Supplemental Information

SMART-MD Journal of Precision Medicine, Summer 2024

www.smart-md.org

Acute Pancreatitis: Assessment and Management in the First 24 Hours

Peter J Lee MBChB[1], Shrinivas Bishu MD PhD[2], Cameron Breze MS[3], Amitabh Chak MD[4], Timothy B. Gardner MD[5], Nalini M. Guda MD[6], Vivek Kaul MD[7], Thiruvengadam Muniraj MD PhD FRCP[8], Georgios I. Papachristou MD PhD[1], Beth Schrope MD PhD[9], Daniel M. Spagnolo PhD[3a], Daniel S. Strand MD[10], Paul Tarnasky MD[11], Jason R. Taylor, MD[12b], C. Mel Wilcox MD[13,c], David C Whitcomb MD PhD[3,14]

[1]Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, The Ohio State University, Columbus Ohio; [2]Division of Gastroenterology and Hepatology, Department of Medicine, University of Michigan, Ann Arbor, MI; [3]Consultant, Ariel Precision Medicine, Pittsburgh, PA; [4]Digestive Health Research Institute, Department of Medicine, Case Western Reserve University, Cleveland, Ohio; [5]Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, NH; [6]GI Associates, St. Luke's Medical Center, Milwaukee, WI; [7]Division of Gastroenterology & Hepatology, University of Rochester Medical Center & Strong Memorial Hospital, Rochester, NY; [8]Division of Digestive Diseases, Department of Medicine, Yale University School of Medicine, New Haven, CT; [9]Department of Surgery, Columbia University College of Physicians and Surgeons, Washington Heights, NY; [10]Department of Gastroenterology and Hepatology, Department of Medicine, University of Virginia, and UVA Health, System Charlottesville, VA; [11]Methodist Digestive Institute, Methodist Dallas Medical Center, Dallas, TX; [12]Division of Gastroenterology and Hepatology, Department of Medicine, Saint Louis University, Saint Louis, MO. [13]Division of Gastroenterology & Hepatology, Department of Medicine, Birmingham, AL; [14]Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh, Pittsburgh, PA

Current affiliation. [a]Artios, Cambridge, England, United Kingdom; [b]BJC HealthCare, Saint Louis, MO. [c]Orlando Health Digestive Health Institute, Orlando, FL

Introduction and expanded definitions.

Systemic Inflammation. Systemic inflammation is a cytokine-driven condition with activation of leukocytes of the innate immune system within the blood stream affecting multiple organs, i.e. the "cytokine storm" [(1-3)]. The condition is diagnosed clinically as the *Systemic Inflammatory Response Syndrome* (**SIRS**) when specific diagnostic criteria are met: heart rate (HR) >90 beats/min, core body temperature of <36°C or >38°C, white blood cell (WBC) count of <4000 or > 12000/mm^3 and respiratory rate (RR) of >20/min or PCO_2 <32 mmHg[(4)]. Thus, it is easy to measure clinically.

SIRS is a clinical syndrome seen in patients with AP, polytrauma, extensive burns and sepsis[5-8], among other insults. It is a non-specific syndrome, but it is a useful indicator in patients with AP, because it informs caregivers that immune response to injury is affecting the *entire body*. In some cases, the symptoms resolve quickly, while in others, SIRS persists. Persistent SIRS (lasting ≥48 hours) is associated with progression to MOF [4, 9]. SIRS appears to be the bridge between local pancreatic inflammation and MOF since the *absence of SIRS* accurately predicts that MOF is unlikely (e.g. negative predictive value, NPV = 0.88 to 0.96 [10]). However, the *presence of SIRS* alone is *highly inaccurate* in predicting MOF (e.g. positive predictive value, PPV = 0.11 to 0.43 [10]). These data indicate that there are additional critical factors linking SIRS to MOF.

Multi-organ Failure (**MOF**). MOF in AP (also called *multi-organ dysfunction syndrome*, MODS) is determined by evaluating clinical biomarkers of dysfunction in three systems: cardiovascular, pulmonary and renal.[4] MOF is diagnosed using the *Modified Marshall Score*[4, 11] with scores of 0 to 4 for progressive dysfunction of the three systems. A score of 2 or more for any of the organ systems is considered organ failure, and severe AP (**SAP**) is defined by (a) Single OF, or (b) MOF (following Banks[4]).

Progression and Evolution. Progression of AP to MOF is dependent on the presence of SIRS, but it also includes additional factors that appear to cause endothelial cell injury and dysfunction leading to capillary leak syndrome (CLS).[12] SIRS is associated with altered capillary permeability allowing albumin to leak out of plasma over the first few days of AP. In contrast, MOF is associated with endothelial cell toxicity resulting in a breakdown of the endothelial barrier and loss of both albumin and large plasma proteins.[12] The loss of post-capillary oncotic pressure minimizes fluid reabsorption from the interstitial space, leading to venous hypovolemia and eventually hypovolemic shock. Transudation of plasma from the vascular compartment to the interstitial space and the "third space" results in pulmonary edema and acute respiratory distress syndrome (ARDS), hypovolemia and cardiovascular shock, pre-renal azotemia with acute kidney injury (AKI), pancreatic hypoperfusion and risk for pancreatic necrosis (PNec).[12] Likewise, hypoperfusion of intestinal epithelial cells leads to increased intestinal permeability with translocation of bacteria and other intestinal contents into the lymphatics that continuously drive

SIRS in a vicious cycle (e.g. >48 hours). Thus, optimal care requires both detecting capillary leak, which develops in a subset of AP patients, and preventing hypovolemia.

Multi-Organ Failure. Once MOF is established, management is primarily supportive. Treatment requires: for pulmonary failure, mechanical ventilation in the intensive care unit (ICU); for cardiac failure, fluid resuscitation and vasopressors; for renal failure, hemodialysis and for gut failure, nasojejunal tube feedings. Pancreatic necrosis (PNec) requires expectant observation and minimally invasive debridement when it becomes infected (i.e. endoscopic, percutaneous catheter placement or laparoscopic following a step-up approach).

Question 3. How is AP diagnosed?

Abdominal imaging. Abdominal imaging is used to detect biliary lithiasis and complications such as an impacted gallstone with ascending cholangitis or persistent cholestasis. CT imaging is seldom required to make the diagnosis of AP[4] and performance of CT scan in patients with persistent SIRS does not result in any change of management.[13] Two scenarios where an contrast enhanced CT imaging may be helpful are 1) Patients with recurrent idiopathic AP where autoimmune pancreatitis needs to be ruled out. One of the cardinal diagnostic criteria of autoimmune pancreatitis is imaging features (the other being histology). 2) Patients 40 years or older in whom obstructive malignancy needs to be ruled out. Evaluation of these potential etiologies should be done after inflammation from AP has subsided.

Question 5 How should severity be determined and predicted in an AP patient?

Revised Atlanta Criteria. Currently, the revised Atlanta criteria (RAC) are widely used to classify the severity of AP into mild, moderate, and severe.[4] Mild AP is characterized by the absence of any local or systemic complications or organ failure. Moderately severe AP is characterized by the presence of local (i.e. pancreatic

necrosis) or systemic complications and/or transient organ failure (<48 hours). Severe AP is characterized by persistent failure of a single or multiple organs (SOF and MOF), where organ failure (or dysfunction) refers to the lungs, cardiovascular system and kidneys using criteria defined by the Modified Marshall scoring system.[4] Pancreatic necrosis is a serious complication of AP and is included in the RAC as moderately severe AP. The RAC also highlights the importance of SIRS in the evolution of pancreatitis, but it is persistent SOF or MOF, rather than persistent SIRS or even pancreatic necrosis[9] that defines severe AP. Furthermore, by definition, severe AP cannot be diagnosed until day 3 of AP (i.e. >48h).

SIRS and MOF. Recent concepts recognize that SIRS as a clinically defined syndrome based on heart rate, body temperature, WBC level and respiratory rate (or PCO_2) that may or may not lead to MOF, depending on the etiology and driving factors of SIRS. In the absence of pre-existing conditions or medications that may alter body temperature, heart rate or WBC, the prognosis of patients with AP without SIRS is excellent. Most of the morbidity and mortality in AP is derived from MOF. This typically develops in a subset of patients with SIRS who progress to an unregulated CLS leading to major fluid shifts with intravascular hypovolemia, visceral organ hypoperfusion with pre-renal azotemia, pancreatic necrosis, pulmonary edema/adult respiratory distress syndrome (ARDS) and hypovolemic shock.[12] These events often lead to metabolic acidosis which can worsen pancreatic injury, thereby providing more substrates to perpetuate SIRS and CLS (i.e., disease-associated molecular patterns -> inordinate immune response -> CLS).[14] Presence of metabolic acidosis can often be recognized by RR >20 as the respiratory system attempts to compensate for the acidosis. CLS often begins in the context of SIRS with the MOF being delayed by 12-24 hours[12], and its onset typically is within the first week. So the absence of MOF on an early examination does not preclude development of MOF a few hours (or days) later. For this reason, a clinical decision support tool to aid bedside forecasting of prognosis and track important prognostic parameters is crucial to early identification of impending MOF.

Bedside clinical decision support tools: However, there are a number of challenges to implementing the available prognostic scores and parameters for bedside use: 1) Currently, there are more than 20 prognostic models developed for use in AP but it is difficult for clinicians to know which one to utilize, let alone compute the

probability of impending MOF. 2) Even though the ER providers are on the frontline to seeing AP patients early in the course, there are no ER specific guidelines to guide them for prognostication of AP and most of the prognostic model studies are published in the GI-specific journals. These barriers to implementation into clinical practice highlight a need for a clinical decision support tool that is accessible, easy to use, and is maintained with a database of prognostic models that can be implemented into clinical practice. To this end, tools such as ADAPT represents a front-runner to bringing prognostic models to the bedside to aid decision making.[15] The ADAPT tool is currently available on a user-friendly web-based platform (https://adapt-demo.arielmedicine.com/) where clinicians can go to the website and enter relevant patient data for computation of 13 prognostic model scores that aids classification of AP patient into predicted severe vs non-severe.[15]

Question 6. Etiology-based evaluation and management.

Ascending cholangitis - persistent bile duct obstruction. Features of the initial history and physical examination suggesting acute biliary pancreatitis include female sex, obesity, older age, sudden onset of pain, prior gallstones or biliary colic, and prior gallstone pancreatitis. Signs of ascending cholangitis include the Charcot's triad of right upper quadrant abdominal pain, jaundice and fever, with the addition of mental confusion and septic shock (Reynold's pentad) being less specific because confusion and shock may overlap with the presentation of severe AP.[16] Further diagnostic evaluation should include assessment of liver injury/function tests (LFT) and abdominal imaging. Following initial resuscitation and stabilization, further evaluation should begin with transabdominal abdominal ultrasound (TUS) to detect biliary sludge, gallstones or dilated common bile duct (e.g. >8mm). When the above imaging tests are inconclusive, endoscopic ultrasound (EUS) is highly sensitive and specific, especially for distal biliary stones or sludge to determine whether an urgent ERCP is indicated[17, 18]. Laboratory indices favoring biliary etiology include elevated serum alanine aminotransferase (ALT) >150 U/L or 2X ULN and acute elevation of direct bilirubin (DBili) or total bilirubin (TBili) above the ULN with no other confounding etiology.[17-19] Elevated WBC does not aid in determining etiology. In one study female sex, age >58 years and serum AST >150 U/L were independent predictive factors for biliary cause of AP.[17] The positive predictive value of ALT value > 150 U/L is 95%, but it lacks sensitivity.[17, 18] Both bile duct dilation (or visualized stone) on

transabdominal ultrasound and a total bilirubin >4 mg/dL have a specificity of approximately 94% for finding a stone at ERCP.[20] For the initial 24 hour assessment, a TUS is recommended, as it is noninvasive (unlike endoscopic procedures), doesn't require nephrotoxic contrast (as in cross-sectional imaging), and is widely available.

The purpose of diagnosing gallstone pancreatitis is to further determine whether there is ascending cholangitis, or a gallstone impacted at the level of the ampulla. Multiple studies and clinical guidance suggest that urgent ERCP is of no added benefit in patients without ascending cholangitis, and around two-thirds of patients could be spared an invasive procedure from which they gain no benefit but could have procedure-associated complications, especially if the patents are unstable from severe AP and have pulmonary edema and evolving ARDS[19] However, there are remaining questions as to whether ERCP is beneficial in patients with biliary pancreatitis without cholangitis or persistent cholestasis. The APEC trial from the Dutch Pancreatitis Study Group[19] concluded that urgent ERCP with sphincterotomy did not reduce the composite endpoint of major complications or mortality, compared with conservative treatment, but the rate of subsequent cholangitis was slightly higher in the conservative management group (10%) than the urgent ERCP with sphincterotomy group (2%, NS). From the same group, the results of the APEC-2 trial, where patients with predicted severe pancreatitis underwent urgent EUS, 58% of patients had gallstones/sludge in the bile duct. All of these underwent immediate ERCP with biliary sphincterotomy. Compared to the control group of APEC-1, no difference in the primary endpoint (~41% in each group), were met, Thus, the results of this study further support that ERCP is not beneficial for patients with predicted severe gallstone pancreatitis even when bile duct disease is present in the absence of cholangitis.[21]

Hypertriglyceridemic acute pancreatitis (HTG-AP). HTG-AP can be defined as the diagnosis of AP with triglyceride (TG) levels of at least 500 mg/dL with other common AP etiologies being excluded.[22] It is likely that HTG both induces AP and also results in more severe AP regardless of etiology. The risk of AP is directly related to fasting TG levels with progressively higher risk for TG levels above >177 mg/dL.[23] The etiology of HTG is also complex with a different mix of genetic, environmental and metabolic factors in different people. Several homozygous or compound heterozygous gene mutations causing familial chylomicronemia syndrome (FCS).[24, 25]

Multifactorial chylomicronemia syndrome (MCS) is common and reflects as complex mix of genetic factors[26-28] with or without environmental or metabolic factors. Other risk factors include medications such as glucocorticoids, poorly controlled diabetes mellitus (DM), alcoholism and obesity.[29, 30]

The diagnosis of HTG-AP should be suspected from the family history, the patients past medical history, medication review, physical examination, and laboratory findings of lipemic serum and elevated TG on a lipid panel. Note that serum amylase may be falsely normal in the setting of marked hypertriglyceridemia. Surprisingly, this key etiology is often overlooked by physicians and follow-up to prevent recurrence is often overlooked.[31] Early identification of HTG-AP is important since there is a high risk of lipotoxicity, which is closely associated with SIRS and MOF due to the types of fatty acids released by circulating pancreatic lipase.[32-34]

Hypercalcemia. Hypercalcemia is considered a risk factor when total ionized calcium levels are ≥12.0 mg/dL or ≥3 mmol/L.[35] Total calcium levels are affected by serum albumin and total protein, and conversion formulas are available to adjust for low serum protein. Approximately 90% of cases of hypercalcemia are caused by primary hyperparathyroidism (PHPT) or hypercalcemia of malignancy, with the rest typically associated with genetic disorders, sarcoidosis, chronic kidney disease (CKD), or other factors.[35, 36] During the acute phase of AP, total serum calcium levels may be deceivingly within normal limits because of concurrently low albumin and/or fat saponification "consumes" calcium. This necessitates the need for measuring its level potentially serially upon recovery especially in patients where etiology is uncertain. For treatment, see text.

Diabetic ketoacidosis (DKA). Diabetic ketoacidosis is a medical emergency defined by elevated blood glucose, elevated blood/urine ketones, and intravascular metabolic acidosis. It is caused by insufficient insulin and seen with type 1 DM, especially during illness or stress. AP may develop in DKA in the presence of metabolic acidosis with serum pH below 7.2 (e.g. pH 7.15 +/- 0.14 in one study[37]).[38-40] The mortality of patients with DKA-AP was found to be 2.3 times higher than for those with AP alone (P<.001; CI 1.8–3.0) in a study of an administrative database, but in the same study HTG-AP was found to have lower risk of mortality than AP alone.[41]

The diagnosis of DKA should be suspected in patients with a history of DM, smell of acetone on the patient's breath, and hyperventilation as a respiratory compensation for metabolic acidosis. The diagnosis is made based on elevated serum blood sugar of >250 mg/dL and presence of ketones in the serum or urine and metabolic acidosis (arterial blood gas [ABG] with pH $\leq$7.3, serum bicarbonate of $\leq$18 mmol/L and anion gap of >10). [(42)] Serum lactate levels should also be measured to evaluate tissue ischemia and hypovolemic shock.

Apart from the "urgent" etiologies discussed above, there are many additional causes of pancreatitis that may be identified by history, laboratory or specialized testing. Assessment for these causes can be pursued in sequential fashion based upon clinical features, though this is not critical early on. Such assessments could include genetic counselling and testing (e.g. for *PRSS1*), IGG subclass analysis (to identify IGG-4 Related disease), EUS (to assess for intraductal papillary mucinous neoplasia or a small pancreatic mass), or a secretin enhanced MRI (particularly w/ recurrent pancreatitis to identify a potential structural cause, such as pancreas divisum). In patients with recurrent pancreatitis where explicit alcohol use is involved, counseling with referral to addiction treatment should be offered to reduce recurrence risk. Where surreptitious alcohol consumption seems likely, testing for carbohydrate deficient transferring (CDT) or phosphatidylethanol may be of use.[(43)]

References

1. Makhija R, Kingsnorth AN. Cytokine storm in acute pancreatitis. J Hepatobiliary Pancreat Surg. 2002;9(4):401-10 D.O.I: 10.1007/s005340200049. PMID: 12483260

2. Siddall E, Khatri M, Radhakrishnan J. Capillary leak syndrome: etiologies, pathophysiology, and management. Kidney Int. 2017;92(1):37-46 D.O.I: 10.1016/j.kint.2016.11.029. PMID: 28318633

3. Castellheim A, Brekke OL, Espevik T, Harboe M, Mollnes TE. Innate immune responses to danger signals in systemic inflammatory response syndrome and sepsis. Scand J Immunol. 2009;69(6):479-91 D.O.I: SJI2255 [pii] 10.1111/j.1365-3083.2009.02255.x. PMID: 19439008

4. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11 D.O.I: 10.1136/gutjnl-2012-302779. PMID: 23100216

5. Dahiya P. Burns as a model of SIRS. Front Biosci (Landmark Ed). 2009;14:4962-7 D.O.I: 10.2741/3580. PMID: 19482598

6. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39(2):165-228 D.O.I: 10.1007/s00134-012-2769-8. PMID: 23361625

7. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med. 2017;45(3):486-552 D.O.I: 10.1097/CCM.0000000000002255. PMID: 28098591

8. Napolitano LM. Sepsis 2018: Definitions and Guideline Changes. Surg Infect (Larchmt). 2018;19(2):117-25 D.O.I: 10.1089/sur.2017.278. PMID: 29447109

9. Buter A, Imrie CW, Carter CR, Evans S, McKay CJ. Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. Br J Surg. 2002;89(3):298-302 D.O.I. PMID: 11872053

10. Mounzer R, Langmead CJ, Wu BU, Evans AC, Bishehsari F, Muddana V, et al. Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. Gastroenterology. 2012;142(7):1476-82 D.O.I: 10.1053/j.gastro.2012.03.005. PMID: 22425589

11. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med. 1995;23(10):1638-52 D.O.I. PMID: 7587228

12. Komara NL, Paragomi P, Greer PJ, Wilson AS, Breze C, Papachristou GI, et al. Severe acute pancreatitis: capillary permeability model linking systemic inflammation to multiorgan failure. Am J Physiol Gastrointest Liver Physiol. 2020;319(5):G573-G83 D.O.I: 10.1152/ajpgi.00285.2020. PMID: 32877220

13. Kamal A, Faghih M, Moran RA, Afghani E, Sinha A, Parsa N, et al. Persistent SIRS and acute fluid collections are associated with increased CT scanning in acute interstitial pancreatitis. Scand J Gastroenterol. 2018;53(1):88-93 D.O.I: 10.1080/00365521.2017.1383510. PMID: 29017354

14. Rumbus Z, Toth E, Poto L, Vincze A, Veres G, Czako L, et al. Bidirectional Relationship Between Reduced Blood pH and Acute Pancreatitis: A Translational Study of Their Noxious Combination. Front Physiol. 2018;9:1360 D.O.I: 10.3389/fphys.2018.01360. PMID: 30327613

15. Paragomi P, Spagnolo DM, Breze CR, Gougol A, Talukdar R, Kochhar R, et al. Introduction and Validation of a Novel Acute Pancreatitis Digital Tool: Interrogating Large Pooled Data From 2 Prospectively Ascertained Cohorts. Pancreas. 2020;49(10):1276-82 D.O.I: 10.1097/MPA.0000000000001686. PMID: 33122514

16. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 2008;57(12):1698-703 D.O.I: gut.2008.152702 [pii]

10.1136/gut.2008.152702. PMID: 18519429

17. Liu CL, Fan ST, Lo CM, Tso WK, Wong Y, Poon RT, et al. Clinico-biochemical prediction of biliary cause of acute pancreatitis in the era of endoscopic ultrasonography. Aliment Pharmacol Ther. 2005;22(5):423-31 D.O.I: 10.1111/j.1365-2036.2005.02580.x. PMID: 16128680

18. Gungor B, Caglayan K, Polat C, Seren D, Erzurumlu K, Malazgirt Z. The predictivity of serum biochemical markers in acute biliary pancreatitis. ISRN Gastroenterol. 2011;2011:279607 D.O.I: 10.5402/2011/279607. PMID: 21991501

19. Schepers NJ, Hallensleben NDL, Besselink MG, Anten MGF, Bollen TL, da Costa DW, et al. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. Lancet. 2020;396(10245):167-76 D.O.I: 10.1016/S0140-6736(20)30539-0. PMID: 32682482

20. Committee ASoP, Buxbaum JL, Abbas Fehmi SM, Sultan S, Fishman DS, Qumseya BJ, et al. ASGE guideline on the role of endoscopy in the evaluation and management of choledocholithiasis. Gastrointest Endosc. 2019;89(6):1075-105 e15 D.O.I: 10.1016/j.gie.2018.10.001. PMID: 30979521

21. Hallensleben ND, Stassen PMC, Schepers NJ, Besselink MG, Anten MGF, Bakker OJ, et al. Patient selection for urgent endoscopic retrograde cholangio-pancreatography by endoscopic ultrasound in predicted severe acute biliary pancreatitis (APEC-2): a multicentre prospective study. Gut. 2023;72(8):1534-42 D.O.I: 10.1136/gutjnl-2022-328258. PMID: 36849226

22. Vipperla K, Somerville C, Furlan A, Koutrompakis E, Saul M, Chennat J, et al. Clinical Profile and Natural Course in a Large Cohort of Patients With Hypertriglyceridemia and Pancreatitis. J Clin Gastroenterol. 2016;51(1):77-85 D.O.I: 10.1097/MCG.0000000000000579. PMID: 27322530

23. Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting Mild-to-Moderate Hypertriglyceridemia and Risk of Acute Pancreatitis. JAMA Intern Med. 2016;176(12):1834-42 D.O.I: 10.1001/jamainternmed.2016.6875. PMID: 27820614

24. Dron JS, Hegele RA. Genetics of Hypertriglyceridemia. Front Endocrinol (Lausanne). 2020;11:455 D.O.I: 10.3389/fendo.2020.00455. PMID: 32793115

25. Chyzhyk V, Kozmic S, Brown AS, Hudgins LC, Starc TJ, Davila AD, et al. Extreme hypertriglyceridemia: Genetic diversity, pancreatitis, pregnancy, and prevalence. J Clin Lipidol. 2019;13(1):89-99 D.O.I: 10.1016/j.jacl.2018.09.007. PMID: 30352774

26. Schaefer EJ, Geller AS, Endress G. The biochemical and genetic diagnosis of lipid disorders. Curr Opin Lipidol. 2019;30(2):56-62 D.O.I: 10.1097/MOL.0000000000000590. PMID: 30720493

27. Dron JS, Wang J, Cao H, McIntyre AD, Iacocca MA, Menard JR, et al. Severe hypertriglyceridemia is primarily polygenic. J Clin Lipidol. 2019;13(1):80-8 D.O.I: 10.1016/j.jacl.2018.10.006. PMID: 30466821

28. Johansen CT, Wang J, Lanktree MB, McIntyre AD, Ban MR, Martins RA, et al. An increased burden of common and rare lipid-associated risk alleles contributes to the phenotypic spectrum of hypertriglyceridemia. Arterioscler Thromb Vasc Biol. 2011;31(8):1916-26 D.O.I: 10.1161/ATVBAHA.111.226365. PMID: 21597005

29. Parhofer KG, Laufs U. The Diagnosis and Treatment of Hypertriglyceridemia. Deutsches Arzteblatt international. 2019;116(49):825-32 D.O.I: 10.3238/arztebl.2019.0825. PMID: 31888796

30. Simha V. Management of hypertriglyceridemia. Bmj. 2020;371:m3109 D.O.I: 10.1136/bmj.m3109. PMID: 33046451

31. Olesen SS, Harakow A, Krogh K, Drewes AM, Handberg A, Christensen PA. Hypertriglyceridemia is often under recognized as an aetiologic risk factor for acute pancreatitis: A population-based cohort study. Pancreatology. 2021 D.O.I: 10.1016/j.pan.2021.02.005. PMID: 33608229

32. Navina S, Acharya C, Delany JP, Orlichenko LS, Baty CJ, Shiva SS, et al. Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. Sci Transl Med. 2011;3(107):107ra10 D.O.I: 10.1126/scitranslmed.3002573. PMID: 22049070

33. Nawaz H, Koutroumpakis E, Easler J, Slivka A, Whitcomb DC, Singh VP, et al. Elevated Serum Triglycerides are Independently Associated With Persistent Organ Failure in Acute Pancreatitis. Am J Gastroenterol. 2015;110(10):1497-503 D.O.I: 10.1038/ajg.2015.261. PMID: 26323188

34. Khatua B, El-Kurdi B, Patel K, Rood C, Noel P, Crowell M, et al. Adipose saturation reduces lipotoxic systemic inflammation and explains the obesity paradox. Sci Adv. 2021;7(5) D.O.I: 10.1126/sciadv.abd6449. PMID: 33514548

35. Whitcomb DC, North American Pancreatitis Study G. Pancreatitis: TIGAR-O Version 2 Risk/Etiology Checklist With Topic Reviews, Updates, and Use Primers. Clin Transl Gastroenterol. 2019;10(6):e00027 D.O.I: 10.14309/ctg.0000000000000027. PMID: 31166201

36. Walsh J, Gittoes N, Selby P, Society for Endocrinology Clinical C. SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: Emergency management of acute hypercalcaemia in adult patients. Endocr Connect. 2016;5(5):G9-G11 D.O.I: 10.1530/EC-16-0055. PMID: 27935816

37. Nair S, Yadav D, Pitchumoni CS. Association of diabetic ketoacidosis and acute pancreatitis: observations in 100 consecutive episodes of DKA. The American journal of gastroenterology. 2000;95(10):2795-800 D.O.I: 10.1111/j.1572-0241.2000.03188.x. PMID: 11051350

38. Bhoomagoud M, Jung T, Atladottir J, Kolodecik TR, Shugrue C, Chaudhuri A, et al. Reducing extracellular pH sensitizes the acinar cell to secretagogue-induced pancreatitis responses in rats. Gastroenterology. 2009;137(3):1083-92 D.O.I: 10.1053/j.gastro.2009.05.041. PMID: 19454288

39. Thrower EC, Gorelick FS, Husain SZ. Molecular and cellular mechanisms of pancreatic injury. Curr Opin Gastroenterol. 2010;26(5):484-9 D.O.I: 10.1097/MOG.0b013e32833d119e. PMID: 20651589

40. Lugea A, Waldron RT, Mareninova OA, Shalbueva N, Deng N, Su HY, et al. Human Pancreatic Acinar Cells: Proteomic Characterization, Physiologic Responses, and Organellar Disorders in ex Vivo Pancreatitis. Am J Pathol. 2017;187(12):2726-43 D.O.I: 10.1016/j.ajpath.2017.08.017. PMID: 28935577

41. Simons-Linares CR, Jang S, Sanaka M, Bhatt A, Lopez R, Vargo J, et al. The triad of diabetes ketoacidosis, hypertriglyceridemia and acute pancreatitis. How does it affect mortality and morbidity?: A 10-year analysis of the National Inpatient Sample. Medicine. 2019;98(7):e14378 D.O.I: 10.1097/MD.0000000000014378. PMID: 30762737

42. Dhatariya KK, Vellanki P. Treatment of Diabetic Ketoacidosis (DKA)/Hyperglycemic Hyperosmolar State (HHS): Novel Advances in the Management of Hyperglycemic Crises (UK Versus USA). Curr Diab Rep. 2017;17(5):33 D.O.I: 10.1007/s11892-017-0857-4. PMID: 28364357

43. Lohr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United European gastroenterology journal. 2017;5(2):153-99 D.O.I: 10.1177/2050640616684695. PMID: 28344786