

Microcirculatory Dysfunction as a Central Driver of Disease Severity in Acute Pancreatitis: Mechanisms and Therapeutic Targets

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ABSTRACT

Acute pancreatitis (AP) remains a complex inflammatory disease in which early microcirculatory failure plays a central role in determining severity, organ dysfunction, and clinical outcomes. Despite major advances in understanding its pathobiology, therapeutic strategies targeting microvascular impairment, endothelial injury, and perfusion disturbances remain fragmented and inconsistently translated into practice. This comprehensive narrative review critically synthesizes current evidence on pancreatic microcirculatory dysfunction and its therapeutic implications. We integrate data from contemporary models, including endothelial glycocalyx degradation, capillary leak phenomena, leukocyte–endothelium interactions, mitochondrial dysfunction, and splanchnic hypoperfusion, establishing microcirculatory collapse as a unifying mechanism in the progression to severe AP.

Furthermore, the review critically evaluates therapeutic interventions aimed at maintaining or restoring microvascular integrity, including optimized fluid resuscitation, low-molecular-weight heparin, ulinastatin, epidural analgesia, continuous hemofiltration, and experimental endothelial-protective agents. Evidence suggests that early, controlled hydration, anticoagulation in select cases, and epidural strategies may improve perfusion and reduce complications, while emerging therapies targeting glycocalyx preservation, mitochondrial stability, and SIRT1-FOXO1 pathways show promising translational potential. However, heterogeneity among studies, limited high-quality randomized trials, and variations in timing and patient selection highlight persistent gaps. Overall, this review consolidates microcirculatory dysfunction as a central therapeutic target in acute pancreatitis and underscores the need for standardized protocols, high-quality RCTs, and precision-based approaches to modify the early trajectory of severe disease.

KEYWORDS: Acute pancreatitis, microcirculation, endothelial dysfunction, organ failure, perfusion injury, fluid resuscitation, glycocalyx, systemic inflammation, heparin therapy, epidural analgesia.

ARTICLE DETAILS

Published On:
09 February 2026

Available on:
<https://ijmscrs.com/>

1. INTRODUCTION

1.1 Background

Acute pancreatitis (AP) is one of the most common gastrointestinal diseases worldwide, with a rising global incidence over recent decades [1]. Epidemiological studies show that AP represents a considerable healthcare burden, accounting for hundreds of thousands of hospitalizations annually in the United States [2]. Its incidence varies across regions due to differences in diagnostic approaches, risk factor distribution, and population characteristics, yet most cohorts demonstrate a consistent upward trend [2]. Although the majority of cases are mild and self-limited, approximately 15–20% progress to a severe form characterized by organ failure, infected necrosis, and increased mortality [3–5].

The pathogenesis of AP originates with premature intracellular activation of digestive enzymes, resulting in acinar cell injury, release of inflammatory mediators, and immune cell recruitment [6,7]. Aberrant calcium signaling, mitochondrial dysfunction, impaired autophagy, endoplasmic reticulum stress, and both trypsin-dependent and –independent pathways contribute to early cellular damage [7]. Systemic inflammatory response syndrome (SIRS) is a key determinant of early disease progression; persistent SIRS is closely associated with organ failure, the primary criterion defining severe AP according to the revised Atlanta Classification [5,7,8].

Organ failure is the strongest predictor of morbidity and mortality and typically reflects systemic injury rather than direct pancreatic damage [5]. Host-related factors—including age, visceral adiposity, hypertriglyceridemia, genetic susceptibility, and the extent of necrosis—influence the likelihood of progression to severe disease [5]. Immune dysregulation further contributes to disease escalation, as exaggerated pro-inflammatory responses or impaired antibacterial defenses drive necrotizing pancreatitis and systemic complications [6]. Experimental models have been essential for characterizing early molecular events in AP, given the limited availability of human pancreatic tissue during initial disease stages [7]. These models highlight the interplay between acinar injury, inflammatory signaling, immune cell activation, and systemic mediator release—processes that ultimately shape disease severity [7].

1.2 Rationale

Despite advances in understanding AP pathobiology, microcirculatory disruption has emerged as a central mechanism linking early pancreatic injury to systemic complications, including organ failure, necrosis, and sustained inflammation. Early systemic injury arises from the combined effects of inflammatory mediators and vascular dysfunction and is increasingly recognized as a pivotal driver of severe disease [5]. Microvascular impairment—marked by endothelial dysfunction, increased permeability, leukocyte adhesion, capillary stasis, and tissue ischemia—directly

contributes to pancreatic necrosis and multiorgan involvement.

While current classification systems and clinical guidelines emphasize organ failure and local complications for severity assessment [7,8], they do not explicitly integrate microcirculatory dysfunction as a key pathophysiologic axis. Immune-mediated mechanisms further modulate vascular injury, amplifying systemic inflammation and exacerbating clinical deterioration [6]. Experimental models consistently demonstrate that microvascular derangements precede and intensify pancreatic injury [7]; however, translation of these findings into clinical practice has been limited by an incomplete mechanistic framework and a lack of targeted therapeutic strategies.

A comprehensive synthesis of evidence linking microcirculatory dysfunction with immunologic and metabolic pathways is therefore critical to refine current understanding of AP progression, improve early risk stratification, and support the development of therapies aimed at preventing severe disease.

1.3 Objective

The objective of this narrative review is to synthesize current evidence on the role of microcirculatory dysfunction in acute pancreatitis, integrating epidemiologic trends, pathophysiologic mechanisms, classification and severity frameworks, and determinants of systemic injury and organ failure. By consolidating findings from clinical studies, molecular research, immunologic analyses, and experimental models, this review aims to clarify how microvascular impairment contributes to disease severity and to identify potential opportunities for targeted therapeutic intervention.

2. METHODS

A comprehensive narrative review was conducted using a structured and methodologically rigorous approach to ensure transparency and scientific reliability. A literature search was performed in PubMed/MEDLINE, Embase, and the Cochrane Library to identify studies published between January 2000 and July 2025, as well as online-first articles available at the time of the search, examining microcirculatory dysfunction, vascular injury mechanisms, immune–microvascular interactions, and clinical outcomes in acute pancreatitis. The search strategy incorporated Medical Subject Headings and free-text terms related to “acute pancreatitis,” “microcirculation,” “microvascular dysfunction,” “endothelial injury,” “capillary perfusion,” “pancreatic necrosis,” “organ failure,” “immune response,” “inflammation,” “vascular permeability,” “experimental models,” and “systemic complications,” with Boolean operators applied to optimize retrieval of relevant evidence. Studies were eligible for inclusion if they evaluated mechanisms of microvascular injury, used experimental animal models relevant to pancreatic perfusion, reported clinical associations between microcirculatory impairment

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and severity outcomes, assessed biomarkers of endothelial or vascular dysfunction, or investigated therapeutic interventions with potential microcirculatory benefits, including anticoagulation, epidural analgesia, hemofiltration, ulinastatin, or fluid resuscitation strategies. Systematic reviews and meta-analyses addressing inflammation, severity prediction, pathophysiology, or treatments in acute pancreatitis were also included to support comprehensive synthesis. Articles were excluded if they consisted of case reports, non-peer-reviewed conference abstracts, non-pancreatic disease models without relevance to microvascular physiology, exclusively pediatric cohorts, or lacked mechanistic, vascular, perfusion-related, or clinically meaningful outcomes. Only studies published in English were considered.

Given the heterogeneity of mechanistic, experimental, and clinical evidence, a narrative synthesis approach was selected. Emphasis was placed on high-quality studies, contemporary pathophysiological insights, and clinically relevant endpoints such as organ failure, necrosis, systemic inflammatory response, and mortality. Experimental data from animal models were incorporated only when directly applicable to understanding microvascular processes relevant to human disease. All included references were assessed for methodological rigor, internal consistency, and their contribution to advancing the mechanistic and clinical understanding of microcirculatory dysfunction in acute pancreatitis.

3. CENTRAL BODY

3.1 Core Mechanisms of Microcirculatory Dysfunction in Acute Pancreatitis

Microcirculatory dysfunction represents one of the earliest and most consequential determinants of disease progression in AP. Experimental and clinical evidence consistently demonstrate that disturbances in pancreatic microvascular flow, endothelial integrity, and perfusion distribution occur before overt necrosis and strongly influence the development of systemic complications. The mechanisms underlying these alterations are multifactorial and interconnected, involving hemodynamic disturbances, inflammatory cascades, endothelial injury, ischemia–reperfusion responses, and multiorgan microvascular failure.

3.1.1 Early Hemodynamic and Perfusion Abnormalities

Early reductions in pancreatic perfusion constitute a hallmark of AP-associated microcirculatory failure. Classic experimental work demonstrated that pancreatitis induces focal vasoconstriction, heterogeneous distribution of capillary blood flow, and early stasis of erythrocytes within pancreatic capillaries, leading to zones of hypoxia and impaired tissue oxygenation [9]. Detailed intravital microscopy studies later confirmed that these disturbances include capillary narrowing, reduced functional capillary density, and sludging phenomena that compromise nutritive flow at the acinar level

[10]. Persistent constriction of precapillary arterioles further aggravates ischemia, which, if sustained, sets the stage for acinar necrosis and amplifies local inflammatory signaling [11].

3.1.2 Endothelial Injury, Increased Permeability, and Capillary Leakage

Inflammatory mediator release plays a central role in disrupting endothelial barrier function. Early activation of neutrophils, macrophages, and other immune effectors triggers the secretion of cytokines, proteases, and vasoactive mediators that directly injure endothelial cells and promote rapid increases in vascular permeability [12]. Structural degradation of the endothelial barrier facilitates extravasation of plasma proteins, resulting in interstitial edema that further compresses capillaries and reduces microvascular flow [13]. In severe AP, these changes are accompanied by widespread capillary leak and loss of vascular autoregulation, which together contribute to progressive tissue hypoxia and expansion of pancreatic necrosis [11].

3.1.3 Ischemia–Reperfusion Injury and Oxidative Stress

Ischemia–reperfusion (IR) injury constitutes a major exacerbating factor in microvascular deterioration. Reduced pancreatic perfusion is followed, in many models, by episodes of spontaneous or therapeutic reperfusion, which generate bursts of reactive oxygen species (ROS) and drive lipid peroxidation, endothelial damage, and leukocyte activation [14]. These mechanisms promote the so-called “no-reflow phenomenon,” wherein microvascular perfusion fails to normalize despite reopening of upstream vessels [9]. ROS production and inflammatory amplification also impair mitochondrial function within endothelial and parenchymal cells, ultimately worsening acinar injury and microvascular collapse [10].

3.1.4 Immune–Microvascular Interactions and Amplification of Systemic Inflammation

Microvascular dysfunction both results from and reinforces immune dysregulation in AP. Inflammatory mediators described early in AP—including TNF- α , IL-1 β , and chemotactic factors—promote endothelial activation, upregulation of adhesion molecules, and extensive leukocyte adhesion to the microvascular wall [12]. Neutrophils, in particular, contribute to capillary plugging, the release of proteolytic enzymes, and microthrombi formation, all of which further obstruct perfusion [9]. The systemic dissemination of these processes helps explain why severe AP frequently progresses to multiorgan involvement. Clinical evidence demonstrates that microvascular injury is not confined to the pancreas; vascular complications such as thrombosis, hemorrhage, and ischemic injury can occur in splanchnic and peripheral circulations, highlighting the systemic reach of these microvascular derangements [13]. Experimental data corroborate that impaired endothelial function and microvascular perfusion contribute directly to

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early organ dysfunction, independent of the degree of pancreatic necrosis [11].

3.1.5 Progression to Local Necrosis and Systemic Organ Failure

The cumulative effect of impaired perfusion, endothelial injury, and immune-driven microvascular obstruction leads to expansion of pancreatic necrosis and initiates events that precipitate systemic organ failure. Reduced functional capillary density and progressive ischemia within pancreatic tissue limit oxygen delivery and hinder removal of toxic metabolites, accelerating cellular death and necrotic transformation [10]. At the systemic level, widespread microcirculatory disturbances—particularly within the renal, pulmonary, and hepatic beds—have been demonstrated experimentally in severe AP, contributing to shock, respiratory dysfunction, and multi-organ impairment [11]. These findings align with clinical observations that severe vascular complications, including splanchnic thrombosis and hemorrhage, represent advanced manifestations of profound microvascular instability [13]. Thus, pancreatic microcirculatory dysfunction acts as both a local pathogenic driver and a systemic amplifier of disease severity.

3.2 Immune–Metabolic and Molecular Mechanisms Underlying Microvascular Injury

Microcirculatory dysfunction in AP arises from a complex interplay of inflammatory, metabolic, endothelial, and neurogenic pathways that converge on the pancreatic and systemic microvasculature. Beyond simple hypoperfusion, the microvascular injury observed in AP reflects a series of tightly interconnected molecular events that amplify vascular permeability, impair capillary integrity, promote intravascular obstruction, and propagate systemic organ dysfunction. Recent advances in immunology, cell biology, and vascular biology have expanded the mechanistic landscape, revealing several key pathways that link early acinar injury to disseminated microvascular collapse.

3.2.1 HMGB1–TLR4–IL-23–IL-17 Axis and Neutrophil-Mediated Microvascular Damage

A pivotal inflammatory cascade driving microcirculatory impairment involves the HMGB1–TLR4–IL-23–IL-17 axis, which promotes robust neutrophil activation and recruitment. HMGB1, released from injured acinar and immune cells, acts as a potent DAMP that binds to TLR4 on myeloid cells, triggering downstream IL-23 release and subsequent expansion of IL-17–producing immune subsets [15]. This amplifies neutrophil chemotaxis, oxidative burst, and degranulation, ultimately exacerbating endothelial injury and capillary permeability. Neutrophils activated through this pathway obstruct the microcirculation via adhesive interactions and intravascular aggregation, intensifying local hypoxia. Evidence from experimental models demonstrates that targeting SIRT1 mitigates this cascade, reducing neutrophil activation and improving pancreatic microvascular

perfusion [15], underscoring the centrality of this axis in microvascular disruption.

3.2.2 Gut–Pancreas Crosstalk and Microbiota-Derived Extracellular Vesicles

Alterations in gut microbiota composition contribute to systemic inflammation and endothelial injury in AP, with extracellular vesicles (EVs) emerging as critical mediators of this gut–pancreas dialogue. Dysbiosis in AP increases the translocation of microbial components and enhances EV release, which can transport inflammatory molecules, microRNAs, and bacterial antigens that modulate host immune responses and vascular integrity [16]. These EVs reinforce systemic inflammation by activating pattern-recognition receptors and promoting cytokine release, thereby aggravating endothelial dysfunction and microvascular permeability. Experimental data indicate that microbiota-derived EVs are capable of shaping inflammatory and metabolic pathways that influence microvascular stability, establishing the gut as a central extra-pancreatic contributor to microvascular pathology in AP [16].

3.2.3 Glycocalyx Degradation as a Driver of Capillary Leakage and Organ Dysfunction

The endothelial glycocalyx—a carbohydrate-rich layer composed of proteoglycans, glycosaminoglycans, and associated plasma proteins—is crucial for maintaining vascular barrier integrity. In severe AP, rapid shedding of the glycocalyx occurs in response to inflammatory mediators, oxidative stress, and enzymatic degradation, particularly by heparanase and metalloproteinases [17]. Loss of glycocalyx structure increases vascular permeability, disrupts shear-dependent signaling, and exposes endothelial adhesion molecules that promote leukocyte binding and microvascular plugging. The resulting capillary leak and interstitial edema compromise effective perfusion and contribute to early organ dysfunction. Degradation of glycocalyx components has been directly linked to the development of multiple organ dysfunction syndrome (MODS) in AP, establishing it as a key upstream driver of systemic microvascular failure [17].

3.2.4 Heparanase-Mediated Extracellular Matrix and Glycocalyx Disruption

Heparanase, an endoglycosidase that cleaves heparan sulfate chains, plays a pathogenic role by degrading both the extracellular matrix and the endothelial glycocalyx during AP. Its upregulation increases microvascular permeability, facilitates inflammatory cell infiltration, and destabilizes endothelial–basement membrane interactions [18]. These effects collectively impair microvascular integrity and accelerate the progression of pancreatic injury. Experimental inhibition of heparanase has demonstrated reductions in inflammation, edema, and microvascular damage, positioning it as a promising therapeutic target for mitigating vascular injury and limiting necrotic progression in AP [18].

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3.2.5 Mitophagy Dysregulation and Oxidative Stress in Endothelial and Acinar Injury

Mitochondrial dysfunction is an early and critical event in AP and contributes significantly to microvascular injury through ROS production and impaired cellular metabolism. Dysregulated mitophagy—failure of damaged mitochondria to be selectively removed—amplifies oxidative stress and perpetuates inflammatory cascades [19]. Key molecular pathways involved include PINK1/Parkin-mediated mitochondrial quality control and BNIP3/NIX-dependent responses, which are disrupted during AP [19]. When mitophagy fails, accumulated dysfunctional mitochondria impair endothelial cell bioenergetics, reduce nitric oxide availability, and exacerbate ROS-mediated vascular injury. These mitochondrial defects also potentiate acinar cell death and sterile inflammation, linking metabolic failure directly to microvascular collapse.

3.2.6 SIRT1–FOXO1 Signaling and Oxidative Stress Modulation

The SIRT1–FOXO1 axis functions as a major regulator of oxidative stress responses and endothelial stability. In severe AP, downregulation of SIRT1 leads to FOXO1 dysregulation, resulting in increased oxidative injury, endothelial apoptosis, and microvascular dysfunction [20]. Resveratrol has been shown to exert protective effects by activating SIRT1, enhancing FOXO1-mediated antioxidant pathways, and reducing inflammatory damage to the microcirculation [20]. Restoration of this axis improves perfusion, reduces edema, and attenuates progression toward necrosis, supporting its role as an immunometabolic checkpoint that modulates vascular injury.

3.2.7 Neurogenic Inflammation and Sensory Neuropeptides in Microvascular Derangements

Neurogenic inflammation represents an additional layer of microvascular dysregulation in AP.

Sensory neurons release neuropeptides such as substance P and calcitonin gene-related peptide (CGRP), which modulate vascular tone, increase endothelial permeability, and promote leukocyte recruitment [21]. Ion channels—including TRPV1 and sodium channel subtypes—are implicated in nociceptive activation and neuropeptide release during pancreatic injury [21]. Excessive neurogenic signaling interacts synergistically with inflammatory pathways to exacerbate capillary leak, edema formation, and local hypoperfusion. These findings highlight the neurovascular interface as a novel contributor to microvascular pathology and a potential therapeutic target in AP.

3.3 Clinical Correlates and Biomarkers of Microvascular Impairment in Acute Pancreatitis Microcirculatory dysfunction exerts profound influence on the clinical progression of acute pancreatitis, shaping the transition from local pancreatic inflammation to necrosis, vascular complications, and systemic organ failure. A combination of

perfusion imaging, vascular injury biomarkers, and established clinical observations demonstrates that microvascular derangements not only precede severe outcomes but also provide measurable indicators of disease trajectory.

3.3.1 Perfusion-Based Predictors of Necrosis and Severity

Impairment of pancreatic perfusion is one of the earliest detectable features of severe disease and serves as a reliable clinical predictor of necrotizing pancreatitis. Perfusion CT studies have shown that decreased pancreatic blood flow and reduced regional blood volume correlate strongly with the subsequent development of pancreatic necrosis, often before structural changes become visible on conventional imaging [22]. These findings highlight the temporal relationship between early microvascular compromise and tissue breakdown, supporting the concept that necrosis emerges as a downstream consequence of sustained ischemia and capillary dysfunction. The ability of perfusion metrics to anticipate severe outcomes underscores their value as early clinical markers of microcirculatory instability.

3.3.2 Vascular Complications as Indicators of Systemic Microvascular Injury

As microvascular injury progresses, it extends beyond the pancreas and contributes to a spectrum of clinically significant vascular complications. Patients with acute pancreatitis may develop splanchnic vein thrombosis, arterial hemorrhage, pseudoaneurysm formation, and ischemic lesions, reflecting widespread endothelial activation and permeability disturbances [13]. These complications represent advanced manifestations of microvascular dysfunction and indicate systemic propagation of the underlying vascular injury. Their presence is associated with worse outcomes and often necessitates invasive or endovascular interventions. Clinically, such vascular events serve as markers of severe disease biology and mirror the extensive endothelial damage documented in experimental and pathological studies.

3.3.3 Circulating Biomarkers of Endothelial Dysfunction

Biochemical markers have emerged as sensitive indicators of microvascular impairment, complementing imaging and clinical assessment. Elevated levels of soluble mannose receptor (sMR/CD206), which reflects macrophage activation and endothelial perturbation, are significantly associated with severe and necrotizing pancreatitis [23]. Similarly, von Willebrand factor (vWF), a key marker of endothelial activation and coagulation pathway engagement, rises early in patients who progress to severe disease and correlates with the risk of necrosis and persistent organ dysfunction [23]. Together, CD206 and vWF provide a measurable biochemical signature of endothelial damage and microcirculatory stress, illustrating the tight linkage between immune activation, vascular injury, and clinical severity.

3.3.4 Microvascular Mechanisms Underlying Organ Failure and Severity Frameworks

Organ failure—the principal

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determinant of mortality in acute pancreatitis—largely reflects systemic microcirculatory collapse rather than direct pancreatic destruction. Early inflammatory mediator release disrupts endothelial function and impairs perfusion in distal vascular beds, contributing to shock, renal dysfunction, and respiratory impairment independent of local pancreatic injury [24]. Contemporary severity classifications reinforce this mechanistic understanding: severe acute pancreatitis is defined by persistent organ failure, acknowledging that systemic microvascular injury drives the clinical course more forcefully than pancreatic necrosis itself [25]. The convergence of endothelial activation, perfusion deficits, inflammatory amplification, and metabolic stress provides a cohesive explanation for the rapid onset and sustained nature of organ dysfunction in high-risk patients.

3.4 Therapeutic Interventions Targeting Microcirculatory Dysfunction in Acute Pancreatitis

Therapeutic strategies aimed at preserving or restoring microcirculatory integrity have gained significant attention as potential modifiers of disease severity in AP. Evidence from experimental models, randomized controlled trials, and meta-analyses demonstrates that multiple pharmacologic and hemodynamic interventions influence endothelial stability, capillary perfusion, inflammatory pathways, and the progression toward necrosis and organ failure. These therapeutic modalities can be broadly categorized into: (1) microvascular-protective pharmacologic agents, (2) anticoagulation-based strategies, (3) epidural analgesia as a perfusion-enhancing intervention, and (4) fluid resuscitation protocols optimizing hemodynamic stability without exacerbating vascular injury.

3.4.1 Pharmacologic Modulators of Endothelial and Microvascular Injury

Several experimental therapies demonstrate the capacity to attenuate microvascular dysfunction by reducing oxidative stress, improving endothelial signaling, or stabilizing structural components of the vascular barrier.

Resveratrol, a SIRT1–FOXO1 activator, has shown robust protective effects against severe AP–induced microcirculatory disturbance. In a well-controlled experimental model, resveratrol significantly improved microvascular flow, reduced neutrophil infiltration, and mitigated oxidative stress by upregulating SIRT1 and modulating FOXO1 activity, thereby attenuating microcirculatory collapse [20].

Targeting the endothelial glycocalyx, a structure essential for vascular permeability and leukocyte–endothelium interactions, has emerged as another promising avenue. Severe AP is associated with marked glycocalyx degradation, leading to tissue edema, impaired perfusion, and systemic organ dysfunction. Recent evidence highlights the glycocalyx as a therapeutic target, demonstrating its central role in the pathogenesis of multiorgan involvement and identifying potential molecular pathways for pharmacologic intervention [17].

Endothelin-1 contributes significantly to microvascular constriction and perfusion heterogeneity. Classical experimental work demonstrated that endothelin receptor blockade restores capillary permeability, enhances pancreatic perfusion, and improves survival in severe AP, highlighting its role as a potent modulator of microvascular tone and endothelial integrity [26].

In addition, heparanase inhibition has been identified as a novel therapeutic target, with experimental findings showing that suppressing heparanase activity reduces acinar injury, inflammatory amplification, and vascular leakage—mechanisms that collectively sustain microcirculatory dysfunction [18].

3.4.2 Anticoagulation Strategies and Microthrombi Prevention

Microvascular thrombosis, impaired flow, and capillary obstruction are well-recognized contributors to tissue ischemia in severe AP. Anticoagulation strategies, particularly with low-molecular-weight heparin (LMWH), have been investigated in clinical settings.

A 2024 comparative clinical study demonstrated that LMWH therapy reduced progression to severe disease and improved inflammatory parameters in AP, emphasizing its ability to modulate the microvascular coagulation pathway and improve perfusion [27].

More recently, a randomized clinical trial conducted in patients with hypertriglyceridemic AP showed that combining LMWH with insulin significantly improved clinical outcomes, reduced the incidence of organ failure, and enhanced recovery, suggesting synergistic benefits in reducing microvascular thrombosis and metabolic injury [28].

These findings support the concept that anticoagulation—whether used alone or in combination with metabolic therapies—may attenuate microvascular obstruction and improve systemic outcomes in select AP populations.

3.4.3 Epidural Analgesia as a Modulator of Pancreatic Perfusion

Beyond its analgesic effects, thoracic epidural analgesia (TEA) has been shown to enhance pancreatic microcirculation. In a controlled experimental trial, TEA significantly improved survival and microvascular perfusion in severe AP by promoting splanchnic vasodilation and reducing inflammation-driven vasoconstriction [29].

Clinical evidence also supports this microcirculatory benefit: an observational study demonstrated improved pancreatic perfusion and reduced disease severity among patients receiving TEA, reinforcing its role as a physiologic modulator of regional blood flow [30]. Subsequent analyses emphasized TEA's capacity to reduce inflammatory responses and mitigate the progression of organ dysfunction in AP [31].

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Collectively, these findings suggest that TEA represents a physiologically sound, perfusion-enhancing intervention with meaningful impact on microvascular stability.

3.4.4 Fluid Resuscitation Strategies and Hemodynamic Optimization

Fluid management is one of the earliest modifiable determinants of microcirculatory health. However, recent high-quality evidence challenges the traditional paradigm of aggressive hydration.

Two comprehensive meta-analyses demonstrated that aggressive intravenous hydration—despite historical recommendations—increases mortality in severe AP and markedly elevates the risk of fluid-related complications in both severe and non-severe disease [32,33]. The increased risk of fluid overload, interstitial edema, and impaired organ perfusion reflects the detrimental impact of excessive volume on capillary leakage and tissue compartment pressures.

Beyond volume, fluid type also influences microvascular behavior. A randomized trial comparing lactated Ringer's (LR) solution with normal saline (NS) found LR to be superior in reducing hyperchloremia, ICU admissions, and length of stay, reflecting its more favorable physiologic profile and lower potential for metabolic acidosis-induced endothelial injury [34]. A triple-blind RCT reinforced these findings, demonstrating that LR significantly reduced inflammatory markers and exerted direct anti-inflammatory effects compared with NS [35].

Taken together, these findings underscore the critical importance of adopting controlled, goal-directed fluid strategies while prioritizing balanced crystalloid solutions to prevent exacerbation of microcirculatory dysfunction.

3.5 Therapeutic Strategies Targeting Microcirculatory Dysfunction in Acute Pancreatitis Microcirculatory dysfunction is increasingly recognized as both a mechanistic driver and a therapeutic target in acute pancreatitis. The following section integrates available evidence on interventions that modulate perfusion, endothelial function, inflammatory mediator load, and microvascular integrity. These therapeutic categories are supported entirely by clinical studies, randomized trials, mechanistic analyses, and translational evidence extracted from the included references.

3.5.1 Epidural Analgesia and Splanchnic Perfusion Modulation

Thoracic epidural analgesia has emerged as a promising adjunctive therapy with direct microcirculatory consequences. Experimental and clinical findings demonstrate that sympathetic blockade improves pancreatic perfusion by redistributing splanchnic blood flow, lowering microvascular resistance, and mitigating ischemic injury. Evidence from Theakarajan et al. shows that epidural analgesia enhances pancreatic blood flow, reduces inflammatory mediator release, and may attenuate organ dysfunction through improved splanchnic hemodynamics [36]. These effects extend beyond analgesia, positioning

epidural blockade as a physiologically targeted intervention capable of modulating microcirculatory failure in severe AP. Although data remain limited, early-phase studies suggest reductions in enzyme elevation, inflammatory markers, and systemic complications in selected patients, while large-scale randomized trials are still lacking. Current evidence supports the physiological rationale for epidural techniques as a microcirculatory therapy, particularly in settings where pain control, splanchnic vasodilation, and perfusion optimization are therapeutic priorities [36].

3.5.2 Vasoactive and Endothelium-Targeted Pharmacologic Strategies

Endothelin-mediated vasoconstriction plays a major role in the early perfusion abnormalities of AP. Classic experimental data from Foitzik et al. demonstrated that endothelin receptor blockade improves pancreatic microcirculation, stabilizes capillary permeability, and increases survival in severe AP models [26]. In this study, pharmacologic antagonism enhanced systemic and pancreatic perfusion, reduced microvascular stasis, and limited edema formation—directly addressing several pathophysiologic components of microvascular collapse.

Beyond endothelin-targeted therapy, other cytoprotective and anti-inflammatory agents have been evaluated. Ulinastatin, a protease inhibitor with endothelial-stabilizing and anti-inflammatory properties, has shown clinical benefit in randomized controlled trials. Wang et al. reported that ulinastatin reduced inflammatory markers, improved clinical severity scores, and mitigated complications in patients with severe AP, suggesting a potential role in protecting endothelial integrity and limiting microvascular injury [37].

Fluid resuscitation strategies also influence microcirculatory stability. A meta-analysis by He et al. compared aggressive versus controlled hydration regimens and underscored the risk of over-resuscitation, including increased vascular leakage and abdominal compartment syndrome, both of which worsen microcirculation [38]. This evidence supports more conservative, physiology-guided resuscitation to prevent exacerbation of endothelial permeability.

Additionally, Yin et al. demonstrated that anticoagulation in splanchnic vein thrombosis—a recognized vascular complication of AP—improves vessel recanalization without increasing major bleeding, reinforcing the importance of addressing coagulation disturbances that impair regional microcirculation [39].

Collectively, these therapies illustrate that pharmacologic modulation of microvascular tone, endothelial stability, inflammatory signaling, and coagulation pathways can meaningfully influence disease progression in AP.

3.5.3 Organ Support and Extracorporeal Therapies Targeting Inflammatory and Microvascular Burden

Severe AP is characterized by systemic endothelial activation, cytokine excess, and microvascular shutdown in multiple organs. Extracorporeal therapies have been explored as a

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means to attenuate inflammatory load and restore microvascular function.

Continuous veno-venous hemofiltration (CVVH) appears particularly advantageous in hyperinflammatory phenotypes. Yadav and Zhang reported that early CVVH reduced the incidence of local pancreatic complications, likely through removal of circulating inflammatory mediators that impair endothelial function and regional perfusion [40]. Similarly, a systematic review by Hu et al. concluded that blood purification techniques improve hemodynamics, oxygenation, and inflammatory profiles, supporting their role in interrupting microvascular deterioration and organ dysfunction [41].

Clinical management frameworks also emphasize the importance of organ support in preserving microcirculatory stability. Lee and Papachristou highlight lung-protective ventilation, careful fluid stewardship, and early identification of organ failure as central strategies to maintain systemic perfusion and reduce endothelial stress [42]. Van den Berg and Boermeester similarly underscore early risk stratification, prevention of over-resuscitation, and timely intervention for complications to minimize microvascular derangements that accelerate severity progression [43]. These findings emphasize that beyond local pancreatic injury, systemic microcirculatory collapse can be mitigated by extracorporeal therapies and supportive strategies that reduce inflammatory overload, maintain endothelial function, and stabilize organ perfusion.

3.5.4 Adjunctive Therapies and Emerging Approaches Targeting Microvascular Repair

Several adjunctive therapies focus on modulating inflammatory responses, protecting endothelial structures, or preventing downstream vascular complications. Ulinastatin (covered above) represents one such intervention, but broader perspectives highlight additional therapeutic avenues.

Antkowiak et al. synthesized available evidence on pharmacologic agents aimed at restoring microvascular flow, including antioxidants, anti-cytokine treatments, and endothelial-targeted therapies such as nitric oxide donors or agents that preserve endothelial glycocalyx integrity [44]. Although clinical translation remains limited, these therapies share a common goal of mitigating capillary leak, reducing leukocyte-endothelial interactions, and maintaining functional capillary density.

Epidural analgesia, discussed in detail in 3.5.1, also belongs to this category as a microcirculatory adjunct capable of reducing vasoconstriction and splanchnic ischemia through sympathetic blockade [36].

Additionally, Zaman and Gorelick outline multiple experimental therapies under investigation—including mitochondrial stabilizers, autophagy modulators, and microvascular regulators—highlighting the expanding landscape of biological targets relevant to endothelial protection and perfusion restoration in AP [45].

Together, these adjunctive and emerging approaches reflect a growing shift toward therapies aimed not only at inflammation control but also at direct preservation of microvascular function. To complement the narrative synthesis and ensure comprehensive coverage of the remaining evidence, **Table 1** summarizes additional key studies addressing perfusion-modulating, endothelial-targeted, or microcirculation-related therapeutic strategies in acute pancreatitis. These investigations, although not incorporated into the core mechanistic sections, provide essential contextual insights into systemic microvascular dysfunction, emerging pharmacologic approaches, fluid stewardship, extracorporeal support, and evolving management paradigms. Together, they broaden the evidentiary foundation of this review and reinforce the central role of microcirculatory impairment in shaping clinical outcomes.

4. DISCUSSION

Microcirculatory dysfunction has long been recognized as a pivotal mechanistic axis in the progression of acute pancreatitis, yet its integration into contemporary diagnostic and therapeutic frameworks remains incomplete. Classic microvascular studies demonstrated early reductions in capillary density, perfusion heterogeneity, and endothelial disruption as key determinants of pancreatic ischemia and subsequent necrosis [9,10]. These foundational observations are reinforced by modern insights into inflammatory cascades, endothelial glycocalyx degradation, heparanase-mediated vascular injury, and immune–microvascular crosstalk, all of which contribute to rapid escalation from local acinar injury to systemic inflammatory response and organ failure [6,12,18,17]. Importantly, the severity of systemic injury often exceeds the anatomical burden of pancreatic necrosis, underscoring that severe acute pancreatitis is fundamentally a vascular and immunometabolic disease rather than a purely glandular disorder [5,25].

The therapeutic implications of this paradigm are substantial. Although fluid resuscitation remains a cornerstone of early management, emerging evidence challenges traditional aggressive hydration strategies and instead supports controlled, goal-directed approaches that mitigate microvascular congestion and endothelial shear stress [32,33,38]. Similarly, the superiority of balanced crystalloids over normal saline in improving perfusion and acid–base homeostasis provides mechanistic rationale beyond clinical efficacy alone [34,35]. Beyond fluids, adjunctive strategies targeting endothelial integrity, coagulation abnormalities, inflammatory pathways, and splanchnic perfusion are gaining traction. Low–molecular-weight heparin, whether used in conventional severe AP or hypertriglyceridemic AP, has shown potential to reduce microthrombi formation and local complications through its anticoagulant and anti-

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inflammatory properties [27,28]. Epidural analgesia represents another promising modality, improving pancreatic perfusion and modulating sympathetic vasoconstriction in both clinical and experimental models [29,30,31,36]. Meanwhile, pharmacologic interventions such as ulinastatin and endothelial-stabilizing agents—including resveratrol and glycocalyx-targeted therapies—demonstrate growing mechanistic and translational relevance [15,20,37].

Despite these advances, significant gaps persist. Current severity scores and guidelines, including the revised Atlanta classification, continue to emphasize organ failure, necrosis, and systemic complications while omitting microcirculatory dysfunction as an explicit dimension of disease assessment [4,8]. Moreover, early biomarkers of vascular injury such as soluble CD206 and von Willebrand factor remain underutilized despite promising predictive performance for severe or necrotizing pancreatitis [23]. Experimental models also reveal substantial heterogeneity in the temporal evolution of microvascular changes, complicating translational interpretation and limiting targeted therapeutic development [7]. Finally, the systemic dissemination of microvascular injury—including splanchnic thrombosis, hemorrhage, and multiorgan hypoperfusion—highlights a need for integrated, multisystem approaches to early intervention [13,14].

Taken together, the accumulated evidence positions microcirculatory dysfunction not as a secondary byproduct of inflammation but as a primary orchestrator of disease progression, linking early acinar injury to systemic complications and mortality. Incorporating vascular pathobiology into risk stratification, therapeutic decision-making, and future clinical trials represents a critical next step toward reshaping the management of acute pancreatitis. By reframing severe AP as a disorder of microvascular failure and immune–endothelial disruption, more precise and earlier interventions may emerge, with the potential to meaningfully reduce the global burden of this increasingly common disease [1,2,3,43,45,46].

5. CONCLUSION

Microcirculatory dysfunction represents a fundamental and early determinant of disease progression in acute pancreatitis, bridging the gap between initial acinar injury and the systemic manifestations that culminate in organ failure. The evidence reviewed demonstrates that endothelial disruption, impaired capillary perfusion, inflammatory amplification, glycocalyx degradation, and ischemia–reperfusion injury form an interconnected cascade that drives pancreatic necrosis and multiorgan involvement. These alterations begin before radiologic or clinical deterioration becomes evident, underscoring the central role of the microvasculature as both a mechanistic origin point and a predictor of severity.

Despite growing mechanistic clarity, current diagnostic and therapeutic frameworks largely overlook microvascular

injury as a clinical target. Yet, emerging interventions—ranging from endothelial-protective strategies to optimized fluid therapy, epidural analgesia, anticoagulation, and extracorporeal blood purification—highlight the potential for restoring microcirculatory integrity as a means to alter the course of severe disease. Integrating microvascular-focused approaches into future research, risk stratification, and clinical trials may shift management toward earlier, mechanism-based intervention and ultimately reduce the burden of severe acute pancreatitis and its systemic complications.

REFERENCES

- I. Iannuzzi JP, King JA, Leong JH, Quan J, Windsor JW, Tanyingoh D, Coward S, Forbes N, Heitman SJ, Shaheen AA, Swain M, Buie M, Underwood FE, Kaplan GG. Global Incidence of Acute Pancreatitis Is Increasing Over Time: A Systematic Review and Meta-Analysis. *Gastroenterology*. 2022 Jan;162(1):122-134. doi: 10.1053/j.gastro.2021.09.043.
- II. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013 Jun;144(6):1252-61. doi: 10.1053/j.gastro.2013.01.068.
- III. Lee PJ, Papachristou GI. New insights into acute pancreatitis. *Nat Rev Gastroenterol Hepatol*. 2019 Aug;16(8):479-496. doi: 10.1038/s41575-019-0158-2.
- IV. Gao W, Yang HX, Ma CE. The Value of BISAP Score for Predicting Mortality and Severity in Acute Pancreatitis: A Systematic Review and Meta-Analysis. *PLoS One*. 2015 Jun 19;10(6):e0130412. doi: 10.1371/journal.pone.0130412. Erratum in: *PLoS One*. 2015 Oct 29;10(10):e0142025. doi: 10.1371/journal.pone.0142025.
- V. Garg PK, Singh VP. Organ Failure Due to Systemic Injury in Acute Pancreatitis. *Gastroenterology*. 2019 May;156(7):2008-2023. doi: 10.1053/j.gastro.2018.12.041.
- VI. Glaubitz J, Asgarbeik S, Lange R, Mazloun H, Elsheikh H, Weiss FU, Sendler M. Immune response mechanisms in acute and chronic pancreatitis: strategies for therapeutic intervention. *Front Immunol*. 2023 Oct 10;14:1279539. doi: 10.3389/fimmu.2023.1279539.
- VII. Rosales-Muñoz GJ, Souza-Arroyo V, Bucio-Ortiz L, Miranda-Labra RU, Gomez-Quiroz LE, Gutiérrez-Ruiz MC. Acute pancreatitis experimental models, advantages and disadvantages. *J Physiol Biochem*. 2025 Aug;81(3):539-556. doi: 10.1007/s13105-025-01091-w. Epub 2025 May 17. Erratum in: *J Physiol Biochem*. 2025
- VIII.

- Aug;81(3):831-832. doi: 10.1007/s13105-025-01102-w.
- IX. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013 Jan;62(1):102-11. doi: 10.1136/gutjnl-2012-302779.
- X. Zhou ZG, Chen YD. Influencing factors of pancreatic microcirculatory impairment in acute pancreatitis. *World J Gastroenterol*. 2002 Jun;8(3):406-12. doi: 10.3748/wjg.v8.i3.406.
- XI. Menger MD, Plusczyk T, Vollmar B. Microcirculatory derangements in acute pancreatitis. *J Hepatobiliary Pancreat Surg*. 2001;8(3):187-94. doi: 10.1007/s005340170015.
- XII. Foitzik T, Eibl G, Hotz B, Hotz H, Kahrau S, Kasten C, Schneider P, Buhr HJ. Persistent multiple organ microcirculatory disorders in severe acute pancreatitis: experimental findings and clinical implications. *Dig Dis Sci*. 2002 Jan;47(1):130-8. doi: 10.1023/a:1013284008219.
- XIII. Bhatia M, Brady M, Shokuhi S, Christmas S, Neoptolemos JP, Slavin J. Inflammatory mediators in acute pancreatitis. *J Pathol*. 2000 Feb;190(2):117-25. doi: 10.1002/(SICI)1096-9896(200002)190:2<117::AID-PATH494>3.0.CO;2-K.
- XIV. Głuszek S, Nawacki Ł, Matykiewicz J, Kot M, Kuchinka J. Severe Vascular Complications Of Acute Pancreatitis. *Pol Przegl Chir*. 2015 Oct;87(10):485-90. doi: 10.1515/pjs-2015-0093.
- XV. Sakorafas GH, Tsiotos GG, Sarr MG. Ischemia/Reperfusion-Induced pancreatitis. *Dig Surg*. 2000;17(1):3-14. doi: 10.1159/000018793.
- XVI. Wang J, Zou Y, Chang D, Hong DQ, Zhang J. Protective effect of Dachengqi decoction on the pancreatic microcirculatory system in severe acute pancreatitis by down-regulating HMGB-TLR-4-IL-23-IL-17A mediated neutrophil activation by targeting SIRT1. *Gland Surg*. 2021 Oct;10(10):3030-3044. doi: 10.21037/gs-21-655.
- XVII. Li Y, Li J, Li S, Zhou S, Yang J, Xu K, Chen Y. Exploring the gut microbiota's crucial role in acute pancreatitis and the novel therapeutic potential of derived extracellular vesicles. *Front Pharmacol*. 2024 Jul 26;15:1437894. doi: 10.3389/fphar.2024.1437894.
- XVIII. Li H, Wen H, Liu J, Luo X, Pei B, Ge P, Sun Z, Liu J, Wang J, Chen H. The glycocalyx: a key target for treatment of severe acute pancreatitis-associated multiple organ dysfunction syndrome. *Hum Cell*. 2025 May 24;38(4):107. doi: 10.1007/s13577-025-01227-6.
- XIX. Khamaysi I, Singh P, Nasser S, Awad H, Chowers Y, Sabo E, Hammond E, Gralnek I, Minkov I, Noseda A, Ilan N, Vlodavsky I, Abassi Z. The Role of Heparanase in the Pathogenesis of Acute Pancreatitis: A Potential Therapeutic Target. *Sci Rep*. 2017 Apr 6;7(1):715. doi: 10.1038/s41598-017-00715-6.
- XX. Zhu L, Xu Y, Lei J. Molecular mechanism and potential role of mitophagy in acute pancreatitis. *Mol Med*. 2024 Sep 3;30(1):136. doi: 10.1186/s10020-024-00903-x.
- XXI. Rong Y, Ren J, Song W, Xiang R, Ge Y, Lu W, Fu T. Resveratrol Suppresses Severe Acute Pancreatitis-Induced Microcirculation Disturbance through Targeting SIRT1-FOXO1 Axis. *Oxid Med Cell Longev*. 2021 Feb 9;2021:8891544. doi: 10.1155/2021/8891544.
- XXII. Wu Y, Han C, Luo R, Cai W, Xia Q, Jiang R, Ferdek PE, Liu T, Huang W. Molecular mechanisms of pain in acute pancreatitis: recent basic research advances and therapeutic implications. *Front Mol Neurosci*. 2023 Dec 22;16:1331438. doi: 10.3389/fnmol.2023.1331438.
- XXIII. Tsuji Y, Takahashi N, Isoda H, Koizumi K, Koyasu S, Sekimoto M, Imanaka Y, Yazumi S, Asada M, Nishikawa Y, Yamamoto H, Kikuchi O, Yoshida T, Inokuma T, Katsushima S, Esaka N, Okano A, Kawanami C, Kakiuchi N, Shiokawa M, Kodama Y, Moriyama I, Kajitani T, Kinoshita Y, Chiba T. Early diagnosis of pancreatic necrosis based on perfusion CT to predict the severity of acute pancreatitis. *J Gastroenterol*. 2017 Oct;52(10):1130-1139. doi: 10.1007/s00535-017-1330-5. Epub 2017 Apr 3. Erratum in: *J Gastroenterol*. 2017 Oct;52(10):1147-1148. doi: 10.1007/s00535-017-1343-0.
- XXIV. Reuken PA, Brozat JF, Quickert S, Ibidapo-Obe O, Reißing J, Franz A, Stengel S, Teichgräber UK, Kiehntopf M, Trautwein C, Stallmach A, Koch A, Bruns T. Soluble mannose receptor CD206 and von Willebrand factor are early biomarkers to identify patients at risk for severe or necrotizing acute pancreatitis. *J Intensive Care*. 2022 Jun 11;10(1):28. doi: 10.1186/s40560-022-00619-2.
- XXV. Madrigal TPR, Panlilio MTT, Burog AILD, Danguilan RA, Chavez JR. Incidence of acute pancreatitis among patients with leptospirosis requiring extracorporeal membrane oxygenation (ECMO): a descriptive study. *BMJ Open Gastroenterol*. 2023 Mar;10(1):e001094. doi: 10.1136/bmjgast-2022-001094.
- XXVI. Boxhoorn L, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, van Santvoort

- HC, Besselink MG. Acute pancreatitis. *Lancet*. 2020 Sep 5;396(10252):726-734. doi: 10.1016/S0140-6736(20)31310-6. Erratum in: *Lancet*. 2021 Nov 6;398(10312):1686. doi: 10.1016/S0140-6736(21)02377-1.
- XXVII. Foitzik T, Eibl G, Hotz HG, Faulhaber J, Kirchengast M, Buhr HJ. Endothelin receptor blockade in severe acute pancreatitis leads to systemic enhancement of microcirculation, stabilization of capillary permeability, and improved survival rates. *Surgery*. 2000 Sep;128(3):399-407. doi: 10.1067/msy.2000.107104.
- XXVIII. Ca S, Gondesí K, K KP, Yarremsetty SV. Efficacy of Low-Molecular-Weight Heparin in the Treatment of Severe Acute Pancreatitis: A Comparative Study at a Tertiary Health Center. *Cureus*. 2024 Jul 30;16(7):e65736. doi: 10.7759/cureus.65736.
- XXIX. He W, Ding L, Liu Z, Hua M, Zhou Y, Gong M, Sheng J, Wu X, Fan H, Shu H, Wang R, Xun L, Huang C, Guo F, Cao C, Zhan Z, Chen H, Qian X, Liu Q, Li Q, Tang Z, Xiong Y, Xie P, Yu B, Wan J, Ke H, Wu Y, Hu Y, Ai J, Huang X, Lei Y, Xiong H, Liu Z, Zhu Y, Luo L, Xia L, Ke L, Cai W, Huang W, Li W, Windsor J, Sutton R, Lv N, Zhu Y; Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG). Low-Molecular-Weight Heparin Plus Insulin in Hypertriglyceridemic Acute Pancreatitis: A Randomized Clinical Trial. *JAMA Netw Open*. 2025 Nov 3;8(11):e2542124. doi: 10.1001/jamanetworkopen.2025.42124.
- XXX. Bachmann KA, Trepte CJ, Tomkötter L, Hinsch A, Stork J, Bergmann W, Heidelmann L, Strate T, Goetz AE, Reuter DA, Izbicki JR, Mann O. Effects of thoracic epidural anesthesia on survival and microcirculation in severe acute pancreatitis: a randomized experimental trial. *Crit Care*. 2013 Dec 5;17(6):R281. doi: 10.1186/cc13142.
- XXXI. Sadowski SM, Andres A, Morel P, Schiffer E, Frossard JL, Platon A, Poletti PA, Bühler L. Epidural anesthesia improves pancreatic perfusion and decreases the severity of acute pancreatitis. *World J Gastroenterol*. 2015 Nov 21;21(43):12448-56. doi: 10.3748/wjg.v21.i43.12448.
- XXXII. Windisch O, Heidegger CP, Giraud R, Morel P, Bühler L. Thoracic epidural analgesia: a new approach for the treatment of acute pancreatitis? *Crit Care*. 2016 May 4;20(1):116. doi: 10.1186/s13054-016-1292-7.
- XXXIII. Li XW, Wang CH, Dai JW, Tsao SH, Wang PH, Tai CC, Chien RN, Shao SC, Lai EC. Comparison of clinical outcomes between aggressive and non-aggressive intravenous hydration for acute pancreatitis: a systematic review and meta-analysis. *Crit Care*. 2023 Mar 22;27(1):122. doi: 10.1186/s13054-023-04401-0.
- XXXIV. Guo J, Hong J, He Y, Li Q, Huang T, Lou D, Zhang J. Comparison of early aggressive versus nonaggressive fluid resuscitation in acute pancreatitis: a meta-analysis. *Therap Adv Gastroenterol*. 2023 Aug 22;16:17562848231192144. doi: 10.1177/17562848231192144.
- XXXV. Lee A, Ko C, Buitrago C, Hiramoto B, Hilson L, Buxbaum J; NS-LR Study Group. Lactated Ringers vs Normal Saline Resuscitation for Mild Acute Pancreatitis: A Randomized Trial. *Gastroenterology*. 2021 Feb;160(3):955-957.e4. doi: 10.1053/j.gastro.2020.10.044.
- XXXVI. de-Madaria E, Herrera-Marante I, González-Camacho V, Bonjoch L, Quesada-Vázquez N, Almenta-Saavedra I, Miralles-Maciá C, Acevedo-Piedra NG, Roger-Ibáñez M, Sánchez-Marin C, Osuna-Ligero R, Gracia Á, Llorens P, Zapater P, Singh VK, Moreu-Martín R, Closa D. Fluid resuscitation with lactated Ringer's solution vs normal saline in acute pancreatitis: A triple-blind, randomized, controlled trial. *United European Gastroenterol J*. 2018 Feb;6(1):63-72. doi: 10.1177/2050640617707864.
- XXXVII. Theakarajan R, Ashuvanth S, Rajagopalan G. From pain relief to organ protection: epidural analgesia in acute pancreatitis-a narrative review of its evolving role. *Clin J Gastroenterol*. 2025 Aug 22. doi: 10.1007/s12328-025-02204-0.
- XXXVIII. Wang SQ, Jiao W, Zhang J, Zhang JF, Tao YN, Jiang Q, Yu F. Ulinastatin in the treatment of severe acute pancreatitis: A single-center randomized controlled trial. *World J Clin Cases*. 2023 Jul 6;11(19):4601-4611. doi: 10.12998/wjcc.v11.i19.4601.
- XXXIX. He K, Gao L, Yang Z, Zhang Y, Hua T, Hu W, Wu D, Ke L. Aggressive versus controlled fluid resuscitation in acute pancreatitis: A systematic review and meta-analysis of randomized controlled trials. *Chin Med J (Engl)*. 2023 May 20;136(10):1166-1173. doi: 10.1097/CM9.0000000000002684.
- XL. Yin Y, Wang L, Gao F, Liu L, Qi X. Anticoagulation Therapy for Splanchnic Vein Thrombosis Associated With Acute Pancreatitis: A Systematic Review and Meta-Analysis. *Clin Appl Thromb Hemost*. 2023 Jan-Dec;29:10760296231188718. doi: 10.1177/10760296231188718.
- XLI. Yadav SC, Zhang B. Effect of Early Continuous Veno-Venous Haemofiltration in Severe Acute Pancreatitis for the Prevention of Local Pancreatic Complications. *Gastroenterol Res Pract*. 2022 Mar 7;2022:7575231. doi: 10.1155/2022/7575231.

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- XLII. Hu Y, Xiong W, Li C, Cui Y. Continuous blood purification for severe acute pancreatitis: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2019 Mar;98(12):e14873. doi: 10.1097/MD.00000000000014873.
- XLIII. Lee PJ, Papachristou GI. Management of Severe Acute Pancreatitis. *Curr Treat Options Gastroenterol*. 2020;18(4):670-681. doi: 10.1007/s11938-020-00322-x.
- XLIV. van den Berg FF, Boermeester MA. Update on the management of acute pancreatitis. *Curr Opin Crit Care*. 2023 Apr 1;29(2):145-151. doi: 10.1097/MCC.0000000000001017.
- XLV. Antkowiak R, Bialecki J, Chabowski M, Domoslawski P. Treatment of Microcirculatory Disturbances in Acute Pancreatitis: Where Are We Now? *Pancreas*. 2022 May 1;51(5):415-421. doi: 10.1097/MPA.0000000000002044.
- XLVI. Zaman S, Gorelick F. Acute pancreatitis: pathogenesis and emerging therapies. *J Pancreatol*. 2024 Mar;7(1):10-20. doi: 10.1097/JP9.0000000000000168.
- XLVII. Sarri G, Guo Y, Iheanacho I, Puelles J. Moderately severe and severe acute pancreatitis : a systematic review of the outcomes in the USA and European Union-5. *BMJ Open Gastroenterol*. 2019 Feb 16;6(1):e000248. doi: 10.1136/bmjgast-2018-000248.

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Table 1. Additional Key Studies Relevant to Microcirculatory or Perfusion-Modulating Strategies in Acute Pancreatitis

Study (Ref)	Design	Intervention / Focus	Microcirculatory Mechanism Targeted	Key Findings	Outcomes Reported	Level of Evidence	Quality Indicators
Garg, 2019 [5]	Narrative review	Organ failure in AP	Systemic endothelial injury and microvascular failure	Establishes organ failure as consequence of systemic microvascular collapse.	Conceptual linking of endothelial dysfunction → OF.	Level V (expert/narrative)	High-quality synthesis; no formal bias assessment.
Antkowiak, 2022 [44]	Narrative review	Treatments for microcirculatory disturbances	Endothelial stabilization, perfusion improvement	Summarizes vasoactive agents, antioxidants, microcirculatory-directed therapies.	Therapeutic mechanisms described; no pooled outcomes.	Level V	Comprehensive expert review; non-systematic.
van den Berg, 2023 [43]	Clinical update	AP management	Clinical decision-making affecting organ perfusion	Highlights fluid strategy, early OF prevention, and complication timing.	Improved severity prediction; management impact summarized.	Level V	Evidence-based narrative; no systematic method.

Lee, 2020 [42]	Clinical review	Severe AP management	Organ perfusion and systemic support	Emphasizes hemodynamic optimization, respiratory support, early organ failure mitigation.	Summaries of mortality, OF risk, and management outcomes.	Level V	Strong clinical reasoning; methodological limitations inherent to reviews.
He, 2023 [38]	Systematic review and meta-analyses	Aggressive vs controlled hydration	Endothelial permeability, vascular leak	Controlled hydration reduces complications associated with fluid overload.	Mortality, SIRS, organ failure, ICU stay.	Level I	PRISMA-guided; moderate heterogeneity across RCTs.
Sarri, 2019 [46]	Systematic review	Severe AP outcomes across US/EU-5	Systemic microvascular complications	Identifies high morbidity/mortality related to systemic inflammatory burden.	Mortality, organ failure, ICU utilization, LOS.	Level II	Clear inclusion criteria; limited by retrospective observational data.

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Zaman, 2024 [45]	Mechanistic review	Emerging experimental therapies	Endothelial and mitochondrial protection	Identifies novel targets: autophagy regulation, mitochondrial stability, endothelial repair.	Mechanistic outcomes; no clinical endpoints.	Level V	High translational relevance; non-clinical evidence predominates.
Yadav, 2022 [2]	Randomized controlled trial	Early CVVH	Cytokine removal; endothelial stabilization	Early CVVH reduces local pancreatic complications and inflammatory mediator load.	↓ local pancreatic complications; ↓ inflammatory biomarkers.	Level II	Moderate-quality RCT; small sample size; some risk of bias.

Abbreviations: AP, acute pancreatitis; OF, organ failure; SIRS, systemic inflammatory response syndrome; CVVH, continuous veno-venous hemofiltration; ICU, intensive care unit; LOS, length of stay; RCT, randomized controlled trial; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.