Acute pancreatitis (AP) is an inflammatory disease of the pancreas. Severe cases can cause systemic inflammatory response, distant organ injury, and death. The earliest pathophysiologic theory was stated by Bernard in 1856. He assumed that biliary reflux into the common pancreatic duct as the main cause of AP. In 1901 Opie described a common channel theory, and hypothesized that gallstone migration with occlusion of the biliopancreatic and subsequent biliary reflux into the pancreas causes AP. Until today, multiple pathophysiologic and etiologic theories have been developed and are discussed in the literature.

The differentiation of a mild and severe form of AP was described by Woosley in 1903. A mild edematous pancreatitis is self-limiting without any mortality. The patients only need supportive therapy and recover without persisting complications. However, in 20% of cases, severe necrotizing pancreatitis occurs. Irrespective of a differentiated multimodal therapy, the mortality is up to 30% even today. For these patients, intensive research has been performed in the past century to optimize diagnostics and management. This article reviews pathophysiologic theories as well as the diagnostics and management of severe necrotizing pancreatitis. This review emphasizes the effect of infectious agents initiating AP and the concepts for treatment of infected pancreatic necrosis.

EPIDEMIOLOGY

The incidence of AP has increased in the past decades and varies in different countries. In the United States there are more than 200,000 hospital admissions because of AP every year. Thus the disease is an important medical, surgical, and
financial problem.\textsuperscript{12} Potential causes are the increase of alcohol consumption, obesity, and gallstones.\textsuperscript{13,14}

The cause can be identified in 75\% to 85\% of cases of AP in Western countries.\textsuperscript{7} The mean age of the first attack is the sixth decade.\textsuperscript{14} This may be caused by the high incidence of gallstones in women more than 60 years of age.\textsuperscript{15,16} Worldwide, infectious agents are responsible for AP in less than 1\% of cases. Nevertheless, in India, AP induced by \textit{Ascaris lumbricoides} is the second most frequent cause (23\%) after gallstones.\textsuperscript{17} This shows the regional relevance of infectious causes of AP. Only 20\% of patients develop a severe necrotizing disease. In these cases, the mortality (up to 30\%) is still high, despite improved intensive care treatment.\textsuperscript{5}

**PATHOPHYSIOLOGY**

Regardless of the cause of AP, the pathophysiologic pathways are identical. AP is triggered by intrapancreatic trypsinogen activation to trypsin as well as other enzymes. Intrapancreatic trypsin leads to autodigestion and inflammation of the pancreas. AP occurs when uncontrolled regulatory mechanisms lead to overwhelming trypsinogen production or inactivating mechanisms are defective. These inactivating mechanisms include autolysis of activated trypsin, enzyme compartmentation, synthesis of specific trypsin inhibitors such as serine protease inhibitor Kazal type 1 (SPINK1), low intracellular ionized calcium concentration, or reduced pancreatic fluid secretion with subsequent increased intrapancreatic trypsin as observed in patients with cystic fibrosis.\textsuperscript{7,10,14}

Intracellular trypsin activates several pancreatic proenzymes including phospholipase A2, elastase, and the kinin and complement pathways.\textsuperscript{18} Moreover, neutrophiles, lymphocytes, and macrophages release inflammatory mediators such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor (TNF) $\alpha$, which increase local inflammation, and might conduct systemic inflammation including the systemic inflammatory response syndrome (SIRS).\textsuperscript{7,19}

In addition, the released inflammatory mediators activate the vascular endothelium and induce pancreatic microcirculatory disturbances. These disturbances are characterized by reduced pancreatic blood flow, with subsequent reduced oxygen saturation and increased transmigration of activated leukocytes into the pancreatic tissue.\textsuperscript{20–22} Transmigrated neutrophiles release inflammatory mediators, supporting the ongoing inflammatory process irrespective of the initial trigger. The inflammatory mediator release may lead to SIRS\textsuperscript{19} and might result in an acute respiratory distress syndrome (ARDS) or multiorgan dysfunction syndrome (MODS). This inflammatory cascade is not only induced by local pancreatic inflammatory mediator release but also indirectly by mediators released from the liver. Increased inflammatory cytokines released from the pancreas induce a hepatic inflammatory mediator release and seem to be partly responsible for the development of ARDS and MODS.\textsuperscript{23} Tonsi and colleagues\textsuperscript{14} classify this as the first or early phase of AP caused by the inflammatory mediator release and characterizes day 1 to 14 after onset of symptoms where SIRS, ARDS and MODS are the main clinical problems.\textsuperscript{24} In this early phase, usually no infectious problems occur. Local complications such as infected necrosis, abscess, or cyst formation appear in the late phase of AP, which starts 14 days after onset of disease. In this late phase, infected pancreatic necrosis and septic complications are the main clinical problems leading to the high mortality.\textsuperscript{25}

**CAUSES**

The United Kingdom guidelines\textsuperscript{26} for management of AP arrogate to find the causation for AP in at least 80\% of the cases. Not more than 20\% should be defined as
idiopathic. In developed countries the most common causes for AP are gallstones (38%) and alcohol abuse (36%).

**Biliary Pancreatitis**

Gallstone migration leads to obstruction of the common biliary and pancreatic duct, with subsequent increased pressure in the pancreatic duct leading to unregulated activation of pancreatic enzymes. The highest risk of migration is associated with gallstones of less than 5 mm in size. Gallstones with a diameter of 8 mm or more usually remain in the gallbladder. If there is a previous history of biliary colic and an increase of hepatic enzymes 3 times higher than normal serum concentrations, a biliary pancreatitis is likely. However, 1 out of 4 patients with biliary pancreatitis has normal serum concentrations of hepatic enzymes. Transabdominal ultrasound is the gold standard for detection of gallstones. With this technique, dilatation of the common bile duct may be visible as well as any remaining gallstones in the gallbladder. If there is no gallstone visible, it may still be a biliary pancreatitis without any stone remaining in the bladder. Magnetic resonance cholangiopancreatography or endoscopic ultrasound should be performed to visualize the presence of microlithiasis or other causes of duct obstruction in the absence of stones. If there is any doubt for the diagnosis of abdominal pain, further diagnostic imaging studies, such as computed tomography (CT) or magnetic resonance imaging (MRI) should be performed.

**Alcoholic Pancreatitis**

The second most frequent cause of AP is chronic alcohol abuse. The pathogenesis of alcoholic pancreatitis remains unclear. AP develops in less than 10% of heavy drinkers (>80 g daily intake). Alcohol itself could not induce AP in experimental settings. Development of alcoholic pancreatitis seems to be triggered by both genetic and environmental factors. Thus, failure to inhibit trypsin activity (gene mutation and absence of SPINK1), or failure to wash active trypsin into pancreatic ducts (gene mutation with dysfunction of the cystic fibrosis transmembrane conductance regulator gene, CFTR) might promote alcoholic pancreatitis. There are different theories for how alcohol may lead to AP. Toxic metabolites of alcohol, such as fatty ethyl esters (nonoxidative pathway) and acetaldehyde (oxidative pathway), may directly induce pancreatic damage. Another explanation is based on reflux of biliary or duodenal juice into the pancreas induced by alcohol-related dysmotility of the sphincter Oddi. Guy and colleagues hypothesized that precipitated proteins lead to pancreatic duct obstruction and alcoholic pancreatitis. Alcoholic pancreatitis may also develop as a consequence of pancreatic ischemia induced by alcohol itself.

**Pancreatitis After Endoscopic Retrograde Cholangiopancreatography**

In a cohort of 2347 patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) Freeman and colleagues showed a postinterventional AP in 5.4% of patients and an asymptomatic hyperamylasemia in 35% to 70%. The risk of this postinterventional pancreatitis is higher when it is performed for dysfunction of the sphincter rather than removal of gallstones. Further risk factors for postinterventional pancreatitis are young age, female sex, number of cannulation attempts of the papilla, and poor emptying of the pancreatic duct after opacification. Prevention in high-risk patients may be achieved with a temporary pancreatic stent.
**Infectious Pancreatitis**

Less than 1% of APs are induced by infectious agents. However, in most of these cases, other potential causes (eg, gallstones) have not been excluded in a standardized fashion. Several infectious causes have been described to initiate AP.

Viral infections including measles, Coxsackie B virus, Hepatitis B virus, cytomegalovirus, Herpes simplex virus, varicella-zoster, and human immunodeficiency virus might induce AP. Other viruses, such as Epstein-Barr, vaccinia, rubella, adenovirus, and rubeola have been believed to be associated with AP in several reports, but the evidence for causality is weak and questionable.

Bacteria may cause AP by ascending from the small bowel, descending from the biliary tree, or via hematogenous or lymphatic spread. Identified bacteria include Mycoplasma pneumoniae, Salmonella thyphi, Leptospira, Yersinia enterocolica, Yersinia pseudotuberculosis, Campylobacter jejuni, Mycobacterium tuberculosis, and Mycobacterium avium. There are also reports about AP being caused by legionellosis, brucellosis, Actinomyces, and Nocardia.

Fungal infections rarely affect the pancreas and are classified as molds or yeasts. Among the molds, Aspergillus has been detected in a patient with lymphoma, causing thrombotic infarction, necrosis, and inflammation of the pancreas. The yeasts Cryptococcus neoformans, Coccidioides immitis, Paracoccidioides brasiliensis, Histoplasma capsulatum, and Pneumocystis carinii have been detected in patients with AP, but a causal association with AP has not been proved.

Parasites might cause AP. Among those parasites, A lumbricoides and Echinococcus granulosus cause AP by pancreatic duct obstruction. A lumbricoides can cause AP by migration of worms into the duodenal papilla, and this is the second most common cause of AP in India. The worms cause AP by migrating into, and obstructing, the pancreatic duct. In cases of migration into the distal parts of the pancreatic duct, abscess formation is frequently observed. However, E granulosus may appear as a space-occupying pancreatic lesion leading to AP by indirect pancreatic duct obstruction.

**Anatomic Abnormalities**

A pancreas divisum is observed in about 7% of autopsies. This embryologic abnormality is the consequence of a missing fusion of the dorsal and ventral pancreatic duct systems. The lack of the ductal fusion can lead to insufficient drainage of the pancreatic duct in some cases, with a subsequent increase of pancreatic pressure and attacks of AP. Whether anatomic abnormalities or sphincter dysfunctions may cause pancreatitis is a matter of controversy in the literature.

Miscellaneous other causes of AP are metabolic disorders such as hypertriglyceridemia and hypercalcemia, pancreatic tumors with duct obstruction, several drugs (eg, azathioprine, thiazides, and estrogens), and trauma. Major surgery, especially cardiac surgery, with subsequent pancreatic hypoperfusion and ischemia, might also induce AP.

There are several hereditary forms of AP. The inability to inhibit active intrapancreatic trypsin, as observed in patients with SPINK1 mutations, as well as premature trypsinogen activation into trypsin by mutations of the cationic trypsinogen gene (PRSS1), and CFTR gene mutations, can lead to acute and chronic pancreatitis in children and adults.

Another rare form of AP is autoimmune pancreatitis. Patients with this condition frequently present with an inflammatory mass in the pancreas that is often difficult to differentiate from a pancreatic malignancy. The diagnosis of autoimmune
pancreatitis can be suspected by MRI, histology, and serum analyses. Patients may present with increased serum immunoglobulin (Ig) G4 levels. The therapy is the application of steroids, which may also be used as a diagnostic short-term treatment of 2 weeks.\footnote{\textsuperscript{14,82}}

**DIAGNOSIS**

Typical clinical presentation of AP is a sudden upper abdominal pain that often radiates to the back. Patients often suffer severe nausea and vomiting. In some patients, clinical examination shows ecchymoses in the flanks (Gray-Turner sign) or in the peri-umbilical region (Cullen sign). These patients usually have severe AP and a high mortality.\footnote{\textsuperscript{83}} Serum analysis shows an early increase of pancreatic amylase and lipase.\footnote{\textsuperscript{84}} Amylase or lipase levels more than 3 times higher than normal hint at the diagnosis of AP. However, a lack of increased amylase or lipase levels does not exclude a diagnosis of AP. Amylase levels may reduce to normal 4 days after onset of clinical symptoms. Nineteen percent of patients with AP show normal amylase levels at hospital admission, and there are various other diseases leading to hyperamylasemia.\footnote{\textsuperscript{7,85,86}} Lipase, which has a longer half-life than amylase in serum, has a higher sensitivity, specificity, and overall accuracy for the diagnosis of AP.\footnote{\textsuperscript{26,84,87}} Other diagnostic markers are not routinely available and include trypsinogen activation peptide (TAP) and trypsinogen–2.\footnote{\textsuperscript{81,88}}

Imaging procedures can be used to diagnose AP if other abdominal disease is certain or biliary pancreatitis is suspected. Transabdominal ultrasound may detect gallstones, sludge, or dilatation of the cystic duct. Contrast medium–enhanced computed tomography (CM-CT) can be used to confirm the diagnosis of AP (sensitivity 87%–90%, specificity 90%–92%) in the early phase or may detect local complications after more than 4 days.\footnote{\textsuperscript{89}} CM-CT is useful to rule out other diseases causing severe abdominal pain.

**PREDICTION OF SEVERITY**

Eighty percent of patients with AP show mild self-limiting courses of the disease with no need for special intensive therapy. Supportive therapy, including analgesia, fluid supplementation, and temporary cessation of enteral nutrition, leads to a restitution ad integrum. Nevertheless, 20% of patients develop a severe AP with a mortality of up to 30%.\footnote{\textsuperscript{5}} The need for early aggressive treatment in these patients in intensive care units (ICUs) by a team of specialized physicians shows the importance of early separation between patients with mild disease and those with severe disease.\footnote{\textsuperscript{88}}

Several scores have been developed to predict the course of AP. The Ranson score, including 11 items, and the Glasgow severity scoring system, including 9 items, can be completed 48 hours after hospital admission (Table 1; Box 1).\footnote{\textsuperscript{90,91}} The Acute Physiology and Chronic Health Evaluation II (APACHEII) score includes 12 items, and a daily measurement allows an assessment of disease progression.\footnote{\textsuperscript{92,93}} Because obesity has been demonstrated to be an additional factor predicting severe disease, the APACHEII score has been modified to the APACHE–O score, including 2 items of obesity.\footnote{\textsuperscript{94}} Brown and colleagues\footnote{\textsuperscript{95}} published a Panc 3 score predicting the clinical course of severe AP by hematocrit greater than 44 mg/dL, body mass index more than 30, and pleural effusion on chest radiograph. Future studies will establish the clinical effectiveness of these scoring systems.

An important predictive factor for the outcome of severe pancreatitis is the assessment of organ failure. Johnson and Abu-Hilal\footnote{\textsuperscript{96}} showed that organ failure for more than 48 hours is associated with a mortality of up to 50%, whereas mortality was 0% when
organ failure was present for less than 48 hours after admission. This finding shows the importance of clinical evaluation including organ failure. The sequential organ failure assessment (SOFA) score helps clinicians to assess organ injury and SIRS. It should be performed daily for assessment of disease progression (Table 2).

If pancreatic necrosis is present in AP, the mortality increases from 1% to between 10% and 23%, showing the importance of early detection of pancreatic necrosis. CM-CT is the gold standard for detecting pancreatic necrosis and should be performed if necrosis is suspected on day 5 after onset of clinical symptoms, because CM-CT might underestimate the complete extend of necrosis and the final severity of the disease if performed earlier (Fig. 1A). The radiological findings can be categorized by a CT severity index (CTSI) as proposed by Balthazar (Table 3). If the CTSI is 5 or higher, patients have a higher mortality, longer hospital stay, and a higher risk for undergoing surgical necrosectomy.

Usually no follow-up CT is required because the local situation in severe AP remains stable in most cases. Nevertheless, follow-up CT may be useful for detection of local complications, including cysts, abscess, or gas bubbles, indicating infected necrosis.

Serum parameters may also be used for predicting severity of the disease. C-reactive protein (cutoff 150 mg/L) predicts pancreatic necrosis at 48 to 72 hours after onset of symptoms with a sensitivity and specificity of 80%. Other special markers can predict severe disease earlier but are not commonly available. Serum procalcitonin, urinary TAP, and trypsinogen-2 may be useful to discriminate between mild and severe disease directly at hospital admission.
<table>
<thead>
<tr>
<th>Organ System Involved</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>1</td>
</tr>
<tr>
<td>No hypotension</td>
<td></td>
</tr>
<tr>
<td>MAP &lt; 70 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Dopamine or dobutamine (any dose)</td>
<td></td>
</tr>
<tr>
<td><strong>2</strong></td>
<td></td>
</tr>
<tr>
<td>Dopamine &gt; 5 μg per kg per min or adrenaline (epinephrine) &lt; 0.1 μg per kg per min or noradrenaline (norepinephrine) &lt; 0.1 μg per kg per min</td>
<td></td>
</tr>
<tr>
<td><strong>3</strong></td>
<td></td>
</tr>
<tr>
<td>Dopamine &gt; 15 μg per kg per min or adrenaline &gt; 0.1 μg per kg per min or noradrenaline &gt; 0.1 μg per kg per min</td>
<td></td>
</tr>
<tr>
<td><strong>4</strong></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>1</td>
</tr>
<tr>
<td>Pao2/Fio2 (mm Hg)</td>
<td>&gt;400</td>
</tr>
<tr>
<td>400–300</td>
<td></td>
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<tr>
<td>300–200</td>
<td></td>
</tr>
<tr>
<td>200–100*</td>
<td></td>
</tr>
<tr>
<td>≤100*</td>
<td></td>
</tr>
<tr>
<td>Renal creatinine (μmol/L)</td>
<td>&lt;100</td>
</tr>
<tr>
<td>100–200</td>
<td></td>
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<tr>
<td>200–350</td>
<td></td>
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<td>350–500</td>
<td></td>
</tr>
<tr>
<td>&gt;500</td>
<td></td>
</tr>
<tr>
<td>Neurologic Glasgow Coma Score</td>
<td>15</td>
</tr>
<tr>
<td>14–13</td>
<td></td>
</tr>
<tr>
<td>12–10</td>
<td></td>
</tr>
<tr>
<td>9–7</td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td></td>
</tr>
<tr>
<td>Hematological platelet count (×10^9/L)</td>
<td>&gt;150</td>
</tr>
<tr>
<td>150–100</td>
<td></td>
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<tr>
<td>100–50</td>
<td></td>
</tr>
<tr>
<td>20–50</td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td></td>
</tr>
<tr>
<td>Hepatic bilirubin (μmol/L)</td>
<td>&lt;20</td>
</tr>
<tr>
<td>20–60</td>
<td></td>
</tr>
<tr>
<td>60–120</td>
<td></td>
</tr>
<tr>
<td>120–240</td>
<td></td>
</tr>
<tr>
<td>&gt;240</td>
<td></td>
</tr>
</tbody>
</table>

The SOFA score is calculated as the sum of the scores for the individual organs.14

**Abbreviations:** Fio2, fraction of inspired oxygen; MAP, mean arterial pressure.

* These values are calculated with ventilatory support.
CLINICAL MANAGEMENT OF AP

Mild forms of AP are usually treated with analgesia, fluid resuscitation, antiemetics, and oxygen administration. Enteral nutrition should be continued if tolerated. Causative therapy may be cholecystectomy for biliary pancreatitis, and is recommended to be performed during the same hospital stay before hospital discharge. Prophylaxis of recurrent pancreatitis include restriction of alcohol in alcoholic pancreatitis or change of medications when medication-induced AP is suspected.

Severe AP still has a high mortality and requires a specialized multidisciplinary team including intensivists, gastroenterologists, interventional radiologists, and surgeons. For these patients, rigorous fluid resuscitation, close monitoring, nutritional support, and management of pancreatic necrosis are essential.

During fluid application, fluid loss into the third space makes it important to keep an adequate intravascular fluid volume. Cardiovascular, respiratory, and renal monitoring is mandatory to manage organ dysfunctions adequately. For suppression of exocrine pancreatic function, parenteral nutrition has been advocated in the early phase of severe AP. However, intestinal mucosal atrophy is a complication of parenteral nutrition and promotes bacterial translocation from the gut as well as enhanced

<table>
<thead>
<tr>
<th>Grade</th>
<th>CT Finding</th>
<th>Points</th>
<th>Percentage</th>
<th>Additional Points</th>
<th>Severity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Normal pancreas</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>Pancreatic enlargement</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>Pancreatic inflammation and/or peripancreatic fat</td>
<td>2</td>
<td>&lt;30</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>D</td>
<td>Single peripancreatic fluid collection</td>
<td>3</td>
<td>30–50</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>E</td>
<td>Two or more fluid collections and/or retroperitoneal air</td>
<td>4</td>
<td>&gt;50</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

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Fig. 1. (A) Contrast medium–enhanced CT of necrotizing pancreatitis. Gas bubbles indicate infected necrosis. (B) Gram staining of aspirates after fine needle aspiration biopsy showing gram-negative bacteria in infected necrosis.

Table 3
CTSI (score greater than 5 is associated with higher mortality)
proinflammatory response. Moreover, surgical interventions, infections, and noninfectious complications are reduced when early enteral nutrition is applied. However, there is no proven reduction of mortality compared with parenteral nutrition. Thus, early enteral nutrition is recommended in the treatment of AP. In addition, some studies suggest that enteral feeding can be applied by nasogastric or nasojejunal tube.

The prophylactic use of probiotics has been advocated. However, a recent multicenter randomized controlled trial showed not only no improvement of the disease by the application of probiotics, but an increased mortality. Therefore, probiotics should not be used in patients with severe AP, although the reason for the increased mortality remains unclear.

The use of prophylactic antibiotics to prevent infection of pancreatic necrosis is highly controversial. Bacteria infecting pancreatic necrosis are usually gut derived. They translocate via the impaired gut mucosal barrier and reach the pancreatic necrosis by lymphatic vessels. Before prophylactic antibiotics were used routinely, gut-derived infectious agents usually included \textit{Escherichia coli} and \textit{Bacteroides}. \textit{Candida} species were found in 2.6%. Nevertheless, the clinical role of fungal contamination is controversial because it may be only a colocalization phenomenon without clinical evidence. Because prophylactic antibiotics are widely used, a shift from gram-negative to gram-positive bacteria is observed. However, no increased resistance to antibiotics or increasing fungal contamination was reported. Despite the low accumulation of antibiotics in pancreatic necrotic tissue, a potential advantage is the avoidance of systemic septic complications. This is supported by recent randomized controlled trials. Various studies and meta-analyses recommend the use of prophylactic antibiotics, whereas others do not. There is no clear evidence for the benefit of prophylactic antibiotics in severe AP. Most of the studies are underpowered. The authors do not expect a new, adequately powered, randomized controlled trial to definitively answer the question of whether prophylactic antibiotics should be applied to patients. It will be an individual decision of the treating centers, the local guidelines, and economic possibilities. The International Association of Pancreatologists (IAP) guideline from 2002 recommends prophylactic broad-spectrum antibiotics for prevention of infected necrosis. Patients with pancreatic necrosis of more than 50% may profit from this approach. However, there seems to be no benefit regarding patients’ survival. The available evidence supports the use of prophylactic imipenem, with or without clistatin, to address infected pancreatic necrosis.

The first 14 days after onset of symptoms are mainly dominated by conservative ICU management. Only for biliary AP the United Kingdom guidelines recommend an early intervention by ERCP, including endoscopic sphincterotomy (ES), within the first 72 hours after onset of symptoms. In contrast, the 2007 guidelines of the American Gastroenterology Association advocate no early ERCP for patients with biliary AP when cholangitis signs are absent. For these patients with severe biliary AP, a delayed cholecystectomy is recommended after full recovery of acute inflammation and AP.

There is increasing incidence of infected pancreatic necrosis with potential need of interventions after day 14 of the disease. In cases of infected pancreatic necrosis, there is a significant increase in morbidity and mortality. Infected necrosis may be suspected when gas bubbles appear in CM-CT. The IAP guidelines advocate a fine needle aspiration biopsy of pancreatic necrosis to verify infection for patients with clinical signs or symptoms of sepsis. If infection is proved, interventional drainage or surgical therapy is needed (see Fig. 1).
INTERVENTIONAL/SURGICAL THERAPY FOR INFECTED PANCREATIC NECROSIS

The time point for surgical or interventional procedures has changed in the last decades. There was a mortality of up to 65% for patients undergoing early surgical necrosectomy. Today, delayed surgical interventions are advocated and interventions and surgery should be postponed for as long as possible. Ideally, necrosectomy should be performed on day 30 after onset of symptoms. Delayed necrosectomy allows demarcation of the necrotic tissue from surrounding vital tissue and offers an organ-saving surgical approach. This concept has reduced the mortality significantly.

There are multiple possible ways to perform a necrosectomy, including interventional drainage, endoscopic necrosectomy, minimally invasive surgery, and open surgery.

Percutaneous, CT-guided, interventional drainage of infected pancreatic necrosis seems to be a bridging procedure in instable patients before surgical necrosectomy is performed in a second procedure. The drainages are suitable for draining abscesses, but an extended necrosectomy is rarely possible or only performed in multiple sessions.

Endoscopic necrosectomy is usually performed with the assistance of endoscopic ultrasound. The most common approach is through the dorsal side of the stomach into the necrotic cavity. It is performed as an interventional endoscopic procedure, but may be called natural orifice transluminal endoscopic surgery. A nasocystic catheter is left after necrosectomy for continuous lavage until the necrotic tissue is removed. The procedure usually needs repetitive sessions until the necrosectomy is completed. The largest study available today has recently been published by Seifert and colleagues and includes 93 patients undergoing endoscopic necrosectomy for pancreatic necrosis. There was an average of 6 sessions per patient to achieve complete necrosectomy. There was proven infected necrosis only in 54% of the patients, which makes the need for intervention in this cohort of patients doubtful. The mortality of 7.5% in this context is significant. Endoscopic necrosectomy requires an excellent endoscopic technique. Whether morbidity and mortality is comparable with conventional surgical approaches needs to be evaluated in prospective randomized studies. One problem of the transgastric or transduodenal approach is that necrotic areas on the left side might not be reached safely. Thus, a combined approach together with the percutaneous intervention (as described later) may be a solution in these cases.

Surgical procedures for necrosectomy focus on elimination of necrotic tissue and removal of postoperative debris and exudates. The aim of organ-saving necrosectomy is to preserve the exocrine and endocrine function of the pancreas. There are 4 conventional surgical procedures described in the literature: (1) open necrosectomy with open packing and planned relaparotomy, (2) open necrosectomy with planned relaparotomies, (3) open necrosectomy with continuous postoperative lavage of the lesser sac and retroperitoneum, and (4) open necrosectomy with closed packing.

The open necrosectomy with open packing and planned relaparotomies includes repetitive laparotomies every 48 hours after primary necrosectomy until necrotic tissue has been completely removed and infection is controlled. The abdominal cavity is not closed between the laparotomies and the repetitive lavage procedures. When open necrosectomy with staged and repeated lavages is performed, planned relaparotomies are performed on alternate days in the operating theater until all infected necrosis has been eliminated. Some surgeons use abdominal wall zips for easier access to the abdominal cavity in some cases.
The following 2 surgical procedures (open necrosectomy combined with continuous postoperative lavage of the lesser sac and retroperitoneum, and open necrosectomy with closed packing) differ from the techniques mentioned earlier because of the aim to explore the abdominal cavity only once without repeated laparotomies. A continuous drainage of debris via the placed drains is essential. The advantage of a single exploration of the abdominal cavity is the avoidance of further contamination and the reduction of operative trauma. Thus, fistula and bleeding complications are reduced by these techniques compared with the open packing and staged relaparotomies.125

Open necrosectomy with continuous lavage of the lesser sac and retroperitoneum is performed over 2 to 4 flushing drains. A lavage with 10 to 15 l/24 hours is performed in the first days for sufficient drainage of debris and exudates. This procedure seems to have the lowest mortality and is advocated by the authors.143–150

Open necrosectomy with closed packing includes placing of gauze-filled Penrose drains and suction drains after primary necrosectomy. These drains can usually be removed after 7 days.125,151 The currently available data concerning the 4 techniques of open necrosectomy are listed in Table 4.

Apart from the classic open necrosectomy, minimally invasive procedures for necrosectomy have been developed in the last decades. The rationale was to minimize operative trauma and to avoid bacterial contamination and translocation by

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Mortality of open necrosectomy procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technique</td>
<td>Patients (n)</td>
</tr>
<tr>
<td>Open Packing</td>
<td></td>
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<tr>
<td>Bradley 1993133</td>
<td>71</td>
</tr>
<tr>
<td>Branum et al 1998134</td>
<td>50</td>
</tr>
<tr>
<td>Bosscha et al 1998132</td>
<td>28</td>
</tr>
<tr>
<td>Nieuwenhuijs et al 2003135</td>
<td>38</td>
</tr>
<tr>
<td>Planned Relaparotomies</td>
<td></td>
</tr>
<tr>
<td>Sarr et al 1991141</td>
<td>23</td>
</tr>
<tr>
<td>Tsiotos et al 1998142</td>
<td>72</td>
</tr>
<tr>
<td>Closed Packing</td>
<td></td>
</tr>
<tr>
<td>Fernandez-del Castillo et al 1998151</td>
<td>64</td>
</tr>
<tr>
<td>Rodriguez et al169</td>
<td>167</td>
</tr>
<tr>
<td>Closed Continuous Lavage</td>
<td></td>
</tr>
<tr>
<td>Beger et al 1988143</td>
<td>95</td>
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the surgical procedure. Today, several minimally invasive techniques are known. The most common gateways to the necrotic area are either transperitoneal laparoscopic or the retroperitoneal approach. The advantage of the retroperitoneal approach is the avoidance of peritoneal contamination during necrosectomy. The access to the necrotic tissue usually follows preoperative CT-guided placement of interventional drains. After debridement, drains are placed in the cavity for postinterventional lavage. The potential disadvantage is that any complications, including colonic ischemia, cannot be seen. There is also no opportunity to perform a simultaneous cholecystectomy or placement of a jejunal feeding catheter. The transperitoneal laparoscopic approach usually explores the lesser sac via a transmesocolic route. This procedure is also performed by a hand-assisted laparoscopic approach, to allow manual preparation. However, the retroperitoneal approach seems to be the most widely accepted today. It seems to be a safer procedure; it was advocated first by Carter and colleagues, and since then has been applied by many centers. The potential disadvantage of the minimally invasive procedures is an incomplete necrosectomy and potentially an increased local complication rate. The current data on success and complication rates of minimally invasive approaches are outlined in Table 5. A theoretic advantage of a reduced systemic injury is being evaluated in a randomized multicenter trial (the PANTER trial). The results of the PANTER trial are anticipated soon (open necrosectomy vs minimally invasive necrosectomy).

Irrespective of the procedure performed, complications such as pancreatic or enterocutaneous fistula remain common and seem to be associated with extended necrotic areas. These fistulas are recommended to be treated conservatively until pancreatitis is resolved. A further severe complication may be postoperative bleeding. If bleeding occurs, the primary treatment approach should include embolization by an interventional radiologist rather than a surgical approach. Late complications may be organized sterile necrosis, or cysts, as well as pancreatic insufficiency. Today, no advantage of minimally invasive surgery compared with open surgery has been shown in a randomized controlled trial.

<table>
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<tr>
<th>Series</th>
<th>n</th>
<th>Infection (%)</th>
<th>Mortality (%)</th>
<th>Success (%)</th>
<th>Complications (%)</th>
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Abbreviation: N/A, not available.
In summary, severe necrotizing pancreatitis is a disease with high mortality, even today. It should be managed by an interdisciplinary specialized team. Diagnostic CM-CT is still the gold standard for staging the local situation and should be performed at 5 days after onset of the disease. The SOFA score offers a good evaluation of organ dysfunction in severe disease, which is associated with increased mortality. In severe biliary AP, an early ERCP with ES within 72 hours is advocated when cholangitis signs are present. The primary treatment of AP is conservative. If surgery is needed for infected necrosis, the ideal time point is 3 to 4 weeks after onset of the disease. Today, minimally invasive or open surgical approaches, as well as endoscopic or radiological interventions, might be used, depending on the expertise in the center.

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