Pathophysiology of pulmonary complications of acute pancreatitis

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Abstract
Acute pancreatitis in its severe form is complicated by multiple organ system dysfunction, most importantly by pulmonary complications which include hypoxia, acute respiratory distress syndrome, atelectasis, and pleural effusion. The pathogenesis of some of the above complications is attributed to the production of noxious cytokines. Clinically significant is the early onset of pleural effusion, which heralds a poor outcome of acute pancreatitis. The role of circulating trypsin, phospholipase A2, platelet activating factor, release of free fatty acids, chemoattractants such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, IL-6, IL-8, fMet-leu-phe (a bacterial wall product), nitric oxide, substance P, and macrophage inhibitor factor is currently studied. The hope is that future management of acute pancreatitis with a better understanding of the pathogenesis of lung injury will be directed against the production of noxious cytokines.

Key words: Acute pancreatitis; Cytokines; Acute respiratory distress syndrome; Complications of pancreatitis; Pleural effusion; Interleukins

INTRODUCTION
Acute pancreatitis (AP), an acute inflammatory process of the pancreas in its severe form, is complicated by the development of multi-organ dysfunction syndrome (MODS) with a mortality of 15%-20%. Regardless of etiology, once AP is initiated the inflammatory events within the acinar cells will progress to a generalized systemic inflammatory response syndrome (SIRS). Amongst the systemic complications, pulmonary complications are the most frequent and potentially the most serious. Recognition of these complications and their pathology may lead to more rapid diagnosis and better therapies. The following is a brief summary of the current researches on each of the possible pulmonary complications ranging from hypoxemia to acute respiratory distress syndrome (ARDS). Hypoxemia may occur without radiological abnormalities in 75% of cases. There is a direct correlation between hypoxemia noted early in the course of AP and mortality. Pleural effusion, once thought to be a marker of AP, is now a noted poor prognostic sign. Atelectasis, a frequent radiological complication, is attributed to a decrease in the quantity of pulmonary surfactant. The most dangerous complication of the pulmonary system is ARDS. The pathophysiology of ARDS and most of the other pulmonary complications is multifactorial. Activated trypsin causes damage to pulmonary vasculature and increases endothelial permeability. Active circulating phospholipase A2 (PLA2) is known to remove fatty acids from phospholipids. One of the main components of surfactant is the phospholipid, dipalmitoylphosphatidylcholine. Many recent studies have assessed the role of platelet activating factor (PAF) which stimulates polymorphonuclear cells (PMNs) regulating the interaction between PMNs and endothelial cells facilitating migration of activated WBC into interstitial spaces. Based on the observation a PAF inhibitor Lexipafant has undergone double blind randomized studies. Another major advance in the understanding of the pathophysiology of pulmonary complications is the explosion of knowledge of cytokines. There are pro-inflammatory cytokines released from the pancreas such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, and IL-8. PMNs also contribute to release of cytokines. Our aim was to help the clinician understand the importance of the many studies looking at the effect of inflammatory modulators in decreasing the severity of AP. Today’s experimental medicine is likely to become a therapeutic modality in the near future.
variable involvement of peripancreatic organs and/or remote organ systems in different degrees. In 10%-20% of AP, it presents in its severe form, which is frequently complicated by the development of MODS with a mortality rate of 15%-20% or more\[1,2]. Recent studies have documented two peaks of mortality in patients with AP, an early mortality due to the effects of SIRS and MODS, and a late mortality caused by the effects of MODS combined with pancreatic sepsis following pancreatic necrosis\[3,4]. About 30% of patients with fatal AP have been diagnosed first at autopsy,\[2,5\] indicating how often we miss the diagnosis and how fast the disease can progress after the onset. Regardless of its etiology, the clinical course follows a pattern of interaction between inflammatory events within the pancreas which initiate a generalized systemic inflammatory response. The mortality and severity of the disease appear to be influenced by events occurring subsequently to the pancreatic injury as a result of release of cytokines and other mediators.

Severe AP is associated with MODS and/or local complications such as necrosis, abscess, pseudocyst, or pancreatic ascites. Fortunately, AP is usually mild.

Pulmonary complications of AP occur in almost 75% of cases, ranging from hypoxemia to ARDS.\[6,7\] The local and systemic complications are listed in Table 1. Of the systemic complications, acute respiratory failure is perhaps the most serious one. In the last two decades, our understanding and management of severe AP have substantially improved. The traditional concept that AP is entirely due to the release of activated proteases from an injured pancreas has been considerably changed. The present view is that the activation of trypsin by intracellular zymogens, trypsin activating chymotrypsinogen, proelastase and prophospholipase A plays an initiating role, but other chains of events predominate in precipitating complications.\[8-10\]

Recent studies using secretagogue-induced models of pancreatitis, caerulein- induced AP in rats, sodium taurocholate- induced AP, choline deficient ethionine-supplemented diet- induced AP in mice and free fatty acid- induced AP in dogs, as well as a number of other models have suggested that pancreatitis is a disease that evolves in 3 phases. The initial phase is characterized by intrapancreatic digestive enzyme activation and acinar cell injury which involves the first few hours of AP. The second phase characterized by an intrapancreatic inflammatory reaction and varying degrees of acinar cell necrosis involves approximately 12-72 h. Finally, the third phase which involves the rest of the progression of AP is characterized by further progression of the pancreatic injury and the appearance of extrapancreatic changes including SIRS and ARDS.\[9,10\]

It is during phase three that pulmonary insult occurs. In this review, we chiefly focus on the many pulmonary complications of AP, their pathogenesis, and clinical significance. This review is an extension of our previous review and other excellent recent reports on the topic.\[10-13\]

The literature search was done by Medline search using the terms ‘pancreatitis’, ‘pleural effusion’, ‘hypoxemia’, and ‘ARDS’ in combination searches in the English language.

Pulmonary complications of AP for ease of explanation are divided into three stages. Stage 1 deals with pulmonary manifestations without any noticeable changes radiologically, stage 2 emphasizes radiologic changes observed and stage 3 discusses ARDS. Following these stages is a discussion on the players in the pathophysiology of the pulmonary complications of AP.

### STAGE 1: HYPOXEMIA WITH NO RADIOLOGICAL ABNORMALITIES

Tachypnea, mild respiratory alkalosis, and hypoxemia are seen in almost two thirds of patients with AP during the first 2 d of admission to the hospital.\[14\] In these patients, physical examination is essentially normal, chest radiographs rarely demonstrate abnormalities (11%), and clinical signs if present, seldom indicate the severity of the hypoxemia.\[10\] Ranson and colleagues\[15\] observed that 52% of patients have arterial oxygen tensions (PaO2) < 71 mmHg. Imrie and co-workers\[6\] showed that 45% of patients have severe arterial hypoxemia (PaO2 < 60 mmHg) and indicated that a PaO2 of < 52.5 mmHg is associated with a mortality of more than 30%. A study conducted several years ago identified that the incidence of pulmonary insufficiency in acute edematous pancreatitis is < 10%, increasing to 47% for acute sterile necrosis and 74% for infected necrosis.\[16,17\] Ranson et al.\[18\] reported that respiratory insufficiency characterized by an arterial pO2 < 75 mmHg and drawn within 48 h of admission is observed in 58%. Recently Lankisch and associates\[19\] studied a group of 204 patients with AP and demonstrated that 63% of the patients have an arterial pO2 < 70 mmHg, and 30% have a pO2 < 60 mmHg, showing that hypoxemia is present early in AP patients. The major cause of hypoxia is ventilation and perfusion mismatch.

### Table 1 Complications of acute pancreatitis

| Local-extrapancreatic |
|-----------------------|
| Involvement of contiguous organs (intraperitoneal hemorrhage, GI bleeding, thrombosis of splenic vein, bowel infarction) |
| 2 Pancreatic ascites |
| 3 Obstructive jaundice |

| Systemic |
|----------|
| 1 Pulmonary |
| a Early arterial hypoxia |
| b Atelactasis, pneumonia, pleural effusion, mediastinal abscess |
| c ARDS |
| 2 Cardiac: shock, pericardial effusion, EKG changes, arrhythmias |
| 3 Hematologic: DIC, TTP/HUS |
| 4 Gastrointestinal: GI bleeding (portal-splenic vein thrombosis, colonic infarction) |
| 5 Renal: azotemia, oliguria |
| 6 Metabolic: hypocalcemia, hyperglycemia, hypertriglyceridemia, acidosis, elevation of free fatty acids |
| 7 CNS: psychosis, pancreatic encephalopathy, Putscher’s retinopathy |
| 8 Peripheral: fat necrosis (skin and bones), arthritis |
| 9 Miscellaneous: rhabdomyolysis |

| Pancreatic |
|------------|
| 1 Necrosis-sterile vs infected |
| 2 Pseudocyst-infection/rupture/hemorrhage |
| 3 Abscess |

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which results in a right intrapulmonary shunting of up to 30% of cardiac output[20]. The most important precipitating factor for MODS during the first week of AP is perhaps the failure to promptly recognize and treat hypoxia and hypovolemia[21]. The incidence of respiratory insufficiency is not related to the etiological factors of AP, severity of the disease, age of the patient, admission serum amylase, serum calcium, the amount or the nature of fluid administered (colloid solutions or blood), or the estimated fluid sequestration, but is seen more often in patients experiencing their first attack of AP.

**Clinical significance**

If pulmonary infiltrates and severe hypoxemia develop concurrently, mortality rate may be as high as 56%[10]. In two studies, Imrie and coworkers[21,24] correlated the overall mortality with the degree of hypoxemia. They found that patients with arterial pO2 below 70 mmHg have a mortality of 3% to 5.9% and when the arterial pO2 decreases below 60 mmHg the mortality rate increases to about 14%. Marked respiratory insufficiency in 22% of the cases of AP is associated with a 60% mortality from uncontrollable hypoxemia[23]. These studies suggest that respiratory insufficiency early in AP represents a risk for future ARDS especially if it is persistent and refractory to oxygen therapy.

**STAGE 2: HYPOXEMIA WITH RADIOLOGICAL ABNORMALITIES**

**Pleural effusion**

In 33% of all patients with AP, respiratory complications are clinically or radiographically detectable[14]. Pulmonary infiltrates or atelectasis (15%), pleural effusions (4%-17%), and pulmonary edema (8%-50%) are the pulmonary manifestations of AP in this category. Mortality and morbidity are significantly higher as compared to Stage 1. Some of these patients require ventilatory assistance. A direct relationship to prognostic factors is observed in this stage.

Presence of pleural effusion is currently considered an indication of severe pancreatitis and not just a marker of the disease[24]. Pancreatic ascites and pleural effusion are rare complications of both chronic and acute pancreatitis, and are associated with a mortality rate of 20% to 30%[25]. Mediastinal pancreatic pseudocysts and acute fluid collections are rare complications of pancreatitis resulting in an increase in morbidity and mortality[26]. Pleural effusions in AP are usually small, occasionally bloody, and are characterized by high amylase (up to 30 times greater than corresponding serum value), protein (>30 gm/L), and lactic acid dehydrogenase (ratio >0.6 serum value) levels[27]. The majority of pleural effusions (68%) are left-sided, 22% are bilateral and 10% are right-sided only. Two main causes of pleural effusion are transdiaphragmatic lymphatic blockage or pancreaticopleural fistulae secondary to leak and disruption of the pancreatic duct or pseudocyst caused by an episode of acute pancreatitis. The leak or disruption is more likely to lead to a pleural effusion if the duct disruption is posteriorly into the retroperitoneum.

The pancreatic enzymes can track up into the mediastinum and then rupture into the pleural cavity either left side or bilaterally and so create a connection between the pancreatic duct and the pleural cavity. Pancreatic pleural effusions may be massive and require treatment[29].

Close to 1/3 of all patients with an internal pancreatic fistula present with pleural effusion[29]. Formation of a posterior mediastinal cyst indicates that a patient is at increased risk of developing pleuropulmonary complications including acute and chronic pleural effusions which can be sympathetic in origin or result from the development of a fistulous tract into the pleural space[28]. Dyspnea and hypoxia, chest pain, atelectasis, cough, and ARDS can develop, worsening the prognosis[29].

Treatment of pleural effusion is usually at first conservative. Pleural effusions which become symptomatic often require thoracentesis, tube thoracotomy, endotracheal intubation, ICU admission, parenteral alimentation, and administration of octreotide. When the intraabdominal etiology is resolved, pleural effusions often resolve as well. Chronic effusions often require drainage of the pseudocyst or abscess or excision of the fistulous tract[27].

**Atelectasis**

Consolidation of lung tissue and atelectasis are frequent radiological observations. In cerulein-induced experimental pancreatitis-associated lung injury, it has been observed that there is a decrease in the production of pulmonary surfactant[31]. A decrease in the quantity of pulmonary surfactant may be a significant cause of atelectasis formation in dependent lung regions. Cerulein-induced pancreatitis appears to cause a decrease in the strength of the muscles of the diaphragm as well as a decrease in the endurance of these muscles[32]. Because the primary lesion is found at the alveolar interstitial level, it is probable that this decreases lung compliance and increases the work of breathing, leading to fatigue of the diaphragm more quickly[32].

There is mounting evidence that the proinflammatory cytokines are the agents behind the systemic complications of AP[33-35]. Cytokines are low molecular weight proteins, secreted by various cell types, that regulate the intensity and duration of immune responses and mediate cell-to-cell communication[36]. During AP IL-1, IL-6, and TNF-α are formed within the pancreas[32]. There is growing evidence that cytokines, mainly TNF-α and IL-1, could be the orchestrators of skeletal muscle dysfunction during sepsis. An experimental study showed that TNF-α at a lower concentration (50-400 ng/mL) causes no diaphragmatic fatigue in rats[37]. However at a higher concentration (10 μg/mL) of the cytokine, fatigue occurs in hamsters[38]. It has been noticed that TNF-α and IL-1 have a synergistic negative inotropic effect on the contractility of the diaphragm[39]. According to Matuszczak et al[39], cytokine levels need to be at a very high concentration to have a physiologic effect. Since the concentrations of cytokines in muscle during sepsis have not yet been quantified, the higher concentration of cytokines used in the study may be achieved in the natural physiologic setting of sepsis[32]. According to Norman et al[31], the intrapancreatic concentration of cytokines achieved in AP is much
higher than the systemic level and this argues in favor of the observation by Matuszczak et al[43] who used higher concentrations of cytokines to achieve the end result of diaphragmatic fatigue. According to these studies, it is possible that if IL-1, IL-6, TNF-α are present at high enough concentrations in the pancreatic juice, they could cause diaphragmatic fatigue. Diaphragmatic impairment may be the pathophysiological cause of atelectasis in the lower regions of the lung via decreased ventilation in these regions[50].

**STAGE 3: ARDS**

The most dangerous complication of the pulmonary system is ARDS. ARDS, a syndrome first described in 1967[49], is observed in association with AP[10]. Of the patients who develop AP, 15% to 20% develop ARDS with an associated mortality of 56%-60%. ARDS usually manifests itself between two to seven days following the onset of AP, but may have a much more rapid course. Clinical features include severe dyspnea and extreme hypoxemia refractory to a high inspired oxygen concentration. Multilobar pulmonary infiltrates in patients with previous normal radiographs and a relatively normal pulmonary capillary wedge pressure (< 18 mmHg) are noted[42,43]. Autopsy studies in patients with AP have shown that morphological changes in the lungs are indistinguishable from those in patients with ARDS caused by other conditions, including shock, sepsis, and severe trauma[44]. The lungs are characterized by increased alveolar capillary permeability with interstitial edema. The complication of ARDS parallels the presence of other poor prognostic signs of AP[15]. Although less often than necrotizing pancreatitis, patients with interstitial edematous pancreatitis are also at risk (10%) of developing respiratory failure[45].

There are three clinical features that must be present in ARDS: widespread bilateral radiographic infiltrates, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2/FiO2) less than or equal to 200 regardless of the positive end-expiratory pressure (PEEP), and no clinical evidence for an elevated left atrial pressure (less than or equal to 18 mmHg)[41,42]. Hypoxia is worse in ARDS. ARDS accounts for 50%-90% of all deaths from pancreatitis[41]. Improved ventilatory and supportive care, has improved the outcome in ARDS. However the underlying etiology remains unclear, keeping the mortality still unacceptably high.

**Pathophysiology**

The pathophysiology of ARDS in AP is poorly understood. Actions of pancreatic enzymes as well as inflammatory mediators released as a result of pancreatic injury play a key role in the pulmonary complications. The pathophysiology of ARDS is described as increased pulmonary vasculature leaking protein-rich transudate into the alveolar space and decreased lung compliance manifested clinically as refractory hypoxemia, and radiologically as diffuse infiltration in the lungs.

In the pathogenesis of systemic complications of AP, the role of active enzymes in circulation, liberation of proinflammatory cytokines, leukoagglutination, migration of neutrophils, activation of leukocytes, complement-mediated injury, and platelet activating factor decreasing the normal defense mechanisms and increased production of Nitric oxide (NO) are studied. The agents which are suspected to play a role in the pathogenesis of AP are noted in Table 2. A number of experimental and clinical studies have helped to elucidate the mechanisms involved in the pathogenesis of lung injury secondary to AP.

**Activated trypsin:** It is a possible source for the cause of pulmonary insufficiency. Trypsin causes damage to the pulmonary vasculature and increases endothelial permeability[48]. In laboratory experiments trypsin has been shown to cause leukostasis in the pulmonary vasculature and thus activated trypsin could intensify intravascular coagulation in the pulmonary microcirculation[49]. In post mortem studies, patients with acute pancreatitis have been shown to have intravascular fibrin thrombi in different tissues, including the lungs[15]. Trypsin is capable of activating different complement factors directly, which can stimulate cytolysis and chemotactic leukocytes. Complement has been shown to produce ARDS raising the possibility of developing respiratory insufficiency.

**Phospholipase A:** As an incriminating factor in pulmonary complications of AP phospholipase A2 (PLA2) has been investigated by many authors. PLA2, which is activated by trypsin in the duodenum, is known for its ability to remove fatty acids from phospholipids. Pulmonary surfactant lines the surface of the alveoli and prevents the alveoli from collapsing by maintaining the surface tension. One of the main components of surfactant is phospholipid dipalmitoylphosphatidylcholine, which is a perfect substrate for PLA2. The basic reason for pulmonary insufficiency and ARDS in AP is due to the destruction of the surfactant. Büchler et al[48,50] showed that there is a strong correlation between serum-activated PLA2 and pulmonary insufficiency. In their prospective study, patients with pulmonary failure demonstrated a notably higher catalytic PLA2 activity during the first week of AP than patients without arterial hypoxemia. Büchler et al[48] and Kortesuo et al[51] observed that there are many isoenzymes of PLA2. The source of IR-PLA2 and group I PLA2 is the pancreas, but has no correlation with the severity of pancreatitis or likelihood of development of pulmonary insufficiency. Group II PLA2, which has an extra-pancreatic source, correlates

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**Table 2: Pathogenic players in respiratory insufficiency**

|   |   |
|---|---|
| 1 | Phospholipase A2 |
| 2 | Trypsin inhibitor |
| 3 | FFA/Lipoprotein lipase |
| 4 | Complement activation (C5a) |
| 5 | MIF |
| 6 | IL-6, IL-8, IL-β |
| 7 | NO |
| 8 | TNF-α |
| 9 | fMet-Leu-Phe (a bacterial wall product) |
| 10 | ICAM-1 |
| 11 | β-2-integrin (CD11b/CD18) |
| 12 | Trypsin |
| 13 | NF-kB |
| 14 | Substance P |

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well with the severity of AP and is probably responsible in part for the pulmonary insufficiency occurring as an extra-pancreatic complication of AP. The role of other isoenzymes of PLAc in AP has yet to be elucidated. Inflammatory cells do not seem to be the source of Group II PLAc, but they cause the pulmonary insufficiency and ARDS in AP. The low molecular weight PLAc inhibitor has been shown to decrease the level of group II PLAc activity and has no effect on group I PLAc activity. The inhibitor also decreases tissue destruction and protects pancreatic acinar cells. This is an area which needs further investigation to improve the outcome of AP.

**Platelet activating factor (PAF):** PAF is a potent biological mediator whose effect is manifested throughout the body. PAF stimulates PMN white cells and regulates the interaction between PMN cells and endothelial cells, facilitating migration of activated white cells into tissue spaces. PAF is a structural component of membrane lipids and is released upon the action of PLAc. In induced experimental pancreatitis (whether induced by immune complex, caerulein, or taurocholate) PAF is released into the pancreas, ascitic fluid, lung and blood. PAF can be controlled via the PAF receptor and PAF antagonists decrease the severity of experimental AP by reducing oxidative injury, morphological changes, white cell infiltration, vascular permeability in pancreas and lungs, pulmonary damage, blood, and peritoneal PAF exudative concentrations. Lexipafant, a computer image analysis generated imidazolyl derivative of Sp2 nitrogen compounds, is a powerful PAF receptor antagonist having an affinity for the receptor seven times more avid than PAF itself. Lexipafant has undergone a randomized double blind phase II clinical trial in human pancreatitis and is very successful in reducing organ failure. However, during phase III clinical trial, Lexipafant is unsuccessful in reducing new organ failure or mortality. In the largest systematic prospective study of severe AP ever undertaken, Johnson et al found that 58% of patients in the placebo group and 57% of patients in the Lexipafant group develop one or more organ failures, indicating that there is no difference between these groups. Systemic sepsis affects fewer patients in the Lexipafant group, the development of pseudocysts is 14% in the placebo group and 5% in the Lexipafant group. IL-8, a marker for neutrophil activation and E-selectin, a marker for endothelial damage, decrease more rapidly in the Lexipafant group than in the placebo group. This adequately powered study showed that antagonism of PAF activity on its own is not sufficient to ameliorate SIRS in severe AP or change mortality rates.

**Free fatty acid:** Another possible cause of pulmonary insufficiency is the release of free fatty acid (FFA). During the inflammatory process, pulmonary lipoprotein lipase is activated and releases FFA from albumin, to which they are physiologically bound. The free fatty acids released from triglycerides (TG), have been shown to damage capillary alveolar wall membranes. Digestive enzymes: In a normal pancreas, potentially harmful digestive enzymes (i.e. protease and phospholipase) are synthesized as inactive proenzyme forms which are only activated after pancreatic secretions reach the duodenum. Enteroctin, a brush border enzyme, cleaves trypsinogen into 2 products, namely N-terminal portion termed tryptsinogen-activation peptide (TAP) and active trypsin. Active trypsin then catalyzes the conversion of other proenzymes secreted by the pancreas into their active forms. Gukovskaya et al demonstrated that neutrophils infiltrate into the pancreas facilitating intrapancreatic trypsin activation during cerulean (cholecytokinin analogue)-induced experimental pancreatitis. The immunocytochemical localization experiments using specific antibodies to TAP indicate that the trypsin activation mediated by neutrophils occurs within the pancreatic acinar cells. Steer, in an excellent hypothesis, suggested that intrapancreatic (i.e., intra-acinar cell) activation of trypsinogen during pancreatitis is itself a 2-phase event. According to this interpretation, the initial phase of trypsinogen activation would be neutrophil-independent and solely dependent on acinar cell events. This initial phase of trypsinogen activation can lead to early acinar cell injury that triggers the pancreatic inflammatory response.

Activated neutrophils throughout the body, are attracted to the pulmonary microvascular network by various factors such as complement activation, cytokine production, alveolar macrophages and the upregulation of adhesion molecules. Chemoattractants such as TNF-α, IL-1, IL-6, IL-8, fMet-Leu-Phe (a bacterial wall product) and complement factor C5a upregulate the beta-2-integrin expression on neutrophils and the ICAM-1 receptor on endothelial cells. The binding of ICAM-1 to beta-2-integrin (CD11b/CD18) can increase the permeability of the pulmonary vasculature, allowing neutrophils to enter the lung parenchyma. Upon entry into the parenchyma, neutrophils release compounds which have been implicated in the damage caused by ARDS. This theory is supported by studies demonstrating that mice deficient in ICAM-1, develop a much less severe form of pancreatitis, and that ICAM-1 expression is increased in mice with pancreatitis. Several compounds released by neutrophils once within the lung parenchyma are discussed in the following paragraphs.

**TNF-α:** High concentrations of TNF-α are found in a variety of locations throughout the body during an episode of AP, and pancreatic parenchyma, ascitic fluid, lymphatic drainage and serum levels can predict disease severity and possible mortality. TNF-α activates neutrophils and increases lung damage levels at higher concentration in the lung. A tetravalent guanylhydrazone compound CNI-1493 has been developed in a research program to prevent the production of macrophage-derived NO. It was then discovered that CNI-1493 blocks the production of inflammatory mediators such as TNF-α, IL-1, IL-6, macroinflammatory peptide (MIP)-1, by preventing the phosphorylation of p38 mitogen-activated (MAP) kinase. If p38 MAP kinase is prevented from being phosphorylated, then TNF-α is not produced or is produced at a significantly lower level. Denham et al reported that CNI-1493 significantly attenuates the increase in pulmonary TNF-α resulting in decreased lung injury, confirming that CNI-1493 inhibits its pancreatic and pulmonary TNF-α gene induction in two models.
of murine pancreatitis. These results also support that pulmonary congestion is decreased when anti-TNF-α antibody is administered after pancreatitis is induced and overall morbidity and mortality are decreased[8,70]. Several recent studies have suggested that TNF-α is one of the agents orchestrating the early stages of AP, especially in recruitment of inflammatory cells, regulation of cytokine production, and promotion of pancreatic acinar cell death by apoptosis[81,86,79]. TNF-α also plays a protective role in preventing the release of proinflammatory cytokines[76,83]. TNF-α induces concomitantly proapoptotic and antiapoptotic mechanisms[93]. Antiapoptotic mechanisms are controlled by NF-B and MAP kinases. Pancreatitis-associated protein (PAP) prevents apoptosis[81,82]. Apoptosis is possibly a more favorable demise for acinar cells than necrosis because it results in a quick removal of damaged cells without loss of plasma membrane integrity as well as decreased recruitment of leukocytes[86]. According to Kaiser et al[83] severe forms of AP demonstrate little apoptosis while edematous pancreatitis shows a higher number of apoptotic cells. There is an interaction between apoptosis and necrosis, with inflammatory cells infiltrating the pancreas and causing necrosis of the apoptotic cells[81,83]. Apoptosis appears to be advantageous over necrosis, but needs to be controlled to prevent excessive tissue loss[81].

Nitric oxide: The role of nitric oxide (NO) in vascular collapse during AP is highly controversial[103,104]. CNI-1493 blocks the production of NO by macrophages, subsequently the level of NO decreases lessening the damage to the lungs[86]. However, Tsukahara et al[83] demonstrated that alveolar macrophages during experimental pancreatitis mediate endothelial injury as well as increase microvascular permeability resulting in lung injury. In contrast, O'Donovan et al[81] showed that administration of sodium nitroprusside, a NO donor, to rats with caerulein-induced pancreatitis decreases lung myeloperoxidase activity, bronchoalveolar lavage protein concentration, and wet-to-dry lung weight, suggesting that NO may be protective against lung injury during pancreatitis. A possible explanation for the contradictory findings between Tsukahara et al[83] and O'Donovan et al[81] is the different experimental models or is possibly attributable to the paradoxic nature of NO[73].

Substance P: Substance P is a neuropeptide which is located in the nerve endings throughout the body and is released into the gap where it acts via the NK1 receptor to mediate pain[12]. It has also been implicated in many inflammatory states, such as immune complex-mediated lung injury, asthma and inflammatory bowel disease[86,88]. Once pancreatitis occurs, there is an increase in substance P levels as well as NK1 receptors on pancreatic acinar cells[12]. Interestingly, mice which have been genetically engineered to be deficient in NK1 receptors are protected from AP[90]. This gives clinical medicine another possibility for preventing AP and thus also for protecting patients against pulmonary complications of AP.

Chemokines: Chemokines are a family of cytokines which are distinguished by the fact that they act on the superfamilies of G-protein–coupled serpentine receptors[12]. There are two subsets of chemokines based on the orientation of the first two cysteines: CC chemokines and C-X-C chemokines. The CC chemokines stimulate monocytes and C-X-C chemokines stimulate neutrophils. IL-8 is a C-X-C chemokine[90]. There is no direct homologue of IL-8, but there is a homologue of growth-related oncogene-alpha (GRO-α) which is cytokine-induced neutrophil chemoattractant (CINC)[93]. CINC (also a C-X-C chemokine) is a specific neutrophil attractant. A recent study reported that anti-CINC antibody reduces lung damage. During the study, anti-CINC was administered to Caerulein-induced pancreatitis mice prophylactically and during Caerulein administration. The results demonstrate that both the prophylactic group and the therapeutic group have a reduction in lung injury, but not a reduction in AP[91].

IL-8: IL-8 is a strong attractant of neutrophils in the lungs and its high concentrations have been observed in the lungs of patients with ARDS[91,92]. Donnelly et al[91] showed that bronchoalveolar lavage (BAL) levels of IL-8 are significantly higher in patients who develop ARDS than in those who do not develop ARDS. However, they have not found a relationship between blood levels of IL-8 and patients with or without ARDS, but found that IL-8 may be a prognostic factor for ARDS. Kurdowska et al[91] took the IL-8 issue one step further to determine if the anti-interleukin 8 and interleukin-8 complex is a marker of patients who are at risk of developing ARDS, and found that anti-interleukin 8 and interleukin-8 complexes may be a maker of patients who may progress to ARDS.

Macrophage migration inhibitory factor (MIF): MIF is a cytokine discovered in 1966 and produced by T lymphocytes and plays a role in preventing random migration by macrophages[95,96]. It is now known that MIF is released not only by T lymphocytes but also by monocytes, macrophages, pituitary corticotrophic cells, and epithelial cells. MIF is currently viewed as an important proinflammatory cytokine[77,97]. MIF has a critical role in regulating the immune system by overriding the anti-inflammatory and immunosuppressive effect of glucocorticoids on macrophages and T cells[99,90]. MIF has been shown to be elevated in several inflammatory diseases such as sepsis, rheumatoid arthritis, bronchial asthma and also in the bronchoalveolar lavage samples of adults with ARDS[103]. It was reported that MIF levels in the lungs of taurocholate (TCA) pancreatitis rats are significantly higher than those in the lungs of normal rats, whereas MIF levels in the pancreas and liver have no differences between the normal and TCA pancreatitis rats[102,100]. There is a possible connection between TNF-α and MIF[103]. Pulmonary TNF-α levels are increased significantly in TCA-induced pancreatitis and the increase can be attenuated by treatment with anti-MIF antibody, but not with the control antibody[103]. Anti-MIF antibody also improves the survival rate in both TCA pancreatitis rats and choline deficient, ethionine-supplemented (CDE) pancreatitis mice[100]. Serum MIF levels are also found to be significantly higher in severe AP than in mild AP or in healthy controls[101]. Combining the increased survivability with anti-MIF antibody, induction of IL-8, stimulus of TNF-α production, ability to override the effects of glucocorticoids and the increased levels of MIF found

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**Table 3 Pro-inflammatory cytokines**

| IL-1β | -major inflammatory mediator, major activator of macrophages and enhances B and T cell activation |
| IL-6 | -acute phase reactant, stimulates B cell differentiation |
| IL-8 | -stimulates the upregulation of adhesion molecules, chemotactic factor for neutrophils and lymphocytes |
| TNF-α | -recruitment of inflammatory cells, regulation of cytokine production, and promotion of pancreatic acinar cell death by apoptosis |

IL-10 is an anti-inflammatory cytokine by inhibiting macrophages releasing inflammatory mediators.

in severe AP, suggests that MIF plays strongly a vital role in AP and lung injury[33-35]. It also raises the possibility of treatment with anti-MIF antibody to prevent lung injury in AP in the future.

**IL-10:** IL-10 is one of the few known anti-inflammatory cytokines in human body which prevents the production of pro-inflammatory mediators particularly TNF-α by macrophages and T cells[106-109]. IL-10 also inhibits the release of IL-6, and IL-1-beta[112,108,110-112] as well as stimulates the synthesis of IL-1 receptor antagonist (IL-1ra) and the release of soluble p75 TNF receptor which inhibits the action of pro-inflammatory cytokines[113]. (Table 3) In particular IL-10 has been shown to inhibit the release of TNF-α from alveolar macrophages, thus implicating that it can decrease the likelihood of developing ARDS[114]. In another study, IL-10 was administered to one group of mice prior to the development of AP. IL-10 was administered to another group of mice 33 hafter the induction of AP. The study showed that mortality is decreased due to AP in both groups[115]. Two other studies showed that both IL-10 and IL-1ra significantly decrease the severity of AP when given after the induction of AP[115,116]. Several studies have shown that IL-10 when given after AP can decrease the severity of AP, which raises the possibility of IL-10 used in clinical treatment of AP[115,116].

**CONCLUSION**

Mortality in AP occurs in two peaks and is usually associated with MODS. Pulmonary dysfunction is perhaps the most critical for all extra-pancreatic manifestations of AP[117]. The pathogenesis of pulmonary complications in AP has been the topic of intense research in the past two decades. In this review, we have evaluated the different types of respiratory complications, with their clinical significance assessed and their pathogenesis discussed. Although the data are predominantly from experimental studies, their clinical relevance is of increasing importance. Hyoxemia occurs in nearly 50%-60% of patients with AP[118,119]. The major cause of hypoxemia is ventilation/perfusion (V/Q) mismatch which results in right to left intrapulmonary shunting. Failure to promptly recognize hypoxemia and hypoxemia may precipitate MODS. Pleural effusion on the left side, once considered just a marker of AP, is indeed a sign of poor prognosis[24]. Atelectasis is noted to be secondary to a decrease in pulmonary surfactant[31]. The role of cytokines has become quite evident in a number of experimental studies of atelectasis[33-35]. The most dangerous pulmonary complication is ARDS[118]. Of the patients who develop ARDS nearly 50% would die[110]. The incidence is much less in edematous pancreatitis. The clinical features of ARDS include widespread bilateral infiltrates in CXR and a ratio of partial pressure of arterial O2 to fraction of inspired oxygen (PaO2/FiO2) ≤ 200 regardless of PEEP with no evidence of elevated left atrial pressure[21,46]. The pathophysiology of ARDS is complex. The action of enzymes in circulation (trypsin, and phospholipase A2, proinflammatory cytokines, leukoagglutination, migration of neutrophils, activation of leukocytes, complement mediated injury, PAF, NO) is noted to play a different role in the pathogenesis.

The future management of AP that currently carries an overall mortality of 5% and 15%-20% in necrotizing pancreatitis includes measures to counteract the proinflammatory agents[24,30]. With the exception of platelet activating inhibitor agents, such as Lexipafant, nothing seems to be clinically relevant at this time[102]. However, a better understanding of the pathogenesis of lung injury and other organ dysfunction is expected to revolutionize the treatment of AP.

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