acceptance widely in the United Kingdom. Again a score of three or more was considered severe. This scoring system was later modified based upon the application of criteria and outcomes in 405 episodes of acute pancreatitis over 7 years. These prognostic criteria have been referred to as Glasgow criteria and Imrie's criteria. An advantage of Imrie's criteria is the validation in different etiologies of pancreatitis and simplification. Ranson's initial study was dominated by ETOH abuse and later would be modified into ethanol and biliary etiologies.

While useful, the nuances of these criteria can be difficult to remember. Additionally, while these clinical scoring systems provide objective tools for prognostic value they have not been shown superior to clinical judgement of experienced physicians. Other simple criteria are correlated to a high risk of complications or death. These include obese body habitus, organ failure, pleural effusion, and ascites. The outcomes of pancreatitis in obese versus non-obese was compared. Obesity was defined as a body mass index (BMI) greater than or equal to 30kg/m^2. Non-obese was BMI <30kg/m^2. The incidence of death (7/19, 37%) and complications (12/17, 71%) in obese patients with pancreatitis was significantly greater than the non-obese group death (4/80, 5%) and complications (5/80, 6%) P=0.0007. Obesity was a predictor for severe disease with a sensitivity of 63% and a specificity of 95%. Pleural effusion, pancreatic ascites, or discrete pericardial effusion were predictive of a local complication (pseudocyst formation) in approximately 40% of patients versus 10% without pleural effusion, ascites or pericardial effusion (P<0.01 pleural effusion and ascites) (P=0.05 pericardial effusion). In multivariate analysis of severe pancreatitis pleural effusion and ascites were predictive of complications or death odds ratio 8.6 (2.3-32.5 CI 95%) and 5.9 (1.5-23.0 CI 95%). Organ failure is associated with increased mortality. Virtually all patients with 4 organ system failure die. The mean multiple organ failure score was 1.4 for survivors versus 3.2 for non-survivors in pancreatitis.

A significant disadvantage of these scoring systems is the inability to provide objective monitoring after the initial 48 hours and delays in recognition of severe pancreatitis. The APACHE II scoring system uses 14 parameters of physiologic activity and biochemical function. These include the temperature, blood pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, potassium, creatinine, hematocrit, white blood cell count, Glasgow Coma Score, age, and chronic health points. The scoring system had previously been validated. The potential advantage of an instantaneous scoring system led investigators to compare the APACHE II to Ranson and Imrie scoring systems. The results are shown below with similar sensitivities, specificity and predictive value.

COMPARISON OF APACHE, GLASGOW, RANSON

	Sensitivity (%)	Specificity (%)	Predictive value positive (%)	Predictive value negative (%)	Percentage Correct
On admission					
APACHE II(>5)	95	54	40	97	64
APACHE II (>7)	68	67	40	87	68
Peak					
APACHE II (> 9)	82	74	50	93	76
APACHE II (> 12)	53	92	69	86	83
Glasgow score	71	88	66	91	84
Ranson score	87	71	49	94	75

Peak APACHE II score =highest score in day 1-3; sensitivity = percentage of all complicated attacks predicted correctly by test; specificity = percentage of all mild attacks predicted correctly by test; predictive value positive = percentage of complicated attacks among predicted severe by test; predictive value negative = percentage of mild attacks among all predicted mild by test; percentage correct = percentage correctly classified

V. RADIOGRAPHIC IMAGING

Poor outcomes with pancreatitis are related to necrosis, which predisposes to multiple organ failure, abscess, pseudocyst, and hemorrhage. CT scanning is an alternative means to recognize suspected severe pancreatitis subgroups. An initial study noted the findings in 83 patients with acute pancreatitis. CT exams were initially obtained in 40 patients within 3 days and between 4-10 days in 43 patients. Findings related to pancreatitis were scored: A, normal pancreas; B, diffuse enlargement of the pancreas; C, enlarged pancreas with peripancreatic edema; D, single ill defined fluid collection; and E, two or more poorly defined fluid collections. Abscesses were seen in (2/17, 11.8%) of patients with C, (2/12, 16.7%) with D, and (14/23, 60.9%) with E. Deaths were seen in D (1/12, 8.3%) and E (4/23, 17.4%). This radiographic scoring criteria is termed Balthazar and Ranson Criteria.

Rapid bolus contrast-enhanced CT scan can demonstrate areas of reduced perfusion and correlates with pancreatic necrosis. This encouraged use of non-invasive techniques to predict patients at risk. A retrospective review of ultrasound and CT compared imaging to surgical findings. Ultrasound recognized necrosis in 35/62. (56.4% accuracy) as compared to 57/67 (85.1% accuracy) with CT. Ultrasound was significantly impacted by meteorism (the presence of gas or air in the abdomen or intestines) which made the test non-diagnostic in 22.6% of patients with necrosis. Pancreatic necrosis correlates with adverse clinical outcomes. CT necrosis was thus correlated with clinical outcomes including the risk of septic complications. The degree of necrosis and the outcomes are shown below for Ranson's clinical scoring system, C-reactive protein, and degree of necrosis on CT scan.

	Ranson	CRP	< 30%	30-50%	>50%
Edematous	1.7	50			
Necrotic Non- Sepsis	3.2	141	9	5	1
Necrotic Sepsis	3.9	192	3	4	10
Necrotic Organ System Failure	3.4	146	3	3	1

Multivariate regression analysis for C-reactive protein, Ranson score, and CT scan for necrosis found only CT necrosis of 30% or greater as predictive for septic complications. The value of CT recognized pancreatic necrosis predicting septic complications was subdivided into percentage of necrosis. Pancreatic necrosis of

greater than 30% had a sensitivity of 82%, specificity of 81%, negative predictive value of 91%, and positive predictive value of 67% for predicting septic complications. The predictive accuracy of CT for septic complications was 81%.

Clinically mild pancreatitis can have some necrosis although it appears infrequently. A correlation of outcomes and necrosis found no deaths and 6% complication rate for interstitial pancreatitis versus 23% mortality and 82% complication rate for necrosis. A caveat to remember is necrosis can appear later. An initially normal contrast enhanced pancreas on CT scan did not exclude the development of late necrosis in 4 of 22 patients. Three of the 4 later died secondary to pancreatic sepsis. All deaths in this subgroup occurred in patients with Stage D or E on Balthazar CT scoring system.

These results suggest the value of a CT scan during admission. However, previous publications had variable times of CT imaging and retrospective approaches. A prospective multicentered trial from France assessed the findings of CT scan within 48 hours of admission on death and pancreatic abscess. Forty-six centers entered 228 patients. Death was associated with pancreatic index less than $1.0cm^2$; nonenhancement of the head; non-enhancement of the neck; non-visualization pancreas; portal vein non-visualized; splenic vein non-visualized; fluid in right anterior pararenal space, left posterior pararenal space, right posterior pararenal space, right mesocolon, mesentery, pelvis; Balthazar score A-D versus E; free intraperitoneal fluid; and abdominal wall infiltration. Abscesses were associated with portal vein non-visualization; splenic vein non-visualization; fluid in left posterior pararenal space, right posterior pararenal space, transverse mesocolon, mesentery, pelvis; Balthazar CT score A-D versus E; extradigestive gas bubbles; heterogeneity of collections; and abdominal wall infiltration. It may be easier to consolidate these findings into the following 1) nonenhancement of the genu and head, 2) portal and splenic vein non-visualization, and 3) fluid collections right anterior pararenal, left posterior pararenal, right mesocolon, mesentery and pelvis, 4) Balthazar CT Score, 5) abdominal wall infiltration.

Pancreatic necrosis increases the risk of pancreatic infections but the risk is only 30-50%. Pancreatic infections are almost always fatal unless surgery is performed. Yet, early necrosectomy within 2 weeks carries a high mortality. Conversely, non-operative strategies on infected necrosis jeopardizes survival. A non-operative approach of CT guided aspiration is a method to distinguish infected necrosis from non-infected necrosis. 60 patients with inflammatory masses underwent sampling. Aspirations were performed on each mass. No complications related to the aspiration occurred. Thirty-six (60%) developed a pancreatic infection. Infections occurred within 7 days in 12 and within 14 days in 12. Thus 55% (20/36) infections occurred within 14 days. Sites of infections were 13/21 pseudocysts, 1 of 2 extrapancreatic fluid collections, and 6/13 pancreatic masses. A total of 42 infections were noted: *Klebsiella,* 13; *Escherichia coli,* 10; *Enterococcus,* 6; *Staphylococcus aureus,* 5; *Proteus,* 3; *Bacteroides melaninogenicus,* 2; *gamma Streptococcus,* 2; *Pseudomonas,* 2; *Serratia* 2; *Streptococcus viridans,* 2; *Peptostreptococcus,* 1; and *Eichenella corrodans,* 1. Elevations in white blood cell count and fever were not predictive of infectious or sterile findings on aspirations. However, the indication for performance of aspiration was fever, leukocytosis, and inflammatory mass on CT scan. All of these cases were either a D or E on Balthazar/Ranson CT scoring.

VI. Microorganism and Antibiotic

The use of antibiotic is appropriate in suspected cholangitis or prophylaxis in severe pancreatitis. Current recommendations regarding antibiotic usage in necrotizing pancreatitis were preceded by failures to show benefit. A retrospective review today would note that these studies failed to recognize the majority of all

attacks (75% depending on etiology) of pancreatitis are self-limited. These cases are at no risk to develop necrosis and thus the outcome will be excellent regardless of intervention. The entry criteria of all patients with a diagnosis of pancreatitis were included in these initial studies. Thus the failure to identify the subgroup of patients who would most likely benefit led to a patient population from which the benefit of prophylactic antibiotics was concealed.

Outcome data correlated with cost analysis of hospital stay identified infections (infected necrosis) as the most frequent cause of death. Clinical criteria including Ranson, Glasgow, Apache Score, organ system failure, focused on identification of this population. The technical advance and widespread use of computerized axial tomography further demonstrated pancreatic necrosis, which correlates with an increased risk of death from pancreatic infections.

Antibiotic therapy to prevent pancreatic abscess is based upon 3 factors: tissue concentration of antibiotic, organisms, and susceptibility of organisms. The most common organisms identified in surgical specimens of humans with pancreatic necrosis are listed below (see table). Treatment of the organism is dependent on the microorganism's sensitivity and the concentration of the antibiotic. The ability of different antibiotics to penetrate the pancreas required investigation. Pancreatic tissue concentrations of antibiotic were measured in humans with acute pancreatitis, chronic pancreatitis, and pancreatic cancer. Interestingly, there was no significant difference in pancreatic concentrations of antibiotics for these different illnesses. An efficacy factor (EF) was proposed which considered the various involved organisms, pancreatic tissue concentrations of antibiotics, and percentage of inhibited bacteriologic strains for each antibiotic. Calculations of these variables are seen in below for the various antibiotics. The fluoroquinolones and imipenem became popular in view of their respective efficacies.

Organism in Pancreatic Infections	Percentage of Infections
E Coli	25.9%
Pseudomonas	15.9%
Staphylococcus Aureus	15.3%
Klebsiella	10.1%
Proteus	10.1%
Streptococcus Faecalis	4.4%
Enterobacter	2.5%
Different Anaerobes	15.6%

Efficacy Factor Analysis	
Netilmicin	0.21
Tobramycin	0.22
Mezlocillin	0.71
Piperacillin	0.72
Ceftizoxime	0.76
Cefotaxime	0.78
Oflaxacin	0.87
Ciprofloxacin	0.86
Imipenem	0.98

An initial study randomized patients with necrotizing pancreatitis to receive antibiotic therapy (imipenem 500mg IV every 8 hours for 14 days) or none. Seventy-four patients were recruited from 6 centers. Etiologies of pancreatitis enrolled included biliary, 37 (50%); alcohol, 24 (32%); and other, 13 (18%). Thirty-three patients were placed in the control arm and 41 were enrolled in the antibiotic arm. The patient population was similar in regard to severity of illness and demographics. Patients, who were in the control arm, received antibiotics if warranted by clinical conditions. Ampicillin and or aminoglycoside for urinary tract infection or pneumonia were administered. The outcomes of death, pancreatic sepsis, and non-pancreatic sepsis were compared.

	Control N==33	Imipenem N=41
Pancreatic Sepsis	10 (30.3%)	5 (12.2%)*
Non-Pancreatic Sepsis	16 (48.5%)	6 (14.6%)*
Death	4 (12.1)	3 (7.3%)

The difference in pancreatic sepsis and non-pancreatic sepsis was significant between the groups $P< 0.01$. Death did not reach statistical difference. The organisms seen in infected necrosis were *Escherichia coli,* 11 (7 control/4 treated group); *Streptococcus faecalis,* 7 (4 control/3 treated); *Pseudomonas,* 4 (4 control); *Candida,* 4 (4 control); *Citrobacter,* 2 (2 treated); *Klebsiella,* 1 control; *Serratia,* 1 treated; *Bacteroides fragilis,* 1 control; *Corynebacterium*, 1 control. All four cases of Candida in this study were in the control treatment arm. The emergent of Candida in pancreatic necrosis is a significant cause of death. Additionally this study demonstrated the percentage of necrosis increased the risk of pancreatic sepsis.

	Pancreatic Sepsis
Necrosis <30%	5/20 (25%)
Necrosis 30-50%	4/11 (36.3%)
Necrosis > 50%	1/ 2 (50%)

There were no pancreatic infections when necrosis was 50% or less in the antibiotic arm. However, 5/14 (35.7%) with more than 50% necrosis developed pancreatic sepsis. This study demonstrated a reduction in complications. The death rate in the control arm was low compared to previous series death rates of 20-70%. A statistical benefit from antibiotic in the prevention of death could not be shown.

A second trial compared cefuroxime to none in patients with necrotizing pancreatitis from ethanol abuse. The entry criteria included an elevated C-reactive protein >120mg/L and low enhancement with dynamic CT scan (necrotizing pancreatitis). The care policy at this center includes the routine prophylaxis of patients with biliary pancreatitis etiology and thus this subgroup was excluded. The results favored antibiotic prophylaxis with a lower mortality, lower mean complications, and urinary tract infections. The mean hospital stay and intensive care unit stay were lower in the antibiotic group but did not reach significance (P=0.24 and P=0.06). The need for surgery was less with antibiotics 8 versus 36 control (P=0.012).

The cause of death was *Staphylococcus epidermidis* with multiple organ failure in 1 antibiotic group and 3 in control group. Sepsis with *Staphylococcus aureus* 1, *Enterococcal faecalis* 1, and shock 2 were seen in the control group.

	Control N=30	Cefuroxime 4.5g/d N=30
Length of Stay	33.2	43.8
ICU days	23.6	12.1
Mean Complications/patient	1.8	1.0 *
Death	7	1 *

P<0.01
P=0.0284

	Control	Cefuroxime 4.5 g/d
Sepsis Culture +	8	4
Urinary tract Infection	17	6 *
Pneumonia/ ARDS	17	11
Pancreatic Infection	12	9
Pts with Complications	20 (67%)	25 (83%)

P=0.0073

The fluoroquinolones appear to have similar efficacy to imipenem. However, a recently published control trial did not find the two equal. The groups were similar in demographic, etiology, and severity of pancreatitis. The study entry required necrosis of 50% of the pancreas. Four centers entered patients with various causes of pancreatitis including biliary, biliary plus ethanol, alcohol, post-ERCP, and idiopathic. The etiology expressed in percentages were biliary, 66.1%; alcohol, 15%; and biliary and ethanol, 14%. The incidence of infected necrosis, extrapancreatic infections and deaths favored imipenem treatment. However, only pancreatic infections reached P<0.05.

	Perfloxacin	Imipenem
Infected Necrosis	10/30 (34%)	3/30 (10%)
Extra Pancreatic Infections	13/30 (43%)	6/30 (20%)
Death	7/30 (24%)	3/30 (10%)

Infected pancreatic necrosis was an indication for surgical intervention. All 3 patients who developed pancreatic infections despite Imipenum antibiotic prophylaxis died. Deaths were associated with multiorgan failure (MOF) and sepsis. One patient had *Candida glabratra*. Infected necrosis resulted in 5 deaths in the Perfloxacin group MOF with *C. glabrata* 3, MOF with *Xanthomonas maltophilia*, and 1 polymicrobial infection with *E. coli* and *Bacteroides fragilis*. The outcome was not different for gram negative or gram-positive infections. Candida non-albicans pancreatic infections were fatal and seen in 4/8 deaths with infected necrosis.

	Perfloxacin	Imipenem
S. Aureus (Methicillin Resist.)	3	2
Candida glabrata	3	1
Pseudomonas Aeruginosa	2	0
E Coli	1	2
B Fragilis	1	0
Xanthomonas maltophilia	1	0
Actineobacter	1	0
Enterococcus	1	0
Klebsiella	1	0

The infections listed above were Polymicrobila in 4 patients: 2 with *P. aeruginosa* and *S aureus*, 1 with *E. coli* and *B fragilis*, 1 with *Kleb* and *Acinetobacter*.

An alternative approach is the selective decontamination of the GI tract. Translocation of bacterial across the intestinal lumen may have a role in the development of infected necrosis. A significant reduction in mortality in rats has been shown with intestinal lavage and intraluminal kanamycin. Patients with severe pancreatitis (n=102) as defined by Imrie (Glasgow) score (>2) or CT (grade D or E on Balthazar scale) were enrolled. Patients were randomized to receive standard care or decontamination. Colistin sulfate and amphotericin was placed per oral cavity, tracheotomy site, and rectal enema. Cefotaxime was given until gram negative bacteria were eliminated from cultures of the oral cavity and rectum. Fifty-two patients were placed in the control group and 50 in the selective decontamination group. The treatment was continued while in the intensive care unit.

Pancreatic infections occurred in 20 patients in the control group and 9 patients in the decontamination group (P=0.03). Gram negative pancreatic infections occurred in 17 (33%) of the control group versus 4 (8%) with decontamination P=0.003. In both groups, all gram negative pancreatic infections were preceded by colonization of the digestive tract by the same bacteria. Laparotomy was performed for necrosectomy or abscess. An average of 3.1 laparotomies were performed per patient versus 0.9 in the selective decontamination group ($p<0.05$). Death was seen in 18 patients in the control group and 11 in the treatment arm P=0.19.

VII. Endoscopic Intervention

Gallstones are a significant cause of pancreatitis. The passage of gallstones through the ampulla has long been postulated as the cause of pancreatitis. Opie in 1901 postulated that gallstone impaction at the ampulla allowed reflux of bile into the pancreatic duct resulting in enzyme activation and pancreatitis. This argument is dependent upon a common channel from the bile duct and pancreatic duct. The common channel finding is seen in only 85% of patients and could not explain all cases. Further problems with this hypothesis include the fact that pancreatic pressure frequently exceeds the biliary pressure, and bile perfused into the pancreatic ductal system does not induce pancreatitis. Occlusion of the pancreatic duct likely is a significant factor. Ligation of the bile duct, pancreatic duct and both suggest the critical role of pancreatic occlusion in pancreatitis. Ligation models of the pancreatic duct have correlated the duration of occlusion with the

severity of necrosis. Further, early decompression of the ductal system prevents progression of disease, thus leading credence to early intervention for biliary pancreatitis.

The observation of impacted stones at autopsy in pancreatitis and at surgery suggested the etiology and a possible role for intervention. A strong argument for the role of gallstone passage was the fecal recovery of multiple gallstones among patients who suffered from acute pancreatitis as compared to the population with biliary colic. Gallstones were recovered in 34 of 36 patients with pancreatitis but in only 3 of 36 with biliary colic. Common bile duct stones and impacted ampullary stones at surgery performed within 48 hours of admission was noted in 62-75% of cases. Delays in surgery decrease the incidence to 3-33% and impacted stones to 5%. Surgical approaches of common bile duct exploration failed to demonstrate a benefit. Rather they suggested that early intervention adversely affects patient outcomes. Early surgery within 48 hours was associated with a mortality rate of 47.8% versus 11.8% in severe pancreatitis. Surgical approaches typically incised the bile duct and remove stones through a biliary incision. A new surgical approach incorporated the use of duodenotomy with sphincteroplasty to remove the stones through the ampulla. In this series only 1 of 46 of patients died (2.9%) versus a historical comparison group of 14/86 (16%) deaths.

The technical advance of endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy in 1974 brought a new therapeutic modality approach for the removal of stones. A significant complication of ERCP is pancreatitis and the use of ERCP was initially considered risky. Thus, endoscopic trials were delayed for 15 years. Endoscopic intervention for acute pancreatitis has been compared in 4 controlled trials. Three articles are published in peer reviewed journals. One has been published only in abstract form and presented at the annual digestive disease week symposium. The results support the use of ERCP in patients with biliary etiology and severe pancreatitis. A significant component of the benefit is the prevention of cholangitis in this population whereas the exclusion of patients with cholangitis and jaundice appears to minimize the therapeutic effects of endoscopic intervention.

An initial trial prospectively randomized patients with pancreatitis (n=121) to urgent ERCP or conservative management within 72 hours. Patients with alcohol abuse or other causes of acute pancreatitis including trauma and hyperlipidemia where excluded from study entry. Sphincterotomy was performed if a stone was identified. ERCP was successful in 32/34 mild pancreatitis cases and 20/25 cases in severe pancreatitis. The arms were compared on an intention to treat basis. The complication rate for mild cases of pancreatitis was not significantly different for intervention, 12% versus 14%. In contrast, the severe pancreatitis group with intervention had complication rates of 24% versus 61% in control population ($P<0.01$). The length of hospital stay was 9.0 with intervention versus 11.0 control group for the mild pancreatitis group. This was not significantly different in this population. However, in the severe pancreatitis group the length of stay was 9.5 versus 17.0 in the control group for a statistical value of $P=0.0346$. Mortality was 2% in the ERCP group versus 8% in the conventional group. The difference was greater in the subset of severe pancreatits 5/28 (17.8%) versus 1/25 (5%) but did not reach statistical difference. This study suggested ERCP in severe acute pancreatitis altered the complication rate for acute pancreatitis but did not influence death. Additionally the performance of ERCP in acute pancreatitis did not increase the complication rate.

A second study compared the intervention of ERCP within 24 hours of admission to conservative therapy. Sphincterotomy was performed if a stone was present. Patients with evidence of cholangitis, shock, or jaundice underwent ERCP in the conservative treatment arm. One hundred and ninety-five patients were randomized. 97 patients were randomized to emergent ERCP. ERCP was unsuccessful in 10 patients (10.3%). Ninety-eight patients were randomized to conservative management. In the conservative group, 9 of

58 with initially mild pancreatitis underwent ERCP (14-57) hours after admission, secondary to the development of cholangitis or shock. However, 18/40 patients with severe pancreatitis who were randomized to conservative treatment underwent ERCP. Six of 16 patients in the severe subgroup were found to have stones. ERCP failed to cannulate in two patients.

Evaluation was performed on an intent to treat basis. Local and systemic complications, sepsis, and other complications were compared for all patients with regard to therapy. Subset analysis was performed regarding whether the pancreatitis was mild or severe. No statistical difference in local or systemic complications could be seen regardless of therapy. The incidence of sepsis was significantly altered in favor of endoscopic intervention with 0 versus 16 (12 acute cholangitis, 1 acute cholecystitis, and 3 pancreatic abscess). The death rate was 5 versus 9, a P value of 0.4 in favor of endoscopy. The virtues of endoscopy continued to be extolled but the benefit appeared to be the prevention of biliary sepsis.

A third study did not find endoscopy to be of benefit. However, the entry criteria were significantly different from the previous trials. This multicenter study was performed involving greater than 22 centers and enrollment of 238 patients. Exclusion criteria were total bilirubin 5mg/dl or cholangitis. The incidence of severe pancreatitis was 16% versus 41-51% in two other prospective studies. The invasive therapy group received ERCP within 72 hours. There was no statistically significant difference between intervention or conservative therapy with regard to complications or deaths. Deaths were 14 in the invasive group versus 7 in the conservative group for a P =0.10. Patients who received early ERCP had higher incidence of respiratory failure 15 versus 5 (P=0.03). The benefits of endoscopic intervention on mortality and morbidity disappeared with the exclusion of cholangitis and jaundice bilirubin 5mg/dl. Critics of this paper point out the lack of severe pancreatitis in this study and question whether the multiple centers lacked the experience and benefits of a dedicated interventional endoscopist. A low patient volume is suggested by 19 centers enrolling only 2 patients per year. The success and complications of ERCP is correlated with procedure volume. Procedure related complications, technical failures, and need for subsequent repeat procedures are improved with high endoscopist volume.

A fourth study has been reported only in abstract form. Patients (n=280) were randomized to receive urgent ERCP with sphincterotomy regardless of findings or conventional therapy. Significantly fewer complications were noted: 17% versus 36% (P, 0.001), and lower mortality rates 2 versus 13%. The benefits appear to extend to both mild and severe pancreatitis subgroups who received endoscopic therapy.

These papers raise questions whether the good outcomes noted in select centers of expertise can be replicated in other centers. Outcome research is the application of data from a large patient population managed at various centers. The results are likely to be consistent with centers without the resources of expertise in pancreaticobiliary disease. The criticism of outcome evaluations is the inability to control patient factors, therapies, and the accuracy of the discharge coding. The alternative is a prospective control trial, which is more expensive and may not readily provide the answer. For example the German study required 22 centers over 5 years to enroll sufficient numbers. Utilizing the Veteran Administration database 2075 patients with biliary pancreatitis from 1988 and 1994 were identified. The patients were divided into initial therapy received (650 ERCP and 1425 cholecystectomy). Biliary endoscopy was associated with significant older age, severe pancreatitis, and non-surgical service admission. Despite the selection bias, the outcome with ERCP appeared similar to the outcome received by cholecystectomy. The death rate for initial ERC was 2% versus 4% for surgical intervention.

The majority of pancreatitis cases in the Veteran administration database appeared to be mild and intervention was generally performed after several days' hospitalization. We presume in cases of mild pancreatitis this time period was spent on expectant observation for spontaneous stone passage. However, the data suggest that early intervention by either endoscopy or cholecystectomy would markedly reduce hospital stay. Virtually every patient received either endoscopy or surgery following their initial episode of pancreatitis. This is consistent with the documented increased incidence of recurrent problems if no definite therapy is rendered. Patients admitted to the surgical service were far more likely to receive cholecystectomy as their initial treatment. This may reflect a thoughtful initial decision to admit the patient to the service best suited to deal with their admitting problems. Less comforting would be the explanation that the initial treatment is more determined by ambiguity than medical consideration. Surgeons would tend to manage patients surgically, while internists would be more inclined to choose an endoscopic approach. This suggests a need for a closer interaction between the two services to improve outcomes. These findings support the contention that endoscopic therapy may decrease mortality in severe pancreatitis. Studies, which include a majority of patients with mild pancreatitis, will be unable to show an outcome difference regarding death with endoscopic intervention. Earlier intervention would reduce hospital stay and reduce costs.

VIII. ETIOLOGY AND EVALUATION

Gallstones are the most common cause of pancreatitis in the United States, Asia, and Western Europe at 45%. Alcohol abuse is second at 35%. Idiopathic and miscellaneous causes represent 10% to 15% each. The evaluation to the cause of pancreatitis should begin with a history and physical, ultrasound of the abdomen, liver function tests, serum triglycerides and calcium level. Idiopathic pancreatitis is a common entity but several evaluations may be helpful in obtaining a diagnosis.

ERCP was initially used for the identification of structural abnormalities in idiopathic causes. A potential cause was identified in 23/73 (31.5%). The recognition of a hypertensive sphincter of Oddi (SO) dysfunction association with pancreatitis was found in 17/116 (14.6%). This technique involves the placement of a catheter across the ampullary zone to measure the pressures with manometry at ERCP. Combining SO Manometery and ERCP findings, 38% of patients were found to have a cause of pancreatitis. A third advance in structural abnormality was the identification of biliary sludge passage as a cause of pancreatitis. Evaluation for microlithiasis with echogenic sludge on abdominal ultrasound or biliary aspiration for crystal analysis was associated with idiopathic pancreatitis in 37/51 (73%) and 23/31 (74%). Older age and abnormal liver function tests are noted more commonly in microlithiasis. Further, treatment with sphincterotomy, ursodeoxycholic acid, or cholecystectomy significantly reduced the incidence of recurrent attacks. Some centers have used this data to develop a policy of idiopathic pancreatitis treatment with initial cholecystectomy. The recent findings of genetic predisposition raised other issues. For example, patients with hereditary pancreatitis have been found to have sphincter stenosis and benefited from sphincterotomy. This finding suggests that sphincter stenosis may be a secondary result. Recently the mutation of CFTR allele was linked to idiopathic pancreatitis in 37% of cases. Currently the finding of a cystic fibrosis allele can not influence treatment but may provide more insight into the pathophysiology of pancreatitis.

When patients with idiopathic pancreatitis should undergo further evaluation is controversial. One center performed ERCP on 20 of 31 patients. They did not find any abnormalities. Follow-up at 36 months had one recurrent pancreatitis attack and two episodes of abdominal pain. This study suggested a low yield of ERCP for the initial evaluation of acute pancreatitis. The high incidence of normal findings is not consistent with

the experience at other centers. Additionally, neither sphincter of Oddi manometry or aspiration of bile for biliary microlithiasis were performed.

An analysis of the cost-utility performed for ERCP following acute pancreatitis provides further recommendations. This study considered only the probability of finding a CBD stone in acute pancreatitis. Previous retrospective series have recorded the incidence of finding bile duct stones in idiopathic pancreatitis at 19%-24%. If gallstones are present the rate increased to 38%. The papers assessing microlithiasis noted a 30-60% incidence of biliary disease with recurrent pancreatitis. A cost-benefit analysis considered the cost of care for no evaluation verus the cost of ERCP. This analysis suggested a 25% incidence of stones as neutral. ERCP performed when the incidence of reversible disease is $\geq$ 25% results in the saving of financial resources. By selecting a population with a higher probability of finding a reversible lesion then ERCP is cost-effective. Currently this author recommends ERCP for patients with recurrent pancreatitis, severe pancreatitis, abnormal liver function test, and older age.

IX. APPENDIX

APACHE-II SEVERITY OF Disease Classification System									
	HIGH ABNORMAL RANGE				LOW ABNORMAL RANGE				
PHYSIOLOGIC VARIABLE	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature-rectal (°C)	≥41°	39°- 40.9°		38.5°-38.9°	36-38.4°	34°-35.9°	32-31.9 °	30-31.9	≤29.9°
Mean arterial pressure (mm Hg)	≥160	130-159	110-129		70-109		50-69		
Heart rate (ventricular response)	≥180	140 -179	110-139		70-109		55-69	40-54	≤39
Respiratory rate (nonventilated or Ventilated	≥50	35 - 49		25-34	12-24	10-11	6-9		≤5
Oxygenation: A-aDO_2 (mm HG)									
a. $FIO_2 \geq 0.5$ record A-aDO_2	≥500	350-499	200-349		<200				
b. $FIO_2 < 0.5$ record only PAO_2					PO_2>70	PO_2 61-70		PO2 55-60	PO2 <55
Arterial pH	>7.7	7.6-7.69		7.33-7.49			7.25-7.32	7.15-7.24	<7.15
Serum sodium (mmol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	<110
Serum potassium (mmol/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum creatinine (mg/100 ml) (Double point score for acute renal failure)	>3.5	2-3.4	1.5-1.9		0.6-1.		<0.6		
Hematocrit (%)	≥6.0		50-59.9	46-49.9	30-45.9		20-29.9		<20
White blood count (total/mm^3) (in 1000s)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow Coma Score (GCS): Score – 15 minus actual GCS									
A Total Acute Physiology Score (APS): Sum of the 12 individual variable points									
Serum HCO_2 (venous –mmol/L) (Not preferred use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	14-17.9	<15

B AGE POINTS

Age (yr)	Points
45-54	2
55-64	3
65-74	5
≥ 75	6

C Chronic health points.

If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows:
For non operative of emergency potoperative patinets – 5 points or
a. For nonoperative of emergency posoperative patien ts – 5 points or
b. For elective postoperative patients – 2 points.
Definitions. Organ insufficiency or immunocompromised state must have been evident prior to this hospital admission and conforms to the following criteria:

Liver. Biopsy proven cirrhosis and documented portal hypertension, episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.

Cardiovascular. NY Heart Association Class IV.

Respiratory. Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, e.g., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mm Hg), or respirator dependency.

Renal. Recurring chronic dialysis.
Immunocompromised. The patient has received therapy that suppresses resistance to infection (e.g., immuno-suppression, chemotherapy, radiation, long-term or recent high-dose steroids) or has a disease that is sufficiently advanced to suppress resistance to infection (e.g., leukemia, lymphoma, AIDS).

Apache-II SCORE
Sum of **A** + **B** + **C**
A APS points _____
B Age points _____
C Chronic Health points _____
Total APACHE-II SCORE _____

Frequency of CT Findings on Initial Study, Relationship of the time of the Initial CT Study to These Findings, and overall Incidence of infected Pancreatic Abscess

CT FINDINGS

	0-3*	4-6*	7-10*	All Patients
Number of patients	40	26	17	83
Per cent CT Grade A†	10.0	26.9	5. 9	14.5
B†	22.5	26.9	17.6	22.9
C†	27.5	15.4	11.8	14.5
D†	17.5	11.5	11.8	14.5
E†	22.5	19.2	53.0	27.7
Per cent abscess	25.0	15.4	23.5	21.6

*Day of initial CT scan.
†CT grade A = normal; B = pancreatic enlargement alone; C = peri-pancreatic inflammation only; D = one fluid collection; E = more than one fluid collection.

Ranson's Criteria
Non-Gallstone Pancreatitis

On admission	Within 48 hours of hospitalization
Age > 55 yr	Decrease in hematocrit > 10 points
White-cell count > 16,000/mm^3	Increase in blood urea nitrogen > 5 mg/dl
Glucose > 200 mg/dl	Calcium <8 mg/dl
Lactic dehydrogenase > 350 U/liter	Partial pressure of oxygen <60 mm Hg
AST >250 IU/L	Base deficit >4 mmol/liter
	Fluid deficit >6 liters

Gallstone Pancreatitis

On admission	Within 48 hours of hospitalization
Age> 70 yr	Decrease in hematocrit >10 points
White-cell count > 18,000/mm^3	Increase in blood urea nitrogen >2 mg/dl
Glucose >220 mg/dl	Serum calcium <8 mg/dl
Lactic dehydrogenase >400 U/liter	Base deficit >5 mmol/liter
Aspartate aminotransferase >500 U/liter	Fluid deficit > 4 liters

Modified Glasgow Criteria

	Within 48 hours of hospitalization
	AST >200IU/L
	White-cell count >15,000/mm^3
	Glucose > 180 mg/dl
	Blood urea nitrogen >45 mg/dl
	Lactic dehydrogenase >600 U/liter
	Albumin < 3.3 g/dl
	Calcium < 8 mg/dl
	Partial pressure of oxygen <60 mm Hg

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