In acute pancreatitis, enzymatic autodigestion of the pancreas very rapidly activates a cascade of mediator substances, producing a primarily abacterial inflammatory reaction. In severe cases, this reaction goes far beyond the borders of the pancreas itself and may develop into a systemic inflammatory response syndrome (SIRS). Because of the fulminant course of this entity, the temporal window for early, goal-directed treatment is very brief. Once this window is past, the treatment is limited to symptomatic measures. In this review article, we will discuss recent findings that reveal the importance of basic historical, clinical, and laboratory data in the management of this disease.

In order to help treating physicians answer 12 key questions, the authors have selectively reviewed the literature on this subject with special attention to the guidelines of the German Society for Digestive and Metabolic Diseases (Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten, DGVS), the German Surgical Society (Deutsche Gesellschaft für Chirurgie, DGCH), and the German Visceral Surgery Society (Deutsche Gesellschaft für Viszeralchirurgie, DGVC) (1), as well as those of the American College of Gastroenterology (2). The current guidelines (1, 2, e7), the references listed in them, and the relevant “hits” of an electronic literature search were selectively consulted in the light of the 12 key questions that were posed.

**Does the patient have pancreatitis?**

The major clinical finding in pancreatitis is severe epigastric pain with band-like radiation to the back. A history of prior attacks of pancreatitis is of prognostic importance, because repeated attacks are less likely to take a severe or necrotizing course than the first attack.
A characteristic feature of pancreatitis is “rubber belly,” i.e., no more than moderate tension of the abdominal wall muscles because of the retroperitoneal location of the pancreas. The pancreatic skin signs, i.e., a livid or brownish discoloration around the umbilicus (Cullen sign) or on the flank (Grey-Turner sign), are rare and prognostically unfavorable.

Among a multitude of laboratory tests, some of which are quite costly, none have been found more useful than the measurement of serum lipase concentration to confirm the diagnosis of pancreatitis. Acute pancreatitis can be diagnosed only on the basis of the typical clinical findings and the elevated serum lipase concentration.

**BOX 1**

**Symptoms of acute pancreatitis**

- Band-like abdominal pain: 90%
- Vomiting: 80%
- Paralytic (sub-)ileus: 70%
- Fever: 60%
- “Rubber belly”: 60%


**BOX 2**

**Causes of pancreatitis**

- Common
  - Gallstones: 50–60%
  - Alcohol: 30–40%
- Rare
  - Hyperlipidemia (types I, IV, V)
  - Viral infection (mumps)
  - Post-ERCP
  - Posttraumatic/postoperative
  - Hypercalcemia
  - Medications (e.g., azathioprine, valproic acid, virustatic agents)
  - Pancreas divisum
  - Hereditary pancreatitis
- Diagnosis of exclusion
  - “Idiopathic”


ERCP = endoscopic retrograde cholangiopancreatography
diagnosis of pancreatitis. The sensitivity and specificity of this test are both in the 82–100% range for a threefold elevation above the norm (1, 2, e1–3). Serum amylase measurement is comparably sensitive, but less specific. The determination of lipase and amylase offers no greater diagnostic yield than that of lipase alone (3). The degree of elevation of lipase, however, cannot be considered a reliable correlate of the severity of pancreatitis; in total pancreatic necrosis, for example, the serum lipase concentration can fall rapidly and even "renormalize" (4).

What is the cause? Is the patient suffering from biliary pancreatitis?

Etiologic diagnosis has consequences both for prognostication (alcoholic pancreatitis carries a worse prognosis) and for therapy (in biliary pancreatitis, treatment involves endoscopic retrograde cholangiography [ERC]). Here, too, the clinical history (alcohol consumption, prior gallstones, colic, loss of stool coloration, dark urine) and the physical examination are of major value. By far the most common causes are gallstones and alcoholism (box 2).

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition of the Ranson criteria</strong>*</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Initial examination</strong></td>
</tr>
<tr>
<td>Age &gt; 55 years</td>
</tr>
<tr>
<td>Leukocyte count &gt; 16 G/l</td>
</tr>
<tr>
<td>GOT &gt; 255 U/l</td>
</tr>
<tr>
<td>LDH &gt; 350 U/l</td>
</tr>
<tr>
<td>Blood sugar &gt; 200 mg/dl</td>
</tr>
<tr>
<td>Total score at 48 hours</td>
</tr>
<tr>
<td>0–2 points</td>
</tr>
<tr>
<td>3–4 points</td>
</tr>
<tr>
<td>5–6 points</td>
</tr>
<tr>
<td>&gt; 6 points</td>
</tr>
</tbody>
</table>

GOT, glutamate-oxaloacetate transaminase; LDH, lactate dehydrogenase.

It is important for biliary pancreatitis to be distinguished from all other forms early on in the course of the illness, because of the availability of directed treatment of this entity with the endoscopic removal of obstructing stones. The diagnosis of biliary pancreatitis is suggested by an appropriate clinical history and further supported by elevation of the cholestasis parameters AP, gamma-GT, and bilirubin, and of the transaminases. Elevation of the GPT to more than 300% of the norm has a 95% positive predictive value (PPV) for a biliary origin of pancreatitis.

In addition to these laboratory parameters, ultrasonography of the gall bladder and biliary pathways is highly sensitive and specific. If biliary pancreatitis cannot be definitively excluded by the laboratory parameters mentioned above and by conventional ultrasonography, endoscopic ultrasonography (EUS) can be of great help. EUS is superior to conventional ultrasonography particularly with respect to the demonstration of prepapillary concretions (5).

**Mild or severe pancreatitis?**

The Ranson and Apache II scores and the CRP have no useful predictive value till 48 hours after the initial examination.

**Laboratory gold standard**

An elevation of the C-reactive protein concentration above 15 mg/dl (150 mg/l) implies the presence of necrotizing pancreatitis.
A recent study on 215 patients with symptomatic cholelithiasis showed that EUS is also superior to diagnostic endoscopic retrograde cholangiopancreatography (ERCP) for the demonstration of this entity. The sensitivity of EUS for bile duct concretions was found to be 97%, as compared to 67% for ERC(P) (a significant difference, with p=0.002). The improvement in sensitivity was particularly marked for concretions less than 4 mm in diameter. Computerized tomography (CT) and costly laboratory testing for markers such as procalcitonin were of no additional diagnostic benefit.

**Does the patient have a severe/necrotizing or a mild/edematous form of pancreatitis?**

This distinction is of major prognostic importance, because severe/necrotizing pancreatitis requires early transfer to an intensive care unit for monitoring and treatment. Despite the major diagnostic advances of the past few decades, early prediction of the severity of pancreatitis continues to be unsatisfactory.

The following methods are used to predict the risk of severe/necrotizing pancreatitis:

- The Ranson criteria (e4, *table 1*) are more than 30 years old and are computed from 5 parameters measured upon the admission of the patient to the hospital and 6 further ones that can only be determined 48 hours later. Thus, a prognosis can only be given 2 days after the initial clinical assessment. Patients with a Ranson score of 3 or above are assumed to have severe pancreatitis.

- The APACHE II score (e5) is a score derived from intensive care medicine incorporating 12 acute parameters, including separate points for age and for prior chronic illnesses (*table 2*). Patients with an APACHE II score of 8 or above are assumed to have severe pancreatitis. Like the Ranson criteria, this relatively complex scoring system cannot be used to formulate a fairly reliable prognosis till 48 hours have elapsed from the patient's admission to the hospital. The APACHE-II score on admission to the hospital, if used to predict severe pancreatitis, has a sensitivity of only 36% and a positive predictive value of only 24% (7).

- Computerized tomography (CT) with the intravenous administration of contrast medium can reveal areas of necrosis in the pancreas, which, unlike the surrounding vital tissue, do not take up contrast medium (e6). It has been shown, however, by the serial examination of 102 patients who underwent CT scanning 2 and 7 days after admission that the initial CT does not pictorially represent the future extent of the disease; thus, CT underestimates the severity of disease in many cases (8) and yields adequate prognostic information only when performed 7 days after admission. In CT scans obtained 2 days after admission, 37% of patients who went on to have mild pancreatitis, and an equal percentage of those who went on to have severe pancreatitis, were found to have no necrotic areas in the pancreas; on day 7, the percentages were 79% and 38%, respectively (p<0.001). Early computed tomography is thus less prognostically reliable than once thought (Balthazar criteria, 1990) and is only rarely needed to make the diagnosis of pancreatitis. CT can be used, however, to exclude other entities in the differential diagnosis. The same holds for magnetic resonance imaging (MRI).

- The laboratory gold standard is C-reactive protein (CRP): an elevation above 15 mg/dl (150 mg/l) is evidence of necrotizing pancreatitis (e7). CRP measurement is a better test than the measurement of cytokines such as IL-1, IL-8, and TNFα and is at least as good as the measurement of IL-6 (e7). Furthermore, CRP measurement is quicker, cheaper, and universally available. There is as yet no evidence to support any additional diagnostic or predictive benefit over the measurement of CRP alone from the measurement of other clinical chemical parameters such as procalcitonin, "pancreatitis-associated protein,"
leukocyte elastase, phospholipase A2, or ribonuclease. Because the rise of CRP is delayed, this parameter is adequately predictive only when measured 2–3 days after the onset of the illness. In summary, it can be stated that the other laboratory parameters mentioned here are of insufficient predictive value to be used in the primary care setting, as they only become useful 48 hours after onset. In primary care, simple historical data and laboratory chemistry are the most important pieces of information available.

The timing of pain onset is very important. Patients with severe pancreatitis are significantly more likely to seek medical help within 24 hours of the onset of pain than patients with edematous pancreatitis. In one study (11), the mean interval from the onset of pain to presentation to the primary care physician was 18 hours in patients who went on to develop severe pancreatitis.

### TABLE 2

**APACHE II score**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>4 points</th>
<th>3 points</th>
<th>2 points</th>
<th>1 point</th>
<th>0 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal temperature (°C)</td>
<td>≥ 41</td>
<td>39–40.9</td>
<td>30–31.9</td>
<td>32–33.9</td>
<td>36–38.4</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>≥ 160</td>
<td>130–159</td>
<td>110–129</td>
<td>50–69</td>
<td>70–109</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>≥ 180</td>
<td>140–179</td>
<td>110–139</td>
<td>55–69</td>
<td>70–109</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>≥ 50</td>
<td>35–49</td>
<td>6–9</td>
<td>25–34</td>
<td>12–24</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>≥ 7.7</td>
<td>7.6–7.69</td>
<td>7.25–7.32</td>
<td>7.5–7.59</td>
<td>7.33–7.49</td>
</tr>
<tr>
<td>Po2 if FIO2 &gt; 0.5:</td>
<td>&lt; 7.15</td>
<td>7.15–7.24</td>
<td>–</td>
<td>–</td>
<td>7.33–7.49</td>
</tr>
<tr>
<td>HCO3⁻ if FIO2 &lt; 0.5:</td>
<td>≥ 52</td>
<td>41–51.9</td>
<td>15–17.9</td>
<td>–</td>
<td>22–31.9</td>
</tr>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>≥ 180</td>
<td>160–179</td>
<td>155–159</td>
<td>150–154</td>
<td>130–149</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>≥ 7</td>
<td>6–6.9</td>
<td>2.5–2.9</td>
<td>3.5–3.4</td>
<td>3.5–5.4</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl) double points in acute renal failure</td>
<td>≥ 3.5</td>
<td>2.0–3.4</td>
<td>1.5–1.9</td>
<td>–</td>
<td>0.6–1.4</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>≥ 60</td>
<td>50–59.9</td>
<td>46–49.9</td>
<td>–</td>
<td>30–45.9</td>
</tr>
<tr>
<td>Leukocytes (G/l)</td>
<td>≥ 40</td>
<td>20–39.9</td>
<td>15–19.9</td>
<td>–</td>
<td>3–14.9</td>
</tr>
<tr>
<td>Glasgow Coma Scale (GCS), from 1 to 15</td>
<td>≥ 55</td>
<td>55–64</td>
<td>45–54</td>
<td>–</td>
<td>&lt; 44 years</td>
</tr>
</tbody>
</table>

5 points for chronic organ failure: NYHA grade IV hepatic cirrhosis, severe COPD, chronic dialysis, or immunosuppression

- **BGA** = blood gas analysis, **NYHA** = New York Heart Association, **COPD** = chronic obstructive pulmonary disease

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**Prognostically unfavorable parameters**

- **Leukocytosis above 16 G/l**
- **Age > 55 years**
- **BMI > 30**
- **Serum calcium concentration < 2 mmol/l**
- **Lactate dehydrogenase > 350 U/l**
develop necrotizing pancreatitis and 38 hours in patients who went on to have edematous pancreatitis. This difference was significant (p=0.005).

- The Ranson criteria already incorporate the finding that hyperglycemia is prognostically unfavorable (e4). A more recent study confirmed this and showed that a blood sugar (BS) above 125 mg/dl has high sensitivity (83%) and a high negative predictive value (NPV = 92%) for the occurrence of necrotizing pancreatitis (13).

- The same holds for elevation of the hematocrit (Hct) (10–12). A hematocrit above 43% in a male patient, or above 39.6% in a female patient, is highly sensitive (74%) and has a high negative predictive value (NPV = 88%) for the occurrence of necrotizing pancreatitis (12).

A further study likewise revealed that a hematocrit above 44% has a high NPV for the occurrence of severe/necrotizing pancreatitis (10) (for the definitions of statistical parameters, see also box 3). Hyperglycemia and elevation of the hematocrit thus both have a high "negative predictive value," i.e., not every patient with these pathological findings will go on to develop necrotizing pancreatitis, but necrotizing pancreatitis is unlikely to occur if neither of these pathological findings is present.

When assessing the predictors discussed above, one should bear in mind that their predictive value changes in the first 2–3 days after admission: it becomes worse for some (BS, Hct), but improves for others (CRP, APACHE-II, CT) (diagram 1).

Further prognostically unfavorable parameters include leukocytosis above 16 G/l, age above 55 years, a body-mass index over 30, a serum calcium concentration below 2 mmol/l, and a lactate dehydrogenase concentration above 350 U/l.

**Must the patient be admitted to the hospital/to the intensive care unit?**

Every patient with acute pancreatitis should be admitted to the hospital because of the risk of a life-threatening disease course and because of the difficulties mentioned above with regard to making reliable prognoses on presentation. Patients at high risk for a necrotizing course should be sent to the intensive care unit as soon as they are admitted.

**Imaging studies**

- A CT should be obtained only if it is expected to have therapeutic consequences, e.g., determining the indication for puncture and drainage.
- Beware of contrast medium nephropathy!
What imaging studies are required?
The value of ultrasonography lies mainly in the visualization of the biliary pathways. The
assessment of the pancreas itself is often not very sensitive because of overlying air shadows
due to paralytic ileus. A CT should be obtained only if it is expected to have therapeutic
consequences (e.g., enabling puncture and drainage). This is rarely the case in the early
phase of the disease. Thus, it is much more reasonable for CT to be performed 7 to 10 days
after admission, if at all (8, 26).

Because of the risk of contrast medium nephropathy, patients with impaired renal
function should be treated prophylactically to prevent this complication (200 mg of
theophylline IV 30 minutes before the study, combined with hydration) (14, 15).

Magnetic resonance imaging (MRI) is an alternative radiological study that yields
comparable data to CT in the assessment of acute pancreatitis (e8), while the gadolinium
that is given as MRI contrast medium is much less nephrotoxic than the contrast media used
for CT. CT, however, is usually more practical, particularly for interventional procedures.

Antibiotics: yes or no?
Antibiotics are not required for the treatment of edematous pancreatitis without cholangitis.
In severe/necrotizing pancreatitis, however, a meta-analysis revealed a significant reduction
of mortality by 12.3% (NNT = 8) and of septic complications by 21.1% (NNT = 5) if
antibiotics were given (16, e9–e11). A very recent study failed to confirm these findings
(17), perhaps because it also included patients who had not been definitely proven to have
necrotizing pancreatitis. The mortality (6%) and median Ranson scores (2–3) were so low
in this study that one can infer that it included too many patients with mild pancreatitis and
would therefore not have been able to demonstrate the usefulness of antibiotic treatment
(with ciprofloxacin and metronidazole) for severe pancreatitis.

Another very recent meta-analysis including the last-mentioned study, among others,
concluded that antibiotic therapy does indeed lower the mortality of severe pancreatitis
(e12). Furthermore, 24 of the 51 bacterial isolates obtained in this study were resistant to
ciprofloxacin. More than half of the organisms isolated were Gram-positive (staphylococci,
enterococci); thus, when initial antibiotic treatment fails, the possibility of Gram-positive
organisms should be considered. Because different antibiotic regimes were used in the few
controlled studies on this subject (e9–e11, 17), it is difficult to recommend any particular
antibiotic drug. Imipenem can be recommended because of its proven penetration of
pancreatic tissue and its broad spectrum of coverage. Well-founded recommendations
regarding the duration of therapy cannot yet be made. A Cochrane review that also showed
reduced mortality with antibiotic use recommended treating for a 10- to 14-day course.
A meta-analysis revealed no evidence of an increased frequency of fungal infection associated
with antibiotic use (e12).

ERC(P): yes or no?
A meta-analysis of 4 studies showed that ERC in biliary pancreatitis reduces both the
complication rate (from 38.2% to 25%; relative risk reduction [RRR] = 34.6%; number
needed to treat [NNT] = 7.6; p<0.001) and mortality (from 9.1% to 5.2%; RRR = 42.9%;
NNT=25.9) (18). A Cochrane meta-analysis (19) showed a reduction of complications only
in severe pancreatitis (odds ratio [OR] = 0.27; 95% confidence interval [CI] 0.14–0.53), but
not in mild pancreatitis (OR = 0.89; 95% CI 0.53–1.49).

Because of the fulminant pathophysiology of severe/necrotizing pancreatitis, ERC
should be performed early when it is indicated. Thus, any patient with documented biliary

Antibiotics
• are not indicated for the treatment of edematous pancreatitis without cholangitis.
• have been shown to lower mortality and the rate of septic complications for patients with severe necrotizing pancreatitis.

ERC
• is indicated as an emergency procedure for patients with cholangitis or cholangiosepsis,
• but visualization of the pancreatic duct is contraindicated because of the risk of further pancreatic irritation.
pancreatitis should be referred immediately to a center with the corresponding expertise. Early endoscopic removal of an impacted gallstone is one of the few ways to provide early, effective and directed treatment of pancreatitis. Visualization of the pancreatic duct itself is contraindicated because of the risk of further irritating the pancreas.

ERC should be performed immediately in case of cholangitis or cholangiosepsis. The most important diagnostic criterion for cholangitis is a more than threefold elevation of the GPT above its normal value. In all other cases of biliary pancreatitis, an ERCP should be performed within 72 hours.

What type of analgesia?
What patients want most of all is prompt relief of pain. There is usually no good alternative to the use of opiates. Many opiates can cause papillary spasm; thus, buprenorphine and pentazocine, two agents that lack this property, are usually recommended.

Parenteral administration of the local anesthetic procaine is a type of analgesic treatment that is performed almost exclusively in the German-speaking countries. Two recent studies have shown that procaine provides inadequate pain relief (20, 21). In one of these studies, the combination of procaine with opiates was not found to enable any lowering of the opiate dose (21).

Because opiates worsen the paralytic ileus that has already been caused by pancreatitis, it would seem reasonable to try other types of analgesic agent instead (peridural anesthesia, ketamine, non-steroidal anti-inflammatory drugs). Adequate controlled data on the use of other agents are, unfortunately, not available.

Parenteral or enteral nutrition?
For decades, the withholding of enteral feeding and the administration of parenteral nutrition were a cornerstone of the treatment of acute pancreatitis. Many studies – usually small, often not controlled, and often with multiple endpoints – seem to reveal an advantage of early enteral nutrition by way of a jejunal feeding tube placed under endoscopic or radiological guidance (e17–e22).

Still more recent studies show no advantage to feeding through a jejunal tube as compared to a gastric tube (6). The current state of the data, however, does not stand up to critical

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**Box 4**

**Causes of intravascular volume deficiency in necrotizing pancreatitis**

- Nausea, insufficient fluid uptake
- Vomiting
- Paralytic ileus
- Ascites
- Pleural effusion
- Inflammatory edema
- Exudation
- Capillary leakage in systemic inflammatory response syndrome (SIRS)

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**Analgesia**

- Opiate administration is usually unavoidable in severe pancreatitis.
- Buprenorphine and pentazocine are the most commonly used agents to prevent papillary spasm.

**Parenteral or enteral nutrition?**

It has been demonstrated that enteral nutrition carries a lower risk of infection than parenteral nutrition in patients with necrotizing pancreatitis.
Most studies included too few patients, were not restricted to patients with severe/necrotizing pancreatitis, and do not permit any general recommendation to be made that early enteral nutrition should be given in this form of the disease. A meta-analysis was, at least, able to show a lower rate of infectious complications with enteral as compared to total parenteral nutrition (e23), but it did not show any reduction of mortality. Nonetheless, the finding of a reduced rate of infection is enough to justify starting enteral nutrition as early as possible. At the same time, the need for central venous catheters should be continually reassessed, and these should be removed as soon as possible because of the risk of infection.

**How much fluid?**

The maintenance of optimal organ perfusion is of decisive importance for the survival of vital tissue in many different diseases, e.g., ischemic stroke and myocardial infarction. The same can be assumed to be the case for pancreatitis, which, very early in its course, causes intravascular hypovolemia (box 4).

In severe pancreatitis, fluid administration is very difficult to titrate to the clinical state of the patient. Most guidelines recommend the parenteral administration of 2 to 4 liters of fluid per day. The clinical assessment of the patient’s intravascular volume status is often influenced by signs of volume excess in extravascular compartments such as the interstitial spaces (leg edema due to capillary leakage) and "third spaces" (pleural effusions, ascites). Fear of pulmonary overhydration often stands in the way of adequate fluid administration.

**How much fluid?**

Patients with acute pancreatitis need large amounts of fluids; the precise amount needed is often difficult to estimate ("dry tongue"/"swollen legs").
The major predictive significance of the hematocrit was mentioned above and implies that it is very important for an adequate intravascular volume to be maintained. Hemodynamic monitoring should be begun as soon as possible in all patients with severe/necrotizing pancreatitis.

Central venous pressure (CVP) is a pressure-based parameter; it estimates preload with the transmural pressure difference between the lumen and the outer surface of the superior vena cava (SVC). Only the pressure within the SVC can be measured directly; atmospheric pressure is taken as a surrogate for the pressure outside the SVC (cf. the method of calibrating systems for CVP measurement). This is correct as long as the pressure on the outer surface of the SVC does not exceed the atmospheric pressure, but it can be elevated by a number of mechanisms, e.g., elevation of the intra-abdominal pressure, mechanical positive-pressure respiration, pleural effusion, and mediastinal edema. The greater these pressure components are, the more the CVP overestimates preload.

Pulmonary artery catheters (PAC) are often recommended for guidance of hydration therapy in necrotizing pancreatitis (NP). PAC is another type of pressure-based method of assessing preload.

Many recent studies have shown that the response to fluid administration can be predicted more effectively by volume-based preload parameters, such as the global end-diastolic

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>EBM grades for the diagnosis of acute pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key questions</td>
<td>Diagnostic testing</td>
</tr>
<tr>
<td>Pancreatitis?</td>
<td>Clinical examination, lipase</td>
</tr>
<tr>
<td>Biliary?</td>
<td>Laboratory tests, ultrasound</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Hematocrit, blood sugar</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>If necrosis is suspected</td>
</tr>
<tr>
<td>When to obtain a CT?</td>
<td>Only if necrosis is suspected and 3 days after onset at earliest</td>
</tr>
<tr>
<td>ERCP?</td>
<td>In biliary pancreatitis</td>
</tr>
<tr>
<td>Antibiotics?</td>
<td>If necrosis is present</td>
</tr>
<tr>
<td>Analgesia?</td>
<td>Opiates better than procaine</td>
</tr>
<tr>
<td>Enteral nutrition</td>
<td>Prevents (central venous catheter) infection</td>
</tr>
<tr>
<td>How much volume?</td>
<td>Hemodynamic monitoring, ITBV, EVLV</td>
</tr>
<tr>
<td>The four &quot;ants&quot;?</td>
<td>No</td>
</tr>
<tr>
<td>Surgery?</td>
<td>Not in sterile necrosis; as rarely and as late as possible</td>
</tr>
</tbody>
</table>

*1 EBM grade A:
Ia, meta-analysis of randomized, controlled studies; Ib, randomized, controlled study; Ila, well-designed controlled study without randomization.
*2 EBM grade B:
IIb, other type of well-designed, quasi-experimental study; III, well-designed, non-experimental descriptive study (comparative or case-control study).
EBM grade C:
IV, expert opinion.
ITBV = intrathoracic blood volume; EVLV = extravascular lung water

The response to fluid administration is easier to predict with the aid of volume-based preload parameters such as GEDV and ITBV as well as stroke volume variation, systolic pressure variation, and pulse pressure variation.
volume (GEDV), intrathoracic blood volume (ITBV), variability of cardiac stroke volume (stroke volume variation, SVV), systolic pressure variation (SPV), and difference between systolic and diastolic blood pressure (pulse pressure variation, PPV), than by the CVP or with a PAC. These variations can be determined automatically by a number of hemodynamic monitoring systems connected to an intra-arterial catheter.

Volume-based parameters can be measured with indicator techniques (injection of cooled saline; transpulmonary thermodilution) or by echocardiography. The assessment of preload with the types of variation mentioned above is possible, however, only in the setting of controlled ventilation and when the heart is in sinus rhythm. Echocardiographic techniques have the advantage of being readily available for individual measurements, but they can only be performed reliably by experienced ultrasonographers. Repeated echocardiographic testing also places heavy demands on hospital personnel.

In view of the disadvantages of CVP, pulmonary artery catheters, and echocardiography mentioned above, and the need for sinus rhythm and controlled ventilation if the parameters SVV and PPV are to be used, it would seem that the most suitable hemodynamic monitoring systems for use in patients with severe pancreatitis are those that employ thermodilution to measure the cardiac minute volume, the systemic vascular resistance (SVR), the global end-diastolic volume (GEDV), and the quantity of extravascular lung water (EVLW), and that additionally employ pulse contour analysis for the continuous measurement of the cardiac minute volume, the stroke volume variation (SVV), and the pulse pressure variation (PPV).

Measurement of the extravascular lung water (EVLW) has the advantage of requiring minimal apparatus (injection of cooled saline through a conventional central venous catheter; measurement of the thermodilution curve through an arterial catheter that is generally already in place, because it is indicated for other reasons anyway) and is a good way to assess volume deficits or to demonstrate excessive fluid administration leading to pulmonary overhydration (diagram 2).

Initial observations in patients with severe/necrotizing pancreatitis have shown that the central venous pressure is a thoroughly unsuitable parameter for the assessment of volume deficits in this patient group. When 100 measurements were made in the first 24 hours after hospital admission, the intrathoracic blood volume (ITBV) was found to be below normal in 45 cases despite a normal or elevated central venous pressure. This pilot study has become the basis of a multicenter, controlled study that is currently in progress.

What is the benefit, if any, of the “four antis”?
In the last 2 decades, owing to considerations of pathophysiology, much hope was placed in treatment with antiproteases/proteinase inhibitors (e.g., aprotinin, gabexate, mesilate), anti-inflammatory agents, antioxidants, and antisecretory agents (somatostatin, octreotide). There has not yet been any demonstration of the therapeutic efficacy of any of these four "antis" in a controlled study.

Surgery: yes or no?
From the early days of pancreatic surgery onward, the preferred form of management of acute pancreatitis – surgical or conservative – has alternated from one of these to the other, and back again, in phases lasting about 20 years each. A series of studies published since 1990 have provided evidence against the previous dogma, according to which the demonstration of necrosis implies that surgery should be performed (22, 23).

At present, most guidelines recommend conservative treatment of necrotizing pancreatitis when no infectious organisms are found in the necrotic areas. Currently available data on the

**Use of the "four antis"**
The therapeutic benefit of antiproteases/proteinase inhibitors, anti-inflammatory agents, antioxidants, and antisecretory agents has not yet been demonstrated in controlled studies.

**When to operate?**
Most guidelines recommend conservative management of necrotizing pancreatitis if no microbial pathogens are found in the necrotic areas.
possible indication for surgery when pathogens are found is inconclusive, because no controlled comparison of surgical and conservative treatment in this situation has been published to date. The principle that conservative management is possible in this situation was demonstrated in an uncontrolled study of 16 patients, among whom 2 died (mortality = 12%) (24). CT-guided puncture and drain insertion (26) and endoscopic microinvasive measures (27, 28) are promising alternatives to surgery. A combination of both of these techniques, which offers the possibility of continuous percutaneous irrigation with outflow through an endoscopically inserted internal drain, is also promising. Nonetheless, for now, these techniques should only be employed in the setting of a controlled study (table 3).

If these measures fail to bring improvement, or if they are technically or anatomically not feasible, surgery may be a reasonable option.

There is a consensus that surgery, if performed at all, should be performed as late as possible, at least 10 to 14 days after the onset of pain (24). A further indication for surgical treatment is intra-abdominal compartment syndrome (26).

Conflict of Interest Statement
PD Dr. Huber has served in an advisory capacity to the firm Pulsion Medical Systems, Munich. Professor Schmid states that he has no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

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For references please refer to the additional references listed below.

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Further Information

This article has been certified by the North Rhine Academy for Postgraduate and Continuing Medical Education.

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The solutions to the following questions will be published in Volume 33/2007. The CME unit “Blood Clotting Disorders” (Volume 21/2007) can be accessed until the 6th July. For Volume 28–29/2007 we plan to offer the topic “Substance Abuse in Children and Adolescents”.

Solutions to the CME questionnaire in Volume 17/2007:

Lewalter T et al.: The Emergency Management of Cardiac Arrhythmia: 1/c, 2/c, 3/d, 4/c, 5/c, 6/c, 7/a, 8/c, 9/e, 10/b

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

**Question 1**

Which of the following is true?

(a) To establish the diagnosis of pancreatitis, amylase and lipase should be measured in every case.

(b) Lipase is the most accurate parameter for the laboratory diagnosis of acute pancreatitis.

(c) The measurement of amylase in addition to lipase brings essentially no diagnostic advantage as compared to the measurement of lipase alone.

(d) The diagnosis of acute pancreatitis is certain, even when the patient does not have typical pain, when the serum lipase is elevated to more than three times the normal value.

(e) Hypocalcemia is a common cause of acute pancreatitis.
Question 2  
Which finding or piece of information is of decisive importance in distinguishing biliary pancreatitis from pancreatitis of another cause?  
(a) The sex of the patient  
(b) MRI  
(c) Cholestasis parameters  
(d) Serum procalcitonin  
(e) Erythrocyte sedimentation rate

Question 3  
Which of the following parameters is of high prognostic value in the first 24 hours after the onset of pain for the differentiation of mild/edematous from severe/necrotizing pancreatitis?  
(a) The Ranson criteria  
(b) The APACHE-II score  
(c) The hematocrit  
(d) Computerized tomography of the abdomen and pelvis without contrast medium  
(e) C-reactive protein

Question 4  
In the prognosis of necrotizing pancreatitis, hyperglycemia has, most importantly, a high  
(a) Negative predictive value.  
(b) Positive predictive value.  
(c) Sensitivity.  
(d) Specificity.  
(e) None of the above.

Question 5  
Which of the following parameters is among the Ranson criteria on admission to the hospital?  
(a) Age < 55 years  
(b) Bilirubin > 3 mg/dl  
(c) Base deficit > 4 mmol/l  
(d) Fall of PaO₂ to 60 mmHg  
(e) LDH > 350 U/l

Question 6  
The main advantage of early enteral feeding in acute pancreatitis is  
(a) Reduced mortality.  
(b) Reduced duration of mechanical ventilation.  
(c) Reduced need for analgesics.  
(d) Reduced rate of infectious complications.  
(e) Reduced frequency of acute renal failure.

Question 7  
Which of the following statements regarding ERC(P) in pancreatitis is true?  
(a) The early endoscopic removal of an impacted gallstone is one of the few ways in which pancreatitis can be treated effectively in its early phase.  
(b) In pancreatitis, visualization of the pancreatic duct is indispensable.  
(c) In patients with cholangitis, ERC should not be performed till 14 days after admission.  
(d) A meta-analysis has shown that ERC is associated with a higher complication rate in biliary pancreatitis.  
(e) None of the above.
**Question 8**
Which of the following statements regarding surgery is true?
(a) Once necrosis has been found, surgery must be performed.
(b) The most opportune time for surgical intervention in necrotizing pancreatitis is within 3 days of presentation.
(c) When sterile necrosis is found, conservative treatment is to be preferred over surgery.
(d) Endoscopic necrosectomy was found to be superior to surgery in a randomized study.
(e) Laparoscopic surgery was found to be superior to open surgery in a randomized study.

**Question 9**
Which of the following prognostic parameters loses its informative value over the course of the first 2–3 days after presentation?
(a) APACHE-II score
(b) Serum CRP
(c) Hematocrit
(d) CT with IV contrast medium
(e) Ranson score

**Question 10**
Which of the following therapeutic measures has been found to lower mortality in a meta-analysis?
(a) Early enteral feeding
(b) Adequate analgesia with procaine
(c) Endoscopic treatment of necroses
(d) ERC in biliary pancreatitis
(e) Early CT

**ADDITIONAL MATERIAL SEE NEXT PAGE**
Case illustration

Acute pancreatitis

Around 4 pm on January 2nd, a 61-year-old janitor came to the hospital complaining of epigastric pain with band-like radiation around the back since the early hours of the morning, accompanied by vomiting. He said that the consistency of his stool and the color of his urine were unremarkable, and that he normally consumed 20 to 40 grams of ethanol per day. He had not suffered from gallstones in the past. Physical examination revealed a patient in poor general condition and in obvious distress because of pain. When asked to rate the intensity of the pain on a scale of 1 to 10 (10 = unbearable pain), he replied, "14," and asked to be put to sleep with a general anesthetic. The abdomen protruded tautly and elastically forward and contained a markedly increased amount of gas. No bowel sounds were heard. The patient had moderately severe leg edema and mildly dilated neck veins, but his tongue was dry. The presumed diagnosis of acute pancreatitis was confirmed by the laboratory finding of a serum lipase concentration of 2 134 U/l. The total calcium concentration was normal, and the total protein concentration was only mildly elevated (8.4 g/dl). The cholestasis parameters were moderately elevated (bilirubin 2.4 mg/dl, AP 461 U/l, gamma-GT 223 U/l), while the transaminases were within normal limits. Other positive laboratory findings included a hematocrit of 51.9%, blood sugar of 202 mg/dl, and leukocytosis with a leukocyte count of 19.5 G/l. The LDH concentration, at 348 U/l, was just below the cutoff value of the Ranson criteria (350 U/l). Because of the patient's age, leukocytosis, and hyperglycemia, he had 3 of
the 5 Ranson criteria upon admission to the hospital. His CRP was markedly elevated at 14.8 mg/dl, but still below the threshold value of 15 mg/dl for severe pancreatitis.

Upper abdominal ultrasonography was technically difficult because of gas in the abdomen and yielded essentially no information about the pancreas. The gall bladder was poorly visualized; it was thought to contain, possibly, several small concretions. Because of these unclear findings, an abdominal CT scan was obtained, which showed edematous pancreatitis, with enlargement but homogeneous perfusion of the pancreas (figure 1). The gall bladder indeed contained several small concretions; therefore, endoscopic ultrasonography was planned for further evaluation. Intravenous procaine and a large amount of opiates provided inadequate pain relief, so the patient was admitted to the intensive care unit before the procedure and intubated at an early phase, in view of the planned endoscopic ultrasonography as well as possible endoscopic retrograde cholangiography. A central venous catheter was also inserted; the measured central venous pressure was markedly elevated (18 mmHg). Because this finding was inconsistent with the elevated hematocrit and the patient’s dry tongue, hemodynamic monitoring was held to be indicated. This revealed evidence of a marked intravascular volume deficit (reduction of the intrathoracic blood volume to 70% of normal). Volume therapy with up to 12 liters of fluid per day was begun.

Endoscopic ultrasonography revealed a 4-mm prepapillary concretion. Endoscopic retrograde cholangiography was then performed, and the concretion was removed through a papillotomy with a basket.

The patient was extubated 5 days after admission and was progressively fed by the enteral route. 13 days after admission, he developed a fever of 39.7°C and elevated laboratory parameters of inflammation. A new CT scan revealed extensive areas of necrosis (figure 2), which were then treated with three drains inserted under CT guidance. The fluid obtained by puncture was sterile, but antibiotics were nonetheless continued for a total of 20 days. At the end of this period, the patient was transferred back to the regular ward. He was discharged to a rehabilitation facility 2 weeks later.