15.26.1 Acute pancreatitis 3209

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CONTENTS 15.26.1 Acute pancreatitis 3209 R. Carter, Euan J. Dickson, and C.J. McKay 15.26.2 Chronic pancreatitis 3218 Marco J. Bruno and Djuna L. Cahen 15.26.3 Tumours of the pancreas 3227 James R.A. Skipworth and Stephen P. Pereira 15.26.1 Acute pancreatitis R. Carter, Euan J. Dickson, and C.J. McKay ESSENTIALS Acute pancreatitis affects 300 to 600 new patients per million popu- lation per year and is most commonly caused by gallstones or al- cohol. Careful imaging reveals that most so-called idiopathic acute pancreatitis is due to small (1–3-mm diameter) gallstones. Diagnosis is made by a combination of a typical presentation (upper abdominal pain and vomiting) in conjunction with raised serum amylase (more than three times the upper limit of normal) and/or lipase (more than twice the upper limit of normal). Several other acute abdominal emergencies can mimic acute pancreatitis and may be associated with a raised serum amylase. In equivocal cases, a CT scan is indicated to exclude other causes and confirm the diagnosis. Initial management is with (1) analgesia, (2) ensuring adequate oxygenation, and (3) intravenous fluid administration. The revision of the Atlanta classification separates patients clinically into (1) mild—with early resolution without complications, (2) moderate—local complications without organ failure, and (3) severe—complications associated with organ failure. Mild acute pancreatitis responds to analgesia and intravenous fluids. If gallstones have been identified, then cholecystectomy (or endoscopic retrograde cholangiopancreatography (ERCP) sphincterotomy where clinically appropriate) should be performed during the same admission, or at least within 2 to 4 weeks to pre- vent recurrent attacks. Severe acute pancreatitis carries a high mortality (up to 20%). Management in the early stages is centred on organ support (respiratory, circulatory, and renal failure). Later management involves surgical or radiological intervention for sepsis, usually within a specialist pancreatic unit. With regard to some specific aspects of management: (1) there is no indication for a nasogastric tube or starvation: en- teral feeding of patients with prolonged illness is associated with fewer risks and side effects than total parenteral nutrition. (2) Antibiotics should not be given until and unless a specific indication arises. (3) ERCP—occasionally cholangitis may be as- sociated with hyperamylasaemia, in which case urgent biliary decompression at ERCP is indicated. (4) There are no pharmaco- logical agents that benefit any form of acute pancreatitis. (5) The case for decompressive laparotomy for abdominal compartment syndrome remains

unproven. Epidemiology Population studies from Scotland and Finland have shown the in- cidence of acute pancreatitis is about 400 patients/million per year. Incidence would appear to be rising, with a 100% increase in the hospitalization rate in the United States of America over the last 20 years, a 75% increase in admissions in the Netherlands, and a 3.1% yearly rise in incidence in the United Kingdom. The mean age at presentation is 53 years with a roughly equal sex distribution, al- though the largest increase in incidence has been among women under 35 years, which may reflect increasing obesity within the population. The disease was most prevalent in those with poorer socioeconomic status, especially where alcohol was the cause. Overall mortality is from 2.0 to 7.5%, highest in those who are over 70 years, obese individuals, and those with comorbidity at the time of onset. Prospective and retrospective studies record 45 to 50% of deaths as occurring in the initial week of the illness secondary to fulminant multiple organ failure. 15.26 Diseases of the pancreas

section 15 Gastroenterological disorders 3210 Clinical features Sudden onset of severe upper abdominal pain focused in the epigas- trium with vomiting is the most common presentation. This tends to progressively lessen in severity over the first 48 to 72 h, and it is not usually a significant factor beyond this time. There may be upper abdominal tenderness and guarding, but these signs are often less marked than might be suspected from the severity of the pain, and bowel sounds are usually absent in the early stages. Vomiting is prevalent in the first 12 h of illness, contributing to hypovolaemia and hypotension. Clinical jaundice is rare on admission, although minor abnormalities of biochemical liver blood tests occur in 80% of patients with a biliary aetiology. Occasionally, hyperamylasaemia occurs in association with cholangitis, which if overlooked may re- sult in irreversible multiple organ failure. The presence of jaundice and pyrexia on the day of admission is therefore an indication for ur- gent endoscopic retrograde cholangiopancreatography (ERCP) and biliary decompression. Pathology The initial phase of acute pancreatitis is characterized by oedema and the development of an acute inflammatory infiltrate, rich in neutrophils, with tiny spots of fatty tissue necrosis, mainly on the surface but also in the intralobular fatty tissue. In mild cases, the changes are most marked in the peripancreatic tissue, but because the initial pancreatic histological change is within the intralobular fat, there is a relationship between extent of necrosis and the amount of fat within the pancreas. In severe disease, intravascular throm- bosis and local enzymic necrosis leads to confluent areas of fat ne- crosis, which extends beyond the pancreas into the peripancreatic fat. Within the pancreas, disseminated ductal and periductal ne- crosis may be evident. Diagnosis and assessment of severity The diagnosis is usually made from the clinical presentation of upper abdominal pain and vomiting associated with an elevation of serum amylase or lipase. A CT scan should be performed when the diagnosis is not clear. This often demonstrates pancreatic oe- dema and peripancreatic inflammatory stranding, fluid collec- tions, and poor contrast enhancement of the gland (Fig. 15.26.1.1). Occasionally, the diagnosis may first be made at laparotomy, when simple washout and closure is all that should be done. The differential diagnosis is that of an acute abdomen (Box 15.26.1.1). A raised amylase may be associated with several of these conditions, but the (near) universal availability of CT has simplified diagnosis when doubt exists. Biochemical abnormalities A multitude of biochemical phenomena are found in acute pan- creatitis. Various pancreatic enzymes are released that are useful as diagnostic markers. Acinar cell disruption leads to high serum levels of amylase, lipase, trypsin, chymotrypsin, phospholipase, elas- tase, trypsinogen activation peptide, and phospholipase activation peptide. These are also elevated in peritoneal and retroperitoneal tissues as well as lymphatic fluid. C-reactive protein, an acute-phase reactant, is of most use for longitudinal monitoring of progress.

Very high concentrations of circulating cytokines occur in the blood at an early stage in the disease, including tumour necrosis factor-α, platelet activating factor, and interleukin 6 with maximal levels in those with severe pancreatitis: these are of research interest rather than clinical value. Grading disease severity Many biochemical scoring systems attempting to objectively grade severity of an attack of acute pancreatitis have been developed, including the Glasgow and Ranson scoring systems. While there is value in directing less experienced clinicians to the multisystem organ dysfunction associated with a severe attack, none are suffi- ciently accurate to direct treatment, and the utility lies in assessing equipoise within clinical trials, with regard to which the APACHE II system has been shown to be useful in the stratification of severity of acute pancreatitis. CT scanning can be useful in demarcating location and ex- tent of pancreatic injury, and a CT severity index has been de- veloped, although CT is more commonly used to monitor the development of evolving complications. In practice, sequen- tial physiological scoring systems (e.g. NEWS) can assist the Fig. 15.26.1.1 CT scan 36 h from onset of pain showing reduced enhancement of neck and body, a perfused pancreatic tail, and peripancreatic stranding. Box 15.26.1.1 Differential diagnosis of acute pancreatitis • Mesenteric ischaemia/infarction • Small-bowel obstruction/perforationa • Renal failure • Macroamylasaemia • Dissecting aortic aneurysm • Diabetic ketoacidosis • Perforated duodenal ulcera • Acute cholangitisa • Acute cholecystitisa • Atypical myocardial infarctiona • Ectopic pregnancya a Amylase is usually normal.

 identification of clinical deterioration and are in common use in most surgical units. Other factors affecting prognosis Other factors affecting prognosis include age and obesity. Many studies have shown that those aged over 70 years have a higher mor- tality. Chronic cardiorespiratory or renal impairment is common in this age group and further increases the risk of death. Acute pan- creatitis carries a significantly higher mortality and morbidity in patients with a body mass index of more than 30 kg/m2, mainly because of an increased risk of hypoxaemia, but also from other associated factors. Aetiology Aetiological factors and rare associations of acute pancreatitis are listed in Boxes 15.26.1.2 and 15.26.1.3. Major factors Biliary disease and alcohol abuse together account for over 80% of patients with acute pancreatitis in most prospective studies. Gallstones Gallstones are the predominant cause of acute pancreatitis and all patients should have an abdominal ultrasound examination to identify these, even where there is a history of alcohol excess. Smaller stones pass through the cystic duct more easily and are at increased risk of precipitating acute pancreatitis. Endoscopic ultrasonography (EUS) is more sensitive than transabdominal ultrasonography in identifying small gallstones (microlithiasis). This may be helpful in demonstrating gallstone aetiology in those patients previously labelled ‘idiopathic’. The mechanism by which gallstones induce acute pancreatitis is not certain, but increased back pressure in the pancreatic duct fol- lowing transient impaction of a migrating gallstone at the ampulla of Vater is considered to be the likely initiating event. Subsequent intracellular events lead to activation of proteases within acinar cells, acinar cell injury, and a local inflammatory response. Alcohol The proportion of patients in whom pancreatitis is due to alcohol abuse is dependent on the population under study: rates may be as high as 70 to 80% (in New York (United States of America) and Helsinki (Finland)). The risk is highest in young males who drink in excess of 80 g of alcohol per day. Smoking is a cofactor in the devel- opment of both acute and chronic pancreatitis. Many patients with a possible alcohol history also have gallstones and the diagnosis of alcohol-induced acute pancreatitis should be one of exclusion. Alcohol probably causes acute pancreatitis through intracellular lysosomal release modulated by elevations in cytosolic and mito- chondrial ionized Ca2+ concentration. Minor factors Drugs The drugs most commonly

implicated in causing acute pancreatitis are valproic acid, azathioprine, l-asparaginase, and corticosteroids. There is equivocal evidence regarding thiazide and other diuretics. However, unless viral titres have been determined, together with adequate biliary investigations including endoscopic examination of the ampulla of Vater, it is unwise to ascribe acute pancreatitis to a particular drug. Repeat exposure to the same drug again causing acute pancreatitis is the strongest evidence of a direct association. Viral infection Viral infection, particularly mumps, Coxsackie B, and viral hepa- titis, can cause acute pancreatitis. One clinical feature that may prove useful is prodromal diarrhoea, which is rare in all other types of acute pancreatitis. Of increasing importance are the effects of HIV infection, where acute pancreatitis may be associated with both the primary viral infection and treatment (antiretroviral drugs). Single combination agent therapy (tenofovir, lamivudine, and efavirenz) is considered the most pancreas friendly, but the evidence for favouring one agent over another is weak. Alcohol abuse is common in many HIV-positive patients, particularly in Africa, and it may be difficult to define a specific causal agent. Box 15.26.1.2 Aetiological factors in acute pancreatitis (according to frequency) Major • Biliary disease • Alcohol abuse Minor • After ERCP • Sphincter of Oddi dysfunction • Hyperparathyroidism • Hyperlipoproteinaemia • Blunt or surgical trauma • Autoimmune pancreatitis • Drugs • HIV-associated pancreatitis • Hereditary (trypsinogen gene defects) • Ampullary or pancreatic tumour • Cancers metastatic to pancreas: — Renal — Stomach — Breast — Ovarian — Lung Box 15.26.1.3 Rare associations with acute pancreatitis • Hypothermia • Coxsackie B virus • Mumps virus • Sclerosing cholangitis • α1-Antitrypsin deficiency • Virus infection (non-HIV) • Worm infestationa • Scorpion biteb • Duodenal duplication a In South-East Asia. b In Trinidad.

section 15 Gastroenterological disorders 3212 Benign pancreatic duct stricture A focal area of pancreatic necrosis in a primary attack of acute pan- creatitis can cause secondary fibrosis with main duct stricture for- mation and segmental ‘upstream’ recurrent attacks of pancreatitis as a consequence. Stricture dilatation or occasionally surgical de- compression or distal pancreatectomy may be required. Congenital or developmental anatomical abnormalities can present with pancreatitis (choledochal cyst, duodenal duplication, anomalous pancreaticobiliary junction). Pancreas divisum (nonunion of main and accessory ducts) occurs in 3 to 5% of people and is not con- sidered to be a primary cause of pancreatitis. Periampullary or obstructive pancreatic tumours Periampullary adenoma or carcinoma resulting in upstream ob- struction of the main pancreatic duct is an important association. Ampullary tumours are best diagnosed with side-viewing endo- scopic biopsy. With the increase in this approach to diagnosis, tu- mours at or close to the ampulla have been shown to cause 0.4% of cases of acute pancreatitis. Effective treatment of the tumour abol- ishes recurrent attacks. This usually involves surgical resection, but endoscopic laser therapy or endoscopic papillectomy can be effective in older and less fit patients. Carcinoma of pancreas can occasionally present with clinical acute pancreatitis and other primary tumours (such as neuroendocrine tumours) or tumours metastasizing to the pancreas (such as renal carcinoma) may present in this way, prob- ably by causing pancreatic duct obstruction. Pancreatitis in association with a side branch intraductal papillary mucinous neoplasm is considered a risk factor for malignant trans- formation and requires assessment for potential resection following resolution. Hyperparathyroidism Hypercalcaemia secondary to hyperparathyroidism is now recog- nized to be an uncommon cause of acute pancreatitis. Removal of a parathyroid adenoma usually prevents further acute pancreatitis since persistent hypercalcaemia appears to be the provoking factor. Hyperlipidaemia Patients with type I and type V hyperlipoproteinaemia may de- velop acute pancreatitis in the absence of alcohol ingestion when triglyceride levels exceed 11 mmol/litre. Both

subtypes are asso- ciated with chylomicrons, of which greater than 90% are trigly- cerides. Dietary restriction of lipids and various lipid-lowering drugs are valuable in therapy. Hyperlipidaemia of any cause where triglyceride levels reach in excess of 2000 mg/dl may cause acute pancreatitis, and acute pancreatitis may rarely complicate hyper- lipidaemia of pregnancy or diabetic ketoacidosis. High triglyceride levels may be present during an attack of acute pancreatitis and identifying high fasting lipid levels following resolution is key to confirmation. Hypothermia This is an important association. In younger patients, this may be associated with alcohol abuse, particularly if patients fall asleep out of doors, or in the elderly in an unheated house. Management is directed at gradual warming and supportive measures for organ compromise. Hereditary This condition is increasingly being studied since the discovery of genetic mutations of the cationic trypsinogen gene (PRSS1), which shed light on the mechanism of acute pancreatitis. A Europe-wide study (EUROPAC) has tracked multiple families in the United Kingdom and Europe, and similar work in Japan and the United States of America is ongoing. The two most common mutations are R122H and N29I. An autosomal dominant pattern of inheritance is seen. Severe acute inflammatory changes are rare and diagnosis is often delayed. Patients usually have a long history of recurrent ab- dominal pain from childhood or adolescence. Changes of chronic fibrosis may be present at diagnosis. Typically, chronic pancreatitis is evident by the age of 20 to 40 years, and the risk of pancreatic car- cinoma in those aged over 60 years is significantly increased. Mutations in the cystic fibrosis transmembrane conductance regulator gene (CTFR) and the pancreatic secretory trypsinogen in- hibitor gene (SPINK1) are also linked to pancreatitis. Trauma Hyperamylasaemia may occur after blunt abdominal trauma, usu- ally from a crush injury to the body of the pancreas against the ver- tebral column. The risk of associated injuries to surrounding organs is high, and in the acute phase these are usually more significant than the pancreatic injury. The identification of a pancreatic injury during a trauma laparotomy should be managed by simple drainage in most cases. When there is transection of the main pancreatic duct, therapeutic options include endoscopic transpapillary stenting and distal pancreatectomy. Late presentation is associated with pseudo- cyst formation due to leakage from the damaged pancreatic duct. Pancreatic manipulation during surgical mobilization for colonic, gastric, or splenic surgery may result in inflammation. Iatrogenic Surgical or endoscopic procedures involving the ampulla of Vater can induce pancreatitis. In recent years, diagnostic ERCP (2% risk of acute pancreatitis) has largely been replaced by noninvasive imaging modalities (EUS and magnetic resonance cholangiopancreatography). This has reduced the overall incidence of postprocedural acute pancreatitis, but EUS fine needle aspiration of pancreatic lesions, particularly close to the main duct, can itself result in pancreatitis. The risk of acute pancreatitis increases to 4 to 6% where a therapeutic endoscopic sphincterotomy has been per- formed and may be as high as 20% in high-risk patients (sphincter of Oddi dysfunction). Iatrogenic perforation should be considered in all patients who develop pancreatitis after therapeutic ERCP, and patients with early organ dysfunction or abdominal signs should undergo a CT without delay if any doubt exists as this will affect management (antibiotics). Autoimmune pancreatitis This is a rare condition, which is considered part of the systemic IgG4-related autoimmune disease spectrum and is associated with other autoimmune diseases (polyarteritis nodosa, systemic lupus erythematosus, other vasculitides) and inflammatory bowel disease (Crohn’s disease and ulcerative colitis). It may present as abdominal pain with obstructive jaundice more typical of chronic than acute pancreatitis. Other features may include (1) an increased IgG4/

 IgG ratio in serum, (2) homogeneous gland enlargement with a well-defined halo on CT, (3) characteristic diffuse abnormality on EUS, and (4) periductal

lymphoplasmacytic infiltrate on biopsy. The latter may also be associated with abnormalities in the extrahepatic biliary tree resembling sclerosing cholangitis (IgG4-associated cholangiopancreatopathy). Focal autoimmune pancreatitis may prove difficult to differentiate from carcinoma. A good response to steroids is diagnostic (HISORt criteria). Worm infestation Ascaris lumbricoides within the ampullary area may manifest as acute pancreatitis clinically, and other worms lodged in this area can produce the same effect. Sphincter of Oddi dyskinesia Rarely, sphincter of Oddi dyskinesia can present with acute ab- dominal pain, although the more common presentation is one of chronic relapsing abdominal discomfort. The attacks associated with hyperamylasaemia are usually mild (except where pancrea- titis follows an ERCP). With regard to functional gallbladder and sphincter of Oddi disorders (SODs), the Rome III diagnostic criteria for functional gastrointestinal disorders require episodes of pain in the epigastrium or right upper quadrant and all of the following: epi- sodes lasting 30 min or longer; recurrent symptoms occurring at different intervals (not daily); the pain builds up to a steady level and is moderate/severe enough to interrupt the patient's daily ac- tivities or lead to a visit to the emergency department; the pain is not relieved by bowel movements, postural change, or antacids; and exclusion of other structural disease that would explain the symp- toms. If these criteria are satisfied, then Rome III allowed further classification into functional gallbladder disorder (SOD I), where the gallbladder is present and biochemical tests are normal; func- tional biliary SOD (SOD II), where amylase and lipase are normal, but association of at least two episodes of pain with elevation of serum transaminases, alkaline phosphatase, or conjugated bilirubin is a supportive criterion; and functional pancreatic SOD (SOD III), characterized by elevation of serum amylase and/or lipase. More re- cently, Rome IV, recognizing good evidence that sphincterotomy is no better than sham treatment in patients previously classified as having SOD III, discarded the use of this term and renamed SOD II 'Functional Biliary Sphincter Disorder'. However, whether this exists as a clinical entity remains a matter of debate, and whether it is a potential cause of acute pancreatitis is controversial. Most clinicians would not recommend pancreatic sphincterotomy in the absence of ampullary stenosis. Classification of severity The original Atlanta classification of acute pancreatitis dichotom- ized clinical behaviour into mild or severe acute pancreatitis, and intervention for necrosis was often focused on early removal of sterile or infected necrosis, usually by open necrosectomy. This oversimplification proved inadequate in clinical practice and the Atlanta criteria were revised in 2013 to address the importance of early systemic organ dysfunction in determining disease severity and outcome (Table 15.26.1.1). The outcome following interven- tion for the management of local fluid or necrotic collections is also heavily influenced by the degree of systemic disturbance, and this is reflected in an additional category of 'moderately severe' pancrea- titis, where collections are present in the absence of organ dysfunc- tion. In addition to disease severity, mortality is strongly associated with age and comorbidity. The significance of infection has been recognized in an addendum adding a category of 'critical', recog- nizing that those patients with sepsis and organ failure have the highest mortality. This classification further separates local complications/collec- tions on the basis of time from presentation (<4 or >4 weeks) and on the presence of necrosis, leading to definitions aimed at permit- ting comparison of case series (Table 15.26.1.2). The 'early' phase is characterized by the initial host response to the pancreatitis, the severity being determined by the magnitude of organ disturbance/ failure, and a 'late' phase typified by the persistence of organ dys- function and the management of local or systemic complications. The vast majority of acute fluid collections without necrosis will re- solve within 4 weeks, and a persistent fluid collection with minimal or no necrotic component ('pseudocyst') is very rare. Collections may be sterile or infected. Most clinically

significant peripancreatic complications are therefore related to either acute necrotic collec- tions (<4 weeks) or walled-off pancreatic necrosis (>4 weeks). This temporal separation is somewhat arbitrary as the clinical manage- ment and surgical approach is determined by multifactorial indi- vidual patient factors. However, this does serve to provide a timeline beyond which, if appropriate, intervention should be delayed. Management General aspects The principles of organ support in critical illness should be followed, ensuring reversal of hypoxaemia, restoration of circulating volume, and maintenance of tissue perfusion ideally within a critical care en- vironment. Early restoration of circulating blood volume is associ- ated with an improved outcome. The combination of fluid lost from vomiting and loss of capillary integrity can be very substantial. The introduction of vasoconstrictor therapy should only be considered after establishing adequate volume resuscitation. Hypoxaemia re- flects disease severity in acute pancreatitis, and while most patients Table 15.26.1.1 Grades of severity of pancreatitis (based on the clinical parameters of the presence or absence of organ failure and/or complications Mild acute pancreatitis • No organ failure • No local or systemic complications Moderately severe acute pancreatitis • Organ failure that resolves within 48 h (transient organ failure) and/or • Local or systemic complications without persistent organ failure Severe acute pancreatitis • Persistent organ failure (>48 h): • Single organ failure • Multiple organ failure Critical acute pancreatitis In addition to the other three categories taken from the Atlanta revision, an additional ‘critical’ category (persistent organs failure and sepsis) was proposed by Petrov et al.

section 15 Gastroenterological disorders 3214 can be managed with supplemental humidified oxygen, assisted ven- tilation may be required in more severe cases. For initial resuscitation, Ringer’s lactate is recommended, with goal-directed intravenous fluid (5–10 ml/kg per hour) to produce 0.5 ml/kg of urine per hour. Renal replacement therapy by haemo- dialysis or haemofiltration may be required if renal failure becomes established. The more severe cases of acute pancreatitis are charac- terized by the development and persistence of a systemic inflam- matory response syndrome, one aspect being the development of a swinging pyrexia. This is often inappropriately taken as evidence of sepsis but is usually a reflection of the inflammatory cascade and the presence of devitalized tissue in the retroperitoneum rather than bacterial infection. Specific aspects ERCP There is no role for early ERCP in mild disease. High fever within the first 24 h is rare and, if associated with jaundice, is suspi- cious of ascending cholangitis where the cholangitis, rather than any pancreatic inflammation, is driving organ dysfunction. This is the only unequivocal indication for ERCP and biliary decom- pression. The role of early ERCP remains controversial in all other circumstances. Several randomized studies and cohort series have looked at the role of early ERCP with endoscopic sphincterotomy compared with conservative management in acute gallstone pan- creatitis. A number of meta-analyses have failed to demonstrate a definite benefit, and early ERCP is difficult to justify in patients who are not jaundiced. Antibiotics The dual peak in mortality in acute pancreatitis is well recognized. The late peak is determined by complications associated with ne- crosis, including the development of pancreatic or peripancreatic infection. The consensus of the most recent systemic reviews/meta-analyses is that there is no evidence supporting the use of prophy- lactic antibiotics in either mild or severe acute pancreatitis, and the recommendation is to avoid their use, using targeted antibiotic therapy for episodes of proven infection. It is, however, reasonable to commence antibiotics in the deteriorating patient with radiological and clinical evidence of sepsis while awaiting culture confirmation. Nutrition support There is no benefit from enteral feeding in mild pancreatitis, and these patients need have no dietary restrictions. Assisted feeding may be

required in severe acute pancreatitis to provide long-term nutritional support. Randomized studies have shown that enteral nutritional support is cheaper and is associated with fewer side ef- fects than total parenteral nutrition. In addition, there is no differ- ence in outcome with nasogastric compared to nasojejunal feeding. In clinical practice, therefore, the mode of nutritional support does not appear to influence the disease process, and the choice of de- livery relates to tolerance and minimizing morbidity associated with the delivery system. Probiotics may be detrimental in acute pancrea- titis and specifically supplemented nutrition should only be admin- istered in the context of clinical trials. It has been suggested that nutritional support may help to pre- serve mucosal function and limit the stimulus to the inflammatory response. The experimental evidence supporting this has not been confirmed in clinical practice and there is no evidence that the mode of feeding alters disease progression. Other approaches Previous randomized studies have failed to provide sufficient evi- dence to recommend the use of antiproteases, antisecretory, anti-inflammatory agents, or antioxidant therapy in patients with acute pancreatitis. There is therefore no proven pharmacological therapy for the treatment of acute pancreatitis. Intervention for postacute pancreatitis fluid and necrotic collections The definitions surrounding acute fluid-predominant and acute nec- rotic collections have been detailed previously in Table 15.26.1.2. Due to the complexity and diversity of an individual patient's clinical course, it is challenging to define specific triggers for intervention. Delayed intervention where possible, along with planned minim- ally invasive sepsis control, has become key to management in most pancreatic units. There is no role for early (week 1) intervention unless vascular complications are suspected. Intervention is most commonly required for suspected or proven sepsis of acute necrotic collections or walled-off necrosis after resolution of the initial in- flammatory phase. Optimal management may involve a number or combination of techniques and require discussion with a specialist regional pancreatic centre. The indication for early (<6 weeks) intervention is for the con- trol of proven or suspected sepsis. Secondary clinical or biochemical deterioration after the initial period of organ compromise should lead to a full bacteriological septic screen and contrast-enhanced CT scan. Gas within an acute necrotic collection or walled-off necrosis are indicative of bacteriological contamination but may result from spontaneous fistulation into the intestine (particularly where there is an air–fluid level). In general, fistulation into the foregut may be associated with clinical improvement despite CT appearances, while Table 15.26.1.2 Local complications in acute pancreatitis (2012 Revised Atlanta Classification) Timescale Necrosis absent Necrosis present <4 weeks Acute peripancreatic fluid collection (peripancreatic fluid associated with interstitial oedematous pancreatitis with no associated peripancreatic necrosis) Acute necrotic collection (a collection containing variable amounts of both fluid and necrosis; the necrosis can involve the pancreatic parenchyma or the extrapancreatic tissues)

> 4 weeks Pancreatic pseudocyst (an encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis) Walled-off necrosis (a mature, encapsulated collection of pancreatic or extrapancreatic necrosis that has developed a well-defined inflammatory wall) Infection Each collection type may be sterile or infected

15.26.1 Acute pancreatitis 3215 hindgut fistulation often results in clinical deterioration mandating intervention. Smaller gas bubbles are more commonly associated with bacterial translocation and require drainage by one of the methods described in the following subsections if clinically indicated (Fig. 15.26.1.2). Sepsis associated with acute necrotic collections or early walled-off necrosis Initial walled-off necrosis The trend in the last 20 years has been towards minimizing the magnitude of any intervention while achieving adequate sepsis control. Initially most methods were aimed at mirroring the open surgical debridement techniques to achieve clearance of any necrotic ma- terial as this was felt to be key to recovery, but the importance of sepsis control over removal of necrosis has increasingly been rec- ognized. This was perhaps the most significant finding within the PANTER trial from the Dutch Pancreatitis Study Group, which not only provided randomized data regarding the management of infected pancreatic necrosis, but also demonstrated that a third of patients (35% within PANTER) with pancreatic or peripancreatic necrosis may resolve completely with simple percutaneous drainage. In this trial, patients requiring surgical intervention for pancreatic necrosis were randomized to either primary open necrosectomy or a ‘step-up’ approach based on percutaneous drainage as the initial intervention, with progression to retroperitoneal debridement with lavage if no improvement was observed. There is now a consensus advocating a principle of early organ support, nutritional optimiza- tion, followed ideally by delayed and selective minimally invasive intervention if required. More recently the role of endoscopic (EUS) transmural cysto gastrostomy in the management of postacute walled-off collections has emerged as an alternative to percutaneous or surgical drainage. The choice between initial percutaneous or endoscopic drainage is determined by several factors including (1) the anatomy of the disease, for example, the position of the collection relative to the stomach, colon, liver, spleen, and kidney; (2) patient physiology, as the ability to perform EUS-guided puncture within an intensive therapy unit setting, without the need for patient transfer to the radiology department for CT-guided drainage, may influence the management decision where a patient is in extremis, and unstable to transfer; and (3) institutional capabilities. Secondary intervention The ‘step-up’ concept is based on staged sepsis control as a bridge to surgery or as definitive treatment in some patients. The require- ment for secondary intervention usually arises from blockage of the percutaneous drain, or cystogastrostomy with solid necrotic ma- terial. Simple replacement, upsizing, or insertion of multiple drains has been proposed rather than embarking on one of the secondary intervention techniques described in ‘Particular interventional techniques’. The Dutch Pancreatitis Study Group compared the success of fur- ther upsizing of percutaneous drainage versus retroperitoneal debridement as the initial enhanced step-up procedure if immediate resolution did not occur and showed that more that 50% of patients in the dilatation-alone group settled without formal necrosectomy. Drawbacks included limited ability to remove necrotic debris, pro- longed hospitalization, and the need for multiple procedures. The use of grasping forceps to extract the debris after sequential tract dilatation has been described in a small series, as has the use of assist devices such as stone retrieval baskets, but these techniques are seldom performed in clinical practice. Probably more important than the method of drainage, a dedicated team of surgeons/radi- ologists prepared to proactively address any undrained sepsis is critical for successful percutaneous management of necrotizing pancreatitis. Particular interventional techniques The open lateral approach initially described in the 1980s utilized a loin/subcostal and retrocolic approach to allow debridement of pan- creatic and peripancreatic necrosis. This open approach was associ- ated with major morbidity (enteric fistula 45%, haemorrhage 40%, and colonic necrosis 15%), and failed to gain popularity. Minimally invasive pancreatic necrosectomy For percutaneous necrosectomy, the catheter is exchanged for a radiological guidewire and then a

low-compliance balloon dilator is inserted into the collection and dilated to 34 FG. Access to the cavity is maintained by an Amplatz sheath through which is passed an operating necroscope to allow debridement under direct vision. The necroscope has an operating channel that permits standard (5-mm) laparoscopic graspers as well as an irrigation/suction channel. The directed, high-flow lavage promotes rapid evacu- ation of pus and liquefied necrotic material, revealing black or grey devascularized pancreatic tissue and peripancreatic fat, which if loose is extracted in a piecemeal fashion until, after several pro- cedures, a cavity lined by viable tissue or granulating pancreas is created. At the end of each procedure an 8 FG catheter sutured to a 24 FG drain is passed into the cavity (Fig. 15.26.1.3a) to allow con- tinuous postoperative lavage of warmed fluid, initially at 250 ml/h. Subsequent conversion of the lavage system to simple drainage may be all that is required prior to recovery, or the procedure may be repeated until sepsis control is achieved and interval CT confirms resolution. Video-assisted retroperitoneal debridement A video-assisted retroperitoneal debridement (VARD) procedure is performed with the patient placed in a supine position with the left side 30 to 40° elevated. A subcostal incision of 5 cm is placed in the
Fig. 15.26.1.2 An acute necrotic collection after 17 days illustrating small gas bubbles, managed initially by EUS-guided cystogastrostomy within a step-up framework.

 left flank at the midaxillary line, close to the exit point of the percu- taneous drain. Using the in situ percutaneous drain as a guide, the retroperitoneal collection is entered. The cavity is cleared of puru- lent material using a standard suction device. Visible necrosis is carefully removed with the use of long grasping forceps, and deeper access under direct vision is facilitated using a 0° laparoscope, and further debridement performed with laparoscopic forceps. As with a percutaneous necrosectomy, sepsis control rather than complete necrosectomy is the aim of this procedure and only loosely adherent pieces of necrosis are removed, minimizing the risk of haemorrhage. Two large-bore single-lumen drains are positioned in the cavity and the fascia closed to facilitate a closed continuous postoperative lavage system. Endoscopic necrosectomy Endoscopic cystogastrostomy was initially reported for the man-agement of a mature pancreatic abscess with minimal necrosis, but the technique has evolved in the last 10 years to become an estab- lished procedure, with endoscopic transmural exploration and de- bridement of the retroperitoneum. Single-step drainage under EUS guidance may be carried out by either a transgastric or (less com- monly) a transduodenal route and is preferred to ‘blind’ drainage as EUS allows for identification of the collection where there is no ob- vious bulge seen within the stomach and helps identify a safe route for puncture, free from intervening vessels (Fig. 15.26.1.3b). The presence of significant walled-off necrosis is no longer considered a contraindication, but concerns do remain regarding the adequacy of endoscopic drainage, particularly in solid predominant or larger collections. The major limitation of this technique is that instru- ments have yet to be developed to facilitate the adequate removal of loose solid material from the cavity when this is compromising drainage through the cystogastrostomy. Where there is extensive necrosis, delayed endoscopic necro sectomy may be required. It is the chapter authors’ practice to defer this for a week following the initial drainage procedure to allow the fluid component to drain and any associated sepsis to improve. A re- cent systematic review of 14 studies including 455 patients found an overall success rate of 81% and mortality of 6%, but these studies are in highly selected patients and all but one was retrospective. One small randomized trial compared endoscopic with surgical drainage and found a reduction in significant complications with the endoscopic approach. Endoscopic necrosectomy is, however, a challenging pro- cedure and not without risk. Major complications including fatal air embolism, bleeding, and perforation

occurred in 26% of patients in the multicentre GEPARD study. The use of carbon dioxide insufflation is therefore now recommended. A persistent problem is the lack of availability of suitable endoscopic devices to achieve necrosectomy, and although endoscopic access to the cyst cavity is now facilitated by metallic stents, piecemeal necrosectomy using standard graspers, baskets, and snares is a time-consuming and painstaking process. One possible modification is the use of intracavity hydrogen peroxide to facilitate necrosectomy, but further experience is required before this can be recommended for routine practice. An early randomized pilot study exploring the outcome of endo- scopic transmural drainage versus minimally invasive intervention (VARD) (the PENGUIN trial) suggested at least equivalence, if not benefit, from endoscopic drainage. This study has been criticized due to very small numbers and an excessive mortality (40%), com- pared to historical results, within the VARD arm. The TENSION trial demonstrated that the endoscopic step-up approach was not superior to the surgical step-up approach in reducing major compli- cations or death. The rate of pancreatic fistulas and length of hospital stay were lower in the endoscopy group and many now favour endo- scopic drainage as the index intervention. Open surgical necrosectomy Worldwide, open necrosectomy is still commonly employed, but increasingly is being superseded by the procedures previously de- scribed, or performed within a ‘step-up’ format after initial percutan- eous drainage has produced sepsis control. Three general variations of open necrosectomy are currently practised; although the proced- ures are broadly similar in terms of the necrosectomy, they differ in terms of how they prevent recurrence of an infected collection within the debridement cavity: (1) open necrosectomy with open or closed packing, (2) open necrosectomy with continuous closed postoperative lavage, and (3) programmed open necrosectomy. (a) (b) Fig. 15.26.1.3 Initial ‘step-up’ drainage using (a) minimally invasive retroperitoneal pancreatectomy percutaneous lavage drain and (b) EUS-guided transgastric cystogastrostomy with a self-expanding metal stent.

 Management of late collections A significant proportion of patients with postacute collections do not develop sepsis-related complication in the early phase, allowing the collection to organize and mature. Failure to thrive, persistent discomfort, and nutritional failure are the common indications for late intervention for walled-off necrosis. Nutritional intake may be limited by a combination of early satiety and postprandial pain. The extent of actual necrosis, as opposed to reduced enhancement of the parenchyma on contrast-enhanced CT, often results in an overesti- mation of the extent of necrosis. Spontaneous resolution of even large collections is not infrequent, hence continued nonintervention is often the best approach, particularly where ongoing maturation of a collection may be anticipated and where the clinical picture is improving. In any individual case, the choice of intervention may be guided by factors including the clinical picture, the position of the collection in relation to the stomach and duodenum, and available expertise. Laparoscopic cystogastrostomy For many years, the conventional approach to the management of late walled-off pancreatic necrosis was open pancreatic cystogastrostomy with necrosectomy. This procedure can now be safely and effectively carried out using a laparoscopic approach, which has the potential advantage of allowing a one-stage removal of any solid component and may also be combined with a cholecystectomy if appropriate. Endoscopic ultrasonography-guided cystogastrostomy/necrosectomy Many reports in the literature describe EUS-guided drainage of ‘pseudocysts’, but it is now recognized that true pancreatic pseudocysts are rare following acute pancreatitis as some degree of necrosis is usually present where collections persist. The revised Atlanta criteria define these collections as walled-off necrosis, but there is still a spectrum of clinical presentations. EUS-guided drainage of these collections is now an established technique in

specialist units and several different modifications to the technique have been described. The frequent requirement for repeated endo- scopic procedures, particularly in the presence of significant ne- crosis, have led to a former preference to select fluid-predominant walled-off necrosis collections for this approach, but this assump- tion is being currently challenged within a randomized trial in the chapter authors’ unit. (a) (c) (b) Fig. 15.26.1.4 Examples of complications following acute pancreatitis. (a) Haemorrhage from the splenic artery into a retroperitoneal collection. (b) Acute necrotic collection with fistulation into the colon. (c) Portal vein thrombosis and cavernous malformation.

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