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Review Paper

Precision medicine in acute pancreatitis

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Abstract

Acute pancreatitis is a common inflammatory condition of the pancreas. Its mortality largely depends on disease severity, with severe cases having a mortality rate of up to 50%. Despite the potential for severe progression and the associated high morbidity and mortality, no specific treatment is currently available for routine use in acute pancreatitis. Precision medicine offers a promising approach, aiming to identify and apply personalized treatment strategies that can effectively reduce the burden of this disease on patients and healthcare systems.

Keywords: Acute pancreatitis, precision medicine, treatment.

Introduction

Acute pancreatitis is currently one of the leading gastrointestinal disorders requiring hospitalization. Its global incidence is approximately 34 cases per 100,000 person-years, and it has been steadily rising worldwide[1]. The clinical course varies widely, from mild cases with excellent recovery to severe pancreatitis associated with mortality rates as high as 50%[2]. Initial management focuses on goal-directed fluid resuscitation, adequate pain control, and nutritional support. Despite extensive research and encouraging preclinical findings, no targeted pharmacological treatments are available, and precision medicine approaches remain underdeveloped compared to other medical conditions.

Precision medicine is not a new concept. Hippocrates, regarded as the Father of Western Medicine, observed that 'different drugs for different patients, for the sweet ones do not benefit everyone, nor do the astringent ones, nor are all the patients able to drink the same things'[3]. Similarly, Canadian physician William Osler remarked, 'If it were not for the great variability among individuals, medicine might as well be a science and not an art'[4].

Precision medicine is defined as the customization of medical treatment based on the unique characteristics of each patient, allowing classification into subgroups that differ in their susceptibility to disease or their response to specific therapies. This enables preventive or therapeutic interventions to be targeted to those most likely to benefit, while avoiding unnecessary costs and side effects in others[5]. An effective precision medicine approach provides clinical decision support for both patients and clinicians, helping address complex conditions.

To generate a precision medicine report, clinicians require integrated information on the patient's signs and symptoms, genetic profile, risk factors, and relevant biomarkers. Additional factors such as environmental exposures, lifestyle, prior injuries, metabolic stressors, comorbidities, and even the microbiome must also be considered**.**

Precision medicine in AP

Recent advances in medicine have made it possible to identify key genomic and molecular patterns that help determine individual risk, enable early diagnosis, assess disease severity, guide prognosis, and inform optimal management strategies. However, the adoption of these technologies has been uneven across various human diseases, with some organ systems benefiting more rapidly than others. Notably, precision medicine research focusing on pancreatic diseases has shown the slowest growth in publication volume and remains the lowest in total among all organ systems studied[6].

While this discrepancy may be attributed to factors such as variations in disease incidence, the absence of targeted therapies, limited research funding, and socioeconomic healthcare challenges, it is evident that the management of pancreatic diseases still lags behind in precision medicine. For example, the first genome-wide association study (GWAS) in asthma was published as early as 2010[7], and although GWAS for chronic pancreatitis followed not long after in 2012[8], a GWAS for acute pancreatitis has yet to be conducted.

Despite extensive ongoing international research and promising preclinical findings, there are currently no approved targeted drug therapies available[9].

This, combined with a marked decline in overall research investment with funding for gastrointestinal inflammatory disorders in the USA falling from 25.7% to 10.7% over the past 50 years, has posed major challenges to advancing precision medicine in pancreatitis. As a result, precision medicine for acute pancreatitis remains at an earlier stage compared to many other conditions. However, significant momentum has now been generated in the field of pancreatology, with numerous national and international collaborative networks and initiatives emerging, positioned to leverage technological advances and drive personalized treatment strategies forward.

Pathophysiology of acute pancreatitis

Although the precise mechanisms underlying acute pancreatitis remain incompletely understood, substantial progress has been made in recent decades toward clarifying the processes involved in pancreatic acinar cell injury[10]. Findings from animal models of acute pancreatitis suggest that the early course of the disease can be divided into four distinct phases: i. an initial phase of cellular injury; ii. a second phase marked by local pancreatic inflammation; iii. a third phase involving systemic inflammatory responses affecting distant organs such as the lungs, liver, and kidneys; and iv. a fourth phase that may occur if pancreatic necrosis becomes infected[11]. It is important to recognize that significant differences persist, as patients with acute pancreatitis are highly diverse, exhibiting genetic and epigenetic variability along with differing environmental exposures all of which contribute to variations in susceptibility, disease severity, and progression.

The first phase: The initial phase of cellular damage

Under normal conditions, digestive enzymes are produced and secreted by pancreatic acinar cells in the form of inactive precursors known as zymogens. Their activation begins in the duodenum, where the brush border enzyme enterokinase converts trypsinogen to trypsin. Since trypsin not only activates itself but also triggers the activation of other digestive enzymes, including chymotrypsinogen, pro-carboxypeptidase, and pro-elastase, it serves as the key regulator of the pancreatic enzyme cascade. Although the molecular mechanisms underlying pancreatitis are complex and not yet fully understood, recent experimental studies suggest that factors such as apical enzyme activation, reduced pH, hydrolase activity, and cytoskeletal disruption contribute to premature trypsinogen activation. Among the central elements implicated are calcium signaling, cathepsin B, and early NF-κB activation.

The second phase in acute pancreatitis: Local inflammation

"The second phase of acute pancreatitis is marked by local inflammation within the pancreas. This phase is characterized by a complex inflammatory response, in which various cytokines are released to recruit, activate, and sequester inflammatory cells such as neutrophils, macrophages, and lymphocytes within the pancreatic tissue. In response to local injury, key mediators including NF-κB, acute pancreatitis-associated protein 1, TNF-α, interleukin-1 (IL-1), IL-6, IL-8, and platelet-activating factor (PAF)are released, while MCP-1 and adhesion molecules such as ICAM-1 and selectins also play important roles. Adding further complexity, an anti-inflammatory response follows the initial proinflammatory phase, partly mediated by IL-10, IL-2, IL-1 receptor antagonists, components of the complement system (e.g., C5a), and the activation of protease-activated receptor-2 (PAR-2). The severity of acute pancreatitis appears to be largely determined by the processes that unfold during this phase.

The third phase in acute pancreatitis: Systemic inflammation

The third phase of acute pancreatitis reflects the systemic effects of elevated chemokine levels on distant organs. This phase is characterized clinically by systemic inflammatory response syndrome (SIRS), which can progress to multiple organ dysfunction syndrome (MODS) and remains a key determinant of mortality. Studies have shown that serum cytokine levels correlate with disease severity. Among the distant organ complications, acute pancreatitis-associated lung injury, often presenting as acute respiratory distress syndrome (ARDS), plays a major role in mortality. In addition to the previously mentioned cytokines, mediators such as protease-activated receptor-2 (PAR-2), monocyte chemoattractant protein-1 (MCP-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage migration inhibitory factor (MIF), nitric oxide (NO), and cyclooxygenase-2 (COX-2) have been identified as contributors to the development of MODS.

The fourth phase in acute pancreatitis: Infection of pancreatic necrosis

The exact mechanism driving the progression from interstitial oedematous acute pancreatitis to necrotizing pancreatitis as well as the timing or whether these two forms follow distinct clinical and pathological pathways after the initial phase remains uncertain. In necrotizing acute pancreatitis, infection of the necrosis occurs in 30–70% of cases, representing the most critical local complication. This significantly worsens the prognosis, as it often leads to severe systemic complications such as sepsis and multiple organ dysfunction syndrome. Patients with infected necrosis face a mortality rate twice as high as those with sterile necrosis. While infection of pancreatic or per pancreatic necrosis typically develops within the first two weeks, it often remains latent or subclinical for 3–4 weeks.

Experimental models of pancreatitis have provided valuable insights into disease pathophysiology and potential therapeutic targets. However, translating these findings into effective clinical treatments remains challenging, largely because animal models fail to fully replicate the complexities of human disease.

Additionally, limited access to pancreatic tissue has posed a major obstacle in studying both benign and malignant pancreatic disorders. This restriction has hindered not only research into disease mechanisms but also the development of methods to track disease progression.

Treatment

Precision medicine aims to tailor treatments to individual patients by considering genetic, environmental, and lifestyle factors. However, despite progress in understanding the pathophysiology of acute pancreatitis (AP), no pharmacological therapy has yet proven effective in changing the disease's natural course. Consequently, treatment remains entirely supportive, focusing on managing complications. Most experimental drugs tested in clinical trials have failed to demonstrate significant benefits in real-world settings (Table 1)[11]. This limitation may arise because therapies in experimental studies are typically administered either early in the course of AP or at the time of pharmacologically induced pancreatitis. In contrast, human patients often present at varying times after symptom onset, meaning treatments are initiated when pancreatic inflammation is already well-established. Therefore, early identification of AP patients is crucial to allow interventions at a stage when the inflammatory cascade can still be modulated. A deeper understanding of cytokine profiles, assessed through comprehensive panels could help determine the disease phase at admission and guide targeted, stage-specific therapies[11].

The AP Working Group, convened at a 2018 National Institute of Diabetes and Digestive and Kidney Diseases-sponsored conference, recommended that future clinical trials stratify AP patients early upon presentation based on etiology, disease severity, and underlying molecular pathways to enable targeted therapeutic testing. Emerging insights from multi-omics approaches including genomic, transcriptomic, proteomic, and metabolomic profiling in AP are currently under investigation. A key example is the RAPID-I trial, which integrates transcriptomic biomarker analysis with mechanistic evaluation of anti-TNF-α therapy in AP. The study enrolls adults newly diagnosed with AP (of any severity) presenting within 24 hours of pain onset. Participants are randomized to receive a blinded infusion of 5 mg/kg infliximab, 10 mg/kg infliximab, or placebo, initiated within 12 hours of admission. The primary endpoint is cumulative CRP levels (measured serially over 28 days), while secondary outcomes include pain severity, nutritional deficits, SIRS criteria, SOFA scores, CT-assessed pancreatic injury, complications, hospital stay duration, and patient-reported outcomes.

Additionally, the trial incorporates transcriptome profiling, cytokine analysis, and leukocyte subset characterization to identify mechanistic pathways and predictive biomarkers for disease severity and treatment response. RAPID-I aims to establish a framework for future precision medicine trials in AP, accelerating progress toward personalized therapeutic strategies.

While most randomized controlled trials (RCTs) seeking effective targeted therapies for acute pancreatitis (AP) have yielded disappointing results, some successful studies have emerged—notably those focusing on well-defined patient subgroups. This observation aligns with the precision medicine approach seen in pancreatic cancer treatment[12]. Presently early treatment of AP entails mostly supportive care, which may involve analgesia, antibiotics, probiotics, ERCP, fluid resuscitation, and enteral nutrition[1].

However, these interventions demonstrate variable efficacy across different AP subpopulations. A prime example is ERCP, where clinical utility depends on careful patient selection. The routine use of ERCP in AP has ended up with conflicting conclusions. RCTs in specific patient subpopulations showed that ERCP with endoscopic sphincterotomy performed early (within 24 h) was beneficial in biliary AP associated with cholangitis, but it was not advantageous generally in any biliary cases[13].

Recent studies have challenged conventional approaches to fluid management in acute pancreatitis (AP). Although current guidelines advocate for goal-directed fluid resuscitation[14], a multicenter randomized controlled trial (RCT) across 18 centers was prematurely terminated after finding that aggressive early fluid administration increased the risk of volume overload without demonstrating clinical benefit[15]. It is important to note that the study involved adult patients diagnosed with acute pancreatitis (AP), who were then randomized to receive either moderate or aggressive fluid resuscitation. This introduces the possibility that some patients, particularly those with fluid depletion, might have benefited from the more aggressive approach, while others, whose fluid balance was stable, could have experienced adverse effects. As a result, combining AP patients with differing fluid status could obscure the potential benefits of aggressive fluid resuscitation in hypovolemic patients, who are at risk of developing multiple organ dysfunction unless their fluid volume is promptly corrected[12].

Predicting the extent of fluid sequestration could help identify patients with acute pancreatitis (AP) who require either more or less aggressive fluid resuscitation. One study found that factors such as younger age, alcohol-related etiology, hematocrit levels, glucose, and the presence of systemic inflammatory response syndrome were significantly linked to higher levels of fluid sequestration within the first 48 hours of hospital admission. Additionally, increased fluid sequestration during this period was strongly associated with longer hospital stays, as well as higher rates of acute fluid collection, pancreatic necrosis, and persistent organ failure[16]. In the early phase of acute pancreatitis, distinguishing infection from systemic inflammatory response syndrome (SIRS) can be challenging.

Table-1: Experimental treatment approaches that have been undertaken in the last two decades.

Target	Treatment	Model/study/method used	Benefit
PI3K	Wortmannin	Rodents/experimental/sec	Potential benefit[19]
Calcium	Calcium chelator BAPTA-AM	In vivo (rat/mice)/ experimental /TCA	Potential benefit[20]
Cathepsin B	Cathepsin B inhibitor-E64d Cathepsin B inhibitor CA-074me	In vivo (mice)/ experimental/	Potential benefit[21]
pH reduction	Chloroquine	In vivo (rat)/experimental/sec.	Potential benefit[22]
NF-kB	Curcumin	In vivo (rat)/experimental/sec.	Potential benefit[23]
COX-2	COX-2 inhibitors	In vivo (mice/rat)/experimental/sec.	Potential benefit[24]
MIF	MIF-antibodies	In vivo (mice)/ experimental/sec.	TCA Potential benefit[25]
TNF-a	TNF-a antibody	In vivo (rat)/experimental/sec.	Potential benefit[26]
ICAM-1	ICAM-1 antibody	In vivo (rat)/experimental/sec.	Potential benefit[27]
PAF	PAF-antibody (lexipafant)	Human phase II/RCT double blind (n=290	No benefit[28]
Protease activation	Anti–protease	Human phase II/RCT double blind (n=223)	No benefit[29]
Exocrine secretion	Somatostatin and analogues (n=302) (octreotide, lanreotide)	Human phase II/RCT double blind	No benefit[30]
NO	Antioxidants (N-acetylcysteine, Ascorbic acid, selenium)	Human phase I/observation study (n=46)	No benefit[31]

A study found no significant differences in the incidence of infected pancreatic necrosis, the need for surgical intervention, or mortality when antibiotic prophylaxis was used[17]. Guidelines do not recommend the routine use of prophylactic antibiotics for preventing infectious complications in acute pancreatitis[14].

However, certain patient subgroups may benefit from the early administration of antibiotics. For instance, antibiotics should be administered if signs of extra-pancreatic infection are present, including cholangitis. In cases of suspected infected pancreatic necrosis, procalcitonin-based algorithms should be considered to guide antibiotic use in the early phase of acute pancreatitis, rather than relying on empirical antibiotic treatment[18].

Conclusion

Precision medicine for acute pancreatitis is still in the early stages of development, primarily hindered by the absence of targeted drug therapies, which can be attributed to previous shortcomings in preclinical research and clinical trial designs. However, significant opportunities exist to address this gap, with the results from major omics studies in acute pancreatitis eagerly anticipated. These studies have the potential to facilitate target identification and biomarker discovery, setting the stage for more effective and successful future trials.

Successful treatments for acute pancreatitis can be identified if we can narrow down the patient population to those most in need of specific therapies, maximizing the benefits of targeted treatments while minimizing the risk of adverse effects.

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