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Review

Pathophysiology, classification and available guidelines of acute pancreatitis

PANCREAS

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ABSTRACT

Acute pancreatitis (AP) constitutes the majority of cases requiring hospital admission in gastroenterology. We are yet to know many things about its pathophysiology which is a certain drawback for the progress in its treatment. Prediction of severity is necessary for the plan of the management. The existing scoring systems are yet to be satisfactory. However our progress in the field was significant in the recent decade and a leap forward is expected in this cumbersome-to-manage condition which has many unmet needs. In this review, we are going to summarize the hitherto data in pathogenesis and would weigh the usefulnes and weaknes of each of existing scoring systems in the management of AP.

Keywords: Acute pancreatitis, guideline, pathophysiology, scoring systems, classifications, insights

Pancreas was first discovered by Herophilus, a Greek anatomist and surgeon, in Chalcedon (now Kadıkoy, Istanbul) in 336 BC. Despite the many years since its discovery, a lot remains unknown about pancreas. The coming decade would, probably, witness several advances in our understanding of pancreas and its diseases.

This review aims to describe the hitherto knowledge in pancreas pathophysiology and classification systems of severity scoring.

PATHOPHYSIOLOGY

The main reason for the lack of successful treatment in acute pancreatitis (AP) is that many aspects of this condition regarding the pathophysiology are still unknown. AP has a severe course in 20% of the cases and may be associated with high morbidity and mortality in 2-3%. Pancreatic autodigestion (trypsinogen-centered) theory has been in use in the AP pathogenesis for over a hundred year. In this theory, premature activation of pancreatic proenzymes (zymogens) induces autolysis, which triggers inflammatory events followed by continued damage to the pancreas and/or non-pancreatic tissues in some way.

Experimental models (1,2) have demonstrated the involvement of trypsin activation in hereditary pancreatitis (3). Along with zymogen activation, natural factor kappa beta (NFkB) activation is also important in the development of AP. Whether both are involved or are independently-acting parallel factors in AP is controversial. It was shown, *in vitro,* that trypsinogen expression did not activate NFkB (4). Conversion of trypsinogen to trypsin within the pancreas is a pathological phenomenon. This, however, may not achieve levels that may cause a clinical pathology, might have been eliminated intracellularly by protective mechanisms or may stimulate an acinar inflammatory response without causing cell destruction. Because experiments with protease inhibitors (whether they specifically target trypsinogen is unclear) did not produce satisfactory results, it was considered that experiments with genetically trypsinogen activation-deprived mice [(trypsinogen-7($T^{-/-}$) and cathepsin CB($^{-/-}$)] would contribute to elucidating the trypsinogen hypothesis (5). Acinar necrosis occurred in wild-type mice with supramaximal cerulein, while acinar cell death was never observed in $T^{-/-}$ mice (6). Nevertheless, there is little belief that trypsinogen is responsible for all of the systemic complications. In experiments with pancreas-specific inducible trypsino-

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gen, maximum expression in homozygotes with continuous and rapid induction results in AP, whereas mild and repeated expressions (in heterozygotes) do not induce AP (7).

Acute pancreatitis may develop with trypsin activation in some of the PRSS1 cationic trypsinogen gene mutations. Other genes that are involved in AP have been determined, i.e. cystic fibrosis transmembrane conductance regulator (CFTR), pancreatic secretory trypsin inhibitor or serine protease kazal type 1, chymotrypsinogen C (CTRC). AP was observed in a very few of the p.R122H mutant PSSS1 mice, although this might be incidental (8). The trypsinogen hypothesis cannot explain the absence of chronic pancreatitis despite the incomplete transition and intermittent course of disease in hereditary pancreatitis (9).

Acinar cells have inflammatory functions along with their integrity, functionality and stability functions (10). The significant involvement of NFkB in inflammatory function has been well established during the last decade. The new insight is that NFkB activation occurs before trypsinogen activation in early AP (4). In addition, local and systemic complicated AP could be induced by activation of adenovirus-transfected NFkB with intraductal injection to acinar cells in genetically modified mice (11).

In genetically IL-6-depleted mice, AP did not develop with cerulein (12). Another study demonstrated that IL-22 was protective against AP (13).

Inhibition of pathologic calcium stimulation through calcineurin activation was able to stop biliary AP development (14). In that study, 1,2-bis (o-aminophenoxy) ethane-N,N,N',N'-tetraacetic acid (acetoxymethyl ester) (BAPTA-AM) or three specific calcineurin inhibitors, i.e. FK506, cyclosporine A or calcineurin inhibitor peptide, prevented acinar cell damage resulting from biliary acid induction.

NFATC3 inhibition from NF-activated cells coded by the *NFATC3* gene was shown to reduce the severity of AP (7).

It has been long known that systemic inflammatory mechanisms causing organ failure in AP are similar to sepsis, burns and multi-trauma (15). During the initial phase of AP, SIRS (systemic inflammatory response syndrome) develops with inflammatory activity, followed by compensatory antiinflammatory activity, which triggers the infectious process through immunosuppression (16). In fact, SIRS was first used in 2006. It requires presence of 2 or more of the 4 criteria, which are fever <36ºC or >38ºC, pulse rate >90/min, respiratory rate: >20/min, WBC: <4,000/mm^3 or >12,000/mm^3 and >10% bands. Apart from pancreatic cells, peritoneal and alveolar macrophages and other inflammatory cells including the Kupffer cells have been shown be activated during different phases in AP (17).

Obese AP patients are more prone to develop complications with, sometimes; fatal outcomes compared to non-obese AP patients (18). Inflammation of the adipose tissue in AP was shown to lead to production of the mediators which contribute to the systemic inflammatory response syndrome (19). Peripancreatic adipose tissue was demonstrated to be a more important factor than BMI and waist circumference in the development of severe AP (20).

There have been recent attempts to enable the use of micro-RNAs in diagnosing AP and determining the disease severity. Although these studies are promising, more time will be needed before micro-RNAs may be used as biomarkers. Micro-RNAs are molecules which are composed of 18-25 nucleotides and regulate post-transcriptional gene expression. They may be detected in tissues, sera and all biologic fluids. miR216a and miR217s were found utilizable in diagnosing drug-induced AP (21). It has been demonstrated that miR-92b, miR-10a and miR-7 could be used in the early diagnosis of AP, and miR-551b-5p in estimating the severity of AP (22). Experiments with mouse models have shown significantly increased plasma levels of miR-216a and miR-216b in arginine-induced AP (23).

INNOVATIONS IN GUIDELINES AND CLASSIFICATIONS

Several scoring systems have been developed to measure the severity of AP. Of these, in Acute Physiology and Chronic Health Examination (APACHE-II), scores higher than 8 and modified Glasgow and Ranson scores higher than 3 indicate severe AP. APACHE-II scoring system is popular currently recommended by the AGA (American Gastroenterology Association). This scoring system includes 12 physiologic parameters as well as additional parameters, such as, age and presence of a chronic condition. The cons of this scoring system include its cumbersome use and poor predictive value over the first 24 hours (24). The Ranson scoring system contains 11 parameters, of which 5 are scored at the time of presentation and 6 during the first 48 hours. Scores <3 indicate 0-3% mortality, scores >3 indicate 11-15% mortality and scores >6 indicate 40% mortality (24). Poor prognostic value of the Ranson scoring system was shown by a meta-analysis of 110 studies (25). The Imrie scoring system (Modified Glasgow) is more practical, can be administered within the first 48 hours and contains 9 parameters (age >55 years, WBC >15.000 mm^3, glucose >180 mg/dL (non-diabetics), urea >45 mg/dL, albumin <3.2g/dL, PaO_2 <60 mmHg, Ca^{++} <8 mg/dL, AST/ALT >100U/L, LDH >600U/L). Presence of 3 or more parameters indicates the severe course. The HAP (Harmless Acute Pancreatitis) scoring system has been in use since 2009. It is a simple and convenient scoring system, which can be used for up to first 48 hours and includes 3 parameters (1 point for each parameter: presence of abdominal rebound tenderness, hematocrit over 44% and increased serum creatinine). Presence of 2 or more indicates non-mild course.

2012 Atlanta revision requires presence of following two of three findings for the diagnosis of AP: 1- Characteristic pain, 2- Serum lipase or amylase levels 3 times of the upper limit of normal, and 3- presence of characteristic images in contrast CT

(or MRI and less frequently USG). The time from onset of pain to the patient's presentation should be noted (26-28).

In fact, none of the available scoring systems is excellent alone in predicting severity, and each needs improvement. They generally have moderate sensitivity and poor negative predictive value (29,30). An ideal scoring system should be simple, practical to use, reproducible and usable within the first 48 hours, and should have high enough sensitivity and specificity to accurately predict severity. In a study performed in our clinic, most of the patients had Imrie scores of ≤5 and HAP scores ≤2 (these scores are normally considered as evidence of severe AP; for mild AP, Imrie score should be <3 and HAP score should be 0), whereas these patients did not develop severe pancreatitis (31).

Another, the bedside index of severity scoring system has been started to use recently (2008) (31). It includes 5 parameters and can be used within the first 48 hours. These parameters are presence of SIRS, BUN >25 mg/dL, age >60 years, variable mental status and presence of pleural effusion. The presence of more than 3 parameters indicates the severity. A recent study has shown that the bedside index of severity scoring system was useful in estimating mortality within the first 24 hours in AP patients (32,33).

The 'determinant based classification' was developed in 2013 for severity estimation in AP (34). The point of origin of this classification was the causes of mortality including infected pancreatic or peripancreatic necrosis and organ failure. Determinants are the causes that coincidentally produce severe states, which may be local or systemic. Local determinants include sterile or infected peripancreatic or pancreatic necrosis. Systemic determinants include organ failures (<24 hours transient, >24 hours persistent) scored ≥2 according to the SOFA scoring system (sepsis-related organ failure assessment) in 3 organ systems (cardiovascular, pulmonary and renal) (cardiovascular: inotropic requirement, renal: ≥2 mg/dL, pulmonary: PaO_2/FiO2 ≤300 mmHg). Thus, severity in AP was limited to 4 categories in the determinant based classification. This 4-category classification was clinically validated by Tandessery et al. (35) in 151 patients. Mortality rates in mild, moderate, severe and critical APs were found as 0; 3.6; 33.8; and 87.5%, respectively. Gastroenterologists, surgeons, intensive care specialists, radiologists and internal medicine specialists from 49 countries contributed to the development of this classification system.

According to the 1992 Atlanta criteria, the severity in AP was divided into two categories as mild and severe. Mild pancreatitis involves no organ failure (systolic BP: TA <90 mmHg, GI bleeding: >500 mL/day, pulmonary: PaO_2 <60%, renal: creatinine >2 mg/dL) or local complication, while severe AP involves both. In the revised Atlanta criteria dated 2013, AP was classified into three categories as mild, moderate and severe (26). Definition of mild AP remained unchanged in the new version compared to the previous one, whereas, in the new classification, presence of organ failure for more than 48 hours indicated severe condition, while moderate AP required presence of local complications and transient organ failure (<48 hours). In modified Atlanta classification, organ failure persisting for more than 48 hours was sought for severe AP. Organ failure was defined according to the Modified Marshall Scoring System, where changes in 3 organ systems (the heart, kidneys and lungs) were given a score from 0 to 4. Scores of 2 and higher for any organ indicates organ failure.

The evidence based guideline of AP published by IAP (International Association of Pancreatology) and APA (American Pancreatic Association) in 2013 recommends using SIRS (systemic inflammatory response syndrome) as the best severity score at presentation and 48th hour (28). In fact, SIRS was first used in 2006. It requires presence of 2 or more of the 4 criteria, which are body temperature <36 ºC or >38 ºC, pulse rate >90/min, respiratory rate: >20/min, WBC: <4000 or >12.000 and >10% bands.

In 2013, the American College of Gastroenterology guideline suggested that severity estimation should be based on patient-specific factors (radiologic and laboratory) rather than depending on a scoring system (27). Age, BMI, elevated hematocrit and BUN levels, SIRS, comorbidity, pulmonary effusion and infiltrate, variable mental state and presence of other findings are critical. SIRS during the first 24 hours has a high sensitivity for identifying organ failure and local complication, while its specificty is low (because it does not indicate persistent SIRS) (Table 1).

The prognostic severity scoring system, first used in 2009 in Japan to estimate intra-hospital mortality, was validated in 17901 patients, and mortality rates in non-serious and serious AP were found as 1.1 and 7%, respectively (36). This scoring system included 9 parameters, with presence of more than 3 considered as severe AP (age >70 years; number of positives in SIRS; LDH, ULN >2; base deficit ≤-3 mEq/L or shock; platelet count ≤100,000/mm^3, CRP; ≥15 mg/dL (ULN: <5 mg/dL); serum Ca^{++} ≤7.5 mg/dL; BUN ≥ 40 mg/dL or creatinine ≥2 mg/dL; PaO_2 <60 mmHg).

Radiological scoring systems first emerged in 1990s. Radiologically, AP is divided into two categories as interstitial edematous AP and necrotizing AP. In necrotizing pancreatitis, CT or MRI shows focal or diffuse necrotic tissue with peri-pancreatic adipose tissue necrosis, resulting from the damage to the microvascular circulation of the pancreas (37). Necrotizing pancreatitis was used to define severe AP in the Atlanta criteria. Balthazar CT scoring system was first used in 1985 and is still in use (38). This scoring system includes 5 grades: grade A: normal, grade B: pancreas enlargement, grade C: inflammation of the pancreas and surrounding tissue, grade D: single peripancreatic fluid accumulation, grade E: two or more peripancreatic fluid

Table 1. Scoring systems for acute pancreatitis

Score	Year	Cutoffs	Parameters	Advantages	Disadvantages
Acute Physiology and Chronic Health Examination (APACHE-II) (24,30)	1981	≥8	12 physiologic parameters plus parameters such as age and presence of chronic disorder	American Gastroenterology Association advices.	Difficult to use and predictive value is not good within first 24-hour.
Modified Glasgow (Imrie score) (47)	1984	≥3	9 parameters	Evaluated within first 48-hour.	
Ranson (25)	1974	≥3	11 parameters; 5 Parameters at hospital admission. 6 parameters at 48-hour.	Evaluated after 48-hour.	It is not a good at prediction of prognossis (it has been shown by a metaanalysis of 110 study).
Harmless acute pancreatitis score (HAPS) (48)	2009	>0	3 parameters (rebound, hematocrit and creatinine)	Can be used within 48-hour, simple and practical usage. It was derived on a cohort of 394 patients and validated in a cohort of 452 patients.	
Bedside Index of Severity (49)	2008	≥3	5 parameters (BUN, impaired mental status, systemic inflammatory response syndrome (SIRS), age, and pleural effusion)	Useful at prediction of mortality within first 24-hour. Validated in 18,256 cases	Can not easily distinguish transient organ dysfunction from persistent organ dysfunction at 24 h.
Sepsis-related Organ Failure Assesment (SOFA) (50)	1996	≥2	6 parameters: respiratory, cardiovascular, central nervous systems, renal, coagulation, and liver	SOFA score performed better with additional advantages of easy applicability and timely assessment	It has been validated to describe the degree of organ dysfunction in patient groups with organ dysfunctions not due to sepsis.
Modified Marshall Scoring (for definition of organ insufficiency) (51)	1995	≥2	Changes in 3 organ (hearth, kidney lung) systems are scored as 0 to 4.	It has the merit of simplicity, universal applicability across international centres, and the ability to stratify disease severity easily and objectively. The modified Marshall scoring system is preferred to the SOFA scoring system, which is for patients managed in a critical care unit and which takes into account the use of inotropic and 16 respiratory support.	
Systemic Inflammatory Response Syndrome (SIRS) (52)	2006	≥2	4 parameters: temperature, heart rate, respiratory rate, WBC.	SIRS scores can be measured quickly and easily at the bedside. Data support use of the score to predict length of stay in the intensive care	
Japan Prognostic Severity Score (for prediction of in-hospital mortality) (36)	2009	≥3	9 parameters: base excess, PaO_2, BUN, LDH, platelet count, serum calcium, CRP, SIRS, age, CT grade based on CT scan with contrast medium to measure pancreatic enhancement and extrapancreatic progression.	Mortality rates are found as 1.1% in mild and 7% in severe acute pancreatitis. Validated in 1790 patients.	
Baltazar CT Severity Index (CTSI) (38)	1985	Grade A,B,C,D,E >5	5 grades	Can be used within 10 days of admission. The CT grading scores correlate better with local complications (pseudocysts and abscesses) than with mortality.	Can not detect necrosis. The CTSI is any more predictive than the grades A through E score.
Contrast Enhanced CT Severity	1990	0: no, 2: <30%, Index (39) 4: 30-50%, 6: 50% necrosis	3 grade (<30%, 30% to 50%, and >50%)	Effective tool for predicting complication and mortality of acute pancreatitis. Therefore, these results suggest that the use of iodinated contrast material is essential in acute pancreatitis.	Risk of iodinated contrast material

Table 1. Continued

Score	Year	Cutoffs	Parameters	Advantages	Disadvantages
Extrapancreatic CT Severity Score (EPIC Score) (40)	2007	≥3	Extrapancreatic organ findings (pleural effusion, mesenteric inflammation and retroperitoneal inflammation).	Interobserver agreement is between moderate and good. Allows accurate estimation of severity and outcome within the first 24-hour. of admission. The EPIC score can easily be calculated without the need for contrast-enhanced CT.	
Modified CT Severity Index (CTSI) (53)	2004	≥6	Based on contrast enhanced CT scan taken after at least 72-hour. This score returns a total score based two grades: a CT grade (normal pancreas, 0; edematous pancreas, 1; mild extrapancreatic changes with pancreatic edema, 2; severe extrapancreatic changes and one fluid collection, 3; multiple collections, 4), and a necrotic grade (no involvement, 0; less than one third of pancreas involved, 2; one third to involved, 6).	Interobserver agreement is only moderate.	The score does not significantly correlate with subsequent development of organ failure and the extrapancreatic parenchymal complications. No significant difference in morbidity and mortality is seen, when using CTSI between patients who have 30-50% necrosis and patients who have more than 50% necrosis half involved, 4; more than half.
Simple Prognostic Score (41)	2007	Increases in parallel with severity. Low, moderate and high risk groups.	3 grades	Within 72h of admission. This simple prediction rule is an additional tool that may help physicians stratifying the severity of AP. Low risk patients would not need special monitoring.	Patients with high risk for complicated AP should be kept under close surveillance.
Multiple organ dysfunction score (MODS) (51)	1996	6 parameters	6 organ systems: respiratory; renal; hepatic; cardiovascular; haematological; central nervous system.	Predicts organ dysfunction.	Should be calculated daily.

APACHE-II: Acute Physiology and Chronic Health Examination; HAPS: harmless acute pancreatitis score; SIRS: systemic inflammatory response syndrome; SOFA: sepsis-related organ failure assessment; MODS: multiple organ dysfunction score

accumulation and/or air accumulation. Grade D and E have a mortality of 14% and morbidity of 54%. This scoring system is administered within the first 10 days following presentation. Unfortunately, it is weak in reference to the severity of necrosis. Therefore, contrast CT and necrosis classification, found by Balthazar, were used simultaneously (CT Severity Index): grade 1: <30%, grade 2: 30-50% and grade 3: >50% necrosis (39). This scoring system was also modified later on. Radiological scoring systems assessing SIRS and organ dysfunction have been developed recently. In the extrapancreatic inflammation CT severity score (EPIC score), extrapancreatic organ findings (pleural effusion, mesenteric inflammation and retroperitoneal inflammation) instead of necrosis were assessed with CT (40).

This scoring system has a moderate to good inter-observer agreement. The simple prognostic scoring system was developed in 2007 (41). In this system, each of the parameters including serum BUN ≥25 mg/dL, LDH ≥900 IU/mL and necrosis with CT within 2 days (each is given one point). As the scores get higher from 0 to 3, so does mortality and morbidity (Table 1).

It is not always easy to document common bile duct stones during the early phase of biliary pancreatitis. Cholestatic enzymes and radiology are also not specific in this respect. Enzymes may be normal in 15-20% of the cases (42). Ultrasonography may fail in obese patients and due to excessive flatulence. CT's sensitivity is low: 40%. ALT levels three times the normal (>150 IU/L) was reported useful in diagnosis (43). Although magnetic resonance cholangiopancreatography (MRCP) is the most frequently used, it may not reveal the stone if the size of the stone is smaller than 5 mm (44). Endosonography (EUS) has a sensitivity of 89% and specificity of 96% for choledochal stone but its use is yet to be widespread (43).

Whether the guidelines are useful and how they influence the medical practice are other topics of interest. For instance, a study comparing the period before 2001 (during which the

French guideline was introduced) and the following seven years revealed that, in AP diagnosis, lipase levels was measured by 83% vs. 99% (before and after 2001), 48-hour CT by 29% vs. 69%, CT Balthazar scoring system was the most commonly used system by 55% vs. 76%, and that antibiotic prophylaxis and enteral artificial nutrition was necessary by 57% vs. 20% in AP and by 25% vs. 58% in necrotizing pancreatitis (45).

A study performed in 2014 revealed a positive relationship between in-hospital AP volume and patients' prognosis and outcome. Lower cost, shorter duration of hospital stay and less mortality were noted (using multiple scoring systems) in hospitals which admit large volumes of AP patients (average: 1-82 patient-years) (46).

In conclusion, acute pancreatitis is the most frequent diagnosis for admission to gastroenterology clinics and the management is costly. Our understanding of its pathogenesis is in evolution and, at this time, we know very little about it which is an impediment for management. Prediction of a severe course is a paradigm in this condition. However we are yet to achieve this: the scoring systems are yet to be sufficient. Finally, the patients managed in high volume centers fare better.

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