CHAPTER 55

Etiology, pathogenesis, and diagnostic assessment of acute pancreatitis

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Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas leading to injury or destruction of acinar components and clinically characterized by abdominal pain and elevated blood levels of pancreatic enzymes (Banks et al, 2013; Sarner & Cotton, 1984). The clinical spectrum is as diverse as its causes and pathogenesis; AP can range from relatively mild to severe with potentially life-threatening complications. In the recent Atlanta classification revision, AP is differentiated into two types: interstitial edematous pancreatitis and necrotizing pancreatitis (Banks et al, 2013). AP is the most common diagnosis for hospitalization among the gastrointestinal conditions in the United States, accounting for as many as 230,000 hospitalizations per year (DeFrances et al, 2007). The incidence is on an increasing trend during the past decades and has ranged from approximately 5 to 35 per 100,000 population per year (Peery et al, 2012, Yadav & Lowenfels, 2006). AP with its associated complications is a major cause of morbidity and mortality worldwide; mortality ranges from approximately 1% to 20% in mild to severe cases, respectively (Cavallini et al, 2004, Hamada et al, 2014). As a result, AP poses a huge financial health care burden as well (Andersson et al, 2013). Management is challenging and centers on diagnosing the etiology, assessing the severity, and treating the disease and its associated complications.

ETIOLOGY AND PATHOGENESIS OF ACUTE PANCREATITIS

Gallstones and alcohol abuse together account for as many as 60% to 80% of all AP cases (Sakorafas & Tsiotou, 2000). The relative frequency of each of these etiologies depends largely on the population being evaluated. In both the East and the West, biliary pancreatitis is more common in women, whereas alcoholic pancreatitis is more common in middle-aged men (Hamada et al, 2014;Yadav & Lowenfels, 2006). Approximately 10% of cases are caused by diverse causes, such as malignancy, hyperlipidemia, hypercalcemia, viral infection, drugs, and iatrogenic causes. As many as 30% of cases are idiopathic (Tan & Sherman, 2013).

Acute Biliary Pancreatitis

Between 4% and 8% of patients with gallstones eventually experience biliary pancreatitis secondary to migratory gallstones (Fig. 55.1A) (Howard, 1987) (see Chapters 32 and 36). The incidence of acute biliary pancreatitis is higher in women than in men (69% vs. 31%), and increases with age (van Erpecum, 2006). The natural history of acute biliary pancreatitis is different from that alcohol-induced disease. There is a spectrum of severity similar to alcoholic pancreatitis, but if the patient recovers, endocrine and exocrine deficiencies are much less likely than in alcoholic patients, and in most cases the gland is histologically normal after clinical recovery (Raraty et al, 1998).

Opie first observed an impacted gallstone at the papilla of Vater in two patients with severe pancreatitis in 1901. Since then, investigations have shown that the pathogenesis of biliary pancreatitis is multifaceted, with ampullary obstruction, biliopancreatic reflux, gallstone-related factors, and genetics each playing a role.

Experimental and clinical studies have shown that ampullary obstruction by gallstones not only initiates but also sustains and aggravates biliary pancreatitis (Acosta et al, 2006; Runzi et al, 1993). On the other hand, Acosta and Ledesma (1974) found small gallstones in the stool of 94% of patients with biliary pancreatitis, compared with 8% of control subjects with gallstones without pancreatitis, demonstrating that the crucial event is probably not the impaction of a stone in the common bile duct (CBD), but rather the passage of a gallstone of a suitable size through the ampulla of Vater. In the absence of an obstructing stone at the ampulla, based on findings of inflamed ampulla in patients operated early (<36 hours after admission) for biliary pancreatitis versus those operated late (>3 months after admission), it is hypothesized that local edema or spasm of the ampulla can also lead to obstruction of the pancreatic duct (Stone et al, 1981). Either way, transient obstruction increases pressures in the pancreatic duct, which then leads to extravasation of pancreatic juice in the interstitium and subsequent injury of the gland. Pancreatic hypersecretion after a meal may then enhance the increasing pressure in an already-obstructed duct from the migrating gallstone and intensify the injury (Foitzik & Buhr, 1997). The causative role of transient obstruction by gallstones in pancreatitis is further supported by the observation that recurrent attacks of biliary pancreatitis can be prevented or reduced by endoscopic sphincterotomy (Hammarstrom et al, 1998). In patients with separate orifices of the CBD and pancreatic duct, biliary pancreatitis can still occur, likely due to the stone in the distal bile duct compressing onto the adjacent pancreatic duct directly, or from the resulting oedema (Jones et al, 1987).

Opie proposed in 1901 that bile reflux into the pancreatic duct caused by stone obstruction of the common biliary pancreatic channel initiates the inflammation. Since then, however, the evidence suggests that the common channel focus is invalid (Lerch et al, 1994). Under physiologic circumstances, the pressure in the pancreatic duct is threefold higher than in the CBD, thereby preventing reflux of bile into the pancreatic duct (Nitsche & Folsch, 1999). During ampullary obstruction, the pressure gradient between the biliary tree and the pancreatic

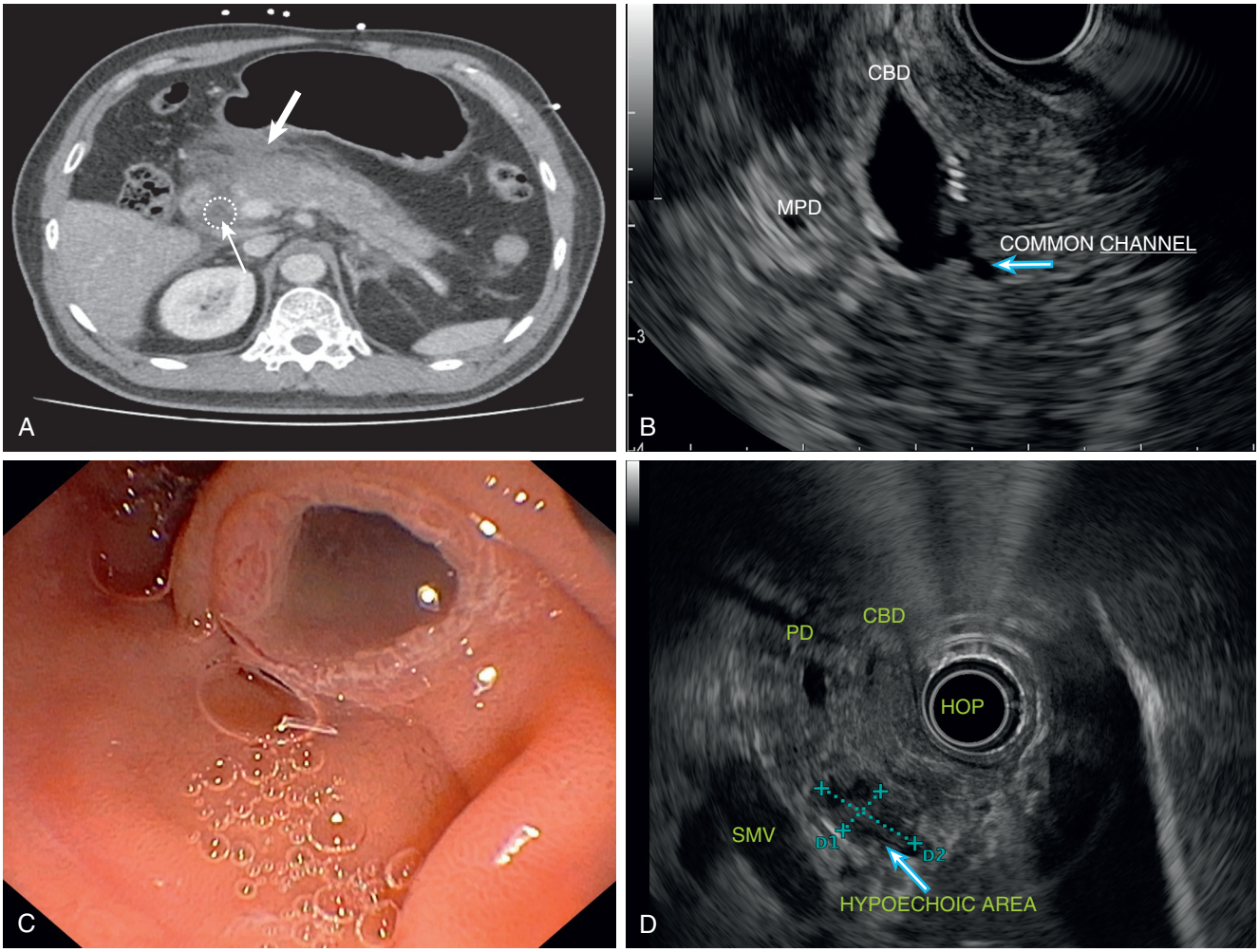

FIGURE 55.1. Causes of acute pancreatitis. **A,** Cross-sectional computed tomography (CT) image of acute biliary pancreatitis. *Thin arrow,* Small gallstones within common bile duct (*circle*); *thick arrow,* edematous head and neck of pancreas with peripancreatic fluid. **B,** Anomalous pancreaticobiliary duct junction (ABPJ) on endoscopic ultrasound (EUS). *Arrow,* Common channel; *CBD,* common bile duct; *MPD,* main pancreatic duct. **C,** Endoscopy picture of fish-mouth papilla with mucus coming out, main duct. Intraductal papillary mucinous neoplasm causing pancreatitis. **D,** Initially diagnosed idiopathic pancreatitis. Cross-sectional imaging (e.g., CT) did not detect a cause of lesion, but further workup with EUS reveals the lesion as a hypoechoic area (*arrow*), which proved to be a pancreatic adenocarcinoma. *HOP,* head of pancreas; *PD,* pancreatic duct; *SMV,* superior mesenteric vein. *(Images courtesy Dr. Damien Tan and Dr. Ser Yee Lee.)*

duct may reverse (Arendt et al, 1999). Nonetheless, although sterile refluxate can cause an increase in the permeability of the pancreatic ductal system through activation of pancreatic enzymes, it does not lead to pancreatitis and would remain a harmless event (Luthen et al, 1993; Nakamura et al, 1996). However, when there is temporary biliary and pancreatic obstruction, followed by decompression and flow of infected bile at high pressure into the pancreatic duct, AP is induced (Arendt et al, 1999).

Contributing to the pathogenesis of biliary pancreatitis are factors that facilitate the passage of gallstones from the gallbladder into CBD and then through the ampulla. A recent study showed that small gallstone diameter (<5 mm), wide cystic duct (>5 mm) and high stone load (>20 gallstones) were significant risk factors for biliary pancreatitis (Sugiyama & Atomi, 2004). Other gallstone-associated features that increase the risk for development of biliary pancreatitis include mulberry shape and irregular surfaces (Diehl et al, 1997; McMahon & Shefta, 1980). Excess cholesterol crystals in the gallbladder and good emptying of the gallbladder are also associated with an increased risk of pancreatitis (Venneman et al, 2005).

In recent years, variations or mutations in the genes that encode pancreatic enzymes or their inhibitors have been suggested as potential risk factors for development of AP. *SPINK1* encodes a potent inhibitor of trypsin activity within the pancreas, and it has been found that mutations in *SPINK1* are significantly higher in patients with AP (all causes) compared to a healthy control group (O'Reilly et al, 2008). A case of recurrent biliary pancreatitis has reportedly been associated with a mutation in *ABCB4* gene, which encodes a multidrug resistance protein involved in the transport of phosphatidylcholine across the canalicular membrane of hepatocytes.

Acute Alcoholic Pancreatitis

Alcoholic pancreatitis is more common in men, which may result from a tendency for males to drink more rather than a gender-based difference in susceptibility (Lankisch et al, 2002). The peak age for presentation of alcoholic pancreatitis is

uniformly 40 to 60 years. Incidence and prevalence also differ in terms of race and geographic distribution (Yadav & Lowenfels, 2006). The average daily alcohol consumption among patients with alcoholic pancreatitis averages 100 to 150 g/day. Although the risk for pancreatitis increases with greater doses of alcohol, epidemiologic studies shows that clinically evident pancreatitis develops in only a minority of heavy drinkers (Sakorafas & Tsiotou, 2000; Steinberg & Tenner, 1994). On the other hand, findings consistent with pancreatitis have been reported in as many as 75% of autopsies performed on alcohol abusers (Dufour & Adamson, 2003). These observations suggest that alcohol alone may not cause pancreatitis unless accompanied by additional genetic and/or environmental factors. As such, it is probable that alcohol sensitizes the pancreas, with these additional genetic and environmental factors then initiating pancreatitis.

The direct effect of alcohol on the pancreas has been studied in its effects on the pancreatic duct and the acinar cells. Alcohol increases secretion of two nondigestive proteins, lithostathine and glycoprotein GP2, in the pancreas, which precipitate out within the ducts and form aggregates that eventually enlarge and calcify to form intraductal calculi (Apte et al, 1996, 1997). Whether these protein plugs and ductal calculi play a role in the initiation of alcoholic pancreatitis is yet to be determined, although it is accepted that these events have the potential to facilitate disease progression. In animal studies, chronic administration of alcohol has been found to increase the pancreatic content of the digestive enzymes trypsinogen, chymotrypsinogen, and lipase as well as the lysosomal enzyme cathepsin B (Apte et al, 1995). Typsinogen can be activated by cathepsin B within acinar cells, leading to a cascade of autodigestion characteristic of pancreatitis (Lindkvist et al, 2006). The pancreas can metabolize alcohol via both oxidative and nonoxidative pathways, yielding the toxic metabolites acetaldehyde and fatty acid ethyl esters (FAEEs), respectively (Gukovskaya et al, 2002; Haber et al, 2004). Oxidative alcohol metabolism results in the generation of reactive oxygen species (ROS) as a byproduct and, at the same time, depletion of the ROS scavenger glutathione. The products of alcohol oxidation (acetaldehyde and ROS) as well as those of nonoxidative metabolism of alcohol (FAEEs) have all been reported to cause acinar cell injury (Lugea et al, 2003; Nordback et al, 1991; Werner et al, 1997). Clinical and experimental studies have demonstrated that oxidant stress from the metabolism of alcohol induces destabilization of zymogen granules and lysosomes, resulting in pancreatic injury. Similarly, FAEEs from nonoxidative metabolism of alcohol destabilize lysosomes in acinar cells, thus increasing the potential for contact between lysosomal and digestive enzymes, leading to their intracellular activation and autodigestion of the gland.

Despite the many pathways of direct toxic injury of alcohol to the pancreas, the low numbers of patients with alcoholism in whom pancreatitis develops who suggest that a susceptibility factor, environmental or genetic, is at play to provide a second hit for triggering clinical pancreatitis. Among the environmental factors studied, smoking has garnered the most interest. A recent cohort study shows that smoking was a dose-dependent risk factor for alcoholic pancreatitis after controlling for age, gender, body mass index (BMI), and alcohol consumption (Lindkvist et al, 2008). As for genetic factors, to date, studies on hereditary factors as well as mutations in genes related to digestive enzymes and their inhibitors have shown no conclusive association with alcoholic pancreatitis. A potential cofactor that does have relevance to the clinical situation is bacterial endotoxemia. A recent study has demonstrated a key role for lipopolysaccharide, an endotoxin found in the cell wall of gram-negative bacteria, in the initiation and progression of alcoholic pancreatitis (Vonlaufen et al, 2007).

Nonbiliary and Nonalcoholic Acute Pancreatitis

Although less frequent, myriad other etiologic factors have been increasingly found to cause AP, accounting for as many as one quarter of the causes. Improved understanding of AP, coupled with advances in genetics, molecular biology, and pathology, has shed new light on its pathogenesis; AP is often the result of a complex interaction between host and environmental factors. This section examines some of these nonbiliary and nonalcoholic causes of AP.

Metabolic Causes

HYPERTRIGLYCERIDEMIA. Hypertriglyceridemia is well documented and accounts for 1% to 10 % of all AP cases (Valdivielso et al, 2014). AP secondary to hypertriglyceridemia seldom occurs unless it is severe (defined as >10 mmol/L fasting), although the exact pathophysiologic mechanism is unclear. This is confounded by the frequent presence of other factors coexisting in some of these patients, such as poorly controlled diabetes mellitus, obesity, alcohol abuse, pregnancy, and hypothyroidism. It is associated with types I, IV, and V hyperlipidemia (Sakorafas & Tsiotou, 2000). A common theory is that excess triglycerides are hydrolyzed by pancreatic lipase and released in the pancreatic microvasculature, resulting in high concentrations of free fatty acids (FFAs), which overwhelm the binding capacity of albumin and self-aggregate to micellar structures with detergent properties. This promotes acinar cell and pancreatic capillary injury, which results in ischemia and forms an acidic milieu that starts the vicious circle of triggering more FFA toxicity. At the same time, the ischemia is exacerbated by the increased viscosity of blood from the elevated levels of chylomicrons. The damage to the acinar cells and microvasculature leads to amplification of inflammatory mediators and free radicals, ultimately leading to necrosis, edema, and inflammation of the pancreas (Scherer et al, 2014; Valdivielso et al, 2014; Zeng et al, 2012).

Mild to moderate hypertriglyceridemia (<5 mmol/L) occurs in almost half of patients in the early phase of AP from any etiology, but some speculate that this is an epiphenomenon rather than a true precipitant because of the high prevalence of hypertriglyceridemia in the general population (Charlesworth et al, 2015; Domínguez-Muñoz et al, 1995). Some studies has proposed a genetic predisposition to hypertriglyceridemic AP. Lipoprotein lipase deficiency associated with chylomicronemia is a rare autosomal recessive disorder caused by multiple/different lipoprotein lipase gene mutations, characterized by high fasting plasma triglyceride levels (Foubert et al, 1996). The frequency of mutations in cationic trypsinogen (*PRSS1*), serine protease inhibitor Kazal type 1 (*SPINK1*), cystic fibrosis transmembrane conductance regulator (*CFTR*), and tumor necrosis factor superfamily member 2 (*TNF2*) genes were studied in 128 patients with hypertriglyceridemia with or without AP. The prevalence of polymorphisms in *CFTR* and *TNF* genes was found to be significantly higher in those with hypertriglyceridemia (Chang et al, 2008).

HYPERCALCEMIA. Hypercalcaemia is a rare cause of AP, with a reported prevalence of 1% to 4% (Etemad & Whitcomb, 2001). There is no clear pathophysiologic mechanism, but elevated parathyroid hormone (parathormone, PTH) and hypercalcemia could be responsible for calcium deposit in the pancreatic ducts. Hypercalcemia-induced cellular injury occurs through activation of pancreatic enzymes by a trypsin-mediated mechanism, resulting in acinar cell damage, pancreatic autodigestion, and subsequent pancreatitis. Another mechanism is the formation of pancreatic calculi which, by modifying pancreatic secretion, may lead to protein plug formation, resulting in ductal obstruction. Acute hypercalcemia also increases the permeability of the pancreatic ductal membrane, allowing enzymes to leak and injure the pancreatic parenchyma. The parathormone may have direct toxic effects on the pancreas as well (Cameron & Clemens, 1993). Coexistence of primary hyperparathyroidism and AP has widely been reported, with a prevalence of 1.5% to 13%, but a causal relationship remains unclear (Biondi et al, 2011; Kota et al, 2103). Hypercalcemia results from calcium infusion during total parenteral nutrition and occurs in patients with myeloma, leukemia, vitamin D poisoning, disseminated cancer, or severe hyperthyroidism, all of which have been associated with pancreatitis (Sakorafas & Tsiotou, 2000). Reciprocally, treatment of the hypercalcemia, regardless of the cause, has been reported to resolve the AP (Biondi et al, 2011).

INBORN ERRORS OF METABOLISM. Acute pancreatitis has been associated with a variety of inborn errors of metabolism; these entities are rare but more common in neonatal and pediatric patients. These familial disorders cause hyperlipidemias, disorders of branched-chain amino acid degradation, homocystinuria, hemolytic disorders, acute intermittent porphyria, and several amino acid transporter defects (Simon et al, 2001). AP also has been reported in patients with type I glycogen storage disease (von Gierke). The mechanism is not clear, but the common physiobiochemical processes are hyperlipidemia, lactic acidosis, hypoglycemia, and hyperuricemia, any of which could initiate pancreatitis (Herman, 1995). Other metabolic conditions associated with AP are maple syrup urine disease, cystathionine β-synthase deficiency, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, pyruvate kinase deficiency, cystinuria, lysinuric protein intolerance, and other cationic aminoacidurias (Baertling et al, 2013). In the majority of these diseases, pancreatitis is not common, and its pathogenesis is poorly understood (Simon et al, 2001).

Chronic Renal Failure and Dialysis-Related Causes

Acute pancreatitis can be caused by and associated with end-stage renal disease, including chronic renal failure and dialysis-related complications. Although rare, AP contributes to significant morbidity and mortality in patients whose health is already compromised. The diagnosis of AP is also confounded by renal dysfunction caused by altered levels of pancreatic enzyme estimation and the contribution of pancreatic damage from dialysis and uremia (Golay & Roychowdhary, 2012). The incidence of pancreatitis is significantly higher in patients undergoing peritoneal dialysis (PD) versus those receiving hemodialysis (HD), in whom the incidence is similar to the general population (Banks, 2002; Lankisch et al, 2008). Based on postmortem studies, pancreatic abnormalities are reported in as many as 60% of patients undergoing long-term dialysis (Bruno et al, 2000). Toxic substances in PD dialysate, alterations in serum calcium and PTH levels, and coexisting bacterial and viral infections are postulated factors that can initiate AP (Joglar & Saade, 1995). The increase in various gastrointestinal hormones in patients with end-stage renal disease, such as cholecystokinin, glucagon, and gastric inhibitory polypeptide, can stimulate hypersecretion of pancreatic enzymes such as trypsin, which can also initiate AP (Owyang et al, 1982). Local culmination of calcium in the pancreas from calcium in the PD solution has also been postulated. Another mechanism is peritoneal infusion of a large amount of nonphysiologic fluid under high intraabdominal pressure, which renders the pancreas more susceptible to parenchymal injury and hypoxemia, inducing premature activation of proteolytic enzymes, with higher risk of AP. These and other factors are cited to explain why the incidence of AP is higher in patients with PD than in patients with HD (Bruno et al, 2000).

Drug-Induced and Toxin-Induced Pancreatitis

Drug-induced pancreatitis (DIP) is a rare entity with a reported incidence of 0.1% to 2% of AP cases (Nitsche et al, 2010). In a World Health Organization (WHO) database, 525 different drugs were listed to cause AP as an adverse effect. Epidemiologic studies report that at-risk populations for DIP include the elderly and pediatric age-groups, females, and patients with inflammatory bowel disease or human immunodeficiency virus (HIV) (Balani & Grendell, 2008, Nitsche et al, 2010). Management and prevention of DIP requires an updated, evidence-based database of drugs associated with pancreatitis because prompt withdrawal of the offending agent is necessary and supportive care. Little is clear and much controversy exists about the precise causes of DIP, and most theories center on a few mechanisms. Accumulation of a toxic metabolite/intermediary and hypersensitivity reactions cause immune-mediated injuries and pancreatic duct constriction (Underwood & Frye, 1993), localized angioedema effect in the pancreas, and arteriolar thrombosis (Kaurich, 2008). Adverse effects of drugs causing hypercalcemia or hypertriglyceridemia are also mechanisms for DIP (Jones, 2015). The family of drugs often reported to cause AP are the angiotensin-converting enzyme (ACE) inhibitors, antidiabetic agents, statins, 5-ASA and derivatives, antibiotics, and valproic acid. Table 55.1 summarizes the various classifications and drugs (Badalov et al, 2007; Hung, 2014; Jones MR, 2015; Karch & Lasagna, 1975; Kaurich, 2008; Mallory & Kern, 1980; Nitsche et al, 2010; Trivedi & Pitchumoni, 2005).

Toxins are reported causes of AP, but this is rare. Many cases may in fact be erroneously labeled "idiopathic pancreatitis." Mechanisms may be similar to how certain drugs can initiate AP. The commonly reported toxins include scorpion's venom (Gallagher et al, 1981), organophosphate anticholinesterase insecticides (Lee, 1989), organic solvents, pentachlorophenol (Table 55.1) (Cooper & Macaulay, 1982), and diethyl glycol (Ellenhorn et al, 1988, Khurana & Barkin, 2001). Data on AP associated with herbal or alternative medicines are limited (Hung & Abreu Lanfranco, 2014). Reports documenting saw palmetto–induced AP postulate that saw palmetto (*Serenoa repens*, extract of American dwarf palm tree fruit) stimulates estrogen receptors, which may result in hypertriglyceridemia or induce a hypercoagulable state that leads to pancreatic necrosis. Saw palmetto also inhibits cyclooxygenase, which is associated with development of AP (Jibrin et al, 2006; Wargo et al, 2010).

TABLE 55.1 Classifications of Drug Induced Acute Pancreatitis (AP) and Common Drugs and Toxins Reported in the Literature

Classes	Class Ia	Class Ib	Class II	Class IIIa	Class IV
Definition Badalov et al, 2007	At least 1 case report, evidence of positive rechallenge Exclusion of other causes of AP	At least 1 case report with positive rechallenge Other causes such as alcohol, gallstones, hypertriglyceridemia, and other drugs were not excluded.	At least 4 case reports with a consistent latency period for 75% or more of cases	At least 2 cases in the literature No consistent latency among cases No rechallenge	Not fitting into cases described earlier Single case report in published literature, without rechallenge
Associations	**Definite**		**Probable**	**Possible**	
Definition Mallory & Kern, 1980	*Criteria* 1. Pancreatitis develops during the treatment with a suspected drug. 2. There is no evidence of any other etiologic factors. 3. Symptoms disappear after withdrawal of the drug. 4. Recurrence of pancreatitis on reintroduction of the pharmacologic agent.		Criteria fulfilled without proof of recurrent pancreatitis after rechallenge of the pharmacologic agent	Single case reports on pancreatitis	
Definition Karch & Lasagna, 1975	1. Drug reaction that follows a reasonable temporal sequence from administration of the drug that follows a known response pattern 2. That is confirmed by cessation of the drug (dechallenge) 3. That is confirmed by reappearance of the symptoms on repeated exposure to the drug (rechallenge)		3. That could not be explained by the known characteristics of patient's clinical state	2. That could have been produced by patient's clinical state or other modes of therapy administered to patient	
Drugs Badalov et al, 2007; Jones MR, 2015; Kaurich, 2008; Hung, 2014; Nitsche et al, 2010; Trivedi & Pitchumoni, 2005; Mallory & Kern, 1980	α-Methyldopa Arabinoside Azodisalicylate Bezafibrate Cannabis Carbimazole Codeine Cytosine Cytarabine Dapsone Enalapril Exenatide Furosemide Isoniazid Mesalamine Metronidazole Pentamidine Pravastatin Procainamide Pyritonol Simvastatin Stibogluconate Sulfamethoxazole Sulindac Tetracycline Valproic acid	All-*trans*-retinoic acid Amiodarone Azathioprine Clomiphene Dexamethasone Ifosfamide Lamivudine Losartan Lynesterol/methoxyethinyl-estradiol Mercaptopurine (6-MP) Meglumine Methimazole Nelfinavir Norethindronate/mestranol Omeprazole Premarin Sulfamethazole Trimethoprim/sulfamethazole	Acetaminophen Chlorthiazide Clozapine Didanosine (ddI) Erythromycin Estrogen L-asparaginase Pegasparagase Propofol Tamoxifen	Aledronate Atorvastatin Carbamazepine Captopril Ceftriaxone Chlorothalidone Cimetidine Clarithromycin Cyclosporin Gold Hydrochloro-thiazide Indomethacin Interferon/ribavirin Irbesartan Isotretinoin Ketorolac Lisinopril Metalozone Metformin Minocycline Mirtazapine Naproxen Paclitaxel Prednisone Prednisolone	ACTH Ampicillin Bendroflu-methiazide Benzapril Betamethazone Capecytabine Cisplatin Colchicine Cyclophosphamide Cyproheptadine Danazol Diazoxide Diclofenac Difenoxylate Doxorubicin Ethacrynic acid Famciclovir Finasteride 5-Fluorouracil Fluvastatin Gemfibrozil Interleukin-2 Ketoprofen Lovastatin Mefenamic acid Nitrofurantoin Octreotide Oxyphenbutazone Penicillin Phenophthalein Propoxyphene Ramipril Ranitidine Rifampin Risperidone Ritonavir Roxithromycin Rosuvastatin Sertaline Strychnine Tacrolimus Vigabatrin/lamotrigine Vincristine

Continued

TABLE 55.1 Classifications of Drug Induced Acute Pancreatitis (AP) and Common Drugs and Toxins Reported in the Literature—cont'd

Associations	Definite	Probable	Possible/ Shown in Animal Studies
Toxins (Sources) Khurana & Barkin, 2001	Ethyl alcohol (antifreeze, organic solvent) Methanol (solvent, nail vanish, gasoline additive) Organophosphate insecticides (pesticide , agricultural sprays, household insecticides, herbicides) Scorpion's venom	Alpha toxin (*Clostridium perfringens, Staphylococcus aureus*) Diesel exhaust fumes (diesel engines) Pentachlorophenol (paper, leather, wood preservatives, fungicide) Tricholorethylene (degreaser for metals, veterinary anesthetic)	Alfatoxin (contaminated food, peanuts, grains) Carbon tetrachloride (organic solvent, dry cleaning, fire extinguishers, refrigerants) Cobalt (metal alloys) Neutral red (coloring agent, tropical viricide)

ACTH, Adrenocorticotropic hormone.

TABLE 55.2 Diagnostic Criteria for Infectious Causes of Acute Pancreatitis

Criteria	Definite	Probable	Possible
Pancreatitis	Evidence of pancreatitis at surgery, autopsy *or* Radiologic evidence	Threefold increase in amylase and/or lipase *and* Characteristic symptoms (e.g., abdominal pain, tenderness)	Threefold increase in amylase and/or lipase without characteristic symptoms
Infection	Organism identified in pancreas or pancreatic duct by stain or culture	Culture of organism from blood or pancreatic juice *or* Serologic diagnosis (Fourfold or greater rise in titer) *with* Characteristic clinical or epidemiologic setting	Culture of organism from other body sites *or* Serologic diagnosis (Fourfold or greater rise in titer)

Modified from Parenti DM, Steinberg W, Kang P, 1996: Infectious causes of acute pancreatitis. Pancreas 13(4):356-371.

Infectious Causes

A variety of bacterial, viral, and parasitic infections have been established to cause AP, but the true incidence is not known. The value of treating the infectious agent to reverse pancreatitis is also not well established. Diagnostic criteria have been defined to evaluate the relationship between the microorganism and AP, based on histologic and imaging evidence of pancreatitis and combined with laboratory data on the infectious agent, after exclusion of the common causes (Table 55.2) (Parenti et al, 1996).

BACTERIAL CAUSES. Pancreatitis caused by bacteria has been reported with hematogenous, lymphatic seeding or ascending infection of the pancreatic duct from the biliary tree or the gastrointestinal tract. *Mycoplasma pneumoniae* has been implicated as a cause of pancreatitis from antibody detection. Studies in the 1970s have reported high *Mycoplasma* antibody titer in patients with AP (Freeman & McMahon, 1978; Leinikki et al, 1973). However, the exact mechanism and relationship between AP and *Mycoplasma* infection remain unclear; postulated factors include ascending infection of *Mycoplasma* organisms, seeding via the hematogenous or lymphatic routes, autoimmune-mediated response to *Mycoplasma* infection, and organ-specific toxin production (Economou & Zissis, 2000). Other pathogenic bacteria, such as *Leptospira interrogans, Campylobacter jejuni, Salmonella typhi, Brucella, Yersinia enterocolitica, Y. pseudotuberculosis, Legionella, Nocardia, Mycobacterium tuberculosis,* and *M. avium,* have been reported as causes of sporadic cases of pancreatitis (Daher et al, 2003; Edwards & Evarard, 1991).

VIRAL CAUSES. Viruses is the first and largest group of infectious agents associated with AP. Diagnosis is based on detection of antiviral antibodies coupled with the clinical diagnosis of pancreatitis after exclusion of the common causes. Mumps (single-stranded DNA paramyxovirus) was implicated as a cause of AP in 1905, when Lemoine and Lapasset described the first case of AP associated with mumps virus infection on autopsy (Wood et al, 1974). Since the mass vaccination of the general population with the measles, mumps, rubella (MMR) vaccine, AP rarely has been reported (Economou & Zissis, 2000; Vanlioglu & Chua, 2011). In 1944, Linsey first described the association between AP and viral hepatitis, which now is well recognized. In most cases, AP is a complication in the course of fulminant liver failure, and AP in nonfulminant viral hepatitis is uncommon, with only isolated case reports (Mishra et al, 1999). Hepatitis B is the hepatitis virus most implicated in AP (Alexander et al, 1988, Amarapurkar et al, 1996, Eugene et al, 1990) (see Chapter 70). Studies have reported pathologic changes in the pancreas of HIV patients. Coexisting conditions such as alcohol use, biliary disease, and malignancies associated with acquired immunodeficiency syndrome (AIDS) (e.g., Kaposi sarcoma, lymphoma) in HIV/AIDS patients; the use of antiretroviral and other medications in their treatment (e.g., corticosteroids, ketoconazole, sulfonamides, pentamidine, metronidazole, isoniazid); and opportunistic infections (e.g., mycobacteria, cytomegalovirus, herpes simplex, cryptosporidiosis) all can contribute to the pathogenesis of AP (Dragovic, 2013). Other viruses reported to cause AP include coxsackievirus type B, cytomegalovirus, varicella-zoster, and herpes simplex

(Economou & Zissis, 2000; Iwasaki et al, 1985; Ozsvar et al, 1992; Ramsingh et al, 1997).

FUNGAL AND PARASITIC CAUSES. Fungal and parasitic infestation is a rare cause of AP. The fungus *Aspergillus* has been reported to cause AP (Parenti et al, 1996). *Ascaris lumbricoides* (nematode) is the most common parasite involved. It is a common infection in developing countries and endemic in certain tropical countries (20%-82% of the population) (Khuroo, 2001). AP is likely triggered by the obstruction of the pancreatic duct, especially in pediatric patients, in whom the duct is much narrower relative to the parasite. Other parasites implicated in causing AP by similar mechanisms include *Clonorchis senensis, Opisthorchis* spp., *Dicrocoelium dendriticum, Fasciola hepatica, Schistosoma haematobium, S. mansoni, Toxoplasma, Cryptosporidium,* and *Paragonimus westermani* (Hung et al, 2014; Parenti et al, 1996) (see Chapter 45).

Iatrogenic or Traumatic Pancreatitis

Post–endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is the most feared and common iatrogenic cause of AP, occurring in approximately 1% to 3% of patients undergoing diagnostic ERCP, 2% to 5% receiving therapeutic ERCP, and as many as 25% having sphincter of Oddi studies (see Chapters 20 and 29). PEP accounts for substantial morbidity and mortality and health care expenditures in excess of $200 million annually in the United States (Elmunzer, 2015). PEP is defined as new or increased abdominal pain that is clinically consistent with AP and associated pancreatic enzyme elevation, at least three times the upper normal limit within 24 hours after the procedure and resulting hospitalization of 2 nights or more. Based on a recent meta-analysis and several large studies, female gender, sphincter of Oddi dysfunction, intraductal papillary mucinous neoplasm (IPMN), previous or recurrent pancreatitis, previous PEP, precut/endoscopic sphincterotomy, difficult cannulation, and main pancreatic duct injection are all independent risk factors for PEP (Ding et al, 2015; Testoni et al, 2010; Vandervoort et al, 2002).

Patients with pancreatic trauma are seen usually with a triad of abdominal pain, leukocytosis, and elevated serum amylase levels. Both blunt and penetrating trauma can injure the pancreas, although these injuries are uncommon because of its retroperitoneal location (see Chapter 123). It occurs in less than 2% of blunt trauma cases but in as many as 12% to 30% of penetrating trauma caused by gunshot or stab wounds (Debi et al, 2013; Fisher & Brasel, 2011). Pancreatic injury is challenging to recognize because of coexisting abdominal injuries and thus requires a high index of suspicion. The damage can be mild to very severe, from a contusion to a severe crush injury or transection of the gland, particularly where the pancreas crosses over the spine, resulting in pancreatic ascites and acute duct rupture. Healing of pancreatic ductal injuries can lead to scarring and stricture of the main pancreatic duct, with resultant obstructive pancreatitis proximally.

Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) is a rare but distinct disorder that has a dramatic response to corticosteroid treatment (Finkelberg et al, 2006; Hart et al, 2015) (see Chapters 54 and 57). The incidence seems to be increasing, probably because of increased recognition of this distinct entity. Radiologically, AIP is characterized by segmental, diffuse, or irregular narrowing of the main pancreatic duct and diffuse enlargement of the pancreas, elevated levels of serum immunoglobulin G (>twice the upper limit of IgG, particularly of the IgG4 subtype), the presence of autoantibodies, and histopathologically by lymphoplasmacytic infiltration and fibrosis. An international consensus on diagnosis based on histopathologic characteristics has been proposed and subdivided AIP into type 1 (lymphoplasmacytic sclerosing pancreatitis, LPSP) and type 2 (idiopathic duct-centric pancreatitis, IDCP). Cardinal features includes imaging of pancreatic parenchyma and duct, serology, extrapancreatic involvement, histology, and an optional criterion of response to corticosteroid therapy. Each feature was categorized as level 1 and 2 depending on the reliability of the diagnosis (Shimosegawa et al, 2011). Types 1 and 2 AIP have similarities but also different clinical features and associations (Table 55.3) (Hart et al, 2015, Kamisawa et al, 2011, 2013,).

Anatomic or Congenital Causes

Anatomic variants or congenital anomalies can lead to AP. Based on autopsy and ERCP studies, *pancreas divisum* (PD) is the most common congenital variation of pancreatic ductal anatomy, occurring in as many as 7% to 12% of individuals (Bernard et al, 1990; Testoni, 2014) (see Chapters 1 and 2). The failure of the derived ventral and dorsal pancreas to fuse embryologically results in separate ductal systems. Partial fusion results in the incomplete PD, and the dorsal duct drains through the major papillae via the ventral duct (DiMagno & Wamsteker, 2011). This communication is generally narrow and may be inadequate for drainage. The inability of minor papillae to accommodate the flow when the pancreas is stimulated or over time leads to relative obstruction and ductal hypertension, causing injury leading to pancreatitis (Bertin et al, 2012). *Annular pancreas* is another rare anatomic condition resulting in the entrapment of both the CBD and duodenum by the annular growth of the pancreas (Testoni, 2014). Approximately one third of patients with annular pancreas have PD, but it is not clear whether pancreatitis depends on the annular variant or the PD. The sphincter of Oddi (SO) is a complex of smooth muscle surrounding the terminal CBD, main pancreatic duct, and common channel. Its main functions are regulating pancreatic and bile flow and preventing reflux of duodenal contents into the ducts. *Sphincter of Oddi dysfunction* (SOD) refers to the abnormality of SO contractility that can manifest clinically as pain, pancreatitis, or deranged liver function tests. *Anomalous pancreaticobiliary duct junction* (APBJ) results in pancreatic reflux in the biliary tree. Reflux of bile into the pancreas seldom occurs because of the higher pressure in the pancreatic duct compared to the bile duct (Fig. 55.1B). Other anatomic lesions that can cause AP include anomalies in the biliary tree such as choledochal cyst, choledochocele (type III choledochal cyst), and duodenal duplication cyst (Sherman, 1996).

Tumors

Pancreatitis can be the first presentation of pancreaticobiliary and periampullary tumors (see Chapter 62). This should be considered in patients with the index pancreatitis episode who are older than 40 years, especially if they have constitutional symptoms such as loss of weight and appetite or new onset of diabetes. The most common pathology associated with pancreatitis are IPMN (Fig. 55.1C), mucinous cystic neoplasms, ampullary tumors, islet cell tumors, and pancreatic adenocarcinoma (Fig. 55-1D). Benign tumors that arise at the

TABLE 55.3 Features of Types 1 and 2 Autoimmune Pancreatitis (AIP)

Clinical Features	Type 1 AIP	Type 2 AIP
Synonyms	Lymphoplasmacytic sclerosing Pancreatitis; AIP without GEL	Idiopathic duct-centric chronic pancreatitis; AIP with GEL
Epidemiology	Asia > USA, Europe	Europe > USA > Asia
Age at diagnosis, mean	Old, 7th decade	Young, 5th decade
Gender	Male predominance, 75% in males	Equal, 50% in males
Clinical presentation	Painless obstructive jaundice	Painless obstructive jaundice; abdominal pain, acute pancreatitis
Serum IgG4 level	Often elevated; ~66%	Normal, occasionally elevated; ~25%
Extrapancreatic involvement	Proximal bile duct, salivary gland, kidney, retroperitoneum; ~50%	No
Inflammatory bowel disease, association with ulcerative colitis	Occasionally	Common; ~10%-20%
Response to corticosteroids	Excellent; ~100%	Excellent; ~100%
Recurrence	High (20%-60%)	Low (<10%)
Associated with IgG4-related disease	Yes	No
Histologic Features		
IgG4 tissue staining	Abundant (>10 cells/hpf)	Scant (<10 cells/hpf)
GEL	−	+++
Lymphoplasmacytic infiltration	++	++
Periductal inflammation	++	++
Obliterative phlebitis	++	+
Storiform fibrosis	++	+

GEL, Granulocytic epithelial lesion; *hpf,* high-power field; *IgG4,* immunoglobulin G4.

From Hart PA, et al:.Recent advances in autoimmune pancreatitis. *Gastroenterology* 149(1):39-51, 2015; and Kamisawa T, et al, 2013: Recent advances in autoimmune pancreatitis: type 1 and type 2. *Gut* 62(9):1373-1380, 2013.

major papillae have the same potential to cause pancreatitis by causing ductal obstruction (e.g., adenoma, lipoma, fibroma, lymphangioma, leiomyoma, harmatoma) (Kim et al, 2001).

Genetic Causes

There is culminating evidence for a genetic basis for pancreatitis (Whitcomb, 2010). This was led by the discovery that gain-of-function mutations in trypsinogen lead to hereditary pancreatitis. Molecular, epidemiologic, and genetic studies have identified several pancreas-targeting factors associated with the susceptibility for acute and chronic pancreatitis. These include *SPINK1*, *CFTR*, *PRSS1*, anionic trypsinogen (*PRSS2*), MCP-1-2518 G allele, calcium-sensing receptor (*CASR*) and chymotrypsinogen C (*CTRC*) (Fig. 55.2) (Masamune et al, 2011; Papachristou et al, 2005; Whitcomb, 2010). Patients with these mutations are at increased risk of pancreatitis caused by a variety of mechanisms involving hypercalcemia and hyperlipidemia. Other mechanisms exist, but most are not well elucidated. Recent studies have also shown that patients with idiopathic AP and idiopathic recurrent pancreatitis may have different genetic backgrounds (Masamune et al, 2011).

Idiopathic Acute Pancreatitis

The cause for AP is unidentifiable in as many as 30% of patients, despite a comprehensive history, physical examination, laboratory investigations, and radiologic evaluation (Tan & Sherman, 2013).These patients are conventionally classified as having idiopathic acute pancreatitis (IAP) (Levy & Gennen, 2001). Idiopathic acute recurrent pancreatitis (IARP) is defined when patients have more than one episode of IAP. Evaluation of IAP/IARP is prudent because most untreated patients with IARP experience recurrent episodes that may result in chronic pancreatitis (Seidensticker et al, 1995). Many of these IAP/IARP cases may in fact be caused by previously unrecognized causes, such as genetic mutations or drugs/toxins. It is hoped that this AP patient group will decrease while our understanding of the disease process improves with time and future studies.

ASSESSMENT OF ACUTE PANCREATITIS

Diagnostic Assessment

The diagnosis of AP is based on the clinical presentation of the patient supported by serum levels of amylase and lipase. History should also focus on possible causes, such as gallstones and heavy alcohol intake. AP is characterized by acute and constant pain localized in the epigastrium or right upper quadrant that usually radiates to the back (Frossard et al, 2008). The pain typically lasts for several days and can be associated with nausea and vomiting. However, in metabolic causes or those associated with alcohol abuse, the pain may be poorly localized and less acute in onset (Whitcomb, 2006). Physical signs depend on the severity of pancreatitis (Frossard et al, 2008). In mild pancreatitis, abdominal examination usually reveals upper abdominal tenderness without features of peritonitis such as rigidity or rebound tenderness. However, in severe cases, pancreatitis may mimic other causes of acute abdominal emergencies. Severe pancreatitis with necrosis may also result in exudates tracking along the falciform ligament and retroperitoneum, resulting in Cullen and Grey Turner signs.

Serum levels of amylase and lipase are frequently obtained for the diagnosis of AP. An elevation exceeding three times the normal upper limit of serum amylase or lipase supports the

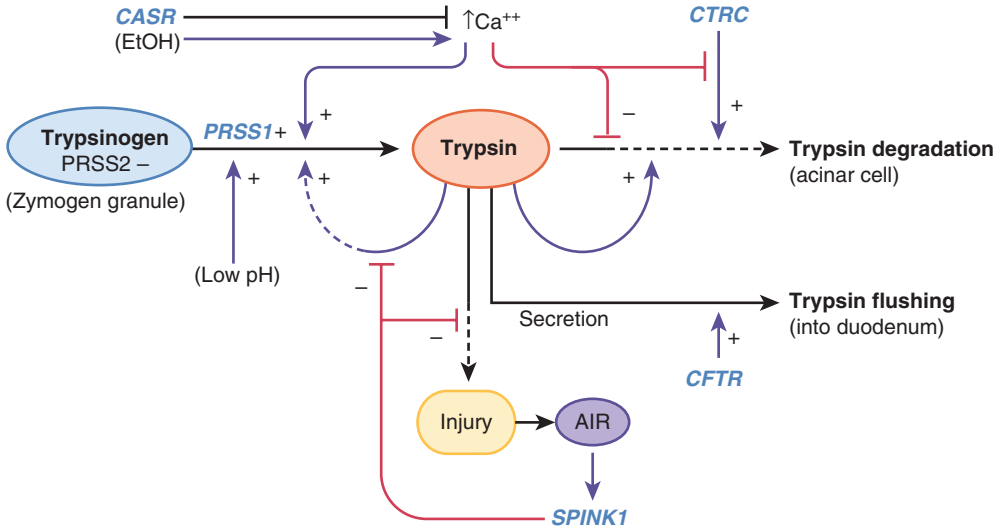

FIGURE 55.2. Genetic basis of acute pancreatitis. Activation of trypsinogen to trypsin within the pancreas is crucial in the pathogenesis of pancreatitis. Trypsinogen activation is promoted by cationic trypsinogen mutations (*PRSS1+*), high calcium (Ca^{2+}), active trypsin, and low pH. Ca^{2+} levels are regulated by calcium-sensing receptor (*CASR*) and dysregulated by alcohol (*EtOH*). Active trypsin degradation is facilitated by cystic fibrosis transmembrane conductance regulator (*CFTR*) and by other active trypsin molecules, but blocked by high Ca^{2+}. Active trypsin leads to pancreatic injury, which leads to an acute inflammatory response (*AIR*). This upregulates expression of serine protease inhibitor Kazal 1 (*SPINK1*), which blocks active trypsin and therefore prevents further activation of trypsinogen and limits further tissue injury. CFTR is an extra–acinar cell mechanism to eliminate trypsin by flushing it out of the pancreatic duct. Mutations in *CFTR* reduce fluid secretion and trypsinogen/trypsin washout. Genes in *blue italic* type indicate that genetic variants are associated with pancreatitis. *(From Whitcomb DC: Genetic aspects of pancreatitis. Annu Rev Med 61:413-424, 2010.)*

diagnosis of pancreatitis. Serum amylase concentrations generally rise within a few hours after symptom onset and return to normal within approximately 5 days (Frossard et al, 2008). It is important to note that amylase levels may not be elevated in as many as 19% of AP patients on admission. Furthermore, amylase levels may also be elevated in the absence of pancreatitis in patients with renal impairment, salivary gland diseases, and other extrapancreatic abdominal conditions (e.g., acute appendicitis, perforated viscus, intestinal obstruction, mesenteric ischemia). Serum lipase levels have the added advantage of remaining elevated during a longer period and have a higher specificity versus amylase. Other laboratory tests, such as trypsinogen activation peptide and trypsinogen-2 levels, have been shown to be more specific than serum amylase or lipase levels, but these tests are not readily available (Whitcomb, 2006; Yokoe et al, 2015).

Occasionally, diagnosis of AP based on the clinical presentation and biochemical investigations alone may be difficult. In these patients, cross-sectional imaging scans such as ultrasound, contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI) should be performed on admission to confirm the diagnosis and exclude other abdominal conditions (Whitcomb, 2006). CT scan has a reported sensitivity of 87% to 90% and specificity of 90% to 92% for detecting pancreatitis (Frossard et al, 2008). Imaging may also identify the cause of pancreatitis and its associated complications.

Definition and Classification of Severity of Acute Pancreatitis

Most episodes of AP have a mild and self-limiting course (Mofidi et al, 2009a). However, approximately 20% of cases may progress to severe pancreatitis, resulting in major local and systemic complications with a significant risk of mortality. The definition and stratification of the severity of pancreatitis are of utmost importance both in clinical practice and for research (Banks et al, 2013; Dellinger et al 2012). In the clinical setting, early identification of patients on admission allows for aggressive treatment. In the secondary care setting, patients needing transfer to a tertiary care center may be identified. Physicians treating severe pancreatitis may triage these patients to optimize and tailor their management accordingly. Targeted therapy such as enteral feeding, endoscopic sphincterotomy, or antibiotics may be initiated at the appropriate time in select patients (Bollen et al, 2012). For research purposes, accurate stratification of patients is important for recruitment in clinical trials and for valid comparison between studies (Dellinger et al, 2012).

The first classification system for pancreatitis was established in Marseille in 1965 (Alsfasser et al, 2013). Since then, the standard tool for defining severe pancreatitis has been the Atlanta classification, proposed in 1992 (Table 55.4) (Bradley, 1993). This was based on clinical, radiologic, and pathologic findings and categorized pancreatitis into mild interstitial and severe necrotizing pancreatitis. However, despite its value, it has several limitations. The main drawback is that no distinction was made between predicted (based on Ranson and APACHE II criteria) and actual (based on organ failure) severity for severe AP. The initial Atlanta classification also failed to recognize that the number of organs failing and the duration of organ failure were important prognosticators for AP (Johnson et al, 2004a).

As a result of the better understanding of the pathophysiology and outcomes of necrotizing pancreatitis and organ failure, the Atlanta classification was revised in 2012 based on an international Internet-based consensus (Table 55.4) (Banks et al, 2013). The updated classification defined three degrees of

TABLE 55.4 Atlanta and Determinant Based Classification Systems for Severity of Acute Pancreatitis

Classification	Mild	Moderate	Severe
Atlanta 2012 (Banks et al, 2013)	No organ failure	Presence of transient organ failure(usually resolves within 48 hrs) *and/or*	Persistent organ failure: may be single or multiple
	No local or systemic complications	Local or systemic complications without persistent organ failure	Usually have ≥1 local complications
	Mortality is very rare.	Mortality is much lower than that of severe acute pancreatitis.	Infected necrosis with persistent organ failure is associated with extremely high mortality, reported as high as 36%-50%.
Atlanta 1992 (Bradley, 1993)	Minimal organ dysfunction and an uneventful recovery Responds to appropriate fluid administration with prompt normalization of physical signs and laboratory values Lacks the described features of severe acute pancreatitis	Not defined	Associated with organ failure and/or local complications, such as necrosis, abscess, or pseudocyst Further characterized by ≥3 on Ranson criteria or ≥8 on APACHE II
Determinant-based classification (Dellinger 2012, et al; Thandassery et al, 2013)	No peripancreatic necrosis No organ failure Mortality 0%	Presence of sterile peripancreatic necrosis *and/or* Transient organ failure Mortality 3.6%	*Severe*: Presence of *either* infected peripancreatic necrosis *or* persistent organ failure Mortality 33.8% *Critical:* Presence of infected peripancreatic necrosis *and* persistent organ failure Mortality 87.5%
		Local Complications	
Definitions	**Organ Failure**	**Early (Within 4 wk)**	**Late (>4 wk)**
Atlanta 2012 (Banks et al, 2013)	Score of ≥2 for one of three organ systems—respiratory, cardiovascular, or renal—using modified Marshall scoring system (Marshall et al, 1995) Score: 0-4 *Respiratory* PaO_2/FiO_2: 400; 301-400; 201-300; 101-200; ≤101 *Renal* Serum creatinine (μmol/L): ≤134; 134-169; 170-310; 311-439; >439 *Cardiovascular* Systolic blood pressure (mm Hg): >90; <90, fluid responsive; <90, not fluid responsive; <90, pH <7.3; <90, pH <7.2	Acute peripancreatic fluid collection: fluid seen usually develops in early phase, associated with interstitial edematous pancreatitis CECT: no well-defined wall, homogeneous, confined by normal fascial planes in retroperitoneum; may be multiple Acute necrotic collection (ANC): containing variable amounts of fluid and necrotic tissue Infected necrosis: diagnosis of infection of ANC or WON suspected by patient's clinical course or by presence of gas within collection on CECT	Pancreatic pseudocyst: fluid collection in peripancreatic tissues, surrounded by well-defined wall with minimal or no necrosis; after onset of interstitial edematous pancreatitis Walled-off necrosis (WON): mature, encapsulated collection of pancreatic and/or peripancreatic necrosis with well-defined inflammatory wall; after onset of necrotizing pancreatitis Infected necrosis: infection of ANC or WON, suspected by patient's clinical course or by presence of gas within collection on CECT
Determinant-based classification (Dellinger et al, 2012)	Persistent organ failure: ≥48 hr Transient organ failure: ≤48 hr Cardiovascular: need for inotropic agent Renal: creatinine: ≥171 μmol/L Respiratory: PaO_2/FiO_2 ≤300 mm Hg Persistent organ failure: organ failure in same organ system for ≥48 hr Transient organ failure: ≤48 hr	Peripancreatic necrosis: nonviable tissue located in pancreas alone and/or in peripancreatic tissues; can be solid or semisolid, without radiologically defined wall Sterile peripancreatic necrosis: absence of proven infection in necrosis Infected peripancreatic necrosis (when at least one of following is present): gas bubbles within peripancreatic necrosis on CT; positive culture of peripancreatic necrosis obtained by image-guided fine-needle aspiration or during first drainage and/or necrosectomy	

APACHE, Acute Physiology and Chronic Health Evaluation points; *CECT*, contrast-enhanced computed tomography.

From Banks PA, et al, Acute Pancreatitis Classification Working Group: Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 62(1):102-111, 2013; and Bradley EL III: A clinically based classification system for acute pancreatitis: summary of the International Symposium on Acute Pancreatitis, Atlanta, 1992. *Arch Surg* 128:586-590, 1993.

severity for AP instead of two and recognized that pancreatitis is an evolving, dynamic condition and that disease severity may change during the course of disease. Another important revision included the definitions for pancreatic and peripancreatic collections and the distinction between collections composed of fluid versus those arising from necrosis, containing solid components.

Parallel to the development of the revised Atlanta classification, the determinant-based classification (DBC) was developed based on a large international survey (Dellinger et al, 2012). In this system, pancreatitis was stratified into four degrees of severity: mild, moderate, severe, and critical (Table 55.4). The DBC was based on two main principles to overcome the limitations of the original Atlanta criteria. First, it was based

on actual factors of severity, such as necrosis and organ failure, rather than predictive factors of severity, such as the APACHE II and Ranson criteria. Second, the factors of severity used in this system had a direct causal association with severity. The DBC was recently validated prospectively, and it accurately stratified the patients according to mortality. Patients classified as mild, moderate, severe, and critical had mortality rates of 0%, 3.6%, 33.8%, and 87.5%, respectively (Thandassery et al, 2013).

At present, it remains uncertain whether the revised Atlanta classification or the DBC will become the dominant classification system in the future (Petrov et al, 2013; Windsor & Petrov, 2013). Both systems have recently been validated in a prospective study (Nawaz et al, 2013) and have been shown to represent an improvement to the original 1992 Atlanta classification.

Clinical Assessment

Prediction of the likely course and outcome of AP is of utmost importance when the patient with pancreatitis is admitted to the hospital. However, this can be challenging, even for experienced clinicians. In the vast majority (75%-80%) of patients, AP is a mild disease with a benign course and without associated mortality. However, the main challenge is to identify patients who are most likely to progress to severe pancreatitis and experience major complications. These patients could potentially benefit from early intensive care monitoring and treatment. In addition to the initial clinical assessment, several prognostic criteria have been developed to aid the clinician in predicting the clinical course of pancreatitis. These prognostic criteria include severity scoring systems based on clinical parameters and laboratory results (e.g., Ranson criteria), radiology-based criteria (e.g., Balthazar score), and single biomarkers (e.g., CRP) (Frossard et al, 2008, Whitcomb, 2006).

Mortality from AP follows a biphasic distribution. Early death is usually from the development of severe and irreversible multiorgan dysfunction, whereas late death occurs in the latter phase of the illness, with organ failure the end result of sepsis and its sequelae. Several authors have reported the important prognostic significance of distinguishing between transient and persistent organ failure for predicting mortality from severe AP (Banks et al, 2013; Dellinger et al, 2012). It has been shown that persistent or deteriorating multiorgan dysfunction in the first 7 days after admission is the most significant predictor of death (Buter et al, 2002, Johnson & Abu-Hilal, 2004; Mofidi et al, 2009a).

Scoring Systems for Assessing Severity of Pancreatitis

Since the 1970s, several scoring systems have been devised to predict the clinical course of AP (Mofidi et al, 2009a). Before severity scoring systems were introduced, patients were assessed solely on clinical progression, which was clearly inadequate. Early prediction of severe disease is important to identify patients who are at greater risk of subsequent severe morbidity and mortality. The first, most widely used scoring system was the Ranson criteria (Ranson et al, 1974). The Ranson criteria were formulated based on the identification of 11 significant prognostic factors from 43 clinical and laboratory variables assessed in 100 acute episodes of pancreatitis (Table 55.5). The main limitations associated with the Ranson criteria were that prognostication was only complete after 48 hours and that it only functioned accurately at the extremes of the scale (less than three criteria predicted survival, and more than three predicted death) and less well at intermediate scores (Mofidi et al, 2009a). Subsequently, several modifications of this system have been proposed, such as the Glasgow (Imrie) severity scoring system. This system was simplified down to nine variables and has been shown to have prognostic accuracy similar to the Ranson criteria (Imrie, 2003; Blamey et al, 1984). In Japan the Japanese Severity Score (JSS) is used to predict severity and mortality from AP (Saitoh et al, 1991; Yokoe et al, 2015).

Currently, the Acute Physiology and Chronic Health Evaluation (APACHE II) system together with the Ranson criteria remain two of the most commonly used systems for the risk assessment of AP (Table 55.5). The APACHE system was not developed specifically for pancreatitis but was devised for patients in the intensive care unit (ICU) (Knaus, 2002) (see Chapter 25). It is a complex, physiologically based classification system based on the most abnormal values of 34 variables, taking into account the patient's baseline health status. The APACHE system was simplified to the APACHE II scoring system, based on 12 physiologic variables, age, and five organ-based chronic health points (Knaus et al, 1985). The APACHE II system has the added utility of not only allowing determination of disease severity on admission, but also allowing daily recalculation and thus assessment of disease progression (Mofidi et al, 2009a). Because obesity has been shown to be an important prognostic factor of mortality from pancreatitis, the APACHE-O scale has been proposed as an improvement to APACHE II and has been shown to improve its prognostic value (Johnson et al, 2004a). Other organ-failure–related scores (e.g., MOF/Goris, Marshall, SOFA) have also been applied to AP but have only been used in a limited number of studies for pancreatitis (Table 55.5) (Alsfasser et al, 2013). Because these scores were not developed specifically for pancreatitis, these systems have several shortcomings and perform variably in ICU versus non-ICU patients (Vincent, 2000).

Most recently, a new scoring system termed the Bedside Index for Severity in Acute Pancreatitis (BISAP) was proposed as simple and accurate method for the early (<24 hours of admission) identification of patients at risk of mortality (Table 55.5) (Singh et al, 2009; Wu et al, 2008). The BISAP was proposed as a model clinicians could use at the bedside with routinely available data. It was developed based on retrospective data on 17,992 patients and validated in another 18,256 patients (Chauhan & Forsmark, 2010; Wu et al, 2009). Subsequent validation studies (Gao et al, 2015; Papachristou et al, 2010; Singh et al, 2009) have demonstrated that although the BISAP is comparable to other scoring systems, its major advantage is its simplicity but not accuracy (Chauhan & Forsmark, 2010). Also, calculation of the BISAP score may not be as simple as it seems, because systemic inflammatory response syndrome (SIRS) calculation requires multiple variables (Singh et al, 2009).

There is still no single system that is completely reliable for AP (Gravante et al, 2009). Existing scoring systems have moderate accuracy and seem to have reached their maximal efficacy in predicting outcomes in AP.

New approaches and biomarkers are needed to improve prognostication (Mounzer et al, 2012). Regular clinical review and timely intervention remains the mainstay of treatment in AP. It is interesting to note that only the 2015 Japanese guidelines (Yokoe et al, 2015) recommend the use of scoring systems in the assessment of pancreatitis (i.e., JSS). Neither the

TABLE 55.5 Acute Pancreatitis (AP) Prognostic Scoring Systems

Scoring Systems	Year	Parameters*
Ranson	1974	At admission: age (>55 yr), WBC (>16,000/mL), glucose (>200 mg/dL), LDH (>350 IU/mL), AST (>250 IU/mL) At 48 hours: hematocrit (decrease >10%), BUN (increase >5 mg/dL), calcium (>8 mg/dL), Pa_{O_2} (>60 mm Hg), base deficit (>4 mEq/L), fluid sequestration (>6 L)
Glasgow	1984	Age (>55 yr), WBC (>15,000/mL), glucose (>180 mg/dL), BUN (>45 mg/dL), Pa_{O_2} (<60 mm Hg), calcium (<8 g/dL), albumin (<3.2 g/dL), LDH (>600 IU/L)
APACHE II Acute Physiology and Chronic Health Evaluation	1989	Temperature, MAP, heart rate, respiratory rate, Pa_{O_2}, arterial pH, bicarbonate, sodium, potassium, creatinine, hematocrit, WBC, GCS score, age, chronic health points
SOFA Sepsis-related Organ Failure Assessment	1996	MAP, Pa_{O_2}/Fi_{O_2}, creatinine, GCS, platelet count, bilirubin Score: 1-5, based on severity of each parameter
SIRS Systemic inflammatory response syndrome	2006	Temperature (<36° C or >38° C), heart rate (>90/min), respiratory rate (>20/min) or Pa_{CO_2} (<32 mm Hg), WBC (<4000/mm^3, >12,000/mm^3, or >10% bands)
POP Pancreatitis Outcome Prediction score	2007	Age, MAP, Pa_{O_2}/Fi_{O_2}, arterial pH, BUN, calcium (these scores use normal ranges)
PANC 3	2007	Hematocrit (>44 mg/dL), body masss index (>30 kg/m^2), pleural effusion
BISAP Bedside Index for Severity in Acute Pancreatitis	2008	BUN (>25 mg/dL), impaired mental status (GCS score <15), SIRS (>2), age (>60 yr), pleural effusion
Haps Harmless Acute Pancreatitis Score	2009	Abdominal tenderness, hematocrit (>43 mg/dL for men or >39.6 mg/dL for women), creatinine (>2 mg/dL)
JSS Japanese Severity Score	2009	Base excess (≤3 mEq/L), Pa_{O_2} (≤60 mm Hg or respiratory failure), BUN (≥40 mg/dL) or creatinine (≥2 mg/dL), LDH (≥2× upper limit of normal), platelet (≤100,000/mm^3), calcium (≤7.5 mg/dL), C-reactive protein (≥15mg/dL), SIRS (≥3), age (≥70 yr)

*At admission and at 48 hours, unless otherwise stated.

AST, Aspartate transaminase; *BUN*, blood urea nitrogen; *GCS*, Glasgow Coma Scale; *LDH*, lactate dehydrogenase; *MAP*, mean arterial pressure; *WBC*, white blood cell count.

From Mounzer R, et al.: Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. *Gastroenterology* 142:1476-1482, 2012.

International Association of Pancreatology (IAP)/American Pancreas Association (APA) guidelines (Working Group IAP/APA, 2013) nor the American College of Gastroenterology (ACG) guidelines (Tenner et al, 2013) presently recommend the use of scoring systems.

Laboratory Assessment

Single-Parameter Biochemical Markers

C-REACTIVE PROTEIN. C-reactive protein (CRP) is an acute-phase protein predominantly synthesized in the liver in response to various infective and noninfectious stimuli, resulting in elevated serum levels (Alsfasser et al, 2013). Because of its easy availability in clinical practice, CRP has been used widely to distinguish mild from severe AP and, at a cutoff level of 150 mg/L, has been shown to have a diagnostic accuracy of 70% to 80% when measured within the first 48 hours of disease onset (Johnson et al, 2004a; Neoptolemos et al, 2000; Wilson et al, 1989). Presently, CRP is frequently considered the "gold standard" single biochemical marker for the risk stratification of AP and is used as the comparison when assessing new potential biomarkers (Alsfasser et al, 2013). A major limitation of CRP is the relatively long delay in achieving peak systematic values at 72 to 96 hours after onset of disease, making very early assessment of severity impossible.

HEMATOCRIT. The hematocrit value has been shown to be a prognostic marker for the severity of AP, and its prognostic significance emphasizes the pathophysiologic role of fluid loss in the severity of pancreatitis and the role of vigorous fluid replacement in the course of disease. A hematocrit of more than 44% on admission or the absence of a fall in hematocrit during the first 24 hours after admission was found to be a clear risk factor for pancreatic necrosis, organ failure, or pancreatic infection (Brown et al, 2000). Hematocrit greater than 50% has also been shown to predict severe pancreatitis (Gan et al, 2004). However, the value of hematocrit remains controversial, because several large studies failed to demonstrate its prognostic value on admission (Alsfasser et al, 2013). Nonetheless, other investigators have reported that hematocrit less than 40% to 44% had a high predictive value of approximately 90% in excluding severe pancreatitis (Khan et al, 2002; Lankisch et al, 2001).

PROCALCITONIN. Procalcitonin (PCT) has been widely used as a biomarker of bacterial infection or sepsis (Alsfasser et al, 2013). At a cutoff level of 1.8 ng/mL, PCT was able to predict the development of infected necrosis in patients with pancreatitis with sensitivity and specificity of more than 90% (Rau et al, 1997). The utility of PCT as a prognostic marker in AP was subsequently confirmed by several other studies. Notably, a prospective international multicenter study in 104 patients with severe pancreatitis reported that PCT was able to predict serious complications such as pancreatic infections and death with a sensitivity of 79% and specificity of 93% at a cutoff level greater than 3.8 ng/mL within 48 to 96 hours from symptom onset (Rau et al, 2007). A meta-analysis of 24 studies demonstrated that the sensitivity and specificity of PCT for the

development of severe AP was 72% and 86%, respectively, although with a significant degree of heterogeneity. The sensitivity and specificity of PCT for prediction of infected pancreatic necrosis were 80% and 91%, respectively, with no significant heterogeneity (Mofidi et al, 2009b). Based on currently available data, PCT is a promising parameter for the early risk stratification of patients at risk for severe complications from pancreatitis.

Other Biomarkers

Other biomarkers, such as the proinflammatory cytokines, have also been proposed as prognostic of disease severity in pancreatitis. A meta-analysis concluded that interleukin-6 (IL-6) and IL-8 may potentially be used as prognostic biomarkers for pancreatitis (Aoun et al, 2009). Trypsinogen and trypsinogen activation peptide (TAP) have also been evaluated as prognostic markers for pancreatitis (Johnson et al, 2004b; Neoptolemos et al, 2000). Urinary TAP concentrations have been reported to correlate well with the severity of AP at admission. Presently, however, measurements of IL-6, IL-8, or TAP are not routinely available outside the laboratory setting, which severely limits their use in clinical practice.

Imaging Assessment

Computed Tomography

There are two main indications of cross-sectional imaging in AP: confirmation of the diagnosis in cases of diagnostic uncertainty and prognostication and detection of complications in the latter course of disease. Dynamic contrast-enhanced CT scan is the imaging modality of choice for staging AP and for detecting complications (see Chapter 18). CT has been reported to detect pancreatic necrosis with a sensitivity of 87% (Arvanitakis et al, 2004; Balthazar, 2002). The morphologic abnormalities and changes associated with pancreatitis are now well recognized, well documented, and defined in the revised 2012 Atlanta classification (Banks et al, 2013). In early-phase inflammation, interstitial edema and fluid collections are recognized on CT. Subsequently, with progression of disease, pseudocysts, acute necrotic collections, and walled-off pancreatic necrosis may develop. These morphologic developments form the basis for current radiologic scoring systems. Presently, CT scoring systems can be stratified into two groups. Unenhanced CT scoring systems evaluate the extent of pancreatic and peripancreatic inflammatory changes, which include the Balthazar grade and pancreatic size index (PSI), or both peripancreatic inflammatory changes and extrapancreatic complications, such as the "mesenteric edema and peritoneal fluid" (MOP) score, extrapancreatic score (EP), and extrapancreatic inflammation on CT (EPIC) score (Bollen et al, 2012). Contrast-enhanced CT scores determine the presence and extent of necrosis, including the CT severity index (CTSI) and the modified CT severity index (MCTSI) (Table 55.6).

The first radiologic scoring system was based on morphologic criteria detected on noncontrast CT (Balthazar et al, 1985). However, with the absence of contrast, important features such as necrosis could not be assessed, and this system was revised by the same group in 1990 and termed the "CT severity index" (Balthazar et al, 1990). Based on the CTSI, the severity of AP is classified into five grades (0-4) on unenhanced CT, whereas the degree of necrosis is measured and given a score of 0 to 6. The sum of these two scores is used to calculate the CTSI, and a score of 7 or greater has been shown to be predictive of high morbidity and mortality (Balthazar et al, 1990). CTSI of 3 or less correlated with a mortality of 3%, versus 92% with CTSI greater than 7 (Alsfasser et al, 2013). A modified CTSI was subsequently proposed (Mortele et al, 2004), which took into account extrapancreatic complications such as pleural effusion and vascular complications (Table 55.6). However, it has not proved to be superior in accuracy to the original CTSI (Alsfasser et al, 2013). In 2007, De Waele and colleagues proposed a CT score based on factors in extrapancreatic inflammation, such as ascites, pleural effusion, retroperitoneal inflammation, or mesenteric inflammation, termed "extrapancreatic inflammation on CT score" (EPIC). The authors demonstrated that with a score of 4 or greater within the first 24 hours, EPIC could predict severe AP and mortality with 100% sensitivity and 71% specificity (Alsfasser et al, 2013). This system also has the added advantage of not requiring the use of contrast-enhanced CT, unlike previous CT-based systems.

A recent study analyzing 159 episodes of AP in 150 patients compared the accuracy of seven CT scoring systems (CTSI, MCTSI, PSI, EP, EPIC, MOP, and Balthazar) with two clinical scoring systems (APACHE II and BISAP) in predicting severity of AP within the first 24 hours of hospitalization (Bollen et al, 2012). It demonstrated that the predictive accuracy of CT scoring systems are similar to the more easily obtainable clinical

TABLE 55.6 Modified Computed Tomography (CT) Severity Index

Points, Grade	Criteria
Evaluation of Pancreatic Morphology	
0, A	Normal pancreas consistent with mild pancreatitis
2, B/C	Focal or diffuse enlargement of the gland, including contour irregularities and inhomogeneous attenuation with or without peripancreatic inflammation
4, D/E	Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis
Additional 2 points	Extrapancreatic complications, one or moreof the following: pleural effusion, ascites, vascular complications, parenchymal complications, or gastrointestinal tract involvement
Scoring Pancreatic Necrosis	
0	No pancreatic necrosis
2	≤30% pancreatic necrosis
4	>30% pancreatic necrosis

Predicting Morbidity and Mortality With the CT Severity Index Combining Scores

Index	Morbidity	Mortality
0-3	8%	3%
4-6	35%	6%
7-10	92%	17%

From Mortele KJ, et al.: A modified CT severity index for evaluating acute pancreatitis: improved correlation with patient outcome. *AJR Am J Roentgenol* 183:1261-1265, 2004.

scoring systems. Therefore based on these findings, the authors concluded that CT scan should not be routinely performed on admission for the assessment of disease severity (Bollen et al, 2012). This finding was concordant with earlier studies that report the utility of CT scan is low early in the course of pancreatitis (Spanier et al, 2010). Presently, CT is recommended in patients with persistent organ failure, for those who have the SIRS or sepsis, for those who do not improve within 6 to 10 days into the disease course, and for those with probable infected pancreatic necrosis (evidence-based medicine recommendation grade B) (Working Party et al, 2005).

Magnetic Resonance Imaging

Although contrast-enhanced, dynamic CT remains the gold standard in imaging for AP, it may be contraindicated in select patients with significant renal impairment on contrast allergies. The utility of MRI in pancreatitis has been investigated in several studies and has been shown to be a useful alternative to CT scan (Zhao et al, 2015).

SUMMARY

Acute pancreatitis is a challenging disease to manage with a myriad of etiologies other than gallstones and alcohol-related causes. In recent years, significant improvement has been achieved in understanding the underlying etiopathogenesis and factors involved in the occurrence of disease because of advanced diagnostic tools ranging from cross-sectional imaging and endoscopic procedures to genetic testing.

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