American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Opinion

Fulminant Necrotizing Pancreatitis, A Sustained Avalanche

Sylvia Frisancho Kiss*

Department of Anaesthesiology, Penta Hospitals, Slovakia

***Corresponding author:** Sylvia Frisancho Kiss, Department of Anaesthesiology, Perioperative and Intensive Medicine, Hospital Bory, Penta Hospitals, Bratislava, Slovakia.

To Cite This Article: *Sylvia Frisancho Kiss*. Fulminant Necrotizing Pancreatitis, A Sustained Avalanche . Am J Biomed Sci & Res. 2025 26(1) AJBSR.MS.ID.003409,* **DOI:** 10.34297/AJBSR.2025.26.003409

Received: March 03, 2025; **Published:** March 06, 2025

Abbreviations: A1AT-Alpha 1 antitrypsin; AI-Artificial intelligence; ICU-Intensive care unit; FNP-Fulminant necrotizing pancreatitis; CR1-Complement regulator one; DAMPs-Danger associated molecular patterns; FFA-Free fatty acids; GIT-Gastrointestinal tract; HMGB1-High mobility group box one; HPA-Hypothalamic pituitary axis; HSP-Heat shock protein; LPS-Lipopolysaccharide; NE-Neutrophil elastase; NLRP3-NLR family pyrin domain containing 3; RAGE-Receptor for Advanced Glycation End Products; ROS-Reactive oxygen species; SS-Somatostatin; SIRS-Systemic inflammatory response syndrome; TLR4-Toll-like receptor four; TREM1-TRIGGERING receptor expressed on myeloid cells 1.

Opinion

"Words shouldn't come out harsh, they shouldn't come as nice clichés, words should echo the true soul and intention". by Oiac. Human patho-physiology is a complex microcosmos, far from perfect, from our perspective. There are matters of homeostasis, adequate or derailed responses to triggers, targeted and collateral damage, hormonal and immune feedback mechanisms and lack of them, matters of proliferation and cell death, which can be inflammatory or silent. Ideally, during disease management, the fluctuations of determinants and influenced parameters should be monitored, understood and interpreted, at least the level of those that are about to be therapeutically influenced. This may become the standard of future intelligent design and AI technologies. Fulminant acute necrotizing pancreatitis is of the most complex, frustrating disease entities in ICU, defined by abrupt and avalanche like culminatory and self-perpetuating cascade of rapidly progressing pathological happenings due to extensive , aberrant pancreatic digestive enzyme activation, severe systemic and local inflammation, with life threatening multiorgan failure , intra-abdominal, particularly retroperitoneal inflammation and necrosis, ultimately with debilitating late complications, high morbidity and long term disability usually of young and middle aged population [1].

The prematurely and excessively activated pancreatic enzymes, with extremely strong catalytic properties, cause autodigestion of local and distant tissues, and simultaneously, self-aggravating systemic inflammatory response [2] culminates in devouring healthy organs, leading to multiorgan failure, and septic complications, and one may hypothize as to what comes first, inflammation or autodigestion? The retroperitoneal pancreatic and peripancreatic necrotic tissue provides an ongoing source of inflammatory mediators, sustaining high levels of SIRS, with acute renal, respiratory and occasionally liver failure. The frequently infected necrotic tissue is undergoing prolonged disposal, eliciting fever and increased capillary leak. Pathogen elimination competes with apoptotic and necrotic bleb clearance [3], placing an extreme burden on the immune system, particularly erythrocyte and innate cell mediated immune complex clearance mechanisms are overloaded, contributing to persistent and profound anaemia [4].The pancreas is embedded in the retroperitoneal space conceded by visceral peritoneum, pro-

viding a rich immune environment to fuel the inflammatory cascade [5,6], resident macrophages and B1B cells producing IgM with excellent affinity towards complement fixation and activation. Elevated NETS for example correlate with disease severity [7].

The multitude of DAMPs, that arise upon cell injury and death have a strong proinflammatory, proapoptotic effect, moreover due to to intimate vicinity of pathogen rich intestinal environment the sterility of inflammation is rarely maintained and the additional problem of pathogen clearance emanates [8].TLRs provide a joint docking site for proinflammatory signaling for DAMPs and pathogens, and they participate in regulating the rate of endocytosis, phagolysosome maturation and antigen presentation [9]. While bacterial phagosome maturation is an inducible event, apoptotic cell phagocytosis is occurring in parallel, constitutively [10]. Similarly, antigen-antibody complexes are taken up via Fc receptors, and after processing in phagosomes, they represented to CD4+T cells. Upon cell injury, extracellular HMGB1 induces pyroptosis via RAGE/NLRP3/IL-1 beta activation, which is aggravated by bacterial LPS [11], and activates the TREM1/ TLR2,4/ Nf-kB pathways significantly enhancing proinflammatory and pro death signature of FNP [12]. Half-life of extracellular HMGB1 spans from 17 min to 10 hours depending on the oxidation state, representing and ongoing trigger, and due to small size, of 25kDa is eliminated by kidneys and continuous renal replacement therapy [13-15]. Proinflammatory mediators are maintained at state of heightened activation due to damage associated molecules, such as HSP 60,70 and HMGB1, released by non-canonical pathway and becoming oxidised in the serum, their effects are elicited upon binding to TLR4 and their levels had been correlated to pancreatitis disease severity, negatively correlated to survival, and pancreatic necrosis [16].

Beyond SIRS, the determinant culprits in FNP pathogenesis are the activated and aberrantly present digestive enzymes in the blood, in retroperitoneal and peritoneal abdominal cavity, where extensive protein, and lipolysis takes place, inducing catabolism, metabolic acidosis, fatty acid cumulation, cleavage of surface cell receptors and tissue demolition. Secondary superinfections further contribute to the destructive phenotype. For example, Pseudomonas aeruginosa, a lately widespread nosocomial pathogen actively cleavesCR1 off erythrocytes, macrophages and neutrophils, similarly to trypsin entering the bloodstream during FNP, depriving the immune system of crucial phagocytic, immune complex clearance and complement regulatory component [17]. Soluble CR1 treatment experimentally diminished FNP associated pancreatic and lung injury [18].

TLR4 is upregulated upon increased free fatty acid production [19], a hallmark of hypertriglyceridemia induced FNP, with deleterious effect on disease phenotype [20]. Overloaded beta oxidation in the mitochondria, creates accumulation of FFA and leads to insulin resistance. FF influences mitochondrial energetics, decreases levels and compromises the mitochondrial electron chain system, impairing cellular breathing, increases ROS production and apoptosis [21]. During FNP, and perhaps SIRS and sepsis in general, early on in innate response proinflammatory and regulatory mediators become upregulated, albeit with differing expression levels. That is why an early, single shot blockade of a regulatory component-such as Tim3, using monoclonal IgG-skews the entire immune response towards a more proinflammatory phenotype [22]. It is only reasonable to apprehend the need to intervene early, preventively to some extent, before autodigestion and SIRS culminates into complete pancreas destruction and into infringement of several organ functions. Surprisingly, comprehensive clinical monitoring and targeted intervention to hold back the avalanche from release are sparse.

Following the straightforward logic of inhibiting pancreatic enzyme release/trypsin, lipase, amylase, chymase/somatostatin is tested occasionally clinically off label. Somatostatin (SS) is a hormone and neuropeptide with widespread actions, produced in hypothalamus, in pancreas, stomach and duodenum, eliciting effects in paracrine and endocrine manners. The established indication for SS analog treatment aretumors with neuroendocrine components, where SS receptors are highly expressed, and its antiproliferative effects are thereby utilized. The indications of periprocedural and fulminant necrotizing pancreatitis treatment with the aim of decreasingself destructive pancreatic enzyme production are less established , with no clear mortality benefit. The problem with efficiency in my opinion is embedded in that somatostatin provides physiological regulation of exocrine pancreatic enzyme release, while during FNP aberrant pancreatic enzyme activation happens, not subject and most likely less responsive to physiological regulation. Moreover, SS has significant functions that, when overexpressed, may present with deleterious, unwanted side effects, such as inhibition of growth hormoneand thyrotropin hormone production from the anterior pituitary, inhibition of the HPA stress axis [23-25]. GIT effects are inhibiting absorption of nutrients and electrolytes, gastrin and gastric acid secretion, smooth muscle contraction, bile flow, causes splanchnic vasoconstriction, and reduces portal blood flow, induces cell cycle arrest in G1 phase, inhibits hepatocellular proliferation and contributes to impaired wound healing [26,27]. Due to antiproliferative effect, SS also influences the immune response and it has diverse effects based on context, SS may skew T cells towards, forbidden phenotypes with aberrant cytokine expressions, and impaired antimicrobial function of T cells reminiscent of T cell phenotype in late, exhausted sepsis phase [28]. Somatostatin levels are generally already increased during experimental sepsis, adding fuel to the fire in sepsis associated central hypothyroidism [29].

Besides the theoretical options of moderating SIRS and regulated pancreatic secretion, it is cogent to consider the blockade of released digestive enzymes. Nf-kB and trypsin had been reported to contribute equally to disease phenotype. Lipase inhibitors are tested in clinical trials. In some regions clinically available trypsin inhibitor, a rather broad proteinase inhibitor, with diverse properties, ulinastatin has been reported to decrease SIRS, trypsin levels, prevent organ failure and improve survival in FNP in single and multi center trials [30]. Ulinastatin is a widespread protease inhibitor from urine, with immunomodulatory and anticoagulative functions, inhibiting trypsin, chymotrypsin, kallikrein, cathepsin

G, neutrophil elastase, thrombin, plasmin, coagulation factors IXa, Xa, XIa, XIaI [31]. Some approaches implement early somatostatin and later phase ulinastatin administration [32]. Another protease inhibitor, produced by the liver, alpha 1antitrypsin(A1AT) deficiency has been shown to aggravate FNP [33,34]. A1AT, with normal serum levels of 1-3g/l, has an extended regulatory effect, providing trypsin and neutrophil elastase neutralization and widespread immunomodulatory functions are attributed to A1AT, such as a complex interaction with ROS production and neutralization and a context dependent proinflammatory cytokine stimulatory or inhibitory role [35,36]. Lung injury is partly attributed for the skewed balance between NE and its inhibitor A1AT, most pronounced in genetic form, induced by SERPINA1 gene mutation leading to lung emphysema and liver fibrosis/cirrhosis [37,38].

The source and driving force of pancreatitis torrents are autodigestion, inflammation and necrosis. Current surgical approaches evolved to become mini-invasive and conservative, with exceptions for open abdomen with negative pressure peritoneal therapy in severe intra-abdominal hypertension, if conservative ways fail to prevent, at the same time endoscopic management of calculous obstructive ductal phenotypes a must [39]. Even Though one may wonder about the extent of possible secondary extraluminal pancreatic duct obstruction caused by the swollen pancreas. In general, depicting the etiology of FNP influences the treatment algorithm [40]. The ongoing catabolic effect of necrotic tissue sustains inflammation and catabolism. Continuous elimination modules may offer advantage, in those the process of elimination is based on the size, rather than the attribute of circulating substances. To progress in standards of care of FNP management, potential perspectives of treatments for fulminant acute pancreatitis in general should undergo further scientific and clinical dissection and clinical validation, starting on the level of individual patients, analysing etiology, with particular attention to treatable viruses, effects on SIRS, hormonal effects, wound healing immune response, and septic complications in differing clinical environments. Assumably, a combination of treatments will bring more satisfactory results, where thorough monitoring, due to the combinatory effects of genesis and therapy is desirable, including the understanding how these interventions affect delayed morbidity and functionality. The aim is an early and aggressive cessation of excessive and unconstrained local and systemic pancreatic enzyme release and activation together with targeted modification of SIRS, to prevent total autodigestion, to functionally preserve pancreatic tissue, while maintaining antibacterial potency, addressing the necrotic tissue, and these goals await clinical realization.

Acknowledgements

None.

Conflicts of Interest

None.

References

1. Watanabe T, Kudo M, Strober W (2017) Immunopathogenesis of pancreatitis. Mucosal Immunol 10(2): 283-298.
2. Liu Q, Li L, Xu D, Zhu J, Huang Z, et al. (2022) Identification of novel immune-related targets mediating disease progression in acute pancreatitis. Front Cell Infect Microbiol 12: 1052466.
3. FitzGerald ES, Luz NF, Jamieson AM (2020) Competitive Cell Death Interactions in Pulmonary Infection: Host Modulation Versus Pathogen Manipulation. Front Immunol 11: 814.
4. Mihoc T, Latcu SC, Secasan CC, Dema V, Cumpanas AA, et al. (2024) Pancreatic Morphology, Immunology, and the Pathogenesis of Acute Pancreatitis. Biomedicines 12(11): 2627.
5. Capobianco A, Cottone L, Monno A, Manfredi AA, Rovere Querini P (2017) The peritoneum: healing, immunity, and diseases. J Pathol 243(2): 137-147.
6. Liu M, Silva Sanchez A, Randall TD, Meza Perez S (2021) Specialized immune responses in the peritoneal cavity and omentum. J Leukoc Biol 109(4): 717-729.
7. Zhou X, Jin S, Pan J, Lin Q, Yang S, et al. (2022) Damage associated molecular patterns and neutrophil extracellular traps in acute pancreatitis. Front Cell Infect Microbiol 12: 927193.
8. Frisancho Kiss S (2021) Innate Recognition and Signaling during Times of Pandemic and Beyond from Intensive Care Perspective. Journal of Advances in Medicine and Medical Research 33(12): 130-143,
9. Underhill DM, Gantner B (2004) Integration of Toll-like receptor and phagocytic signaling for tailored immunity. Microbes Infect 6(15): 1368-1373.
10. Torchinsky MB, Garaude J, Blander JM (2010) Infection and apoptosis as a combined inflammatory trigger. Curr Opin Immunol 22(1): 55-62.
11. Wang G, Jin S, Huang W, Li Y, Wang J, et al. (2021) LPS-induced macrophage HMGB1-loaded extracellular vesicles trigger hepatocyte pyroptosis by activating the NLRP3 inflammasome. Cell Death Discov 7(1): 337.
12. Tammaro A, Derive M, Gibot S, Leemans JC, Florquin S, et al. (2017) TREM-1 and its potential ligands in non-infectious diseases: from biology to clinical perspectives. Pharmacol Ther 177: 81-95.
13. Zandarashvili L, Sahu D, Lee K, Lee YS, Singh P, et al. Real-time kinetics of high-mobility group box 1 (HMGB1) oxidation in extracellular fluids studied by in situ protein NMR spectroscopy. J Biol Chem 288(17): 11621-11627.
14. Li Y, Chen Y, Yang T, Chang K, Deng N, et al. (2023) Targeting circulating high mobility group box-1 and histones by extracorporeal blood purification as an immunomodulation strategy against critical illnesses. Crit Care 27(1): 77.
15. Wu J, Ren J, Liu Q, Hu Q, Wu X, Wang G, et al. (2019) Effects of Changes in the Levels of Damage-Associated Molecular Patterns Following Continuous Veno-Venous Hemofiltration Therapy on Outcomes in Acute Kidney Injury Patients with Sepsis. Front Immunol 9: 3052.
16. Mattke J, Darden CM, Lawrence MC, Kuncha J, Shah YA, et al. (2024) Toll-like receptor 4 in pancreatic damage and immune infiltration in acute pancreatitis. Front Immunol 15: 1362727.
17. Frisancho Kiss S (2023) Portrayal of the Multitasking Complement Regulator One in Critical Illness, Trans Med 13(2): 1000288.
18. Hartwig W, Klafs M, Kirschfink M, Hackert T, Schneider L, et al. Interaction of complement and leukocytes in severe acute pancreatitis: potential for therapeutic intervention. Am J Physiol Gastrointest Liver Physiol 291(5): G844-850.

19. Chen L, Yu CX, Song B, Cai W, Liu C, et al. (2018) Free fatty acids mediates human umbilical vein endothelial cells inflammation through toll-like receptor-4. Eur Rev Med Pharmacol Sci 22(8): 2421-2431.

20. Rajalingamgari P, Khatua B, Summers MJ, Kostenko S, Chang YH, et al. (2024) Prospective observational study and mechanistic evidence showing lipolysis of circulating triglycerides worsens hypertriglyceridemic acute pancreatitis. J Clin Invest 135(1): e184785.

21. Lipke K, Kubis Kubiak A, Piwowar A (2022) Molecular Mechanism of Lipotoxicity as an Interesting Aspect in the Development of Pathological States-Current View of Knowledge. Cells 11(5): 844.

22. Frisancho Kiss S, Davis SE, Nyland JF, Frisancho JA, Cihakova D, et al. Cutting edge: cross-regulation by TLR4 and T cell Ig mucin-3 determines sex differences in inflammatory heart disease. J Immunol 178(11): 6710-6714.

23. Yamamoto M, Ben Shlomo A, Kameda H, Fukuoka H, Deng N, et al. (2018) Somatostatin receptor subtype 5 modifies hypothalamic-pituitary-adrenal axis stress function. JCI Insight 3(19): e122932.

24. Haugen BR (2009) Drugs that suppress TSH or cause central hypothyroidism. Best Pract Res Clin Endocrinol Metab 23(6): 793-800.

25. Frisancho Kiss S (2022) Fine-tuning Mast Cells is Essential for the Maintenance and Regulation of the Systemic and Immune Homeostasis, Journal of Integrative Medicine 10(2): 60.

26. Vockel M, Pollok S, Breitenbach U, Ridderbusch I, Kreienkamp HJ, et al. (2011) Somatostatin inhibits cell migration and reduces cell counts of human keratinocytes and delays epidermal wound healing in an ex vivo wound model. PLoS One 6(5): e19740.

27. Baykal A, Ozdemir A, Renda N, Korkmaz A, Sayek I (2000) The effect of octreotide on postoperative adhesion formation. Can J Surg 43(1): 43-7.

28. Levite M, Chowers Y (2001) Nerve-driven immunity: neuropeptides regulate cytokine secretion of T cells and intestinal epithelial cells in a direct, powerful and contextual manner. Ann Oncol 2: S19-25.

29. Yelich MR, Witek Janusek L (1994) Glucose, lactate, insulin, and somatostatin responses to endotoxin in developing rats. Shock 2(6): 438-444.

30. Wang SQ, Jiao W, Zhang J, Zhang JF, Tao YN, et al. (2023) Ulinastatin in the treatment of severe acute pancreatitis: A single-center randomized controlled trial. World J Clin Cases 11(19):4601-4611.

31. Lagoo JY, D Souza MC, Kartha A, Kutappa AM (2018) Role of Ulinastatin, a trypsin inhibitor, in severe acute pancreatitis in critical care setting: A retrospective analysis. J Crit Care 45: 27-32.

32. Yang X, Li Y, Han F (2024) Effect of Ulinastatin Combined with Somatostatin on Inflammatory Markers, Hemodynamics and Immune Cells in the Treatment of Severe Pancreatitis. Altern Ther Health Med AT10234.

33. Lin K, Gao F, Chen Q, Liu Q, Chen S (2015) Framework for interpretation of trypsin-antitrypsin imbalance and genetic heterogeneity in pancreatitis. Saudi J Gastroenterol 21(4): 198-207.

34. Guttman O, Baranovski BM, Schuster R, Kaner Z, Freixo-Lima GS, et al. (2015) Acute-phase protein α1-anti-trypsin: diverting injurious innate and adaptive immune responses from non-authentic threats. Clin Exp Immunol 179(2): 161-172.

35. Dau T, Sarker RS, Yildirim AO, Eickelberg O, Jenne DE (2015) Autoprocessing of neutrophil elastase near its active site reduces the efficiency of natural and synthetic elastase inhibitors. Nat Commun 6: 6722.

36. Mazzuca C, Vitiello L, Travaglini S, Maurizi F, Finamore P, et al. (2024) Immunological and homeostatic pathways of alpha -1 antitrypsin: a new therapeutic potential. Front Immunol. 15: 1443297.

37. Erion DM, Liu LY, Brown CR, Rennard S, Farah H (2025) Editing Approaches to Treat Alpha-1 Antitrypsin Deficiency. Chest 167(2): 444-452.

38. Stockley RA, Parr DG (2024) Antitrypsin deficiency: still more to learn about the lung after 60 years. ERJ Open Res 10(4): 00139-2024.

39. Leppäniemi A, et al. (2019) WSES guidelines for the management of severe acute pancreatitis. World Journal of Emergency Surgery 14: 27.

40. Rawla P, Bandaru SS, Vellipuram AR (2017) Review of Infectious Etiology of Acute Pancreatitis. Gastroenterology Res 10(3): 153-158.