New insights into acute pancreatitis

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Abstract | The incidence of acute pancreatitis continues to increase worldwide, and it is one of the most common gastrointestinal causes for hospital admission in the USA. In the past decade, substantial advancements have been made in our understanding of the pathophysiological mechanisms of acute pancreatitis. Studies have elucidated mechanisms of calcium-mediated acinar cell injury and death and the importance of store-operated calcium entry channels and mitochondrial permeability transition pores. The cytoprotective role of the unfolded protein response and autophagy in preventing sustained endoplasmic reticulum stress, apoptosis and necrosis has also been characterized, as has the central role of unsaturated fatty acids in causing pancreatic organ failure. Characterization of these pathways has led to the identification of potential molecular targets for future therapeutic trials. At the patient level, two classification systems have been developed to classify the severity of acute pancreatitis into prognostically meaningful groups, and several landmark clinical trials have informed management strategies in areas of nutritional support and interventions for infected pancreatic necrosis that have resulted in important changes to acute pancreatitis management paradigms. In this Review, we provide a summary of recent advances in acute pancreatitis with a special emphasis on pathophysiological mechanisms and clinical management of the disorder.

Mitochondrial permeability transition pores
Proteins located in the inner membrane of the mitochondrion, which when open can cause rapid mitochondrial depolarization and dysfunction.

Calcium release-activated channels
Calcium ion channels that are activated when calcium stores are depleted from the endoplasmic reticulum.

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https://doi.org/10.1038/s41575-019-0158-2

Acute pancreatitis is an inflammatory disorder of the pancreas that is associated with substantial morbidity and mortality. Well-known causes of acute pancreatitis such as pancreatic ductal obstruction secondary to gallstones (the most common cause), alcohol, endoscopic retrograde cholangiopancreatography (ERCP) and various drugs trigger pathological cellular pathways and organelle dysfunction that culminate in the hallmarks of acute pancreatitis — acinar cell death and local and systemic inflammation[1–3]. The global incidence of acute pancreatitis is 34 affected individuals per 100,000 person-years, and it has been increasing worldwide[4]. Acute pancreatitis is currently one of the most common gastrointestinal disorders to cause hospitalization in the USA and costs the health-care system $9.3 billion annually[5–7]. The worldwide obesity epidemic might also contribute to the increasing global incidence of acute pancreatitis[8]. Several complications of obesity that are rising in incidence, including cholelithiasis, hypertriglyceridaemia and diabetes, are independently associated with acute pancreatitis[9,10].

Acute pancreatitis-related mortality has decreased over the past decade from 1.6% to 0.8%[11]. This trend is probably due to improvements in timely and accurate diagnoses, as well as in the care of critically ill patients with acute pancreatitis. However, morbidity and long-term sequelae remain substantial[12–14]. For example, up to 40% of patients develop new-onset prediabetes or diabetes after their first episode of acute pancreatitis, and a quarter of all patients with acute pancreatitis develop exocrine pancreatic insufficiency[15,16]. Necrotizing pancreatitis represents the most severe form of parenchymal injury in acute pancreatitis, and it occurs in 5–10% of patients[3]. In the USA, one in two patients with necrotizing pancreatitis files for disability within a year, and quality of life after acute pancreatitis is generally reported to be markedly reduced[12,14]. Additionally, ~18% of those with acute pancreatitis experience recurrence, and 8% develop chronic pancreatitis, both of which lead to additional financial burden on the health-care system[17,18]. The annual health-care cost attributable to readmissions owing to acute pancreatitis exceeded $3.8 billion in 2013 in the USA[6].

Despite the global burden of disease, currently, no effective therapeutic agents exist to treat or prevent acute pancreatitis. Nevertheless, important basic science advances have been made to identify new cellular targets for potential drug development. For example, elucidation of calcium signalling pathways in acute pancreatitis led to the discovery of mitochondrial permeability transition pores and calcium release-activated channels[19–21], both of which hold promise as therapeutic targets. Recognition of mitochondrial dysfunction as a key driver of acute pancreatitis culminated in a multicentre trial examining the effect of early high-energy enteral nutrition on outcomes, which is currently ongoing[22]. The

Key points

- The incidence of acute pancreatitis is 34 per 100,000 people in the general population, and it is rising worldwide.
- In addition to premature trypsinogen activation, dysfunctional calcium signalling, impaired autophagy, endoplasmic reticulum stress, the unfolded protein response and mitochondrial dysfunction are key cellular processes in the pathogenesis of acute pancreatitis.
- Well-designed, adequately powered trials are needed to define and examine the efficacy of aggressive fluid resuscitation.
- Infected walled-off pancreatic necrosis should be managed with an endoscopic step-up strategy.
- Diabetes and exocrine pancreatic insufficiency are common complications after an episode of acute pancreatitis, occurring in up to one in five patients following acute pancreatitis.
- Acute pancreatitis impairs long-term quality of life, and many patients experience repeated hospitalizations.

mechanism of obesity-mediated pancreatitis severity has also been elucidated[9]. Free fatty acids appear to mediate end-organ failure and have been shown to be released from the lipolysis of triglycerides stored in the intrapancreatic and peripancreatic adipose tissue[23–25]. Clinically, several landmark trials have addressed key management questions in acute pancreatitis, including the timing and mode of nutrition, timing of cholecystectomy in gallstone-related acute pancreatitis and management of infected necrosis. In this Review, we describe important advancements made in our understanding of the mechanisms of acute pancreatitis and highlight important potential therapeutic targets. Additionally, informed by the latest evidence, we discuss current management of acute pancreatitis.

Diagnosis and nomenclature

Diagnostic criteria

Diagnosis of acute pancreatitis is made when two of the three following criteria are met: typical abdominal pain; serum amylase and/or lipase elevation more than three times the upper limit of normal; and imaging findings consistent with acute pancreatitis.

No standardized reference range exists for serum amylase or lipase levels owing to different laboratory techniques in measuring these enzymes. The upper limit of normal ranges between 100 and 300 U/l for amylase and 50 and 160 U/l for lipase. The limitations of serum amylase and lipase as diagnostic tests for acute pancreatitis deserve mention. Amylase levels can be normal in patients with alcoholic or hypertriglyceridaemic pancreatitis; therefore, diagnosis might be challenging in these populations[26,27]. Furthermore, bowel perforation, infarction, obstruction and abdominal aortic aneurysm can also increase amylase levels. Similarly, lipase can be elevated in acute intestinal pathologies, cholecystitis, peptic ulcer disease and biliary obstruction[27]. Thus, imaging modalities complement diagnostic work-up for acute pancreatitis when diagnosis is in doubt. These diagnostic criteria are agreed upon by all published guidelines for acute pancreatitis[27–30]. Aetiologies of acute pancreatitis are shown in TABLE 1.

CT of the abdomen is the most commonly used imaging modality to diagnose acute pancreatitis. Findings can range from gland oedema and peripancreatic fat stranding (that is, hazy interface between the pancreatic parenchyma and surrounding fat on a CT scan; interstitial pancreatitis) to lack of contrast enhancement in the parenchyma (necrotizing pancreatitis) and peripancreatic fluid collections. A contrast-enhanced CT scan is required to diagnose necrotizing pancreatitis, and necrosis might not develop until 72 hours after symptom onset. For this reason, obtaining a CT scan within 72 hours of symptom onset is discouraged by published guidelines including those of the American College of Gastroenterology and American Gastroenterology Association[3,27,28,30].

Nomenclature for local complications

Local complications mainly refer to collections that can form in and/or around the pancreas. The nomenclature for these complications, which are broadly labelled pancreatic fluid collections, has been updated by the revised Atlanta classification in 2013 (REF.[3]). Collections that consist purely of fluid with minimal or no solid debris are called acute fluid collections. Collections that contain necrotic debris from pancreatic and/or peripancreatic necrosis are defined as acute necrotic collections. The terms pseudocyst and walled-off pancreatic necrosis (WOPN) are used when these collections persist for 4 weeks or longer and become organized and encapsulated, respectively. This nomenclature aims to simplify and unify the definitions of local pancreatic complications, with each term carrying distinct implications for management[3].

Pathophysiology

Cellular events central to the pathogenesis of acute pancreatitis include pathological calcium signalling[2,20,31,32], mitochondrial dysfunction[19,33,34], premature trypsinogen activation within the acinar cells and macrophages[35–41], endoplasmic reticulum (ER) stress, impaired unfolded protein response (UPR)[33,42–44] and impaired autophagy[33,45]. These events are triggered by common acinar cell toxins, such as alcohol, nicotine and bile acids. Intraductal events, such as increased pressure caused by ductal obstruction, luminal acidification and ductal cell exposure to bile acid, can also indirectly trigger these events. The crosstalk between acinar cells and the immune system perpetuates an inflammatory response[46–48]. At a locoregional level, the mediatory role of intrapancreatic and peripancreatic fat saponification and ischaemia-conditioned mesenteric lymph in acute pancreatitis severity has been recognized[23,24,49–52]. Characterization of these mechanisms has enabled identification of several potential therapeutic targets for future drug studies in acute pancreatitis (TABLE 2).

Animal models

Owing to the practical challenges of obtaining human pancreatic tissue during an acute pancreatitis episode, all the early cellular events during acute pancreatitis have been investigated using animal models[53]. Animal models help identify pathophysiological mechanisms to develop and test therapeutic agents. The choice of model type is determined by the pathophysiological

Local complications
A collective term to denote collections that form within and/or around pancreatic parenchyma as a result of acute pancreatitis.

Unfolded protein response
(UPR). A collective term to denote a set of compensatory cellular responses to endoplasmic reticulum stress

Autophagy
An orderly mechanism that processes, degrades and recycles various unwanted cellular components.

Table 1 | **Common and uncommon aetiologies of acute pancreatitis**

Aetiology	Examples	Suggestive clinical data
Gallstone	NA	Choledocholithiasis; ALT over three times the upper limit of normal, which is variable in different laboratories; cholelithiasis when other causes have been ruled out
Alcohol	NA	Drinking history >35 standard drinks per week for >5 years
Trauma	• ERCP • EUS with FNA • Aortic surgery • Pancreatic resection	Pancreatitis following one of the listed procedures
Pre-malignant and malignant conditions	• Intraductal papillary mucinous neoplasm • Ductal adenocarcinoma	• Pre-existing cyst with recurrent idiopathic episodes; dilated pancreatic duct in a patient without prior history of chronic pancreatitis • Mass with duct dilatation; weight loss; diabetes diagnosis
Metabolic	• Hypertriglyceridaemia[272] • Hypercalcaemia	• Triglyceride level >1,000 mg/dl • Elevated calcium level when no other cause is apparent
Genetic	*PRSS1*, *SPINK1*, *CFTR*, *CASR*, *CTRC*	First-degree family history of pancreatitis or pancreatic cancer; pancreatitis onset <30 years of age
Autoimmune pancreatitis	NA	Diagnostic criteria have been published elsewhere[272]
Drugs	Mesalamine, furosemide, azothioprine, losartan	When all other causes are ruled out, if the patient is on a class I drug[273] and a temporal relationship between exposure and acute pancreatitis is feasible
Infections	Viral, bacterial and parasitic	When pancreatitis occurs in the context of other clinical features of the infection
Idiopathic	NA	When all causes have been ruled out

ALT, alanine aminotransferase; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; NA, not applicable.

mechanism of interest as well as the disease phase of interest. Currently, owing to low-cost and available strains with genetic deletions, mice are the most widely utilized species[53].

The cerulein-induced pancreatitis model in rodents is commonly used to investigate early cellular events during acute pancreatitis. This model helped characterize the processes of impaired autophagy, pathological calcium signalling and ER stress, which are central to the pathogenesis of acute pancreatitis[21,33,44,54]. In this model, acute pancreatitis is induced by administering supraphysiological doses of cerulein (a cholecystokinin analogue) at repeated intervals. The effects of cerulein on the pancreas are dose-dependent. At a high dose, it causes acinar cells to release digestive enzymes. At a supramaximal dose, it inhibits enzyme release and causes premature digestive enzyme activation[55]. Cerulein-induced pancreatitis models are popular owing to their low cost and high reproducibility. Severe acute pancreatitis can be studied by modifying the cerulein administration protocol to increase acute pancreatitis severity. The disadvantages of this model include a clinically irrelevant initiating mechanism (an excessive cholinergic stimulus is analogous only to scorpion venom toxicity in humans) and a different distribution of parenchymal injury to that seen in humans (diffuse in rodents versus patchy in humans)[53,56].

Alcohol and lipopolysaccharide can be administered in rodents to simulate a model relevant to alcohol-related pancreatitis. This model was used to ascertain mechanisms of alcohol-induced changes in acinar cell lipid metabolism and subsequent acinar cell injury[57,58], but it is primarily used to study chronic pancreatitis. Some investigators utilize models that involve pancreatic duct manipulation to study intraductal events and their association with acute pancreatitis initiation[59,60]. American opossums have been used to elucidate the pathophysiological mechanism of gallstone-associated pancreatitis because of the similarity of their pancreaticobiliary ductal anatomy to that of humans[61,62]. Studies using this model revealed the importance of pancreatic ductal obstruction as the central initiator of gallstone acute pancreatitis. However, opossums cannot be bred in the laboratory, and there is also a high intra-animal variability, limiting its popularity as a model[63,64].

Ductal cannulation and infusion methods are used to study the pathophysiology of post-ERCP pancreatitis and gallstone pancreatitis in rodents and guinea pigs[59]. The drawbacks of these models include the need for surgery and anaesthesia. Although animal-based experimental models have improved our understanding of the pathogenesis of acute pancreatitis, obvious differences exist between human and rodent pancreatitis; therefore, the extrapolation of findings from animal studies to human pancreatitis should be done cautiously considering these limitations[53]. Encouragingly, several ex vivo human studies showed that many of the mechanisms identified in the animal studies are applicable to human pancreatitis models[1,65]. For example, when acinar cell responses to a muscarinic agonist and bile acids were examined in human acini extracted from cadaveric pancreata, trypsinogen activation, ER stress, dysfunctional autophagy and mitochondrial dysfunction were identified, similar to the responses seen in animal models[1].

Updates on cellular mechanisms

Calcium signalling. Pathological elevation of Ca^{2+} concentration in acinar cells is a central event in acute pancreatitis that mediates pro-cell death and pro-inflammatory pathways such as premature trypsinogen activation, activation of nuclear factor-κB (NF-κB) and mitochondrial dysfunction[48,66,67] (FIG. 1). In a physiological state, Ca^{2+} is released from the ER as part of a signalling mechanism that initiates zymogen exocytosis and stimulates production of ATP in the mitochondria[21]. However, the increase in cytosolic Ca^{2+} concentration is only transient, as two ATP-dependent calcium channels rapidly clear the cytosolic calcium: the smooth ER Ca^{2+} channels (SERCAs) move Ca^{2+} back into the ER, and the plasma membrane Ca^{2+} channels (PMCAs) exude Ca^{2+} out of the cell[21]. Alcohol and bile acids can disrupt this homeostasis and cause a global, sustained pathological cytosolic Ca^{2+} elevation through the inositol 1,4,5-trisphosphate receptor ($Ins(1,4,5)P_3R$) signalling pathway. For example, palmitoleic acid ethyl

ER stress
A state in which the demand of cellular machinery overwhelms the capacity of the endoplasmic reticulum (ER), leading to accumulation of misfolded proteins.

Cholecystokinin
A hormone that causes gallbladder contraction and pancreatic enzyme secretion.

Nuclear factor-κB
(NF-κB). A transcription factor that can cause production of pro-inflammatory cytokines and chemokines.

Inositol 1,4,5-trisphosphate receptor
($Ins(1,4,5,)P_3R$). A glycoprotein complex located in the endoplasmic reticulum that can operate as a calcium channel.

Table 2 | **Potential therapeutic targets and target pathways in acute pancreatitis**

Agent	Target	Target pathway	Status
GSK-7975A	ORAI1	Store-operated calcium entry channel; calcium signalling pathway	Preclinical[20,31]
CM4620	Calcium release-activated calcium channel	Store-operated calcium entry channel; calcium signalling pathway	Phase II[274]
TRO40303	Mitochondrial permeability transition pore	Mitochondrial dysfunction	Preclinical[19]
Disaccharide trehalose	Unknown	Autophagy	Preclinical[33]
HMG-CoA inhibitors	HMG-CoA	Unfolded protein response	Commercially available; clinical trial in progress[97]
Lactated Ringer's solution	G_i protein-coupled receptor 81	NLRP3 inflammasome pathway; binds free fatty acid	Pilot clinical trial completed[133,138,195]
Pentoxifylline	Synthesis of TNF	Phosphodiesterase; inflammatory response	Pilot clinical trial in progress[144]
Orlistat	Unsaturated free fatty acids	Hydrolysis of triglycerides to free fatty acids; lipotoxicity	Commercially available; no trials conducted
Tocilizumab	IL-6	Inhibition of IL-6 receptor; inflammatory response	Preclinical in acute pancreatitis in progress; successful clinical trials in other diseases[145,147,275]

HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; NLRP3, LRR- and pyrin domain-containing 3; ORAI1, calcium release-activated calcium channel protein 1.

ester is a non-oxidative, metabolic product of alcohol by the acinar cells that open Ins(1,4,5)P_3Rs, which are Ca^{2+} channels located in the ER[21]. This pathway results in excessive Ca^{2+} release from the major intracellular Ca^{2+} store, the ER lumen[20,31,66,68]. Ca^{2+} concentration build-up causes calcium release-activated calcium channel protein 1 (ORAI1) to promote Ca^{2+} entry into the cell from the outside, further increasing and sustaining a toxic cellular Ca^{2+} concentration[2,69]. Ductal obstruction, which can occur in post-ERCP pancreatitis and gallstone pancreatitis, is thought to cause an increase in Ca^{2+} entry from outside the cell through PIEZO1 — a plasma membrane mechanoreceptor that has cation channel properties and is activated by pressure[70].

The cellular Ca^{2+} concentration overload causes the mitochondrial permeability transition pores to open in a high-conductance state, and this process results in the loss of the membrane potential needed to generate ATP[34,67,71]. ATP depletion perpetuates the toxic Ca^{2+} concentration by disrupting the ATP-dependent SERCAs and PMCAs from clearing excessive cytosolic calcium and impairs cytoprotective mechanisms that need ATP such as autophagy and the UPR[21,33]. Thus, the mitochondrial dysfunction secondary to cellular calcium toxicity ultimately leads to acinar cell necrosis.

On the basis of the central importance of Ca^{2+} concentration toxicity, ORAI1 channel inhibitors that prevent calcium entry into the acinar cells have been developed[20,31]. ORAI1 inhibitors have been shown to prevent necrosis in animal models of acute pancreatitis and human acinar cells, reducing both the local and systemic extent of injury[20]. Preventing ATP depletion through inhibition of mitochondrial permeability transition pore opening with 3,5-seco-4-nor-cholestan-5-one oxime-3-ol (TRO40303) also has therapeutic potential. TRO40303 prevented membrane potential loss and necrosis in alcohol-related acute pancreatitis animal models and human acinar cells[19,34]. TRO40303 has been found to be safe and well-tolerated by patients when tested in patients with acute myocardial infarction undergoing intervention. Thus, it could be efficiently examined in patients with acute pancreatitis[72,73]. The benefits of ATP replenishment through high-calorie nutrition supplementation are also being explored in a multicentre trial of acute pancreatitis[22].

Premature trypsinogen activation. Premature trypsinogen activation is another important pathological cellular event that can lead to acinar cell necrosis. Various pancreas insults (for example, trauma, pancreatic ductal obstruction and alcohol) can initiate fusion of the lysosome with the zymogens within the acinar cells, a process called colocalization[37,40] (FIG. 2). Colocalization occurs in the context of other toxin-provoked intra-acinar cell events, such as decreased exocytosis of protease-containing zymogen granules secondary to cytoskeletal dysfunction and increased synthesis of lysosomal and digestive enzymes[74]. Once the zymogen granule fuses with the lysosome, cathepsin B, a key lysosomal enzyme, activates trypsinogen to trypsin[40]. The mechanism of trypsin and cathepsin B release from the vacuoles remains elusive. Some have suggested that trypsin causes membrane fragility leading to leaky endocytic vacuoles that release trypsin and cathepsin B[36]. Other studies have suggested that vacuoles might rupture against the cytoskeleton and/or organelles[37]. Lysosomal and zymogen granule membranes can also become fragile from the metabolic products of alcohol and the loss of membrane-stabilizing glycoprotein 2, respectively[75,76].

Once released, trypsin causes autodigestion within and outside the acinar cells, and cathepsin B release causes necroptosis, a regulated form of necrosis[36,77]. Necroptosis is mediated via the receptor-interacting protein kinase (RIP), including RIP1–RIP3, and mixed lineage kinase

Zymogen granules
Vesicles that contain various pancreatic enzyme precursors.

Cathepsin B
A lysosomal protease.

Necroptosis
A regulated form of cell death.

Receptor-interacting protein kinase
(RIP). A type of protein kinase that is implicated in regulation of cell death.

domain-like (MLKL) pathway[78,79], in which MLKL is phosphorylated by RIP3, leading to its oligomerization. MLKL oligomers then translocate to the plasma membrane and ultimately cause plasma membrane puncture, resulting in spillage of cellular contents and necroptosis[80]. Inhibition of the RIP1–RIP3 pathway by genetic modulation or necrostatin (an inhibitor of RIP1) decreases severity of acinar cell injury and therefore represents a potential target for acute pancreatitis therapy[77,80]. Intracytosolic protease activation also causes lysosomal membrane disruption, and this process leads to activation of caspase 3 through mitochondrial release of cytochrome *c*[78]. Caspase 3 subsequently mediates apoptosis. Macrophages are among the first immune cells to respond to the chemoattractants released by damaged acinar cells during pancreatitis. Interestingly, trypsinogen activation also occurs within macrophages in response to pancreatitis and results in macrophages becoming pro-inflammatory[41]. This finding challenges the long-held notion that premature trypsinogen activation occurs exclusively within the acinar cells.

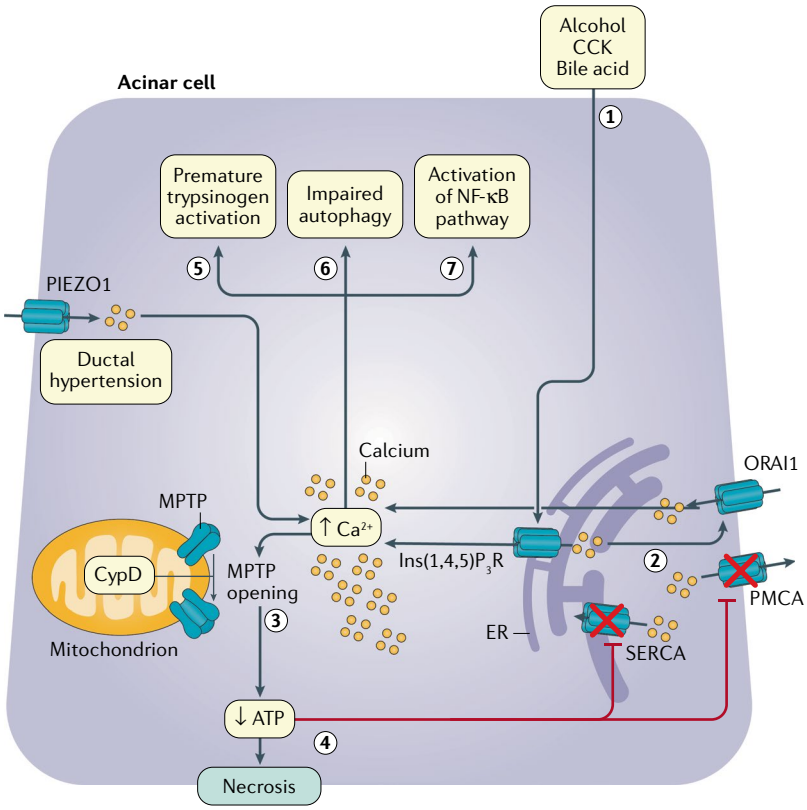

Fig. 1 | **Calcium-mediated mitochondrial dysfunction and cell death in acute pancreatitis.** In acinar cells, alcohol, cholecystokinin (CCK) and bile acid cause inositol 1,4,5-trisphosphate receptor ($Ins(1,4,5)P_3R$)-mediated calcium release from the endoplasmic reticulum (ER) (1). The resulting low calcium concentration in the ER triggers opening of calcium release-activated calcium channel protein 1 (ORAI1), through which calcium enters the cell from the extracellular space (2). This results in pathological global calcium concentration elevation. Calcium elevation results in opening of mitochondrial permeability transition pores (MPTPs) to a high-conductance state, and loss of membrane potential across the mitochondrial membrane ensues (3). This process results in mitochondrial dysfunction and necrosis. Mitochondrial dysfunction leads to ATP depletion, which impairs ATP-dependent mechanisms to reduce cytosolic calcium (4). This process then accentuates and perpetuates the pathological calcium toxicity. Pathological calcium elevation also causes other cytotoxic pathways (5), including premature trypsinogen activation, autophagy impairment (6) and activation of the nuclear factor-κB (NF-κB) pathway (7). The NF-κB pathway leads to production of pro-inflammatory mediators. The PIEZO1 mechanoreceptor, which contains cation channel properties and is activated by pressure, also promotes increased calcium entry from outside the acinar cell (8). CypD, cyclophilin D; PMCA: plasma membrane Ca^{2+} channel; SERCA, smooth ER Ca^{2+} channel.

Autophagy, endoplasmic reticulum stress and the unfolded protein response. Pathogenesis of acute pancreatitis is also driven by impaired cytoprotective mechanisms, such as autophagy and the UPR. Macroautophagy is a cytoprotective mechanism that processes and recycles various cytoplasmic contents, which are aged, defective or damaged[45]. Selective macro-autophagy refers to processing and recycling of specific damaged organelles and misfolded proteins. Acinar cells are highly efficient in producing proteins. Thus, the protein processing and transporting machinery and the mechanism of unimpaired autophagy are critical to the survival of acinar cells. Autophagy is completed through a series of steps that start with the enucleation of cytosolic contents within an open double membrane formed from the ER, Golgi apparatus and plasma membrane[54] (FIG. 3). The double membrane edges meet to form an autophagosome; this step is mediated by autophagy-related proteins (ATGs). Fusion of the autophagosome with the lysosome and degradation of the enclosed contents are the final steps[33,45]. Genetic knockout of ATG5, ATG7 and lysosome-associated membrane proteins has resulted in pancreatitis with extensive inflammation in mouse models of acute pancreatitis[45,81,82]. Additionally, impaired autophagy results in trypsinogen activation, ER stress and mitochondrial dysfunction, and as a result, acinar cells become more susceptible to other insults and death[33,43,78,83,84]. Thus, restoration of efficient macro-autophagy in the acinar cell seems to be an attractive therapeutic target. The disaccharide trehalose, which increases the efficiency of autophagy, reduces pancreatic injury and acute pancreatitis severity in animal models and holds promise as a potential therapeutic agent in acute pancreatitis[33]. However, the mechanism by which trehalose induces autophagy has not been established[85].

ER stress refers to the accumulation of misfolded and/or unfolded proteins within the ER lumen. It occurs when the capacity of the ER to efficiently process and eliminate proteins is overwhelmed[86]. When ER stress devastates the protective cellular responses, apoptosis ensues[87]. Given the heavy protein production of acinar cells, the pancreas is particularly vulnerable to ER stress, which occurs frequently in acinar cells in acute pancreatitis[33,43,83,88]. Common pancreas toxins (for example, alcohol and its metabolites) cause ER stress by both increasing the demand for the production of proteins such as trypsinogen, chymotrypsinogen, lipase and lysosomal enzyme cathepsin B and reducing the cellular ability to process and recycle unwanted proteins (that is, dysfunctional autophagy and mitochondrial dysfunction)[33,43]. During ER stress, acinar cells activate the UPR to restore cellular homeostasis. The UPR alleviates ER stress by upregulating the ER degradation machinery for

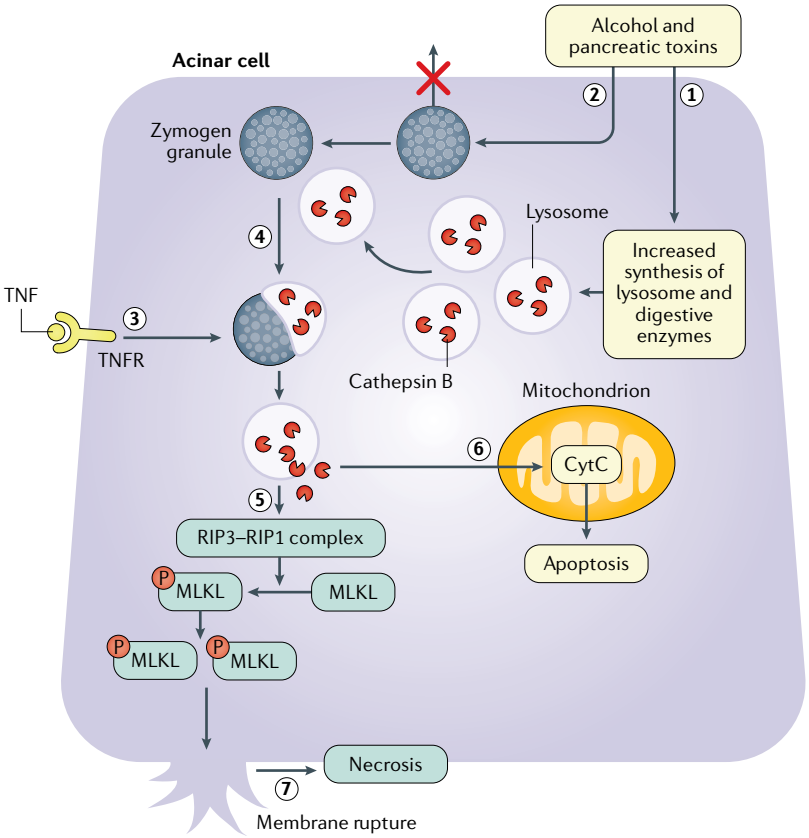

Fig. 2 | **Premature trypsinogen activation in acute pancreatitis.** In acinar cells, alcohol and other pancreatic toxins increase synthesis of lysosomes and digestive enzymes, as well as impair zymogen granule apical exocytosis in the acinar cells by causing microtubule dysfunction (1). This process results in accumulation of zymogen granules (2). TNF can also cause premature trypsinogen activation by activating the TNF receptor (TNFR) (3). Preceding events culminate in colocalization in which lysosomes and zymogen granules fuse (4). Cathepsin B activates trypsinogen to trypsin once colocalization occurs. Cathepsin B and trypsin are released into the cytosol. Cathepsin B activates the receptor-interacting protein kinase (RIP), including RIP1–RIP3, and mixed lineage kinase domain-like (MLKL) pathway, which involves oligomerization of MLKL (5). Intracytosolic protease release also leads to activation of the apoptosis executioner caspase 3 through release of cytochrome *c* (CytC) from mitochondria (6). Phosphorylation and oligomerization of MLKL translocate it to the cell membrane, causing membrane rupture and cell necrosis (7).

unwanted proteins and improves its capacity and efficiency of protein synthesis and folding[44,86,87,89] via three important pathways that respond by acutely decreasing protein synthesis. The three functional pathways of the UPR are the inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6) and protein kinase RNA-like ER kinase (PERK) pathways[44,87]. The downstream events of the IRE1 and ATF6 pathways culminate in activation of transcription factors such as ATF6, and spliced X-box binding protein 1 (sXBP1). These transcription factors promote the synthesis of substrates needed for ER expansion, ER chaperones for protein folding and components of the ER protein degradation machinery[45,54]. They also initiate autophagy to eliminate and recycle unfolded and misfolded proteins[90]. When these responses fail to restore homeostasis, the UPR eventually activates the apoptotic pathway. The PERK pathway is the terminal response, whereby its downstream effectors, such as transcriptional factor CEBP homologous protein (CHOP), promote apoptosis and inflammation[87,91]. Although CHOP can induce autophagy, it eventually promotes cell death during prolonged ER stress. Interestingly, widely available 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) inhibitors promote the UPR[92,93]. Statin use has been associated with lower incidence and severity of acute pancreatitis in observational studies[94–96], and a randomized controlled trial is currently ongoing to examine the effects of HMG-CoA inhibitors, such as simvastatin, in preventing recurrent attacks of acute pancreatitis[97].

Ductal cell dysfunction and intraductal events. Both transmembrane water channels (for example, aquaporin 1 in acinar and ductal cells) and cystic fibrosis transmembrane regulator (CFTR) channels are vital to physiological pancreatic fluid secretion[98,99]. Alcohol has been shown to markedly reduce CFTR function and the amount of bicarbonate secretion, which acidifies the intraductal environment and leads to intraductal fluid stasis, promoting premature enzyme activation within the duct[100–102]. Bile acid-mediated and pancreatic inflammation-mediated reductions in aquaporins also contribute to this intraductal fluid stasis[98]. Different intraductal events might also mediate acinar cell injury and death leading to acute pancreatitis[59]. These events include increased intraductal pressure, ductal cell exposure to bile acids and intraductal acidification[60,70,103,104].

Increased pressure inside the pancreatic duct can activate the mechanoreceptor PIEZO1 in the acinar cells to trigger the pathological calcium signalling described earlier[70]. Ductal hypertension can also cause calcineurin-mediated acinar cell injury by promoting inflammation and activation of the signal transducer and activator of transcription 3 (STAT3) pathway[105]. Clinical examples of ductal hypertension include papillary oedema, acidic contrast injection into the pancreatic duct during ERCP and gallstone obstruction of the duct. Acidification of the pancreatic ductal lumen has been shown to activate transient receptor potential vanilloid 1 (TRPV1) in the primary sensory neurons and cause acute pancreatitis[60]. As such, luminal acidification can occur when an acidic contrast agent is used for pancreatography during ERCP, and PIEZO1-mediated, calcineurin-mediated and TRPV1-mediated mechanisms of acute pancreatitis are highly relevant to post-ERCP and gallstone pancreatitis[60,70,106]. Additionally, bile acid can cause mitochondrial dysfunction in a dose-dependent manner in the ductal cells[101]. The resulting ATP depletion causes decreased ATP-dependent bicarbonate secretion, and it can also cause ductal cell death. Breakdown of ductal cells exposes acinar cells to the bile acids, with resultant cell injury and death[103,107,108]. This mechanism is hypothesized to be relevant to gallstone pancreatitis, in which a lodged gallstone in the papilla can expose ductal cells to bile acids by creating a common channel. However, under physiological conditions, pressure within the pancreatic duct is substantially greater than in the bile duct — thus, the hypothetical mechanism by which bile acids might travel against this pressure gradient has not been delineated[109,110].

Cystic fibrosis transmembrane regulator (CFTR). A chloride channel located in pancreatic duct cells that enables passage of anions and water.

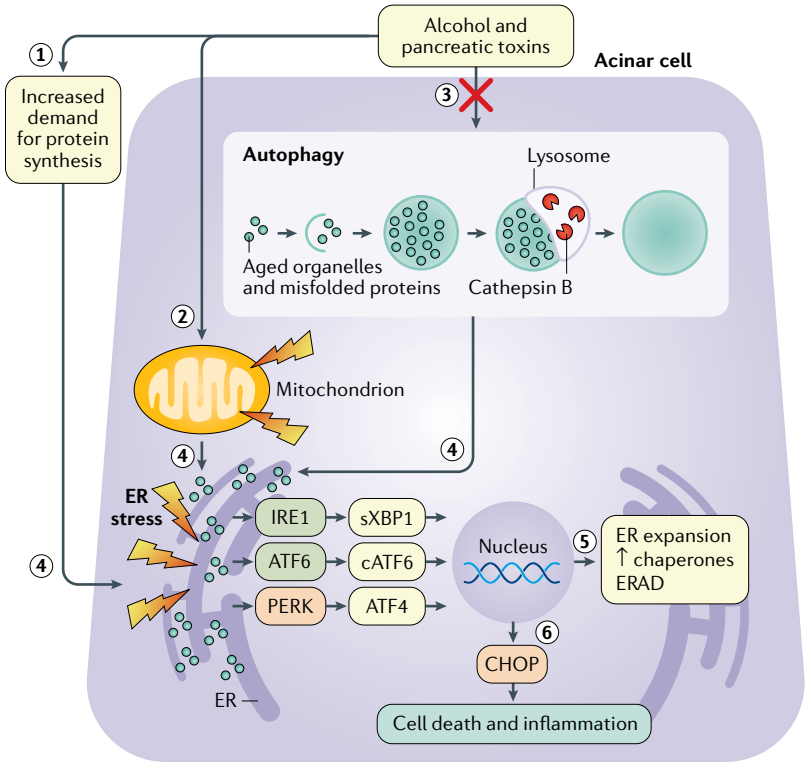

Fig. 3 | **Endoplasmic reticulum stress, the unfolded protein response and autophagy in acute pancreatitis.** In acinar cells, toxins such as alcohol cause an increased demand for protein synthesis (1), mitochondrial dysfunction (2) and impaired autophagy (3). Under physiological conditions, autophagy processes and recycles various aged and defective cytoplasmic contents. Autophagy first enucleates cytosolic contents within an open double membrane. The double membrane edges meet to form an autophagosome, which fuses with a lysosome to form an autolysosome. Hydrolases in the lysosome then degrade the enclosed contents for recycling. The previous events (1–3) result in endoplasmic reticulum (ER) stress, which occurs when demand for protein synthesis and build-up of misfolded or unfolded proteins in a cell overwhelm the ER capacity to process them (4). Transmembrane proteins such as inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6) and protein kinase RNA-like ER kinase (PERK) sense misfolded proteins in the ER lumen. The IRE1 and ATF6 pathway effectors spliced X-box binding protein 1 (sXBP1), ATF6 and cleaved ATF6 (cATF6) are transcription factors for genes involved in ER expansion, molecular chaperone processes and ER-associated degradation (ERAD), which enable the ER to meet the metabolic and protein synthesis demands of the cell (5). Under extreme ER stress, the unfolded protein response (UPR) PERK pathway results in apoptosis and inflammation mediated by CEBP homologous protein (CHOP) (6). Although CHOP can induce autophagy, it eventually promotes cell death and inflammation during prolonged ER stress.

Monocyte chemoattractant protein 1
(MCP1). A chemokine that is involved in facilitating migration and recruitment of monocytes.

Damage-associated molecular patterns
(DAMPs). A variety of substances released by damaged cells that can activate an immune response.

Role of immune system. Injured acinar cells release chemokines, cytokines and various adhesion molecules that recruit and mediate infiltration of immune cells into the site of injury[21,48,111,112] (FIG. 4). Among these chemokines, monocyte chemoattractant protein 1 (MCP1) facilitates the inflammatory monocyte trafficking, and macrophage inflammatory protein 2α (MIP2α) and CXC-chemokine ligand 1 (CXCL1) recruit neutrophils[1,113]. Illustrating their importance in the pathogenesis of acute pancreatitis, inhibition of chemokines and their receptors has been shown to prevent pancreatic and distant organ injury in animal models[114–122]. Increased serum MCP1 levels also correlate with severe acute pancreatitis in humans[123].

Once immune cells infiltrate the pancreas, the cellular contents released from necrotic and injured cells activate monocytes and neutrophils and further propagate the inflammation[54,124,125]. Neutrophilic NADP oxidase causes oxidative stress and increased intra-acinar trypsinogen activation[39,126]. Neutrophils also produce neutrophil extracellular traps, which are adhesive webs composed of granular proteins, DNA and histones that can cause ductal obstruction, activate pro-inflammatory signals and prematurely activate trypsinogen[2,47].

Activated monocytes are central to systemic inflammation and worsening tissue injury in acute pancreatitis. Important mediators of monocyte activation are damage-associated molecular patterns (DAMPs), which are cellular contents that are released from the necrotic acinar cells. DAMPs mediate their effects by binding to different receptors on the immune cells[127–130]. For example, the DAMPs high-mobility group box protein 1 (HMGB1), heat shock protein 70 (HSP70) and double-stranded DNA signal through Toll-like receptors (TLRs) to activate the NF-κB pathway. NF-κB mediates the gene expression of pro-inflammatory cytokines, chemokines and adhesion molecules. Other DAMPs, such as ATP and NAD, bind to P2X7 receptors to activate the inflammasome. Subsequently, pro-IL-1β and pro-IL-18 mature into their biologically active forms through proteolytic cleavage. These pathways amplify the production of pro-inflammatory cytokines including TNF, IL-1β, IL-6 and IL-18, among others[112,131,132].

Macrophages at distant organs are also activated and worsen systemic inflammation and distant organ injury in acute pancreatitis, although the mechanisms of distal organ injury underlying this effect have not been fully elucidated. Given the central importance of these pathways in driving and accentuating inflammatory responses in acute pancreatitis, inhibitors of NF-κB and the inflammasome pathway have been developed and are being tested for efficacy in animal models[48,133–137]. Of these, MCC950, a potent inhibitor of the inflammasome pathway, is being tested in other diseases such as ischaemic stroke, hepatitis and hepatic fibrosis in which inflammasome activation also has a crucial pathogenic role[135,136]. Additionally, lactate, administered in the form of the widely available lactated Ringer's solution, holds promise, as it downregulates the inflammasome pathway and reduces pancreatic injury in acute pancreatitis animal models[133]. Lactated Ringer's solution also showed promise in clinical trials (discussed later)[133,138,139].

Serum TNF and IL-6 levels have consistently been associated with increased severity of acute pancreatitis and acute lung injury[140–143]. TNF also causes direct acinar cell necrosis[46]. Pentoxifylline is a nonselective phosphodiesterase inhibitor that reduces synthesis of TNF by downregulating the NF-κB pathway. A pilot double-blind placebo-controlled randomized trial in 28 patients found that oral pentoxifylline three times a day reduced length of hospital stay[144]. These promising findings are currently being validated in a larger scale clinical trial. Tocilizumab, a commercially available IL-6 receptor antagonist, is another potential therapeutic agent[145,146]. Administration of tocilizumab after induction of severe acute pancreatitis improved outcomes in

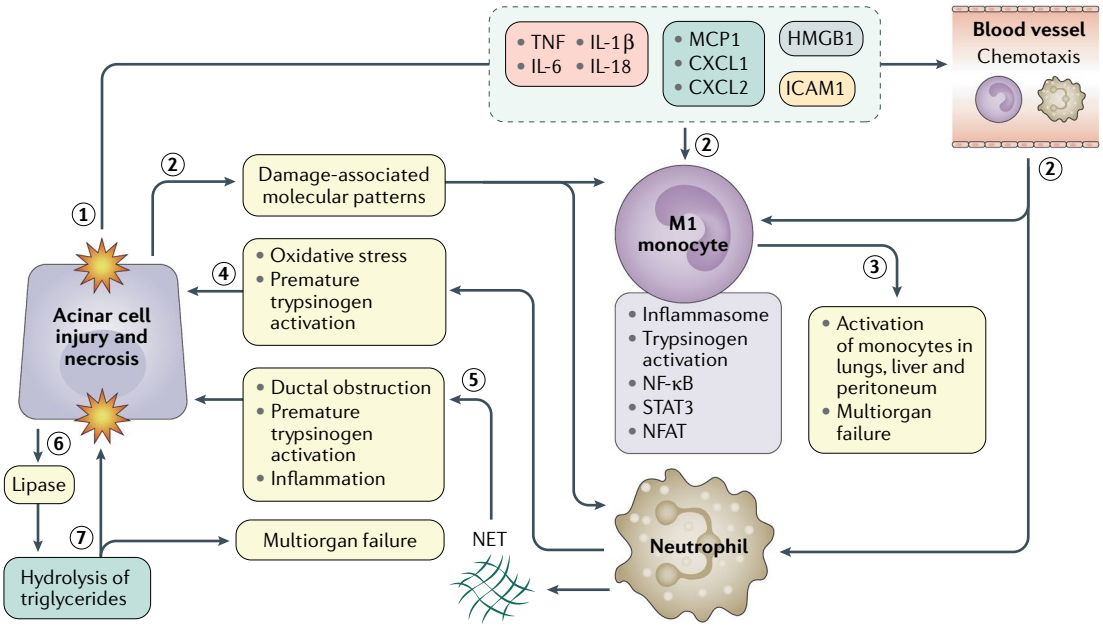

Fig. 4 | **Immune response to acinar cell injury and necrosis in acute pancreatitis.** Injured acinar cells produce cytokines, chemokines and adhesion molecules to recruit immune cells to the site of injury (1). Once recruited, chemokines and cytokines from the acinar cells, and damage-associated molecular patterns, activate immune cells to amplify an inflammatory response (2). Pathways activated within the M1-polarized monocytes include nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3). Monocytes activate monocytes in other organs, causing remote organ injury (3). Neutrophils cause premature trypsinogen activation and oxidative stress to the acinar cells by releasing oxidizing substances (4). Neutrophils also release neutrophil extracellular traps (NETs), which cause ductal obstruction, premature trypsinogen activation and inflammation (5). Owing to a disrupted basolateral barrier, which results from acinar cell injury from a variety of toxins, intrapancreatic fat is exposed to lipase, which is secreted to the interstitium (6). Triglyceride-rich intrapancreatic and peripancreatic fats are hydrolysed by lipase (7). This reaction releases toxic free fatty acids that can cause further acinar cell injury and organ failure. CXCL, CXC-chemokine ligand; HMGB1, high-mobility group box protein 1; ICAM1, intercellular adhesion molecule 1; MCP1, monocyte chemoattractant protein 1; NFAT, nuclear factor of activated T cells.

an animal study[147]. Tocilizumab is probably ready for a clinical trial in human acute pancreatitis given its established safety record and efficacy in patients with other diseases such as giant cell arteritis, rheumatoid arthritis and graft-versus-host disease[146,148,149].

The pro-inflammatory phase in acute pancreatitis is followed by the compensatory anti-inflammatory response syndrome, which is characterized by a predominance of anti-inflammatory cytokines such as TGFβ, IL-4 and IL-10 (REFS[131,150,151]). IL-10 is produced by acinar cells, monocytes, B cells and T cells. It acts at the transcriptional level to reduce the production of pro-inflammatory cytokines via inhibition of the STAT3 pathway and T cell expansion[152]. Animal studies of acute pancreatitis have shown improved outcomes with the use of insulin-like growth factor 1 and IL-4, which enhance IL-10 production[153,154]. During the anti-inflammatory response period, patients with acute pancreatitis are susceptible to developing infection of pancreatic necrosis[155].

Genetic mutations. Several mutations have been identified that have pathogenic roles in acute pancreatitis, including mutations in protease serine 1, serine protease inhibitor Kazal type 1, chymotrypsin C, *CFTR*, claudin 2 and calcium-sensing receptor genes[156]. An in-depth review of clinical implications of these genetic mutations is beyond the scope of this Review, but a review has been published that summarizes the genetics of acute pancreatitis[157].

Role of unsaturated fatty acids. Obesity and hypertriglyceridaemia are established risk factors for severe acute pancreatitis[9,158]. Studies have illuminated the pathophysiological mechanisms by which obesity and hypertriglyceridaemia mediate severe acute pancreatitis. During an acute pancreatitis episode, several mechanisms disrupt the normal apical secretary path of the zymogen granules. Alcohol inhibits apical secretion and instead promotes basolateral secretion[57]. Acinar cell necrosis also causes liberation of enzymes to areas of the pancreas otherwise shielded from exposure to digestive enzymes. For example, lipase is freely released through the basolateral membranes into the interstitium, peripancreatic region and bloodstream[25,159–161]. Lipase hydrolyses circulating triglycerides and those stored in the intrapancreatic and peripancreatic adipocytes into saturated and unsaturated free fatty acids (UFAs). UFAs such as linoleic, oleic and linolenic acids cause cytotoxicity by inhibiting the mitochondrial complexes I and V and increasing the levels of TNF and other chemokines augmenting the inflammatory response[9,23,162,163]. In clinical studies, patients with acute pancreatitis with increased visceral adiposity and elevated serum triglycerides on admission

Systemic inflammatory response syndrome (SIRS). A host immune response to an inflammatory or infectious insult that is often characterized by fevers, leukocytosis, tachycardia, tachypnea and hypotension.

were found to be at increased risk of multisystem organ failure and pancreatic necrosis, substantiating the findings of mechanistic studies[24,164–166]. Prevention of triglyceride hydrolysis through lipase inhibitors seems to be a promising therapeutic strategy in acute pancreatitis[159,167].

Mesenteric lymph. The course of acute pancreatitis can be further worsened by pathological changes in the intestines. These changes include ileus and ischaemia–reperfusion injuries, which result in translocation of bacteria through the intestinal barrier and changes in the microbiome[168]. More recently, the importance of toxin-containing lymph drainage has been highlighted[52,169–171]. Ischaemia-conditioned mesenteric lymph has been associated with cardiac dysfunction and multisystem organ failure in animal acute pancreatitis studies[49,52]. The responsible constituent in the mesenteric lymph has not yet been identified[170]. However, ligation of the thoracic duct mitigated the deleterious effects of the mesenteric lymph in mouse studies[49,171,172]. Currently available percutaneous techniques and endoscopic ultrasonography methods have shown promise in safely accessing the thoracic duct[173–175]. Pending improvements in techniques for accessing the thoracic duct in humans, redirecting mesenteric lymph flow during an acute pancreatitis attack might be an approach to prevent remote organ failure.

Assessment of severity

Revised classifications

The revised Atlanta and determinant-based classifications of acute pancreatitis have been developed to classify patients into severity categories that carry prognostic significance. These classifications have been extensively validated[3,176,177]. The similarities and differences between the two classification systems are shown in TABLE 3. The two systems reflect important advancements in the understanding of the main determinants of morbidity and mortality in acute pancreatitis. Contrary to the traditionally held notion that pancreatic necrosis itself is an independent determinant of mortality, there is now convincing evidence that necrosis without superimposed infection or organ failure has similar survival to interstitial pancreatitis, which carries a 1–2% mortality[3,178,179]. Persistent organ failure (lasting >48 hours) seems to be the most important determinant of mortality, which can be as high as 43%[3]. Duration of organ failure beyond 48 hours does not seem to affect mortality among patients with pancreatic necrosis[180]. Although patients with sterile pancreatic necrosis and/or peripancreatic fluid collections have low mortality, they nevertheless experience a complicated hospital course compared with those with interstitial pancreatitis, and they frequently require prolonged hospitalization and frequent readmissions[177,179].

Prediction of severity

Severe pancreatitis, defined as persistent organ failure, carries a mortality of up to 43% during the first attack[181]. Many prognostication models have been developed to predict severe pancreatitis early in the disease course, ranging from simple laboratory markers[182–184] and biomarkers[123,142,185,186] to clinical scoring systems[123,140,182,187–189]. However, despite a plethora of predictive tools being available, none has been shown to be clearly superior to any other technique in large, head-to-head comparison studies[189–191]. Thus, our ability to predict severe disease early in acute pancreatitis is still modest (accuracy ~80%). Simple and accurate clinical predictors of severity include blood urea nitrogen elevation[182,184], persistent systemic inflammatory response syndrome (SIRS)[192] and haemoconcentration[193]. These scores have strong advantages over other cumbersome scoring systems in that they are readily available and can be serially followed.

Management of acute pancreatitis

Early management in the first 72 hours

Once the diagnosis of acute pancreatitis is made in the emergency room, a predictive tool can help triage patients on the basis of predicted severity. Of all the prognostic tools, SIRS is a commonly used, validated predictor of acute pancreatitis severity and mortality[192,194]. It can be easily calculated, and its components (body temperature, heart rate, white blood cell count and respiratory rate) are readily available clinical variables. Other important factors of early management include fluid resuscitation, nutritional support, identification of aetiology and analgesia (FIG. 5).

Intravenous fluid resuscitation. Society guidelines agree that early, adequate fluid administration is the cornerstone of management in acute pancreatitis[27–30]. One pilot randomized controlled trial compared 20 ml/kg bolus of lactated Ringer's solution followed by 3 ml/kg per hour versus 10 ml/kg bolus followed by 1.5 ml/kg per hour in 60 patients with predicted mild acute pancreatitis[195] (TABLE 4). The aggressive resuscitation group was associated with a 70% clinical improvement rate compared with 42% in the conservative group. It is worth emphasizing that the trial focused on patients with mild acute pancreatitis and was not designed to examine the role of fluid volume in preventing necrosis, organ failure and mortality.

In patients with predicted severe acute pancreatitis, some data suggest that aggressive fluid resuscitation might be harmful. In a randomized controlled clinical trial that included 115 patients, rapid haemodilution to <35% within 48 hours with fluid therapy was associated with increased mortality and occurrence of sepsis of 34% and 79% compared with 15% and 58%, respectively, in the slow-dilution group[196]. However, observational data from the past few years suggest that aggressive fluid resuscitation might improve morbidity and survival[197–199]. Owing to differences in study design, patient population and definition of interventions, it is difficult to determine the effect of fluid volume on acute pancreatitis outcomes. Well-designed, large-scale randomized trials are sorely needed[200].

Lactated Ringer's solution is currently preferred over other crystalloids as the fluid type of choice in acute pancreatitis. This preference is based on a small pilot randomized clinical trial, which showed that administration of lactated Ringer's solution is associated with

a significant reduction in SIRS by 84% ($P = 0.035$) compared with normal saline[138]. Mechanistic evidence might also support this finding[133]. In a mouse study, administration of lactated Ringer's solution reduced the severity of acute pancreatitis by inhibiting the inflammasome and NF-κB pathways[133]. Additionally, lactated Ringer's solution contains calcium, which binds to UFAs and potentially mitigates their toxic effects[9]. In another in vitro study, lactated Ringer's solution inhibited macrophage polarization towards an inflammatory phenotype and inhibited NF-κB activation[201]. Larger studies are needed to see whether these findings translate to meaningful clinical outcomes in humans.

When administering intravenous fluid therapy, it is important to closely follow the intravascular volume status of the patient to prevent volume overload. In patients who are at risk of fluid sequestration, close monitoring of volume status is critical because they can develop life-threatening abdominal compartment syndrome, which is characterized by end-organ dysfunction caused by increased abdominal pressure[202]. A paucity of data exist on which parameter should guide fluid resuscitation and on the role of maintenance fluid therapy in acute pancreatitis[200]. These areas warrant further studies.

Nutritional support. Evidence supports the safe early introduction of a solid, low-fat diet in patients with mild or moderately severe pancreatitis without taking a stepwise approach (that is nil by mouth followed by liquid and then solid diet)[203–205]. For those patients who can tolerate an oral diet, an initial low-fat solid diet is preferred[203,205]. These early and aggressive approaches to feeding reduce the length of hospital stay in patients with mild or moderately severe pancreatitis. In patients with mild–moderate acute pancreatitis who do not tolerate oral feeding within 3–5 days, enteral tube feeding should be considered. Nasojejunal feeding has traditionally been preferred over nasogastric feeding because it should theoretically be better tolerated by patients[206]. Positioning the feeding tube in the jejunum past the duodenum limits the stimulation of the already inflamed pancreas, causing less pain. However, studies comparing nasogastric with nasojejunal feeding did show similar tolerance rates[207,208].

In patients predicted to have severe pancreatitis, however, early enteral feeding (enteral tube feeding within 24 hours of presentation) has not been shown to improve outcomes when compared with oral feeding starting at 72 hours[209]. In a rigorously designed, randomized controlled trial in 208 patients with predicted severe acute pancreatitis, patients were assigned either to early enteral tube feeding or to start oral diet at or after 72 hours (on-demand approach). Both groups developed major infections at similar rates of approximately 25% (TABLE 4). Additionally, there was no mortality benefit to early enteral tube feeding compared with the on-demand, oral diet approach[209]. Thus, in patients who are predicted to have severe acute pancreatitis, it is reasonable to wait at least 72 hours and attempt an oral diet. Enteral feeding might not be feasible in patients who develop ileus as a complication of acute pancreatitis and opioid analgesia. This outcome can pose a substantial challenge to the management of acute pancreatitis. Thus, efforts should be made to optimize patient bowel function by monitoring and correcting electrolyte disturbances, judiciously using opioid analgesia and encouraging mobility when feasible. Parenteral nutrition is considered the last resort because of its association with an increased rate of infection and mortality when compared with enteral feeding[210,211].

Analgesia. A paucity of studies have assessed the effect of analgesia on outcomes in acute pancreatitis. Narcotic analgesia is frequently used in the USA and seems to be effective[212]. Interestingly, one animal study showed that morphine use was associated with increased acute pancreatitis severity and the prevention of pancreatic regeneration[213]. In a large propensity score-matched observational study with 1,003 patients from intensive care units, epidural analgesia, predominantly containing non-narcotic anaesthetics (for example, bupivacaine), was associated with substantially lower mortality than standard care among patients with severe acute pancreatitis[214]. Purported benefits of this approach include improved splanchnic and pancreatic blood flow and anti-inflammatory effects[215,216]. A multicentre, randomized controlled trial is underway to elucidate the benefits of epidural analgesia among critically ill patients with acute pancreatitis[217]. Given the risk of patients becoming dependent on opioid medications, other modes of effective analgesia such as non-steroidal anti-inflammatory agents need to be explored as first-line analgesic agents in acute pancreatitis.

Management after the first 72 hours

Identification of aetiology and its management. In patients with mild biliary pancreatitis, cholecystectomy during their index hospitalization prevents recurrence (risk ratio as low as 0.28) and is cost-effective[218]. Thus, it should be the standard of care[218–221] (TABLE 4). Timing

Table 3 | **Comparison between revised Atlanta classification and determinant-based classification**

Classification	Mild	Moderately severe	Severe	Critical
Revised Atlanta classification[3]	No organ failure, local complications or exacerbation of comorbid condition	Transient organ failure (<48 hours), local complications and/or exacerbation of comorbid condition	Persistent organ failure	NA
Determinant-based classification[276]	No organ failure and no (peri) pancreatic necrosis	Sterile (peri)pancreatic necrosis and/or transient organ failure (<48 hours)	Persistent organ failure (>48 hours) or infected (peri) pancreatic necrosis	Persistent organ failure (>48 hours) and infected (peri) pancreatic necrosis

NA, not available.

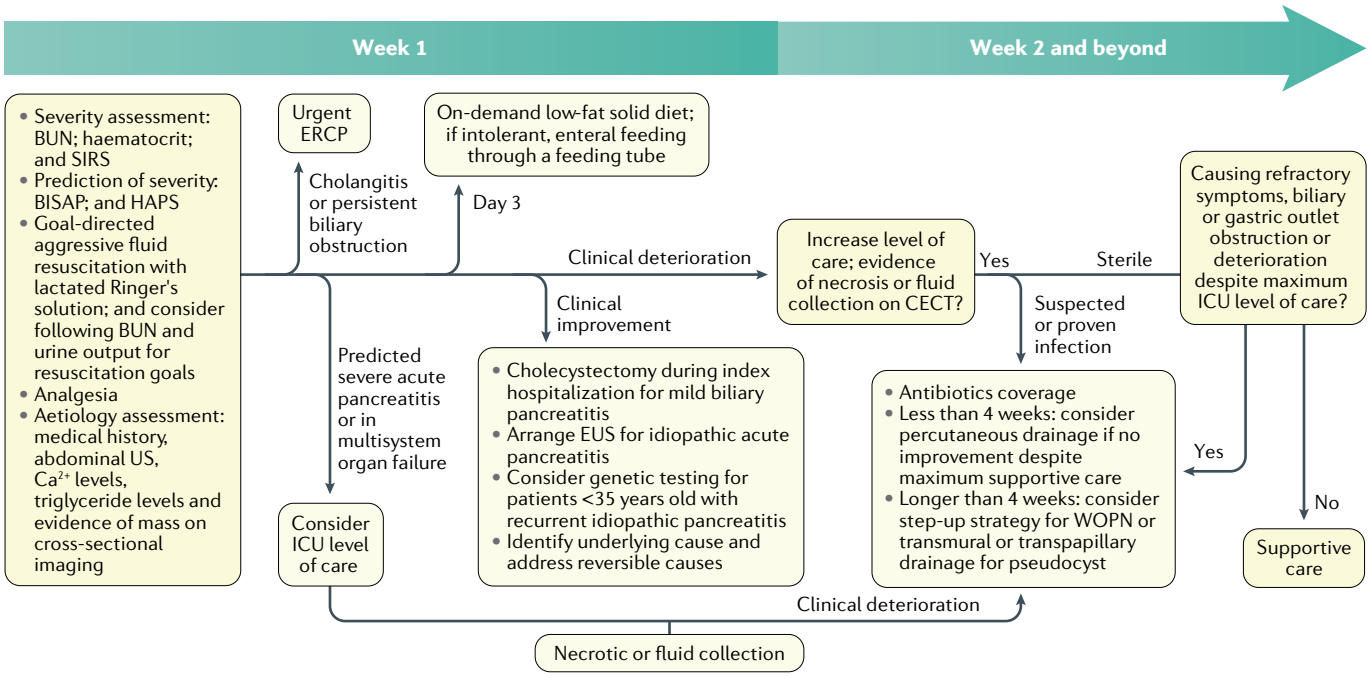

Fig. 5 | **Acute pancreatitis management algorithm.** The goals of acute pancreatitis management in the first week are to assess severity and assign an appropriate level of care, to ascertain aetiology and address reversible cause, to optimize nutrition and to arrange appropriate follow-up for the majority of patients being discharged. Up to 80% of patients with acute pancreatitis will recover and be discharged within a week. Beyond week 1, however, 20% will deteriorate and will need more long-term care depending on the driver of severity. Hence, goals for patients who deteriorate include identifying the determinant of severity, and if the deterioration is attributable to a necrotic collection, infection status and maturity of collection will determine management strategy. If the determinant of morbidity is organ failure, organ support is the most critical goal of care. BISAP, Bedside Index of Severity in Acute Pancreatitis; BUN, blood urea nitrogen; CECT, contrast-enhanced CT; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; HAPS, Harmless Acute Pancreatitis Score; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; US, ultrasonography; WOPN, walled-off pancreatic necrosis.

of cholecystectomy in patients with moderately severe and severe pancreatitis warrants further investigation. Although data are lacking, owing to concerns that early surgery in this setting increases surgical morbidity, waiting at least 6 weeks to enable maturation or resolution of fluid collections is recommended[222–224].

Well-designed studies have shown that interventions to promote alcohol and smoking cessation reduce acute pancreatitis recurrence and readmission rates[225–227]. Serum triglyceride levels need to be checked and treated accordingly when above 1,000 mg/dl, as emerging evidence suggests that even mild to moderate non-fasting hypertriglyceridaemia might contribute to acute pancreatitis severity[228]. However, the benefit of treating non-fasting hypertriglyceridaemia to prevent recurrence needs to be investigated further.

In patients with a dilated pancreatic duct in the absence of prior history of pancreatitis or chronic pancreatitis, main-duct intraductal papillary mucinous neoplasm (IPMN) should be considered as an aetiology. Main-duct IPMNs have high malignant potential, so it is essential to recognize and treat them accordingly. Pancreatic cancer is another important cause that accounts for approximately 1% of all acute pancreatitis causes[229]. For patients over the age of 40 years, a follow-up imaging study or endoscopic ultrasonography is important to rule out a mass.

Role of endoscopic retrograde cholangiopancreatography. The benefit of performing urgent ERCP (within 48 hours) in the setting of severe biliary acute pancreatitis and concomitant cholangitis and/or persistent biliary obstruction is well established[27,30,223]. However, in most patients with biliary pancreatitis, the common bile duct stone has already passed at the time of presentation; therefore, the majority of patients with biliary acute pancreatitis do not require ERCP. An ongoing randomized controlled trial aims to further evaluate the role of urgent ERCP in patients with predicted severe biliary acute pancreatitis[230].

Antibiotic prophylaxis. Many trials have examined the potential benefit of prophylactic antibiotics in patients with either severe pancreatitis or necrotizing pancreatitis. However, no clear benefit has been demonstrated in the body of evidence, and therefore, guidelines recommend against routine antibiotic prophylaxis in acute pancreatitis[27,29,30].

Local complications

Acute necrotic collections and WOPN

The management of pancreatic necrotic collections has evolved over the years. The surgical literature has debated about the indication, timing and mode of intervention for several decades[231]. Available interventions include minimally invasive surgery (video-assisted

Table 4 | **Landmark randomized clinical trials in acute pancreatitis management**

Trial	*n*	Year	Main findings
Goal-directed fluid resuscitation versus standard fluid resuscitation[138]	40	2011	SIRS reduction: normal saline 0% versus lactated Ringer's solution 84%; $P=0.035$
Aggressive fluid resuscitation versus standard fluid resuscitation in mild acute pancreatitis[195]	60	2017	• Clinical improvement[a] at 36 hours: aggressive fluid resuscitation 70% versus standard fluid resuscitation 42%; $P=0.03$ • Persistent SIRS: aggressive fluid resuscitation 7.4% versus standard fluid resuscitation 21.1%; adjusted OR 0.12 (95% CI 0.02–0.94)
Early enteral feeding versus on-demand oral feeding in predicted severe acute pancreatitis[209]	208	2014	Major infection[b] or death at 6 months: early feeding 30% versus on-demand feeding 28%; $P=0.76$
Cholecystectomy during index hospitalization for mild gallstone pancreatitis[218]	266	2015	• Readmission from recurrent gallstone-related complication[c]: same admission cholecystectomy 5% versus delayed cholecystectomy 17%; $P=0.002$ • No differences in surgical complications
Efficacy of pentoxifylline in treatment of predicted severe acute pancreatitis[144]	28	2015	• ICU admission: pentoxifylline 0% versus placebo 28%; $P=0.098$ • Length of stay >4 days: pentoxifylline 14% versus placebo 57%; $P=0.046$
Step-up strategy versus direct necrosectomy[238]	88	2010	Major complication[d] or death: step-up strategy 40% versus open necrosectomy group 69%; $P=0.006$
Endoscopic step-up versus surgical step-up in WOPN[240]	98	2018	• Major complications[e] or death at 6 months: endoscopic step-up 43% versus surgical step-up 45%; $P=0.88$ • Pancreatic fistula: endoscopic step-up 5% versus surgical step-up 32%; $P=0.0011$

ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; WOPN, walled-off pancreatic necrosis. [a]Clinical improvement defined by decreased epigastric pain and decrease in blood urea nitrogen, haematocrit and creatinine. [b]Major infection defined by infected pancreatic necrosis, bacteraemia or pneumonia. [c]Recurrent gallstone-related complication defined by pancreatitis, cholangitis, cholecystitis, choledocholithiasis needing endoscopic intervention, biliary colic or mortality. [d]Major complications defined by new-onset multiple organ failure or multiple systemic complications, perforations of a visceral organ or enterocutaneous fistula or bleeding. [e]Major complications defined by new-onset organ failure, bleeding requiring intervention, perforation of visceral organ requiring intervention, enterocutaneous fistula and incisional hernia.

retroperitoneal debridement or laparoscopy), endoscopic cystenterostomy with or without direct endoscopic necrosectomy and percutaneous catheter drainage. Several landmark trials conducted in the past decade have helped to clarify the role of each of these modalities in the context of managing pancreatic necrosis (TABLE 4).

Indication. Given the substantial morbidity and mortality associated with the procedure, invasive intervention is indicated only when a necrotic collection becomes infected or causes symptoms, such as gastric outlet obstruction, failure to thrive, biliary obstruction or intractable pain[30,232]. The role of interventions has been most rigorously studied in patients with suspected or proven infected pancreatic necrosis[223]. Thus, an intervention should be avoided in patients with sterile necrosis without symptoms, regardless of the size of the collection.

Timing. Observational studies and a randomized clinical trial have suggested that delaying the pancreatic intervention is associated with lower morbidity and mortality[223,233–236]. In patients with infected pancreatic necrosis early in the disease course (that is, <4 weeks from onset of disease) who become clinically unstable despite the administration of intravascular antibiotics, a percutaneous drain placement for decompression is advised[237]. Beyond 4 weeks from the acute pancreatitis onset, endoscopic cystenterostomy with or without necrosectomy or minimally invasive surgery can be considered.

Mode of intervention. A step-up approach using minimally invasive endoscopic intervention is the most beneficial mode of intervention, as illustrated in well-designed randomized clinical trials[238–240]. The step-up approach takes a graded approach to WOPN, starting with the least invasive measure first (drainage of collection using percutaneous catheter or by formation of cystenterostomy). An intervention would be stepped up to the most invasive option (necrosectomy) when a patient's clinical response is not optimal to the less invasive approach. This step-up approach reduced rates of new organ failure by 28% (absolute risk reduction) and the occurrence of a composite end point of major complications, multiple organ failure, perforation, fistula or death by 29%[238]. In a randomized controlled trial, drainage alone led to a resolution of WOPN in 40% of patients without the need for subsequent necrosectomy[241]. Data from a randomized clinical trial in 2018 support use of the endoscopic step-up over the surgical step-up approach. Specifically, the endoscopic step-up strategy led to a lower rate of pancreaticocutaneous fistula formation and shorter length of hospitalization than the surgical step-up approach[240]. Notably, in all the above randomized clinical trials, the majority of the enrolled patients had proven infected WOPN[239–241]. By contrast, data on the management of symptomatic sterile WOPN have mainly been derived from observational studies[242].

Endoscopic ultrasound-guided transmural drainage through cystenterostomy can be used safely once

Cystenterostomy
The creation of a connection between a cyst wall and the wall of the gastrointestinal tract.

the maturation of the collection wall occurs. Metal or plastic stents can be used, but a high-quality comparison of effectiveness data is lacking[243]. The lumen-apposing metal stents for drainage of WOPN have gained popularity owing to their ease of deployment and effectiveness[244–247]. However, long-term safety data are lacking, and there are emerging reports of increased incidence of delayed bleeding with the placement of lumen-apposing metal stents[248–250].

Disconnected duct syndrome

Disconnected duct syndrome is a complication in which the integrity of the pancreatic duct is lost following an attack of necrotizing pancreatitis[251]. Up to 50% of patients with pancreatic fluid collections might have an underlying disconnected duct that can lead to abdominal pain, recurrent acute pancreatitis or recurrent pancreatic fluid collections[252,253]. Disconnected duct syndrome is best recognized using secretin-stimulated magnetic resonance cholangiopancreatography. In such patients, studies have proposed transmural double pigtail stents to be left indefinitely in the collection with the aim of maintaining the patency of the pancreaticoenterostomy[237,254,255]. This approach was found to be safe, with a decreased risk of recurrence when compared with patients without indefinite stents (recurrence rate 17.4% versus 1.7%; $P < 0.001$) in one large observational study of 361 patients with pancreatic fluid collections[253]. Thus, this approach might become a first-line technique when compared with pancreatic surgical drainage, which carries a substantial risk of morbidity and new-onset diabetes.

Vascular complications of acute pancreatitis

Splanchnic vascular complications (SVCs) in acute pancreatitis include venous thrombosis and arterial and/or venous pseudoaneurysms[256]. Severe acute pancreatitis and pancreatic necrosis constitute risk factors for the development of SVCs. Splanchnic vein thrombosis occurs in approximately 15% of patients with acute pancreatitis[216]. The splanchnic vein recanalizes in a third of patients[257,258]. On the basis of available data, most SVCs in acute pancreatitis do not require anticoagulation therapy given their benign natural history[259–261]. On rare occasions, splenic vein thrombosis might lead to local portal hypertension with isolated gastric varices or superior mesenteric vein thrombosis with ascites. Pseudoaneurysms are thought to be a rare complication of pancreatitis; however, in the era of transmural metal stents, iatrogenic pseudoaneurysms have also been reported to occur ten times more frequently[248]. Despite being rare, pseudoaneurysms can be life threatening when not recognized and addressed in a timely fashion with coil embolization via interventional radiology.

Box 1 | Future areas of research in acute pancreatitis

Knowledge gaps or future directions

- Collaborative networks
  - Build multicentre, collaborative networks with infrastructure to conduct large-scale clinical trials
- Recruitment of patients
  - Increase public awareness about acute pancreatitis; develop collaborations with emergency departments for efficient, early recruitment of patients
- Analgesia
  - Compare narcotic versus non-opioid; epidural versus intravenous or oral opioid analgesics
- Fluid therapy
  - Study the optimal type and rate and define goals of fluid therapy
- Endoscopic retrograde cholangiopancreatography
  - Assess the benefit of urgent biliary decompression in predicted severe biliary pancreatitis
- Endoscopic drainage and necrosectomy
  - Compare endoscopic therapy in symptomatic sterile necrosis versus conservative management
- Late complications of acute pancreatitis
  - Study the mechanisms of diabetes mellitus and exocrine pancreatic insufficiency following acute pancreatitis

Long-term complications and follow-up

Disease progression

Recurrent acute pancreatitis (RAP) occurs in 18% of patients after an episode of acute pancreatitis and results in impairment of patient quality of life[13,18,262,263]. Accumulating evidence suggests that patients with RAP are at substantially increased risk of chronic pancreatitis[18,264]. Idiopathic aetiology, active alcohol intake and smoking are the strongest risks for progression to RAP and chronic pancreatitis[18,264,265]. Population-based cohort studies have suggested that acute pancreatitis might be a risk factor for pancreatic cancer[229,266–268], but the risk seems to be confined to patients with acute pancreatitis who progress to chronic pancreatitis[269].

Endocrine and exocrine complications

Until recently, endocrine and exocrine complications of acute pancreatitis were not well established. Now, studies support the idea that approximately one-third of patients will develop prediabetes or diabetes within 5 years of an index episode of acute pancreatitis[15,270], but the mechanisms and risk factors remain to be defined. Similarly, exocrine pancreatic insufficiency is common after acute pancreatitis, occurring in 24–40%[12,16,270,271]. Reported risk factors for exocrine pancreatic insufficiency following acute pancreatitis include pancreatic necrosis, severe acute pancreatitis and alcohol-related aetiology[16,270].

Quality of life

One prospective observational study has reported that long-term health-related quality of life is reduced among patients who survived acute pancreatitis when compared with age-matched and sex-matched individuals without pancreatitis[14]. Patients who experience multisystem organ failure, persistent abdominal pain requiring analgesia and/or disability are at increased risk of diminished quality of life. Importantly, among patients who experience extensive pancreatic necrosis, 53% become registered as disabled at 1 year following their discharge from the hospital[12].

Conclusions

Acute pancreatitis is a common and potentially life-threatening inflammatory disorder of the pancreas. Patients who survive the condition frequently develop long-term devastating consequences such as diabetes

mellitus, exocrine pancreatic insufficiency, chronic pancreatitis and poor quality of life. This substantial burden is noticeable at the health-care system level, and the increasing incidence of acute pancreatitis highlights the urgent need for therapeutic agents designed to alter its natural history. For decades, the exact pathophysiological mechanisms of acute pancreatitis remained an enigma other than recognizing that it might be an autodigestive disease. A rich body of work derived from animal models uncovered several important pathophysiological mechanisms that could represent therapeutic targets, and several agents are already in development. Landmark clinical trials have provided insight into aspects of clinical management, such as nutritional support, fluid therapy for mild acute pancreatitis, prevention of recurrence in mild gallstone pancreatitis and management of infected necrosis.

Despite the progress, several important research gaps remain. Many of the potential therapeutic targets identified in translational work need to be tested in phase I clinical trials. Translational work is required to investigate mechanisms of endocrine and exocrine failures after acute pancreatitis. But most importantly, well-designed, large studies are needed to examine the safety and effectiveness of early, goal-directed fluid therapy; to clarify the goals of fluid resuscitation; and to determine the optimal analgesic regimen, the role of early biliary decompression in predicted severe biliary acute pancreatitis and the optimal endoscopic management of symptomatic sterile pancreatic necrosis. Unfortunately, conducting large-scale trials has been extremely challenging owing to a lack of existing collaborative platforms to execute large clinical trials and difficulty with recruiting patients early in the course of acute pancreatitis. Efforts focusing on constructing a collaborative network of hospitals to conduct clinical trials with a strong emphasis on recruiting patients very early in their disease course are urgently needed. More mechanistic studies are also needed to characterize mechanisms of tissue reconstitution and resolution of pancreatic inflammation following acute pancreatitis, with an emphasis on endocrine and exocrine dysfunction (see BOX 1).

Published online 28 May 2019

1. Lugea, A. et al. Human pancreatic acinar cells: proteomic characterization, physiologic responses, and organellar disorders in ex vivo pancreatitis. *Am. J. Pathol.* **187**, 2726–2743 (2017).
2. Gukovskaya, A. S., Pandol, S. J. & Gukovsky, I. New insights into the pathways initiating and driving pancreatitis. *Curr. Opin. Gastroenterol.* **32**, 429–435 (2016).
3. Banks, P. A. et al. Classification of acute pancreatitis — 2012: revision of the Atlanta classification and definitions by international consensus. *Gut* **62**, 102–111 (2013).
4. Petrov, M. S. & Yadav, D. Global epidemiology and holistic prevention of pancreatitis. *Nat. Rev. Gastroenterol. Hepatol.* **16**, 175–184 (2018).
5. Peery, A. F. et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. *Gastroenterology* **149**, 1731–1741 (2015).
6. Munigala, S. et al. Predictors for early readmission in acute pancreatitis (AP) in the United States (US) — a nationwide population based study. *Pancreatology* **17**, 534–542 (2017).
7. Wadhwa, V. et al. Health care utilization and costs associated with acute pancreatitis. *Pancreas* **46**, 410–415 (2017).
8. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* **390**, 2627–2642 (2017).
9. Khatua, B., El-Kurdi, B. & Singh, V. P. Obesity and pancreatitis. *Curr. Opin. Gastroenterol.* **33**, 374–382 (2017).
10. Camilleri, M., Malhi, H. & Acosta, A. Gastrointestinal complications of obesity. *Gastroenterology* **152**, 1656–1670 (2017).
11. Krishna, S. G., Kamboj, A. K., Hart, P. A., Hinton, A. & Conwell, D. L. The changing epidemiology of acute pancreatitis hospitalizations: a decade of trends and the impact of chronic pancreatitis. *Pancreas* **46**, 482–488 (2017).
12. Umapathy, C. et al. Natural history after acute necrotizing pancreatitis: a large US tertiary care experience. *J. Gastrointest. Surg.* **20**, 1844–1853 (2016).
13. Yadav, D., O'Connell, M. & Papachristou, G. I. Natural history following the first attack of acute pancreatitis. *Am. J. Gastroenterol.* **107**, 1096–1103 (2012).
14. Machicado, J. D. et al. Acute pancreatitis has a long-term deleterious effect on physical health related quality of life. *Clin. Gastroenterol. Hepatol.* **15**, 1435–1443 (2017).
15. Das, S. L. et al. Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. *Gut* **63**, 818–831 (2014).
16. Hollemans, R. A. et al. Pancreatic exocrine insufficiency following acute pancreatitis: systematic review and study level meta-analysis. *Pancreatology* **18**, 253–262 (2018).
17. Vipperla, K. et al. Risk of and factors associated with readmission after a sentinel attack of acute pancreatitis. *Clin. Gastroenterol. Hepatol.* **12**, 1911–1919 (2014).
18. Ali, U. A. et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clin. Gastroenterol. Hepatol.* **14**, 738–746 (2016).
19. Javed, M. A. et al. TRO40303 ameliorates alcohol-induced pancreatitis through reduction of fatty acid ethyl ester-induced mitochondrial injury and necrotic cell death. *Pancreas* **47**, 18–24 (2018).
20. Wen, L. et al. Inhibitors of ORAI1 prevent cytosolic calcium-associated injury of human pancreatic acinar cells and acute pancreatitis in 3 mouse models. *Gastroenterology* **149**, 481–492 (2015).
21. Criddle, D. N., McLaughlin, E., Murphy, J. A., Petersen, O. H. & Sutton, R. The pancreas misled: signals to pancreatitis. *Pancreatology* **7**, 436–446 (2007).
22. Marta, K. et al. High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): protocol of a multicentre randomised double-blind clinical trial. *BMJ Open* **7**, e015874 (2017).
23. Noel, P. et al. Peripancreatic fat necrosis worsens acute pancreatitis independent of pancreatic necrosis via unsaturated fatty acids increased in human pancreatic necrosis collections. *Gut* **65**, 100–111 (2016).
24. Bradbury, K. E. et al. Lipolysis of visceral adipocyte triglyceride by pancreatic lipases converts mild acute pancreatitis to severe pancreatitis independent of necrosis and inflammation. *Gastroenterology* **15**, 100–111 (2017).
25. Acharya, C. et al. Fibrosis reduces severity of acute-on-chronic pancreatitis in humans. *Gastroenterology* **145**, 466–475 (2013).
26. Al-Bahrani, A. Z. & Ammori, B. J. Clinical laboratory assessment of acute pancreatitis. *Clin. Chim. Acta* **362**, 26–48 (2005).
27. Tenner, S., Baillie, J., DeWitt, J. & Vege, S. S. & of Gastroenterology, A. C. American College of Gastroenterology guideline: management of acute pancreatitis. *Am. J. Gastroenterol.* **108**, 1400–1415 (2013).
28. Crockett, S. D., Wani, S., Gardner, T. B., Falck-Ytter, Y. & Barkun, A. N. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. *Gastroenterology* **154**, 1096–1101 (2018).
29. Isaji, S. et al. Revised Japanese guidelines for the management of acute pancreatitis 2015: revised concepts and updated points. *J. Hepatobiliary Pancreat. Sci.* **22**, 433–445 (2015).
30. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* **13**, e1–e15 (2013).
31. Gerasimenko, J. V. et al. Ca^{2+} release-activated Ca^{2+} channel blockade as a potential tool in antipancreatitis therapy. *Proc. Natl Acad. Sci. USA* **110**, 13186–13191 (2013).
32. Murphy, J. A. et al. Direct activation of cytosolic Ca^{2+} signaling and enzyme secretion by cholecystokinin in human pancreatic acinar cells. *Gastroenterology* **135**, 632–641 (2008).
33. Biczo, G. et al. Mitochondrial dysfunction, through impaired autophagy, leads to endoplasmic reticulum stress, deregulated lipid metabolism, and pancreatitis in animal models. *Gastroenterology* **154**, 689–703 (2018).
34. Mukherjee, R. et al. Mechanism of mitochondrial permeability transition pore induction and damage in the pancreas: inhibition prevents acute pancreatitis by protecting production of ATP. *Gut* **65**, 1333–1346 (2016).
35. Aghdassi, A. A. et al. Cathepsin D regulates cathepsin B activation and disease severity predominantly in inflammatory cells during experimental pancreatitis. *J. Biol. Chem.* **293**, 1018–1029 (2018).
36. Talukdar, R. et al. Release of cathepsin B in cytosol causes cell death in acute pancreatitis. *Gastroenterology* **151**, 747–758 (2016).
37. Dawra, R. et al. Intra-acinar trypsinogen activation mediates early stages of pancreatic injury but not inflammation in mice with acute pancreatitis. *Gastroenterology* **141**, 2210–2217 (2011).
38. Wartmann, T. et al. Cathepsin L inactivates human trypsinogen, whereas cathepsin L-deletion reduces the severity of pancreatitis in mice. *Gastroenterology* **138**, 726–737 (2010).
39. Gukovskaya, A. S. et al. Neutrophils and NADPH oxidase mediate intrapancreatic trypsin activation in murine experimental acute pancreatitis. *Gastroenterology* **122**, 974–984 (2002).
40. Halangk, W. et al. Role of cathepsin B in intracellular trypsinogen activation and the onset of acute pancreatitis. *J. Clin. Invest.* **106**, 773–781 (2000).
41. Sendler, M. et al. Cathepsin B-mediated activation of trypsinogen in endocytosing macrophages increases severity of pancreatitis in mice. *Gastroenterology* **154**, 704–718 (2018).
42. Zeng, Y., Wang, X., Zhang, W., Wu, K. & Ma, J. Hypertriglyceridemia aggravates ER stress and pathogenesis of acute pancreatitis. *Hepatogastroenterology* **59**, 2318–2326 (2012).

43. Wu, J. S., Li, W. M., Chen, Y. N., Zhao, Q. & Chen, Q. F. Endoplasmic reticulum stress is activated in acute pancreatitis. *J. Dig. Dis.* **17**, 295–303 (2016).
44. Lugea, A. et al. Adaptive unfolded protein response attenuates alcohol-induced pancreatic damage. *Gastroenterology* **140**, 987–997 (2011).
45. Antonucci, L. et al. Basal autophagy maintains pancreatic acinar cell homeostasis and protein synthesis and prevents ER stress. *Proc. Natl Acad. Sci. USA* **112**, 6166 (2015).
46. Sendler, M. et al. Tumour necrosis factor alpha secretion induces protease activation and acinar cell necrosis in acute experimental pancreatitis in mice. *Gut* **62**, 430–439 (2013).
47. Merza, M. et al. Neutrophil extracellular traps induce trypsin activation, inflammation, and tissue damage in mice with severe acute pancreatitis. *Gastroenterology* **149**, 1931 (2015).
48. Jakkampudi, A. et al. NF-kappaB in acute pancreatitis: Mechanisms and therapeutic potential. *Pancreatology* **16**, 477–488 (2016).
49. Shanbhag, S. T. et al. Acute pancreatitis conditioned mesenteric lymph causes cardiac dysfunction in rats independent of hypotension. *Surgery* **163**, 1097–1105 (2018).
50. Mole, D. J. et al. Tryptophan catabolites in mesenteric lymph may contribute to pancreatitis-associated organ failure. *Br. J. Surg.* **95**, 855–867 (2008).
51. Mittal, A. et al. The proteome of mesenteric lymph during acute pancreatitis and implications for treatment. *JOP* **10**, 130–142 (2009).
52. Flint, R. S. et al. Acute pancreatitis severity is exacerbated by intestinal ischemia-reperfusion conditioned mesenteric lymph. *Surgery* **143**, 404–413 (2008).
53. Gorelick, F. S. & Lerch, M. M. Do animal models of acute pancreatitis reproduce human disease? *Cell. Mol. Gastroenterol. Hepatol.* **4**, 251–262 (2017).
54. Gukovskaya, A. S., Gukovsky, I., Algul, H. & Habtezion, A. Autophagy, inflammation, and immune dysfunction in the pathogenesis of pancreatitis. *Gastroenterology* **153**, 1212–1226 (2017).
55. Lampel, M. & Kern, H. F. Acute interstitial pancreatitis in the rat induced by excessive doses of a pancreatic secretagogue. *Virchows Arch. A* **373**, 97–117 (1977).
56. Pandol, S. J., Gukovsky, I., Satoh, A., Lugea, A. & Gukovskaya, A. S. Animal and in vitro models of alcoholic pancreatitis: role of cholecystokinin. *Pancreas* **27**, 297–300 (2003).
57. Criddle, D. N. The role of fat and alcohol in acute pancreatitis: a dangerous liaison. *Pancreatology* **15**, S6–S12 (2015).
58. Huang, W. et al. Fatty acid ethyl ester synthase inhibition ameliorates ethanol-induced Ca^{2+}-dependent mitochondrial dysfunction and acute pancreatitis. *Gut* **63**, 1313–1324 (2014).
59. Hegyi, P., Pandol, S., Venglovecz, V. & Rakonczay, Z. J. The acinar-ductal tango in the pathogenesis of acute pancreatitis. *Gut* **60**, 544–552 (2011).
60. Noble, M. D., Romac, J., Vigna, S. R. & Liddle, R. A. A. pH-sensitive, neurogenic pathway mediates disease severity in a model of post-ERCP pancreatitis. *Gut* **57**, 1566–1571 (2008).
61. Lerch, M. M. et al. Acute necrotizing pancreatitis in the opossum: earliest morphological changes involve acinar cells. *Gastroenterology* **103**, 205–213 (1992).
62. Senninger, N., Moody, F. G., Coelho, J. C. & Van Buren, D. H. The role of biliary obstruction in the pathogenesis of acute pancreatitis in the opossum. *Surgery* **99**, 688–693 (1986).
63. Runkel, N. S., Rodriguez, L. F., Moody, F. G., LaRocco, M. T. & Blasdel, T. *Salmonella* infection of the biliary and intestinal tract of wild opossums. *Lab. Anim. Sci.* **41**, 54–56 (1991).
64. Senninger, N. & Runkel, N. in *Essentials of Experimental Surgery: Gastroenterology* Ch. 23 (eds Gregerson, H. et al.) (Gordon and Breach Publishing Group, 1995).
65. Dolai, S. et al. Pancreatitis-induced depletion of syntaxin 2 promotes autophagy and increases basolateral exocytosis. *Gastroenterology* **154**, 1805–1821 (2018).
66. Kruger, B., Albrecht, E. & Lerch, M. M. The role of intracellular calcium signaling in premature protease activation and the onset of pancreatitis. *Am. J. Pathol.* **157**, 43–50 (2000).
67. Maleth, J. & Hegyi, P. Ca^{2+} toxicity and mitochondrial damage in acute pancreatitis: translational overview. *Phil. Trans. R. Soc. B* **371**, 20150425 (2016).
68. Zhang, S. L. et al. STIM1 is a Ca^{2+} sensor that activates CRAC channels and migrates from the Ca^{2+} store to the plasma membrane. *Nature* **437**, 902–905 (2005).
69. Lur, G. et al. InsP(3)receptors and Orai channels in pancreatic acinar cells: co-localization and its consequences. *Biochem. J.* **436**, 231–239 (2011).
70. Romac, J. M.-J., Shahid, R. A., Swain, S. M., Vigna, S. R. & Liddle, R. A. Piezo1 is a mechanically activated ion channel and mediates pressure induced pancreatitis. *Nat. Commun.* **9**, 1715 (2018).
71. Elmunzer, B. J. et al. Rectal indomethacin alone versus indomethacin and prophylactic pancreatic stent placement for preventing pancreatitis after ERCP: study protocol for a randomized controlled trial. *Trials* **17**, 2 (2016).
72. Atar, D. et al. Effect of intravenous TRO40303 as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: MITOCARE study results. *Eur. Heart J.* **36**, 112–119 (2015).
73. Le Lamer, S. et al. Translation of TRO40303 from myocardial infarction models to demonstration of safety and tolerance in a randomized phase I trial. *J. Transl Med.* **12**, 38 (2014).
74. Saluja, A. K. et al. Secretagogue-induced digestive enzyme activation and cell injury in rat pancreatic acini. *Am. J. Physiol.* **276**, G835–G842 (1999).
75. Wilson, J. S. et al. Both ethanol consumption and protein deficiency increase the fragility of pancreatic lysosomes. *J. Lab. Clin. Med.* **115**, 749–755 (1990).
76. Haber, P. S., Wilson, J. S., Apte, M. V., Korsten, M. A. & Pirola, R. C. Chronic ethanol consumption increases the fragility of rat pancreatic zymogen granules. *Gut* **35**, 1474–1478 (1994).
77. Louhimo, J., Steer, M. L. & Perides, G. Necroptosis is an important severity determinant and potential therapeutic target in experimental severe pancreatitis. *Cell. Mol. Gastroenterol. Hepatol.* **2**, 519–535 (2016).
78. Han, J., Zhong, C.-Q. & Zhang, D.-W. Programmed necrosis: backup to and competitor with apoptosis in the immune system. *Nat. Immunol.* **12**, 1143–1149 (2011).
79. He, S. et al. Receptor interacting protein kinase-3 determines cellular necrotic response to TNF-alpha. *Cell* **137**, 1100–1111 (2009).
80. Wang, G., Qu, F.-Z., Li, L., Lv, J.-C. & Sun, B. Necroptosis: a potential, promising target and switch in acute pancreatitis. *Apoptosis* **21**, 121–129 (2016).
81. Diakopoulos, K. N. et al. Impaired autophagy induces chronic atrophic pancreatitis in mice via sex- and nutrition-dependent processes. *Gastroenterology* **148**, 626–638 (2015).
82. Mareninova, O. A. et al. Impaired autophagic flux mediates acinar cell vacuole formation and trypsinogen activation in rodent models of acute pancreatitis. *J. Clin. Invest.* **119**, 3340–3355 (2009).
83. Lugea, A. et al. The combination of alcohol and cigarette smoke induces endoplasmic reticulum stress and cell death in pancreatic acinar cells. *Gastroenterology* **153**, 1674–1686 (2017).
84. Zelic, M. et al. RIP kinase 1-dependent endothelial necroptosis underlies systemic inflammatory response syndrome. *J. Clin. Invest.* **128**, 2064–2075 (2018).
85. Lee, H.-J., Yoon, Y.-S. & Lee, S.-J. Mechanism of neuroprotection by trehalose: controversy surrounding autophagy induction. *Cell Death Dis.* **9**, 712 (2018).
86. Ron, D. & Walter, P. Signal integration in the endoplasmic reticulum unfolded protein response. *Nat. Rev. Mol. Cell. Biol.* **8**, 519–529 (2007).
87. Kim, I., Xu, W. & Reed, J. C. Cell death and endoplasmic reticulum stress: disease relevance and therapeutic opportunities. *Nat. Rev. Drug Discov.* **7**, 1013–1030 (2008).
88. Seyhun, E. et al. Tauroursodeoxycholic acid reduces endoplasmic reticulum stress, acinar cell damage, and systemic inflammation in acute pancreatitis. *Am. J. Physiol. Liver Physiol.* **301**, 773 (2011).
89. Pandol, S. J., Gorelick, F. S. & Lugea, A. Environmental and genetic stressors and the unfolded protein response in exocrine pancreatic function — a hypothesis. *Front. Physiol.* **2**, 8 (2011).
90. Richardson, C. E., Kooistra, T. & Kim, D. H. An essential role for XBP-1 in host protection against immune activation in *C. elegans*. *Nature* **463**, 1092–1095 (2010).
91. Xu, C., Bailly-Maitre, B. & Reed, J. C. Endoplasmic reticulum stress: cell life and death decisions. *J. Clin. Invest.* **115**, 2656–2664 (2005).
92. Chen, J. C., Wu, M. L., Huang, K. C. & Lin, W. W. HMG-CoA reductase inhibitors activate the unfolded protein response and induce cytoprotective GRP78 expression. *Cardiovasc. Res.* **80**, 138–150 (2008).
93. Morck, C. et al. Statins inhibit protein lipidation and induce the unfolded protein response in the non-sterol producing nematode. *Caenorhabditis elegans*. *Proc. Natl Acad. Sci. USA* **106**, 18285–18290 (2009).
94. Wu, B. U., Pandol, S. J. & Liu, I. L. Simvastatin is associated with reduced risk of acute pancreatitis: findings from a regional integrated healthcare system. *Gut* **64**, 133–138 (2015).
95. Gornik, I., Gasparovic, V., Vrdoljak, N. G., Haxiu, A. & Vucelic, B. Prior statin therapy is associated with milder course and better outcome in acute pancreatitis—a cohort study. *Pancreatology* **13**, 196–200 (2013).
96. Lee, P. J. et al. Association of statins with decreased acute pancreatitis severity: a propensity score analysis. *J. Clin. Gastroenterol.* **52**, 742–746 (2017).
97. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02743364 (2019).
98. Venglovecz, V. et al. The importance of aquaporin 1 in pancreatitis and its relation to the CFTR Cl(-) channel. *Front. Physiol.* **9**, 854 (2018).
99. Pallagi, P., Hegyi, P. & Rakonczay, Z. J. The physiology and pathophysiology of pancreatic ductal secretion: the background for clinicians. *Pancreas* **44**, 1211–1233 (2015).
100. Hegyi, P. et al. CFTR: a new horizon in the pathomechanism and treatment of pancreatitis. *Rev. Physiol. Biochem. Pharmacol.* **170**, 37–66 (2016).
101. Hegyi, P. & Petersen, O. H. The exocrine pancreas: the acinar-ductal tango in physiology and pathophysiology. *Rev. Physiol. Biochem. Pharmacol.* **165**, 1–30 (2013).
102. Maleth, J. et al. Alcohol disrupts levels and function of the cystic fibrosis transmembrane conductance regulator to promote development of pancreatitis. *Gastroenterology* **148**, 427–439 (2015).
103. Venglovecz, V. et al. Effects of bile acids on pancreatic ductal bicarbonate secretion in guinea pig. *Gut* **57**, 1102–1112 (2008).
104. Vigna, S. R., Shahid, R. A., Nathan, J. D., McVey, D. C. & Liddle, R. A. Leukotriene B4 mediates inflammation via TRPV1 in duct obstruction-induced pancreatitis in rats. *Pancreas* **40**, 708–714 (2011).
105. Wen, L. et al. Transient high pressure in pancreatic ducts promotes inflammation and alters tight junctions via calcineurin signaling in mice. *Gastroenterology* **155**, 1250–1263 (2018).
106. Orabi, A. I. et al. Targeted inhibition of pancreatic acinar cell calcineurin is a novel strategy to prevent post-ERCP pancreatitis. *Cell. Mol. Gastroenterol. Hepatol.* **3**, 119–128 (2017).
107. Maleth, J. et al. Non-conjugated chenodeoxycholate induces severe mitochondrial damage and inhibits bicarbonate transport in pancreatic duct cells. *Gut* **60**, 136–138 (2011).
108. Perides, G., Laukkarinen, J. M., Vassileva, G. & Steer, M. L. Biliary acute pancreatitis in mice is mediated by the G-protein-coupled cell surface bile acid receptor Gpbar1. *Gastroenterology* **138**, 715–725 (2010).
109. Elliot, D. W., Williams, R. D. & Zollinger, R. M. Alterations in the pancreatic resistance to bile in the pathogenesis of acute pancreatitis. *Ann. Surg.* **146**, 662–669 (1957).
110. Lerch, M. M. & Aghdassi, A. A. The role of bile acids in gallstone-induced pancreatitis. *Gastroenterology* **138**, 429–433 (2010).
111. Rakonczay, Z. J., Hegyi, P., Takacs, T., McCarroll, J. & Saluja, A. K. The role of NF-kappaB activation in the pathogenesis of acute pancreatitis. *Gut* **57**, 259–267 (2008).
112. Watanabe, T., Kudo, M. & Strober, W. Immunopathogenesis of pancreatitis. *Mucosal Immunol.* **10**, 283–298 (2017).
113. Griffith, J. W., Sokol, C. L. & Luster, A. D. Chemokines and chemokine receptors: positioning cells for host defense and immunity. *Annu. Rev. Immunol.* **32**, 659–702 (2014).
114. Zhou, G.-X. et al. Protective effects of MCP-1 inhibitor on a rat model of severe acute pancreatitis. *Hepatobiliary Pancreat. Dis. Int.* **9**, 201–207 (2010).
115. Bhatia, M. et al. Treatment with neutralising antibody against cytokine induced neutrophil chemoattractant (CINC) protects rats against acute pancreatitis associated lung injury. *Gut* **47**, 838–844 (2000).
116. Malla, S. R. et al. Effect of oral administration of AZD8309, a CXCR2 antagonist, on the severity of experimental pancreatitis. *Pancreatology* **16**, 761–769 (2016).
117. Saeki, K. et al. CCL2-induced migration and SOCS3-mediated activation of macrophages are involved in cerulein-induced pancreatitis in mice. *Gastroenterology* **142**, 1010–1020 (2012).
118. Bhatia, M. & Hegde, A. Treatment with antileukinate, a CXCR2 chemokine receptor antagonist, protects

mice against acute pancreatitis and associated lung injury. *Regul. Pept.* **138**, 40–48 (2007).
119. Pastor, C. M. et al. Role of macrophage inflammatory peptide-2 in cerulein-induced acute pancreatitis and pancreatitis-associated lung injury. *Lab. Invest.* **83**, 471–478 (2003).
120. Frossard, J. L. et al. Role of CCL-2, CCR-2 and CCR-4 in cerulein-induced acute pancreatitis and pancreatitis-associated lung injury. *J. Clin. Pathol.* **64**, 387–393 (2011).
121. Gerard, C. et al. Targeted disruption of the beta-chemokine receptor CCR1 protects against pancreatitis-associated lung injury. *J. Clin. Invest.* **100**, 2022–2027 (1997).
122. He, M., Horuk, R. & Bhatia, M. Treatment with BX471, a nonpeptide CCR1 antagonist, protects mice against acute pancreatitis-associated lung injury by modulating neutrophil recruitment. *Pancreas* **34**, 233–241 (2007).
123. Papachristou, G. I. Prediction of severe acute pancreatitis: current knowledge and novel insights. *World J. Gastroenterol.* **14**, 6273–6275 (2008).
124. Jakkampudi, A. et al. Acinar injury and early cytokine response in human acute biliary pancreatitis. *Sci. Rep.* **7**, 2 (2017).
125. Gu, H. et al. Necro-inflammatory response of pancreatic acinar cells in the pathogenesis of acute alcoholic pancreatitis. *Cell Death Dis.* **4**, e816 (2013).
126. Ushio-Fukai, M. Compartmentalization of redox signaling through NADPH oxidase-derived ROS. *Antioxid. Redox Signal.* **11**, 1289–1299 (2009).
127. Eppensteiner, J., Davis, R. P., Barbas, A. S., Kwun, J. & Lee, J. Immunothrombotic activity of damage-associated molecular patterns and extracellular vesicles in secondary organ failure induced by trauma and sterile insults. *Front. Immunol.* **9**, 190 (2018).
128. Yasuda, T. et al. Significant increase of serum high-mobility group box chromosomal protein 1 levels in patients with severe acute pancreatitis. *Pancreas* **33**, 359–363 (2006).
129. Sharif, R. et al. Impact of toll-like receptor 4 on the severity of acute pancreatitis and pancreatitis-associated lung injury in mice. *Gut* **58**, 813–819 (2009).
130. Hoque, R. et al. TLR9 and the NLRP3 inflammasome link acinar cell death with inflammation in acute pancreatitis. *Gastroenterology* **141**, 358–369 (2011).
131. Lee, B., Zhao, Q. & Habtezion, A. Immunology of pancreatitis and environmental factors. *Curr. Opin. Gastroenterol.* **33**, 383–389 (2017).
132. Hoque, R. Update on innate immunity and perspectives on metabolite regulation in acute pancreatitis. *Curr. Opin. Gastroenterol.* **32**, 507–512 (2016).
133. Hoque, R., Farooq, A., Ghani, A., Gorelick, F. & Mehal, W. Z. Lactate reduces liver and pancreatic injury in Toll-like receptor- and inflammasome-mediated inflammation via GPR81-mediated suppression of innate immunity. *Gastroenterology* **146**, 1763–1774 (2014).
134. Primiano, M. J. et al. Efficacy and pharmacology of the NLRP3 inflammasome inhibitor CP-456,773 (CRID3) in murine models of dermal and pulmonary inflammation. *J. Immunol.* **197**, 2421–2433 (2016).
135. Mridha, A. R. et al. NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. *J. Hepatol.* **66**, 1037–1046 (2017).
136. Gao, L. et al. NLRP3 inflammasome: a promising target in ischemic stroke. *Inflamm. Res.* **66**, 17–24 (2017).
137. Li, G. et al. TLR4-mediated NF-kappaB signaling pathway mediates HMGB1-induced pancreatic injury in mice with severe acute pancreatitis. *Int. J. Mol. Med.* **37**, 99–107 (2016).
138. Wu, B. U. et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. *Clin. Gastroenterol. Hepatol.* **9**, 717 (2011).
139. Choi, J. H., Kim, H. J., Lee, B. U., Kim, T. H. & Song, I. H. Vigorous periprocedural hydration with lactated Ringer's solution reduces the risk of pancreatitis after retrograde cholangiopancreatography in hospitalized patients. *Clin. Gastroenterol. Hepatol.* **15**, 92 (2017).
140. Aoun, E. et al. Diagnostic accuracy of interleukin-6 and interleukin-8 in predicting severe acute pancreatitis: a meta-analysis. *Pancreatology* **9**, 777–785 (2009).
141. Zhang, H. et al. IL-6 *trans*-signaling promotes pancreatitis-associated lung injury and lethality. *J. Clin. Invest.* **123**, 1019–1031 (2013).
142. Sathyanarayan, G., Garg, P. K., Prasad, H. & Tandon, R. K. Elevated level of interleukin-6 predicts organ failure and severe disease in patients with acute pancreatitis. *J. Gastroenterol. Hepatol.* **22**, 550–554 (2007).
143. Dianliang, Z., Jieshou, L., Zhiwei, J. & Baojun, Y. Association of plasma levels of tumor necrosis factor (TNF)-alpha and its soluble receptors, two polymorphisms of the TNF gene, with acute severe pancreatitis and early septic shock due to it. *Pancreas* **26**, 339–343 (2003).
144. Vege, S. S. et al. Pentoxifylline treatment in severe acute pancreatitis: a pilot, double-blind, placebo-controlled, randomized trial. *Gastroenterology* **149**, 318–320 (2015).
145. Stone, J. H. et al. Trial of tocilizumab in giant-cell arteritis. *N. Engl. J. Med.* **377**, 317–328 (2017).
146. Schirmer, M., Muratore, F. & Salvarani, C. Tocilizumab for the treatment of giant cell arteritis. *Expert Rev. Clin. Immunol.* **14**, 339–349 (2018).
147. Chen, K.-L. et al. Effects of tocilizumab on experimental severe acute pancreatitis and associated acute lung injury. *Crit. Care Med.* **44**, e664–e677 (2016).
148. Yucebay, F. et al. Tocilizumab as first-line therapy for steroid-refractory acute graft-versus-host-disease: analysis of a single-center experience. *Leuk. Lymphoma* **15**, 1–7 (2019).
149. Pablos, J. L. et al. Efficacy of tocilizumab monotherapy after response to combined tocilizumab and methotrexate in patients with rheumatoid arthritis: the randomised JUST-ACT study. *Clin. Exp. Rheumatol.* (in the press).
150. Friess, H. et al. Enhanced expression of TGF-betas and their receptors in human acute pancreatitis. *Ann. Surg.* **227**, 95–104 (1998).
151. Deviere, J. et al. Interleukin 10 reduces the incidence of pancreatitis after therapeutic endoscopic retrograde cholangiopancreatography. *Gastroenterology* **120**, 498–505 (2001).
152. Hutchins, A. P., Diez, D. & Miranda-Saavedra, D. The IL-10/STAT3-mediated anti-inflammatory response: recent developments and future challenges. *Brief. Funct. Genomics* **12**, 489–498 (2013).
153. Lin, R. et al. Interleukin-10 attenuates impairment of the blood-brain barrier in a severe acute pancreatitis rat model. *J. Inflamm.* **15**, 4 (2018).
154. Warzecha, Z. et al. IGF-1 stimulates production of interleukin-10 and inhibits development of caerulein-induced pancreatitis. *J. Physiol. Pharmacol.* **54**, 575–590 (2003).
155. Sharma, D. et al. Association of systemic inflammatory and anti-inflammatory responses with adverse outcomes in acute pancreatitis: preliminary results of an ongoing study. *Dig. Dis. Sci.* **62**, 3468–3478 (2017).
156. Hasan, A., Moscoso, D. I. & Kastrinos, F. The role of genetics in pancreatitis. *Gastrointest. Endosc. Clin. N. Am.* **28**, 587–603 (2018).
157. Zator, Z. & Whitcomb, D. C. Insights into the genetic risk factors for the development of pancreatic disease. *Therap. Adv. Gastroenterol.* **10**, 323–336 (2017).
158. Krishna, S. G. et al. Morbid obesity is associated with adverse clinical outcomes in acute pancreatitis: a propensity-matched study. *Am. J. Gastroenterol.* **110**, 1608–1619 (2015).
159. Navina, S. et al. Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. *Sci. Transl Med.* **3**, 107ra110 (2011).
160. Fallon, M. B. et al. Effect of cerulein hyperstimulation on the paracellular barrier of rat exocrine pancreas. *Gastroenterology* **108**, 1863–1872 (1995).
161. Gaisano, H. Y. et al. Supramaximal cholecystokinin displaces Munc18c from the pancreatic acinar basal surface, redirecting apical exocytosis to the basal membrane. *J. Clin. Invest.* **108**, 1597–1611 (2001).
162. Durgampudi, C. et al. Acute lipotoxicity regulates severity of biliary acute pancreatitis without affecting its initiation. *Am. J. Pathol.* **184**, 1773–1784 (2014).
163. Umpaichitra, V., Banerji, M. A. & Castells, S. Postprandial hyperlipidemia after a fat loading test in minority adolescents with type 2 diabetes mellitus and obesity. *J. Pediatr. Endocrinol. Metab.* **17**, 853–864 (2004).
164. Natu, A. et al. Visceral adiposity predicts severity of acute pancreatitis. *Pancreas* **46**, 776–781 (2017).
165. Halleux, C. M. et al. Secretion of adiponectin and regulation of apM1 gene expression in human visceral adipose tissue. *Biochem. Biophys. Res. Commun.* **288**, 1102–1107 (2001).
166. Nawaz, H. et al. Elevated serum triglycerides are independently associated with persistent organ failure in acute pancreatitis. *Am. J. Gastroenterol.* **110**, 1497–1503 (2015).
167. Patel, K. et al. Lipolysis of visceral adipocyte triglyceride by pancreatic lipases converts mild acute pancreatitis to severe pancreatitis independent of necrosis and inflammation. *Am. J. Pathol.* **185**, 808–819 (2015).
168. Ammori, B. J. et al. Early increase in intestinal permeability in patients with severe acute pancreatitis: correlation with endotoxemia, organ failure, and mortality. *J. Gastrointest. Surg.* **3**, 252–262 (1999).
169. Blenkiron, C. et al. MicroRNAs in mesenteric lymph and plasma during acute pancreatitis. *Ann. Surg.* **260**, 341–347 (2014).
170. Landahl, P., Ansari, D. & Andersson, R. Severe acute pancreatitis: gut barrier failure, systemic inflammatory response, acute lung injury, and the role of the mesenteric lymph. *Surg. Infect.* **16**, 651–656 (2015).
171. Peng, H. et al. Blocking abdominal lymphatic flow attenuates acute hemorrhagic necrotizing pancreatitis -associated lung injury in rats. *J. Inflamm.* **10**, 9 (2013).
172. Zhang, D., Tsui, N., Li, Y. & Wang, F. Thoracic duct ligation in the rat attenuates lung injuries in acute pancreatitis. *Lymphology* **46**, 144–149 (2013).
173. Toliyat, M. et al. Interventional radiology in the management of thoracic duct injuries: anatomy, techniques and results. *Clin. Imaging* **42**, 183–192 (2017).
174. Girotra, M., Horwhat, J. D., Settle, T. L. & Parasher, V. K. Endoscopic ultrasound-guided transesophageal thoracic duct puncture in a Swine model: a survival study. *J. Laparoendosc. Adv. Surg. Tech. A* **23**, 588–591 (2013).
175. Parasher, V. K. et al. Lymph sampling and lymphangiography via EUS-guided transesophageal thoracic duct puncture in a swine model. *Gastrointest. Endosc.* **59**, 564–567 (2004).
176. Choi, J.-H. et al. Revised Atlanta classification and determinant-based classification: Which one better at stratifying outcomes of patients with acute pancreatitis? *Pancreatology* **17**, 194–200 (2017).
177. Zubia-Olaskoaga, F. et al. Comparison between revised Atlanta classification and determinant-based classification for acute pancreatitis in intensive care medicine. Why do not use a modified determinant-based classification? *Crit. Care Med.* **44**, 910–917 (2016).
178. Talukdar, R., Clemens, M. & Vege, S. S. Moderately severe acute pancreatitis: prospective validation of this new subgroup of acute pancreatitis. *Pancreas* **41**, 306–309 (2012).
179. Vege, S. S. et al. Low mortality and high morbidity in severe acute pancreatitis without organ failure: a case for revising the Atlanta classification to include 'moderately severe acute pancreatitis'. *Am. J. Gastroenterol.* **104**, 710–715 (2009).
180. Schepers, N. J. et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. *Gut*. https://doi.org/10.1136/gutjnl-2017-314657 (2018).
181. Petrov, M. S., Shanbhag, S., Chakraborty, M., Phillips, A. R. J. & Windsor, J. A. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology* **139**, 813–820 (2010).
182. Wu, B. U. et al. Blood urea nitrogen in the early assessment of acute pancreatitis: an international validation study. *Arch. Intern. Med.* **171**, 669–676 (2011).
183. Brown, A., Orav, J. & Banks, P. A. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. *Pancreas* **20**, 367–372 (2000).
184. Koutroumpakis, E. et al. Admission hematocrit and rise in blood urea nitrogen at 24h outperform other laboratory markers in predicting persistent organ failure and pancreatic necrosis in acute pancreatitis: a post hoc analysis of three large prospective databases. *Am. J. Gastroenterol.* **110**, 1707–1716 (2015).
185. Karpavicius, A., Dambrauskas, Z., Sileikis, A., Vitkus, D. & Strupas, K. Value of adipokines in predicting the severity of acute pancreatitis: comprehensive review. *World J. Gastroenterol.* **18**, 6620–6627 (2012).
186. Deng, L. H. et al. Plasma cytokines can help to identify the development of severe acute pancreatitis on admission. *Medicine* **96**, e7312 (2017).
187. Mentula, P. et al. Early prediction of organ failure by combined markers in patients with acute pancreatitis. *Br. J. Surg.* **92**, 68–75 (2005).
188. Zhang, Y.-P. et al. Early prediction of persistent organ failure by serum angiopoietin-2 in patients with acute pancreatitis. *Dig. Dis. Sci.* **61**, 3584–3591 (2016).
189. Di, M.-Y. et al. Prediction models of mortality in acute pancreatitis in adults: a systematic review. *Ann. Intern. Med.* **165**, 482–490 (2016).
190. Mounzer, R. et al. Comparison of existing clinical scoring systems to predict persistent organ failure in

patients with acute pancreatitis. *Gastroenterology* **142**, 1476 (2012).
191. Forsmark, C. E. & Yadav, D. Predicting the prognosis of acute pancreatitis. *Ann. Intern. Med.* **165**, 523–524 (2016).
192. Mofidi, R. et al. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. *Br. J. Surg.* **93**, 738–744 (2006).
193. Lankisch, P. G. et al. Hemoconcentration: an early marker of severe and/or necrotizing pancreatitis? A critical appraisal. *Am. J. Gastroenterol.* **96**, 2081–2085 (2001).
194. Singh, V. K. et al. Early systemic inflammatory response syndrome is associated with severe acute pancreatitis. *Clin. Gastroenterol. Hepatol.* **7**, 1247–1251 (2009).
195. Buxbaum, J. L. et al. Early aggressive hydration hastens clinical improvement in mild acute pancreatitis. *Am. J. Gastroenterol.* **112**, 797–803 (2017).
196. Mao, E. Q. et al. Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis. *Chin. Med. J.* **123**, 1639–1644 (2010).
197. Wall, I. et al. Decreased mortality in acute pancreatitis related to early aggressive hydration. *Pancreas* **40**, 547–550 (2011).
198. Singh, V. K. et al. An international multicenter study of early intravenous fluid administration and outcome in acute pancreatitis. *United European Gastroenterol. J.* **5**, 491–498 (2017).
199. Yamashita, T. et al. Large volume fluid resuscitation for severe acute pancreatitis is associated with reduced mortality: a multicenter retrospective study. *J. Clin. Gastroenterol.* **53**, 385–391 (2018).
200. Haydock, M. D. et al. Fluid therapy in acute pancreatitis: anybody's guess. *Ann. Surg.* **257**, 182–188 (2013).
201. de-Madaria, E. et al. Fluid resuscitation with lactated Ringer's solution versus normal saline in acute pancreatitis: a triple-blind, randomized, controlled trial. *United European Gastroenterol. J.* **6**, 63–72 (2018).
202. van Brunschot, S. et al. Abdominal compartment syndrome in acute pancreatitis: a systematic review. *Pancreas* **43**, 665–674 (2014).
203. Larino-Noia, J. et al. Early and/or immediately full caloric diet versus standard refeeding in mild acute pancreatitis: a randomized open-label trial. *Pancreatology* **14**, 167–173 (2014).
204. Zhao, X. L. et al. Early oral refeeding based on hunger in moderate and severe acute pancreatitis: a prospective controlled, randomized clinical trial. *Nutrition* **31**, 171–175 (2015).
205. Vaughn, V. M. et al. Early versus delayed feeding in patients with acute pancreatitis: a systematic review. *Ann. Intern. Med.* **166**, 883–892 (2017).
206. Machicado, J. D. et al. Practice patterns and utilization of tube feedings in acute pancreatitis patients at a large US referral center. *Pancreas* **47**, 1150–1155 (2018).
207. Eatock, F. C. et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. *Am. J. Gastroenterol.* **100**, 432–439 (2005).
208. Petrov, M. S., Correia, M. I. T. D. & Windsor, J. A. Nasogastric tube feeding in predicted severe acute pancreatitis. A systematic review of the literature to determine safety and tolerance. *JOP* **9**, 440–448 (2008).
209. Bakker, O. J. et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *N. Engl. J. Med.* **371**, 1983–1993 (2014).
210. Al-Omran, M., Albalawi, Z. H., Tashkandi, M. F. & Al-Ansary, L. A. Enteral versus parenteral nutrition for acute pancreatitis. *Cochrane Database Syst. Rev.* **1**, CD002837 (2010).
211. Yao, H., He, C., Deng, L. & Liao, G. Enteral versus parenteral nutrition in critically ill patients with severe pancreatitis: a meta-analysis. *Eur. J. Clin. Nutr.* **72**, 66–68 (2018).
212. Basurto Ona, X., Rigau Comas, D. & Urrutia, G. Opioids for acute pancreatitis pain. *Cochrane Database Syst. Rev.* **7**, CD009179 (2013).
213. Barlass, U. et al. Morphine worsens the severity and prevents pancreatic regeneration in mouse models of acute pancreatitis. *Gut* **67**, 600–602 (2018).
214. Jabaudon, M. et al. Thoracic epidural analgesia and mortality in acute pancreatitis: a multicenter propensity analysis. *Crit. Care Med.* **46**, e198–e205 (2018).
215. Bachmann, K. A. et al. Effects of thoracic epidural anesthesia on survival and microcirculation in severe acute pancreatitis: a randomized experimental trial. *Crit. Care* **17**, R281 (2013).
216. Richards, E. R., Kabir, S. I., McNaught, C.-E. & MacFie, J. Effect of thoracic epidural anaesthesia on splanchnic blood flow. *Br. J. Surg.* **100**, 316–321 (2013).
217. Bulyez, S. et al. Epidural analgesia in critically ill patients with acute pancreatitis: the multicentre randomised controlled EPIPAN study protocol. *BMJ Open* **7**, e015280 (2017).
218. da Costa, D. W. et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. *Lancet* **386**, 1261–1268 (2015).
219. da Costa, D. W. et al. Cost-effectiveness of same-admission versus interval cholecystectomy after mild gallstone pancreatitis in the PONCHO trial. *Br. J. Surg.* **103**, 1695–1703 (2016).
220. Young, S.-H. et al. Cholecystectomy reduces recurrent pancreatitis and improves survival after endoscopic sphincterotomy. *J. Gastrointest. Surg.* **21**, 294–301 (2017).
221. Noel, R. et al. Index versus delayed cholecystectomy in mild gallstone pancreatitis: results of a randomized controlled trial. *HPB* **20**, 932–938 (2018).
222. Nealon, W. H., Bawduniak, J. & Walser, E. M. Appropriate timing of cholecystectomy in patients who present with moderate to severe gallstone-associated acute pancreatitis with peripancreatic fluid collections. *Ann. Surg.* **239**, 741–751 (2004).
223. van Dijk, S. M. et al. Acute pancreatitis: recent advances through randomised trials. *Gut* **66**, 2024–2032 (2017).
224. Tang, E., Stain, S. C., Tang, G., Froes, E. & Berne, T. V. Timing of laparoscopic surgery in gallstone pancreatitis. *Arch. Surg.* **130**, 496–500 (1995).
225. Nikkola, J., Laukkarinen, J., Huhtala, H. & Sand, J. The intensity of brief interventions in patients with acute alcoholic pancreatitis should be increased, especially in young patients with heavy alcohol consumption. *Alcohol Alcohol.* **52**, 453–459 (2017).
226. Xiang, J.-X. et al. Impact of cigarette smoking on recurrence of hyperlipidemic acute pancreatitis. *World J. Gastroenterol.* **23**, 8387–8394 (2017).
227. Nordback, I. et al. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. *Gastroenterology* **136**, 848–855 (2009).
228. Pedersen, S. B., Langsted, A. & Nordestgaard, B. G. Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. *JAMA Intern. Med.* **176**, 1834–1842 (2016).
229. Munigala, S., Kanwal, F., Xian, H., Scherrer, J. F. & Agarwal, B. Increased risk of pancreatic adenocarcinoma after acute pancreatitis. *Clin. Gastroenterol. Hepatol.* **12**, 1143–1150 (2014).
230. Schepers, N. J. et al. Early biliary decompression versus conservative treatment in acute biliary pancreatitis (APEC trial): study protocol for a randomized controlled trial. *Trials* **17**, 5 (2016).
231. Bradley, E. L. 3rd & Dexter, N. D. Management of severe acute pancreatitis: a surgical odyssey. *Ann. Surg.* **251**, 6–17 (2010).
232. Gosnell, F. E., O'Neill, B. B. & Harris, H. W. Necrotizing pancreatitis during pregnancy: a rare cause and review of the literature. *J. Gastrointest. Surg.* **5**, 371–376 (2001).
233. Sun, J. et al. Conservative treatment and percutaneous catheter drainage improve outcome of necrotizing pancreatitis. *Hepatogastroenterology* **62**, 195–199 (2015).
234. Mouli, V. P., Sreenivas, V. & Garg, P. K. Efficacy of conservative treatment, without necrosectomy, for infected pancreatic necrosis: a systematic review and meta-analysis. *Gastroenterology* **144**, 333–340 (2013).
235. van Santvoort, H. C. et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology* **141**, 1254–1263 (2011).
236. Mier, J., Leon, E. L., Castillo, A., Robledo, F. & Blanco, R. Early versus late necrosectomy in severe necrotizing pancreatitis. *Am. J. Surg.* **173**, 71–75 (1997).
237. Arvanitakis, M. et al. Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. *Endoscopy* **50**, 524–546 (2018).
238. van Santvoort, H. C. et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N. Engl. J. Med.* **362**, 1491–1502 (2010).
239. Bakker, O. J. et al. Endoscopic transgastric versus surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA* **307**, 1053–1061 (2012).
240. van Brunschot, S. et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. *Lancet* **391**, 51–58 (2018).
241. Kumar, N., Conwell, D. L. & Thompson, C. C. Direct endoscopic necrosectomy versus step-up approach for walled-off pancreatic necrosis: comparison of clinical outcome and health care utilization. *Pancreas* **43**, 1334–1339 (2014).
242. Guo, J. et al. A multi-institutional consensus on how to perform endoscopic ultrasound-guided peri-pancreatic fluid collection drainage and endoscopic necrosectomy. *Endosc. Ultrasound* **6**, 285–291 (2017).
243. Gurusamy, K. S., Pallari, E., Hawkins, N., Pereira, S. P. & Davidson, B. R. Management strategies for pancreatic pseudocysts. *Cochrane Database Syst. Rev.* **4**, CD011392 (2016).
244. Hammad, T. et al. Efficacy and safety of lumen-apposing metal stents in management of pancreatic fluid collections: are they better than plastic stents? A systematic review and meta-analysis. *Dig. Dis. Sci.* **63**, 289–301 (2018).
245. Siddiqui, A. A. et al. Fully covered self-expanding metal stents versus lumen-apposing fully covered self-expanding metal stent versus plastic stents for endoscopic drainage of pancreatic walled-off necrosis: clinical outcomes and success. *Gastrointest. Endosc.* **85**, 758–765 (2017).
246. Sharaiha, R. Z. et al. Endoscopic therapy with lumen-apposing metal stents is safe and effective for patients with pancreatic walled-off necrosis. *Clin. Gastroenterol. Hepatol.* **14**, 1797–1803 (2016).
247. Siddiqui, A. A. et al. EUS-guided drainage of peripancreatic fluid collections and necrosis by using a novel lumen-apposing stent: a large retrospective, multicenter U.S. experience (with videos). *Gastrointest. Endosc.* **83**, 699–707 (2016).
248. Stecher, S. S. et al. Delayed severe bleeding complications after treatment of pancreatic fluid collections with lumen-apposing metal stents. *Gut* **66**, 1871–1872 (2017).
249. Bang, J. Y., Hasan, M., Navaneethan, U., Hawes, R. & Varadarajulu, S. Lumen-apposing metal stents (LAMS) for pancreatic fluid collection (PFC) drainage: may not be business as usual. *Gut* **66**, 2054–2056 (2017).
250. Brimhall, B. et al. Increased incidence of pseudoaneurysm bleeding with lumen-apposing metal stents compared to double-pigtail plastic stents in patients with peripancreatic fluid collections. *Clin. Gastroenterol. Hepatol.* **16**, 1521–1528 (2018).
251. Larsen, M. & Kozarek, R. A. Management of disconnected pancreatic duct syndrome. *Curr. Treat. Opt. Gastroenterol.* **14**, 348–359 (2016).
252. Rana, S. S. et al. Prevention of recurrence of fluid collections in walled off pancreatic necrosis and disconnected pancreatic duct syndrome: Comparative study of one versus two long term transmural stents. *Pancreatology* **16**, 687–688 (2016).
253. Bang, J. Y. et al. Impact of disconnected pancreatic duct syndrome on the endoscopic management of pancreatic fluid collections. *Ann. Surg.* **267**, 561–568 (2018).
254. Tellez-Avina, F. I. et al. Permanent indwelling transmural stents for endoscopic treatment of patients with disconnected pancreatic duct syndrome: long-term results. *J. Clin. Gastroenterol.* **52**, 85–90 (2018).
255. Rana, S. S., Bhasin, D. K., Rao, C., Sharma, R. & Gupta, R. Consequences of long term indwelling transmural stents in patients with walled off pancreatic necrosis & disconnected pancreatic duct syndrome. *Pancreatology* **13**, 486–490 (2013).
256. Ahmed, M., Aziz, M. U., Mansoor, M. A. & Anwar, S. Vascular complications in cases of acute pancreatitis — CT scan based study. *J. Pak. Med. Assoc.* **66**, 977–989 (2016).
257. Harris, S., Nadkarni, N. A., Naina, H. V. & Vege, S. S. Splanchnic vein thrombosis in acute pancreatitis: a single-center experience. *Pancreas* **42**, 1251–1254 (2013).
258. Gonzelez, H. J., Sahay, S. J., Samadi, B., Davidson, B. R. & Rahman, S. H. Splanchnic vein thrombosis in severe acute pancreatitis: a 2-year, single-institution experience. *HPB* **13**, 860–864 (2011).
259. Easler, J. et al. Portosplenomesenteric venous thrombosis in patients with acute pancreatitis is associated with pancreatic necrosis and usually has a benign course. *Clin. Gastroenterol. Hepatol.* **12**, 854–862 (2014).

260. Xu, W., Qi, X., Chen, J., Su, C. & Guo, X. Prevalence of splanchnic vein thrombosis in pancreatitis: a systematic review and meta-analysis of observational studies. *Gastroenterol. Res. Pract.* **2015**, 245460 (2015).
261. Toque, L. et al. Predictive factors of splanchnic vein thrombosis in acute pancreatitis: a 6-year single-center experience. *J. Dig. Dis.* **16**, 734–740 (2015).
262. Machicado, J. D. & Yadav, D. Epidemiology of recurrent acute and chronic pancreatitis: similarities and differences. *Dig. Dis. Sci.* **62**, 1683–1691 (2017).
263. Cote, G. A. et al. Recurrent acute pancreatitis significantly reduces quality of life even in the absence of overt chronic pancreatitis. *Am. J. Gastroenterol.* **113**, 906–912 (2018).
264. Sankaran, S. J. et al. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. *Gastroenterology* **149**, 1490–1500 (2015).
265. Sliwinska-Mosson, M. et al. The effect of smoking on expression of IL-6 and antioxidants in pancreatic fluids and tissues in patients with chronic pancreatitis. *Pancreatology* **12**, 295–304 (2012).
266. Kirkegard, J., Cronin-Fenton, D., Heide-Jorgensen, U. & Mortensen, F. V. Acute pancreatitis and pancreatic cancer risk: a nationwide matched-cohort study in Denmark. *Gastroenterology* **154**, 1729–1736 (2018).
267. Shinzeki, M. et al. Serum immunosuppressive acidic protein levels in patients with severe acute pancreatitis. *Pancreas* **35**, 327–333 (2007).
268. Chung, S.-D., Chen, K.-Y., Xirasagar, S., Tsai, M.-C. & Lin, H.-C. More than 9-times increased risk for pancreatic cancer among patients with acute pancreatitis in Chinese population. *Pancreas* **41**, 142–146 (2012).
269. Rijkers, A. P. et al. Risk of pancreatic cancer after a primary episode of acute pancreatitis. *Pancreas* **46**, 1018–1022 (2017).
270. Nikkola, J. et al. The long-term prospective follow-up of pancreatic function after the first episode of acute alcoholic pancreatitis: recurrence predisposes one to pancreatic dysfunction and pancreatogenic diabetes. *J. Clin. Gastroenterol.* **51**, 183–190 (2017).
271. Das, S. L. M. et al. Relationship between the exocrine and endocrine pancreas after acute pancreatitis. *World J. Gastroenterol.* **20**, 17196–17205 (2014).
272. Shimosegawa, T. et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* **40**, 352–358 (2011).
273. Badalov, N. et al. Drug-induced acute pancreatitis: an evidence-based review. *Clin. Gastroenterol. Hepatol.* **5**, 648–661 (2007).
274. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT03401190 (2019).
275. Bae, S.-C. & Lee, Y. H. Comparison of the efficacy and tolerability of tocilizumab, sarilumab, and sirukumab in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. *Clin. Rheumatol.* **37**, 1471–1479 (2018).
276. Dellinger, E. P. et al. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. *Ann. Surg.* **256**, 875–880 (2012).

Author contributions
P.J.L. researched data for the article. Both authors contributed equally to all other aspects of the manuscript.

Competing interests
The authors declare no competing interests.

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Reviewer information
Nature Reviews Gastroenterology & Hepatology thanks F. Gorelick, P. Hegyi and J. Mayerle for their contribution to the peer review of this work.