AKI Associated with Acute Pancreatitis

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Abstract
Acute pancreatitis is a common disorder of the pancreas. It is the most frequent gastrointestinal cause for hospitalization and one of the leading causes of in-hospital deaths. Its severity ranges from mild self-limited disease to severe acute necrotizing pancreatitis characterized by systemic complications and multiorgan failure. Severe acute pancreatitis develops in about 20% of patients with acute pancreatitis and may be associated with multiorgan failure (respiratory, cardiovascular, and kidney). AKI is a frequent complication of severe acute pancreatitis and develops late in the course of the disease, usually after the failure of other organs. It carries a very poor prognosis, particularly if kidney replacement therapy is required, with mortality rates exceeding 75%. The exact pathophysiology of AKI in acute pancreatitis remains unclear but appears to result from initial volume depletion followed by complex vascular and humoral factors. Here, we provide an overview of the epidemiology, pathogenesis, causes, and management of AKI in patients with severe acute pancreatitis.

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Introduction
Acute pancreatitis is an inflammatory condition associated with a high complication rate and an increased risk of death. The diagnosis can be made by history, physical examination, and results of diagnostic tests (Table 1) (1). The revised Atlanta criteria classified acute pancreatitis according to type, severity, and phase of the disease (Table 2) (1). Imaging plays an important role in the diagnosis and staging of acute pancreatitis, establishing the cause and identifying its complications. Contrast-enhanced computed tomography is the most useful imaging technique especially when performed after 72 hours to assess the extent of the disease (1,2).

The severe form of acute pancreatitis is associated with multiorgan failure and poor outcome. AKI has long been recognized as a common and important complication of acute pancreatitis. Unfortunately, there has been scarce information about this entity in the literature. In this review, we will provide an overview of epidemiology, pathophysiology, and management of AKI in patients with acute pancreatitis.

Epidemiology and Outcome
The prevalence of AKI in acute pancreatitis is not well documented (Table 3) (3–8). Previous studies highlighted the high prevalence of AKI in acute pancreatitis and its dismal prognosis. Most of these were limited by small samples and retrospective design. However, in a comprehensive, retrospective, observational study utilizing the National Inpatient Sample, Devani et al. reported an overall AKI prevalence of 7.9% among 3,466,493 patients hospitalized with acute pancreatitis (3). The mortality rate among AKI subgroup was significantly higher (8.8% in AKI group versus 0.7% in non-AKI; P<0.01). Prospective studies clearly needed to determine the actual incidence and prognosis of AKI in acute pancreatitis.

AKI develops late in the course of acute pancreatitis, usually after failure of other organs (4,5). Remarkably, the kidney was the first organ to fail in only 8.9% of patients with AKI, and only a minority of patients develop isolated AKI (4,5,9). Retrospective studies reported risk factors for AKI in acute pancreatitis but not the need for kidney replacement therapy (KRT) (3–6). Li et al. reported history of kidney disease, hypoxemia, and abdominal compartment syndrome as risk factors (6), whereas Devani et al. found older age, male gender, sepsis, respiratory failure, intensive care unit admission, and history of CKD to increase risk for AKI (3). Of these, abdominal compartment is likely the only modifiable risk factor.

The mortality rate of patients with AKI and acute pancreatitis varied between 25% and 75% (5,7). However, Devani et al. found a three-fold fall in mortality rate among patients with AKI over the past decade (3).

Pathophysiology
The pathophysiology of AKI in acute pancreatitis is not well studied. However, a key pathophysiologic process involves premature activation of pancreatic enzymes within the acinar cells. This leads to autodigestion of the pancreas and surrounding tissues, triggering a cascade of events that contribute to AKI (Figure 1) (10). Release into the systemic circulation of activated enzymes and proteases may cause endothelial damage leading to extravasation of fluids from the vascular space, hypovolemia, hypotension, increased abdominal pressure, intense kidney vasoconstriction, hypercoagulability, and fibrin deposition in the glomeruli. Moreover, acinar injury from autodigestion stimulates cytokine release and production of oxygen free radicals (Figure 2) (11–13).
Hypovolemia plays a critical role in causing AKI early during acute pancreatitis. This was first documented in dogs with experimental acute pancreatitis (11). At 4 hours after bile infusion and the development of pancreatitis, GFR fell by 40% and the plasma volume by 26% compared with the control group. There were no morphologic abnormalities in kidney biopsies, but the decline in GFR was prevented by plasma infusion. However, at 24 hours, kidney failure became unresponsive to further volume expansion. Remarkably, these results were reproduced by the infusion of trypsin, chymotrypsin, elastase, and phospholipase A2 (PLA2) into normal dogs. The authors speculated that released enzymes caused increased vascular permeability and leakage of protein-rich fluid into the interstitial compartment, leading to hypovolemia. In similar experiments in dogs, there was a rapid accumulation of ascites, increased hematocrit level, and decreased arterial pressure, suggesting hypovolemia (12). These experiments demonstrated the role for hypovolemia in AKI, at least in the initial 24 hours after the onset of acute pancreatitis (Figure 2).

Role of Toxic Substances Released from the Necrotic Pancreas

Substances released from the necrotic pancreas were implicated in the pathogenesis of AKI. These include trypsin, chymotrypsin, bradykinin, histamine, and prostaglandin E, as well as endotoxins and bacteria (11,12). Østaf et al. (14) reported that histamine release in the pancreatic exudate of dogs with experimental acute pancreatitis caused increased vascular permeability, hypovolemia, and hypotension. In patients with acute pancreatitis and AKI, urine output improved by peritoneal lavage, suggesting that dialysis may remove substances that contributed to AKI (15). To investigate this further, Satake et al. (12) collected ascitic fluid from experimental dogs with acute pancreatitis and injected 10 ml intravenously in healthy dogs. The dogs developed transient hypotension that was not caused by hypovolemia as evidenced by lack of changes in hematocrit level. There was a significant decrease in kidney blood flow, GFR, urine output, and an increase in kidney vascular resistance, even after hypotension resolved. Kidney vasoconstriction was also documented in patients with acute pancreatitis despite adequate extracellular volume, suggesting increased sympathetic activity (16). Thus, although hypotension and hypovolemia may be the initial culprits in causing AKI early during acute pancreatitis, toxic substances in the pancreatic exudate may subsequently contribute to AKI.

Inflammation

Cytokines may contribute to the pathogenesis of AKI. TNF-α acts directly on glomeruli and tubular capillaries,
Table 3. Prevalence and outcomes of AKI in acute pancreatitis in previous studies

<table>
<thead>
<tr>
<th>First Author/Country</th>
<th>Year</th>
<th>No. of Patients with Acute Pancreatitis</th>
<th>% of ICU Admissions</th>
<th>% of Patients with AKI</th>
<th>Definition of AKI</th>
<th>% of Patients with AKI who Received KRT</th>
<th>Mortality in Patients with Acute Pancreatitis and AKI</th>
<th>Scoring System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tran/Netherlands (4)</td>
<td>1993</td>
<td>267</td>
<td>44</td>
<td>16</td>
<td>Cr &gt; 3.2 mg/dl or a two-fold creatinine rise in patients with CKD</td>
<td>26% (11/42), all died</td>
<td>81% (34/42) hospital mortality</td>
<td>Ranson score (1 ± 1.2 in non-AKI, 3.9 ± 1.5 in AKI)</td>
</tr>
<tr>
<td>Kes/Croatia (5)</td>
<td>1996</td>
<td>563</td>
<td>35</td>
<td>14</td>
<td>NA</td>
<td>62% (49/79), 95.9% died</td>
<td>74.7% (59/79) overall mortality</td>
<td>Ranson score (1.1 ± 0.7 in non-AKI, 3.8 ± 1.4 in AKI) APACHE II score (9.65 ± 4.40 in non-AKI, 11.71 ± 5.60 in AKI)</td>
</tr>
<tr>
<td>Li/China (6)</td>
<td>2010</td>
<td>228</td>
<td>NA</td>
<td>18.4%</td>
<td>Urine output &lt;400 ml/d or Cr &gt;2 mg/dl</td>
<td>NA</td>
<td>66.6% (28/42) overall mortality</td>
<td>Ranson score (1.1 ± 0.7 in non-AKI, 3.8 ± 1.4 in AKI) APACHE II score (9.65 ± 4.40 in non-AKI, 11.71 ± 5.60 in AKI)</td>
</tr>
<tr>
<td>Lin/Taiwan (7)</td>
<td>2011</td>
<td>1734</td>
<td>100</td>
<td>15.0</td>
<td>On the basis of ICD-9-CM codes</td>
<td>NA</td>
<td>23.8% (62/261) ICU mortality</td>
<td>NA</td>
</tr>
<tr>
<td>Zhou/China (8)</td>
<td>2015</td>
<td>414</td>
<td>100</td>
<td>69.3</td>
<td>Absolute increase of serum Cr &gt;0.3 mg/dl or 50% increase</td>
<td>53.3% (153/287), 58.1% died</td>
<td>44.9% (128.8/287) ICU mortality</td>
<td>APACHE II score 17 ± 7.9</td>
</tr>
<tr>
<td>Devani/United States (3)</td>
<td>2018</td>
<td>3,466,493</td>
<td>NA</td>
<td>7.9</td>
<td>On the basis of ICD-9-CM codes</td>
<td>NA</td>
<td>8.8% (24,099/ 273,852) inpatient mortality</td>
<td>NA</td>
</tr>
</tbody>
</table>

Overall mortality indicates that authors did not specify time or location of death. ICU, intensive care unit; KRT, kidney replacement therapy; Cr, serum creatinine; NA, not available; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICD-9-CM, International Classification of Disease, ninth revision, Clinical Modification.

*Denotes incidence. All studies are retrospective in nature.
leading to ischemia and tubular necrosis. It also stimulates release of other cytokines, such as IL-1β, IL-8, and IL-6, which act on endothelial cells leading to kidney ischemia, thrombosis, and release of oxygen free radicals (13). A study of 60 patients with acute pancreatitis found high levels of IL-6 and IL-8 in patients who developed AKI (17).

PLA2 rapidly deposited in proximal tubular cells of rats with experimental acute pancreatitis, causing tubular necrosis. A prospective study of 31 patients with acute pancreatitis found a positive correlation between serum PLA2 activity, as measured early during acute pancreatitis, and urinary N-acetyl-β-glucosaminidase-to-creatinine ratio, suggesting that PLA2 may hydrolyze tubular epithelial cell membrane and contribute to AKI (18). PLA2 also increases vascular permeability and generation of AA, which produces thromboxane. This potent vasoconstrictor and platelet aggregation promoter leads to microthrombi and vascular occlusion. This may be complicated by an increase in platelet-activating factor, which induces platelet activation, aggregation and generation of inflammatory mediators (13).

**Figure 1.** Premature activation of pancreatic enzymes within the acinar cells leads to autodigestion of the pancreas and release of enzymes and proteases which trigger a cascade of events that contribute to the pathogenesis of AKI.

**Figure 2.** AKI in severe acute pancreatitis usually results from volume depletion due to extravasation of fluids from the vascular space followed by complex interactions between inflammatory, vascular and humoral factors.
Inflammatory mediators may increase mucosal permeability leading to translocation of endotoxin and bacteria from the colon. Endotoxins contribute to the development of AKI by increasing endothelin level, which causes vasoconstriction, decreased kidney blood flow, and tubular necrosis (19). Also, oxygen free radicals may react with proteins and enzymes, leading to lipid peroxidation of the cell and organelar membranes, protein denaturation and increased capillary permeability, ischemia, and direct kidney cell membrane injury (13).

Finally, apoptotic cell death may also play a role in AKI. A Japanese group detected DNA fragmentation in Madin-Darby canine kidney cells exposed to pancreatitis-associated ascitic fluid. They also found nuclear and DNA fragmentation in Wistar rat kidneys after intraperitoneal injection of pancreatitis-associated ascitic fluid, indicating that ascitic fluid contains factor(s) that induce apoptosis (20).

**Vascular Effects of Acute Pancreatitis**

Increased kidney vascular resistance was demonstrated in dogs with experimental acute pancreatitis (21). Werner et al. found an increase in kidney vascular resistance in 11 patients with acute pancreatitis. All patients became hypertensive indirectly implicating a vasopressor substance release (16). Patients with acute pancreatitis had six-fold higher plasma renin values than normal, which could be attributed to hypovolemia (22). However, plasma trypsin and kallikrein activate prorenin to renin, which in turn increases angiotensin II levels, leading to increased kidney vascular resistance, decreased effective kidney blood flow, and decline in GFR (22,23).

**Abdominal Compartment Syndrome**

Abdominal compartment syndrome develops when intra-abdominal pressure increases to >20 mm Hg (24,25). Patients with severe acute pancreatitis are at risk of developing abdominal compartment syndrome because of increased intra-abdominal contents by ileus, ascites, and intra-abdominal bleeding. Moreover, interstitial fluid accumulation due to increased capillary permeability and endothelial damage from volume administration, acidosis, sepsis, transfusion, coagulopathy, as well as reduced abdominal wall compliance due to edema, may play a role (24,25). The mechanism of intra-abdominal hypertension induced AKI is not clear, but intra-abdominal hypertension may compress and compromise the kidney blood flow in both the arterial and venous vasculature, leading to decreased perfusion pressure, increased venous pressure, decreased venous blood flow, and increased kidney parenchymal pressure. This results in decreased glomerular filtration pressure, and impaired microvascular function and oxygen delivery, and precipitates ischemic kidney injury.

**Causes of AKI**

The causes of AKI are speculative according to the above-proposed pathophysiology. Hypovolemia and sepsis can lead to prekidney AKI, acute tubular necrosis and, rarely, bilateral kidney cortical necrosis (26). As mentioned above, intra-abdominal hypertension is very common in patients with acute pancreatitis and can lead to kidney impairment. AKI also can result from associated diseases such as autoimmune disease, hemolytic-uremic syndrome, or thrombotic thrombocytopenic purpura, as well as from drugs causing acute pancreatitis and AKI, but this information is limited and on the basis of a few case reports published in the literature. Unfortunately, patients with acute pancreatitis and AKI are usually critically ill, and as a result, a kidney biopsy is rarely performed.

**Management**

Management of AKI in severe acute pancreatitis involves intravenous fluid administration, avoidance of nephrotoxic agents, the minimizing intra-abdominal pressure, and providing KRT when indicated. The routine use of prophylactic antibiotic is not recommended unless there is evidence of active infection. If antibiotic is given, nephrotoxic ones should be avoided (Figure 3) (2,10). Similarly, not all patients with acute pancreatitis need to undergo contrast-enhanced computed tomography particularly those with mild pancreatitis and those who improve rapidly to reduce the risk of contrast nephrotoxicity. Magnetic resonance imaging can be an alternative as it has excellent soft tissue contrast, but gadolinium administration has been implicated in the development of nephrogenic systemic fibrosis. Abdominal ultrasound has little value in the diagnosis of pancreatitis or its complications, but can be useful in detecting gallstones or biliary duct stones (1,2).

Diagnosis of AKI is currently according to the Kidney Disease Improving Global Outcomes criteria. However, recent studies have suggested that biomarkers of kidney injury, such as urine concentrations of neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, IL-18, angiopoietin 2, and procalcitonin, may help in earlier diagnosis of AKI (27,28). Procalcitonin level was superior to other inflammatory mediators in predicting AKI in patients with acute pancreatitis and in identifying patients at risk of worsening kidney function (28). Currently, there are no data to indicate that these biomarkers perform better in AKI associated with acute pancreatitis than other types of AKI. Further research will be required before biomarkers can be used to predict the onset of AKI and to guide its early management.

**Fluid Management**

An essential initial step in the management is the administration of ample intravenous fluids. Few human studies evaluated the optimal type, rate, duration, complications, and outcomes of fluid administration in acute pancreatitis (2). Although some clinical trials have shown a clear benefit of aggressive hydration, others reported that aggressive hydration might be associated with increased morbidity and mortality (2). The American College of Gastroenterology recommends that early aggressive intravenous hydration is most beneficial in the first 12–24 hours, but does have a little benefit beyond this time (2). The goal of fluid resuscitation is to improve the mean arterial pressure, central venous pressure, and urine output. Patients with severe hypovolemia may initially require 500–1000 ml of fluids per hour, whereas those with
less severe volume depletion may require 300–500 ml per hour (10). However, infusion rate should be reduced in patients with heart failure, liver cirrhosis, and oliguric/anuric AKI. Fluid balance is commonly positive in critically ill patients with AKI and should be avoided as it can lead to increased morbidity and mortality due to pulmonary edema, tissues hypoxia, increased need for mechanical ventilation, and cardiac dysfunction (29). In these patients, loop diuretics can be considered.

In a retrospective study of 99 patients with severe acute pancreatitis in Sweden, patients who received 4000 ml or more of fluids during the first 24 hours developed significantly higher respiratory complications rates (66% versus 53%; P<0.001), and admission to intensive care units was also more common compared with patients who received <4000 ml (47% versus 20%; P<0.001, but there was no difference in patients’ outcomes (30). Aggressive volume resuscitation (>7.5 L within 6 hours from hospital admission) was also found to be an independent predictor of developing abdominal compartment syndrome (31). Another study of 179 patients with moderately severe acute pancreatitis showed that aggressive fluid resuscitation (>4 L) was associated with an increased incidence of AKI compared the nonaggressive group (53.12% versus 25.64%; P=0.008), and longer AKI lasting time (P=0.04) (32).

By contrast, a recent four-center retrospective cohort study of 1010 patients with acute pancreatitis divided fluid administered from arrival to the emergency room to 4 hours after diagnosis of acute pancreatitis into tertiles: nonaggressive (<500 ml), moderate (500–1000 ml), and aggressive (>1000 ml). Compared with the nonaggressive fluid group, the moderate and aggressive resuscitations were associated with lower rates of complications and invasive interventions (33). Thus, although adequate intravenous fluid administration in the first 24 hours is indicated, excessive fluid administration beyond this period may be harmful and should be avoided.

It is unclear what type of fluids is most beneficial for patients with acute pancreatitis. Observational studies reported that chloride-rich solutions are associated with a higher risk of AKI and the need for KRT than balanced solutions (34). In a retrospective study of 145 patients with moderately severe and severe acute pancreatitis, hyperchloremia was associated with an increased incidence of AKI. On multivariable analysis, the increase in serum chloride was independently associated with AKI (odds ratio, 1.32; 95% confidence interval, 1.00 to 1.74; P=0.04). The authors suggested that chloride-rich solutions decreased kidney blood flow and GFR via tubuloglomerular feedback activation (35). However, randomized, controlled trials have not demonstrated the superiority of balanced solutions over chloride-rich solutions (36). The American College of Gastroenterology and International Association of Pancreatology (IAP)/American Pancreatic Association (APA) guidelines suggest that lactated Ringer solution might be the preferred fluid replacement (2,37). In a prospective, multicenter, randomized study, Wu et al. (38) reported that lactated Ringer solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Although it is unlikely that lactated Ringer solution, which contains 4 mEq/L of potassium, will cause hyperkalemia, we recommend close monitoring of serum potassium level.
<table>
<thead>
<tr>
<th>First Author/ Country</th>
<th>Study Design (Year)</th>
<th>No. of Patients with Acute Pancreatitis</th>
<th>Blood Purification Modality</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oda/Japan (40)</td>
<td>Prospective observational (2005)</td>
<td>17</td>
<td>Continuous hemodiafiltration</td>
<td>Intra-abdominal pressure and IL-6 were significantly lower after 24 h of continuous hemodiafiltration initiation. High-volume CVVH and early CVVH improved hemodynamics and survival in patients with acute pancreatitis more than low-volume CVVH and late CVVH.</td>
</tr>
<tr>
<td>Jiang/China (41)</td>
<td>Randomized controlled (2005)</td>
<td>37</td>
<td>Low-volume versus high-volume CVVH, early versus late CVVH</td>
<td>High-volume CVVH and early CVVH improved serum concentrations of TNF-α, IL-1β, and IL-6 more efficiently than low-volume CVVH and late CVVH. CVVH improved APACHE II score and SOFA score significantly, and effectively improved gut barrier dysfunction.</td>
</tr>
<tr>
<td>Chen/China (42)</td>
<td>Prospective observational (2007)</td>
<td>20</td>
<td>CVVH</td>
<td>The APACHE II score improved significantly after CVVH with improvement in endothelial dysfunction. CVVH improved APACHE II score and SOFA score significantly, and effectively improved gut barrier dysfunction.</td>
</tr>
<tr>
<td>Zhang/China (43)</td>
<td>Randomized controlled (2010)</td>
<td>63</td>
<td>CVVH versus standard medical therapy</td>
<td>High-volume CVVH significantly reduced plasma inflammatory cytokines concentrations including those of IFN-γ, TNF-α, IL-1, IL-2, IL-5, and IL-13. Peripheral CD4+ and CD8+ T cells, monocyte count, and HLA-DR expression increased significantly only in the high-volume CVVH group.</td>
</tr>
<tr>
<td>Gong/China (44)</td>
<td>Prospective nonrandomized (2010)</td>
<td>12</td>
<td>High-volume CVVH versus standard medical therapy</td>
<td>The APACHE II score of the combined CVVH and peritoneal dialysis significantly decreased compared with the control group. Inflammatory cytokines (IL-6, IL-8, and TNF-α) decreased significantly at days 1 and 2 compared with control group.</td>
</tr>
<tr>
<td>Yang/China (45)</td>
<td>Randomized controlled (2010)</td>
<td>51</td>
<td>Combined CVVH and peritoneal dialysis versus traditional therapy</td>
<td>Inflammatory cytokines (IL-6, IL-8, and TNF-α) decreased significantly at days 1 and 2 compared with control group. The APACHE II score of the combined CVVH and peritoneal dialysis significantly decreased compared with the control group.</td>
</tr>
<tr>
<td>Zhu/China (46)</td>
<td>Prospective nonrandomized (2011)</td>
<td>75</td>
<td>High-volume CVVH versus conventional treatment</td>
<td>The 28-d survival rate was higher in patients who accepted high-volume CVVH, especially in those without AKI. After 72 h of therapy, patients who accepted high-volume CVVH had significantly better APACHE II scores.</td>
</tr>
<tr>
<td>Chu/China (47)</td>
<td>Randomized controlled (2013)</td>
<td>30</td>
<td>Pulse high-volume hemofiltration versus CVVH</td>
<td>The levels of IL-6, IL-10, and TNF-α decreased in the pulse high-volume hemofiltration group more significantly than the control group. Pulse high-volume hemofiltration group was superior to the control group in APACHE II score, C-reactive protein, SOFA score, and SAPS II score.</td>
</tr>
<tr>
<td>Guo/China (48)</td>
<td>Prospective nonrandomized (2014)</td>
<td>61</td>
<td>High-volume CVVH versus optimal standard therapy</td>
<td>High-volume CVVH was associated with a significant reduction in the incidence of kidney failure, infected pancreatic necrosis, length of hospitalization, mortality, as well as duration of kidney, respiratory, and hepatic failure. APACHE II score, C-reactive protein, and IL-6 levels were significantly reduced by high-volume CVVH on days 1, 3, and 7.</td>
</tr>
</tbody>
</table>
Nutrition
The paradigm has shifted dramatically over the past decade, with new evidence suggesting that early enteral feeding is beneficial in acute pancreatitis. Delayed feeding for >24 hours is associated with higher rates of infected peripancreatic necrosis, multiple organ failure, and necrotizing pancreatitis (2). It was hypothesized that enteral nutrition protects the mucosal barrier of the gut and reduces bacterial translocation. Parenteral nutrition should be avoided unless the enteral route is not possible. To our knowledge, there are no studies that specifically examined the nutritional needs of patients with AKI and acute pancreatitis.

Monitoring Intra-Abdominal Pressure
Close monitoring of intra-abdominal pressure is essential in all patients with acute pancreatitis. This can be measured directly by an intraperitoneal catheter, or indirectly by gastric or urinary bladder pressure. However, transduction of bladder pressure remains the gold standard (24). Percutaneous drainage of ascites or continuous hemodi
filtration may decrease intra-abdominal pressure, but some patients require decompressive laparotomy, particularly in patients with intra-abdominal pressure >25 mm Hg (25).

The Working Group IAP/APA Acute Pancreatitis Guidelines to decrease intra-abdominal pressure in acute pancreatitis recommend: (1) nasogastric drainage, prokinetics, rectal tubes, and if necessary, endoscopic decompression; (2) volume resuscitation on demand, if volume overloaded either ultrafiltration or diuretics can be used; and (3) adequate analgesia and sedation to decrease abdominal muscle tone, and if necessary, neuromuscular blockade (37).

KRT
Indications and timing of KRT in patients with AKI after acute pancreatitis are not different from those of other critically ill patients with AKI. Urgent indications for KRT include severe hyperkalemia, severe metabolic acidosis (pH<7.1) and pulmonary edema unresponsive to diuretic therapy, irrespective of kidney function. The timing of elective initiation of KRT is debatable. A randomized, controlled trial failed to show a significant difference in the 90 days mortality between early and late initiation groups (39). The patient’s hemodynamic status usually dictates the choice of KRT modality. Intermittent hemodialysis, extended daily dialysis, or slow low-efficiency daily dialysis are reserved for hemodynamically stable patients, whereas continuous RRT (CRRT) is preferred in hemodynamically unstable patients. A few clinical trials have specifically examined the benefits of one modality of KRT over the other in these patients. A possible advantage of CRRT is its ability to decrease serum cytokine levels (Table 4). However, a low-intensity CVVH may not be adequate because of the large amount of circulating inflammatory mediators in patients with severe acute pancreatitis. In this regard, limited data suggest that high-volume CVVH, particularly when started early, may be more effective (Table 4). However, the evidence so far is not strong enough to recommend its routine use for such patients.

Research Needs and Conclusions
AKI is a frequent complication of acute pancreatitis and usually develops after the failure of other organs. It carries a
poor prognosis, particularly if KRT is required. There is a need for prospective studies to establish the true incidence and risk factors for AKI in acute pancreatitis. The exact pathophysiology of AKI remains unclear, but appears to result from initial hypovolemia followed by complex interactions between inflammatory, vascular, and humoral factors. More studies are clearly needed particularly on the nephrotoxic potential of toxic substances released from the necrotic pancreas and inflammatory cytokines. There is also a lack of human biopsy studies in this condition because most patients are acutely ill. Prospective clinical studies that examine the impact of various therapeutic modalities on patients’ outcomes, including type and volume of intravenous fluid resuscitation, nutritional support, and KRT, are needed.

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