CHAPTER 21

Diseases of the pancreas

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The ageing pancreas

The pancreas has considerable functional reserve, so any anatomical changes associated with age have little, if any, effect on pancreatic function. Morphological changes, however, do occur as part of the ageing process. Ectasia of the main pancreatic duct and pancreatic atrophy can sometimes be noted, both of which can cause confusion in the interpretation of cross-sectional imaging. Ageing may also be associated with impaired pancreatic blood supply due to atherosclerosis, although the implications of this remain unclear.

Pancreatic function studies have been carried out on elderly patients and compared with those on younger patients. The volume of pancreatic secretion falls in the elderly, as do the outputs of lipase, trypsin, and phospholipase.[1] However, there does not appear to be a corresponding fall in fat absorption.

Inflammatory diseases of the pancreas

Acute pancreatitis

In the United States, the incidence of acute pancreatitis increased from 65 to 81 per 100,000 adults annually between 2001 and 2014. In the hospital, case fatalities have decreased from 1.68 to 0.69%, but mortality rates were higher in persons older than 65.[2]

Although alcohol abuse is a major cause of acute pancreatitis in adults, it is somewhat less common as a cause in the elderly. Acute pancreatitis, however, occurs with increasing frequency in the elderly because of an increased prevalence of gallstones and biliary sludge. In addition to alcohol and gallstones, other predisposing factors for acute pancreatitis in the elderly include hypercalcemia (usually due to hyperparathyroidism), hypertriglyceridemia, and obstruction to pancreatic flow caused by a pancreatic tumour. Acute pancreatitis occurs in some patients following cardiac bypass and cardiac valve surgery, although asymptomatic elevations in lipase or amylase are more common and may not be of clinical significance. 15–25% of pancreatitis episodes are categorized as idiopathic. Cholecystectomy has been shown to reduce recurrence of idiopathic pancreatitis, suggesting that some 'idiopathic' pancreatitis may be due to microlithiasis.

In the elderly – and indeed, in all patients – medications are often considered as a possible cause of pancreatitis when no other cause is identified. In fact, with the exception of a small group of anti-retroviral and immunomodulator medications, true drug-related pancreatitis is likely very uncommon. Most reports of drug-related pancreatitis are anecdotal, and the potential severity of the disease precludes drug challenges. A large retrospective German study of acute pancreatitis implicated drugs as a possible cause in only 1.4% of pancreatitis patients.[3]

Finally, autoimmune pancreatitis can be seen in the elderly, but rather than presenting as acute pancreatitis more often presents as a suspected pancreatic mass, with or without painless jaundice, raising concern for adenocarcinoma.[4] There are two recognized entities of this condition: Type 1 and 2. Type 1, also known as IgG4-related pancreatitis, is more prevalent in the older population. On imaging, it is typically characterized by a diffuse 'sausage-shaped' pancreatic enlargement with an irregular narrow pancreatic duct. Histologically, there is lymphoplasmacytic infiltrate with 'swirling fibrosis' and obliterative phlebitis. The tissue stains positive for IgG4-positive cells. Serum levels of IgG4 are often elevated (typically to at least two times the upper limit of normal). Extra-pancreatic involvement can be seen, including biliary stricturing, retroperitoneal fibrosis, mediastinal lymphadenopathy, and infiltration of the kidneys, salivary glands, and parotids. This condition is typically highly responsive to steroid treatment.

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Pathophysiology of acute pancreatitis

The underlying pathophysiological mechanism in acute pancreatitis varies based on the inciting event. The central theory of pancreatitis revolves around the activation of intrapancreatic trypsinogen, resulting in acinar cell damage and cytokines and other pro-inflammatory markers that play a role in the subsequent systemic inflammatory response that results in tissue damage.[5] In the majority of patients, the process is self-limiting. However, in some patients, the disease process accelerates rapidly and can lead to pancreatic necrosis and generalized organ failure. Pancreatic necrosis can sometimes become infected by gut bacteria, which further increases the risk of mortality.

Presentation of acute pancreatitis

Patients with acute pancreatitis characteristically present with moderate to severe abdominal pain, often leading to hospital admission. The pain of pancreatitis usually occurs in the epigastrium and radiates through to the back and may be relieved by sitting forward. However, this presentation may differ in the elderly, and therefore pancreatitis may be confused with myocardial infarction or a perforated abdominal viscus.

The physical signs are those of an acute abdomen. Vomiting, fever, tachycardia, and hypotension may occur. Jaundice may also be a feature if there is concomitant biliary obstruction or cholangitis. Rarely, haemorrhagic pancreatitis can lead to retroperitoneal haemorrhage, causing bruising in the flanks (Grey Turner's sign), around the umbilicus (Cullen's sign) or even below the inguinal ligament (Fox's sign).

Diagnosis of acute pancreatitis

Pancreatitis is diagnosed in patients with (i) characteristic abdominal symptoms, (ii) elevated serum amylase and/or lipase, and/or (iii) imaging demonstrating pancreatic inflammation. At least two of those three criteria must be met to render a diagnosis. Serum lipase is more specific than amylase. Lipase levels elevated three times the upper limit of normal, with characteristic abdominal pain, is considered diagnostic of pancreatitis. The serum lipase rises within 4–8 hours, peaks at 24 hours, and returns to normal in 8–14 days; but serum enzyme levels are not helpful in tracking the clinical course of the illness after the initial diagnosis is made, and daily lipase measurements are not helpful in monitoring the clinical course of pancreatitis patients.

Thoughtful use of radiologic imaging is essential in pancreatitis. An abdominal ultrasound is a helpful first step if aetiology is uncertain, to determine if gallstones or biliary dilation is present. A computed tomography (CT) scan is often performed in the early evaluation of pancreatitis, but we suggest that this should often not be necessary if the diagnosis is clear from other clinical parameters. A CT scan is often more valuable if performed on or after day 5 of a severe clinical course, at which point the presence or absence of pancreatic necrosis may be noted and has important prognostic implications. In elderly patients with mild pancreatitis, a CT scan, either at initial presentation or at four- to eight-week follow-up (once inflammation has completely diminished), can be important to rule out the rare possibility of tumour. In patients with persistent symptoms after weeks, a CT scan may also reveal the presence of a pseudocyst or walled-off necrosis. The role of magnetic resonance cholangiopancreatography (MRCP) has expanded significantly over the years. MRCP can visualize biliary and pancreatic duct obstructions, occult lesions, microlithiasis, autoimmune pancreatitis, and complications of severe pancreatitis, e.g. peripancreatic fluid collections, necrosis, and pancreatic duct disruption. Due to its non-invasive nature, it has largely replaced diagnostic endoscopic retrograde cholangiopancreatography (ERCP) for the investigation of suspected bile duct stones or other biliary or pancreatic ductal pathology. ERCP is now recognized as a high-risk technique that is better suited to therapeutic indications.

In select patients, ERCP is indicated when there is a high pre-test probability for choledocholithiasis, cholangitis, and biliary obstruction. Endoscopic ultrasound (EUS) is another highly sensitive diagnostic modality to visualize the biliary system, pancreatic duct, and parenchyma; it has had a growing role, in conjunction with MRCP, in ruling out biliary stones or sludge as a cause of pancreatitis.

Assessment of the severity of acute pancreatitis

Recognizing the disease severity of acute pancreatitis has important implications for both management and prognosis. Based on the revised Atlanta criteria, pancreatitis can be classified into mild, moderately severe, and severe disease. These categories are based on objective parameters of organ failure and local complications, e.g. peripancreatic fluid collections, pseudocyst, and necrosis. In the absence of organ failure and/or local complications, pancreatitis is considered mild. Moderately severe pancreatitis presents with transient organ failure (<48 hours) and/or the presence of local complications. Finally, severe pancreatitis is characterized by persistent organ failure beyond 48 hours. As expected, organ failure is one of the strongest predictors of prolonged hospitalization and mortality.[6] Additionally, individual lab parameters, such as elevated hematocrit and blood urea nitrogen (BUN), can also help predict outcomes. Advanced age also carries a poor prognosis. Several scoring systems have been developed to predict disease severity and clinical outcomes, including the Ranson and Glasgow scores.[7,8] Such prognostic indices

are of proven value in predicting severe disease but suffer from the disadvantage that data collection is complex and must occur over 48 hours. In 2008, a simplified bedside clinical scoring system, the Bedside Index for Severity in Acute Pancreatitis (BISAP) score, was introduced. It was intended to simplify the prognostication of disease severity and predicting mortality by assessing only five variables: BUN, impairment of mental status, systemic inflammatory response (SIRS), age, and presence of pleural effusion. In a validation study, its performance was comparable to previous scoring systems.[9] Patients with a BISAP Score >0 had an increased risk of mortality. A score of 5 predicts a mortality rate of 22%. A radiologic assessment of disease activity using CT scanning (Balthazar score) has also been studied and showed a good correlation with local complications and mortality.[10]

Management of acute pancreatitis

The majority of patients with pancreatitis present with mild disease and require only observation, IV fluids, and symptom control with analgesia and anti-emetics. Antibiotics are rarely indicated. Patients with a BISAP score greater than 2 should generally be triaged to an intensive care unit for more careful monitoring.

Nutrition is another key therapeutic component. As opposed to delayed nutrition, early initiation of nutrition has shown improved outcomes, preferably using oral feeding.[11] In patients with mild pancreatitis, early initiation of a low-fat diet (versus a clear liquid diet) has been shown to reduce length of hospital stay. Patients with moderate or severe pancreatitis may not be in a clinical condition to tolerate oral feeding within 48–72 hours, so enteral feeding using a nasogastric or nasojejunal tube is recommended and should be initiated within 72 hours when possible. Several randomized controlled trials and meta-analyses report no differences in pre-pyloric versus post-pyloric feeding.[12] Parenteral nutrition is considered the last option for nutrition if caloric goals cannot be met through enteral means. Compared to enteral feeding, parenteral nutrition is associated with a significantly higher risk of infection in this patient population, including bacteraemia and infected necrosis.

Routine antibiotic therapy in severe acute pancreatitis is not recommended unless there is evidence of infected necrosis or persistent clinical instability concerning sepsis.[13] In patients with bile duct stones, endoscopic duct clearance by ERCP is recommended, although this need not be performed urgently except in cholangitic patients. There is now clear data that patients with gallstones who develop mild acute pancreatitis should undergo cholecystectomy during their index admission to reduce the likelihood of repeated attacks and subsequent complications.[14]

Figure 21.1 Acute necrotizing pancreatitis, with a bilobed walled-off necrosis occupying the body and tail of the pancreas.

Acute pancreatic fluid collections and pancreatic necrosis, which may develop in the first four weeks, are generally best managed conservatively. If these collections persist beyond four weeks, they can become walled off as pseudocysts (fluid) or walled-off pancreatic necrosis (solid debris) (see Figure 21.1). Walled-off collections can be drained/debrided endoscopically if symptomatic using a variety of well-supported techniques. Radiologic drainage or surgery should be uncommonly required in the modern era. In particular, surgery performed for pancreatic necrosis is associated with high morbidity and mortality and should be performed only by surgical teams with strong experience in this area.

Chronic pancreatitis

Chronic pancreatitis is a progressive inflammatory condition that leads to histological changes, including an increase in intralobular fibrous tissue, atrophy of the acini, and a chronic inflammatory infiltrate.[15] Macroscopically, ductal changes can occur, mainly ductal irregularity with intermittent strictures and dilatation. Calcifications and pancreatic atrophy may also be present (Figure 21.2). In clinical practice, the diagnosis of chronic pancreatitis relies on a combination of symptoms, pancreatic function testing, and morphological appearance of the pancreas, rather than biopsy confirmation.

In the United States, the prevalence of chronic pancreatitis is 40–50 per 100,000 population.[16] The incidence of chronic pancreatitis in the elderly is uncertain, but it is unusual for symptomatic chronic pancreatitis to be diagnosed for the first time after the age of 65. Post-mortem examinations reveal that pancreatic stones/calcifications occur in ~15% of patients over the age of 90 and that

Figure 21.2 Atrophied pancreas with dilated, irregular pancreatic duct and intraductal stone.

changes of chronic pancreatitis are seen. The significance of these findings is uncertain as there may be no correlation with clinical disease.[14]

Causes of chronic pancreatitis

Drinking alcohol and smoking cigarettes are the commonest causes of chronic pancreatitis. In the elderly, autoimmune pancreatitis can also be considered. Pancreatic insufficiency of unknown cause can occur uncommonly in older persons without other symptoms of pancreatitis. Chronic pancreatitis changes may also be present due to chronic ductal obstruction such as that caused by a pancreatic or periampullary tumour; therefore, a careful history and good-quality imaging evaluation are required to exclude mass lesions, particularly in patients without other risk factors for chronic pancreatitis

Clinical presentation of chronic pancreatitis

Abdominal pain, a characteristic of chronic pancreatitis in younger patients, may be less severe or even absent in the elderly.[17] Weight loss, new-onset diabetes, and steatorrhea (representing fat malabsorption) are often the presenting symptoms in elderly patients. Occasionally, chronic pancreatitis is recognized as an incidental finding when pancreatic calcifications are noted on abdominal CT or, more rarely, abdominal X-rays.

Clinical examination is usually normal, although there may be localized tenderness in the epigastrium. Signs of malnutrition occur late in the disease.

Diagnosis of chronic pancreatitis

Establishing a diagnosis is often challenging, especially early in the disease course. Serum amylase and lipase levels are usually normal or only slightly elevated. If there is associated obstruction of the intrapancreatic bile duct, bilirubin and alkaline phosphatase levels may be elevated. Diagnosis relies on clinical signs and symptoms, pancreatic function tests, and radiologic evaluation.

Both direct and indirect pancreatic function tests can be used to evaluate steatorrhea resulting from exocrine insufficiency. Direct tests are those that require hormonal stimulation as part of the test protocol, whereas indirect tests do not.

Our opinion is that the best and most widely available indirect test of pancreatic function is the faecal pancreatic elastase. Faecal elastase levels fall with ageing and are a sensitive diagnostic test for malabsorption. However, faecal elastase can be falsely positive in unformed stool, and sensitivity is low early in the disease.[18] Measurement of serum vitamin A and β-carotene can be used to screen for fat malabsorption.[19] Steatorrhea can potentially be recognized by Sudan staining of the stool, although this test has very limited specificity. The 72-hour faecal fat collection can be more effective in quantifying steatorrhea if performed correctly, but this test is rarely ordered in practice due to its very cumbersome nature, requiring a daily diet of 100 g of fat and appropriate stool collection by the patient.

Among the direct function tests, the most sensitive are the cholecystokinin and secretin stimulation tests, which typically require upper endoscopy to collect duodenal aspirates (to measure the concentration of pancreatic enzymes or bicarbonate) as part of the test protocol. Although highly sensitive, direct function tests are limited by their invasive nature and are performed only in specialized centres.

Imaging procedures

Radiologic evaluation has generally superseded function studies in the diagnosis of chronic pancreatitis. Other than the rarely-used abdominal X-ray, abdominal ultrasound is the least expensive and most widely available modality for assessing the pancreas; however, the sensitivity of ultrasound for detecting chronic pancreatitis changes is less than that of CT or MRCP. In about two-thirds of chronic patients, ultrasonography may show swelling of the gland or duct dilatation, but abdominal ultrasound may not be able to view the entire pancreas because of intervening bowel gas.

CT scanning provides similar information and is more sensitive in detecting parenchymal atrophy, ductal dilation, and calcifications, especially in advanced disease. Compared to other imaging modalities, MRCP gives the most detailed visual of pancreatic ductal anatomy, such as filling defects,

main and side branch duct dilations, and irregularity of the main pancreatic duct. Administration of IV secretin during MRCP can provide data on duct compliance and even pancreatic flow, which may be helpful surrogates for pancreatic exocrine function, thus enhancing the sensitivity of detecting early chronic pancreatitis.[20]

Endoscopic ultrasound (EUS) is another diagnostic modality that has gained support in diagnosing early chronic pancreatitis. It also evaluates parenchymal and ductal changes, utilizing a variety of EUS imaging criteria. However, there is a lack of standardization regarding EUS scoring tools for chronic pancreatitis, along with significant inter-operator interpretation variance.

When chronic pancreatitis is suspected, our preference is to use CT or MRCP as the first-line imaging modality, depending on local preference and experience.

Complications of chronic pancreatitis

A primary complication of chronic pancreatitis is pain, the management of which will be discussed below. Nutritional issues, in particular fat malabsorption, can be seen in severe chronic pancreatitis and may lead to obvious steatorrhea and weight loss. Diabetes due to chronic pancreatitis, sometimes termed *type 3c diabetes*, is relatively uncommon but can be more difficult to control due to both insulin and glucagon insufficiency. Episodes of hyper- and hypo-glycaemia are more likely. They can be further exacerbated by concomitant exocrine insufficiency, resulting in malabsorption. While diabetes is relatively uncommon in chronic pancreatitis, it is a nearly inevitable consequence of major pancreatic resection such as Whipple surgery (see Chapter 86).

Management of chronic pancreatitis

Pain is relatively less common in the elderly with chronic pancreatitis, but when it occurs, it impairs the quality of life. Opiate drugs should be avoided because of the risks of narcotic medications in the elderly, including narcotic dependence. Non-steroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, and neuromodulators (e.g. gabapentin) are often first-line therapies.

If drug therapy fails to control pain, other options, such as deafferentation techniques (e.g. celiac axis block), have been tried with variable success. If imaging shows clinically significant pancreatic duct strictures or large obstructing pancreatic duct stones, ERCP can be an option before surgical techniques are considered. In general, surgery for chronic pancreatitis should be rare, and the best outcomes are generally in the subgroup of patients with a distinct pancreatic ductal stricture causing a ductal obstruction that can be relieved surgically. Surgical pancreatic resections or total pancreatectomy with islet autotransplantation (TPIAT) have gained increasing success in the younger population for the treatment of CP; however, they have not been well studied in the older population.

Attempts to control steatorrhea by orally administered pancreatic enzymes are worthwhile, and the dose should be titrated to achieve a normal bowel movement frequency. Malabsorption of fat-soluble vitamins occurs and should be treated with appropriate supplements.

Pancreatic cysts and tumours

Cystic lesions of the pancreas

Cystic lesions of the pancreas are very common findings in the era of modern cross-sectional imaging and are usually discovered incidentally. Recent studies have shown that up to 40% of adults will have a small pancreatic cyst noted incidentally on abdominal MRI scans.[21]

Broadly speaking, pancreatic cysts can be divided into neoplastic and non-neoplastic categories. Of the non-neoplastic cysts, the majority are inflammatory lesions, most commonly pseudocysts, which can be encountered as a sequalae of acute pancreatitis. These inflammatory cysts are variably symptomatic, and depending on their anatomical location and morphology, EUS sampling or drainage may be indicated and should be referred for evaluation by a gastroenterologist. Other non-neoplastic cysts are fairly rare but include true cysts, retention cysts, mucinous non-neoplastic cysts, and lymphoepithelial cysts, all of which may be difficult to definitely diagnose and are beyond the scope of this chapter.

Neoplastic cysts are quite common, and certain categories of pancreatic cystic neoplasms may require surveillance or even consideration of resection because of malignancy risk. The two most common types of pancreatic cystic neoplasms are intraductal papillary mucinous neoplasms (IPMNs), which are precancerous and typically require surveillance, and serous cystadenomas (SCAs), which are typically benign and may not require surveillance. There are several other, less common, pancreatic cystic neoplasms, including mucinous cystic neoplasm (MCN) and pseudopapillary neoplasm, extensive discussion of which is beyond the scope of this chapter.

As a general rule, any pancreatic cystic lesion greater than 1 cm should, even if incidentally discovered, be referred to a gastroenterologist to help determine appropriate additional testing and/or surveillance modality and interval. If there is uncertainty regarding the nature of a pancreatic cyst <1 cm in size, then interval MRCP imaging (typically at 6–12 months) or referral to a gastroenterologist are both reasonable considerations; however, the clinical significance of a diminutive pancreatic cyst in an elderly patient is questionable, particularly if other chronic health conditions are present.

Table 21.1 Pancreatic endocrine tumours.

Type	Age at diagnosis (years)	Five-year survival rate (%)	Clinical characteristics
Insulinoma	50–60	90	Fatigue, hypoglycaemia
Gastrinoma	60–70	55	Gastric pain, weight loss
Glucagonoma	50–60	90	Weight loss, diabetes, rash
Somatostatinoma	60–70	30	Diabetes, gallstones, weight loss, steatorrhea
VIPoma	40–60	45	Flushing
Pancreatic peptideomas	40–60	40	None

Endocrine tumours of the pancreas

Endocrine tumours of the pancreas are rare. These tumours are classified according to the hormone they excrete, which typically correlates with the clinical presentation, although some low-grade pancreatic neuroendocrine tumours may be found incidentally on imaging without clinical symptoms. Table 21.1 describes the common pancreatic endocrine tumours and their clinical characteristics.[22]

Most pancreatic neuroendocrine tumours have malignant potential and may be part of the multiple endocrine neoplasia syndrome. Suspicion of a pancreatic neuroendocrine tumour, either on clinical grounds or based on imaging findings, should generally prompt referral to a multidisciplinary team including a gastroenterologist and surgeon. Endoscopic-ultrasound guided biopsy is typically the first step in the diagnostic approach.

Pancreatic adenocarcinoma

Exocrine pancreatic cancer is diagnosed in over 56,000 people in the US each year. 85% of these are adenocarcinomas.[23] Early diagnosis can be difficult because symptoms may be absent or vague in the early stages of the disease. Thus only ~15–20% of patients have tumours amenable to surgical resection at presentation. The overall five-year survival rate is less than 10%, but it is higher for patients diagnosed at earlier stages.

The predominant risk factor is age, although there is a relationship to cigarette smoking. Genetic and general medical conditions such as familial breast cancer, hereditary pancreatitis, chronic pancreatitis, and diabetes are also risk factors.

Clinical features

Cancer of the head of the pancreas presents with jaundice, often with epigastric or back discomfort. Later in the clinical course, other symptoms of cholestatic jaundice such as itching, pale stools, and dark urine occur. Anorexia and weight loss are common. Tumours of the body and tail of the pancreas present more insidiously and are often recognized only when distal spread of the disease has occurred.

Figure 21.3 Hypoenhancing lesion with a central cystic component at the pancreatic neck with associated upstream mild dilatation of the pancreatic duct.

Diagnosis of pancreatic cancer

Following an initial assessment with blood work, tumour marker CA19-9, CT scan, and ultrasonography are typically the first imaging steps. Ultrasound may reveal biliary dilation in the setting of a pancreatic head cancer but is otherwise insensitive to the presence of a pancreatic mass in many cases. CT scan is a much more accurate imaging modality and also has the benefit of providing vascular staging information.

CT scanning may also help identify tumour expansion outside the confines of the gland, such as a metastatic tumour in the liver or adjacent lymph nodes (Figure 21.3). Diagnosis is now most commonly confirmed by endoscopic ultrasound with fine-needle biopsy. ERCP may also be indicated for biliary stent placement in the setting of obstructive jaundice.

Management of pancreatic cancer

Surgery alone offers the hope of cure and, even if performed, offers a five-year survival rate of only 20%. Adjuvant therapy with a fluorouracil-based chemotherapy protocol (e.g. FOLFIRINOX) is the first-line systemic therapy. In patients with unresectable disease, chemoradiation can be used. Gemcitabine is the standard of care in locally advanced unresectable pancreatic adenocarcinoma, and the agent may also be used as part of a combined chemotherapy protocol.[24]

Despite significant ongoing advances in efficacy and tolerability of treatment approaches, many patients with pancreatic adenocarcinoma, including those who could be curable, are not referred for multidisciplinary oncologic evaluation. In general, our recommendation is that even in the elderly or chronically ill patient who may decline treatment, a formal consultation with an oncology team is important to ensure that patients and families are aware of all treatment options, ranging from potentially curative to palliative.

Key points

- Although pancreatic morphological change occurs in the elderly, it may not correlate with pancreatic dysfunction.
- Acute pancreatitis associated with gallstone disease is the commonest cause of acute pancreatitis in the elderly.
- Pancreatic cysts are found incidentally in up to 40% of cross-sectional imaging scans, and referral to gastroenterology is reasonable for cysts >1 cm in size.
- Pancreatic cancer remains a challenging condition to treat, but treatment options are expanding rapidly, and elderly patients should be offered formal oncologic consultation.

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