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Evidence-based management of pancreatitis

Review Article

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Abstract: Introduction. We review the most recent advances in the management of pancreatitis following publication of the latest clinical practice guidelines. The most significant innovations have taken place in the surgical treatment of pancreatitis, specifically regarding when a patient should be intervened and what procedure should be used. Moreover, changes that have occurred in the classification of pancreatitis seek to harmonize diagnostic criteria and facilitate comparisons among centers. Methods. We reviewed three of the latest guidelines and review articles published since 2008 following an electronic search through Medline, Embase and the Cochrane Library. Conclusions. Although diverse guidelines and review articles coincide on many key points, they need to be updated with regard to the numerous surgical innovations that have emerged recently in the management of pancreatitis.

Keywords: *Pancreatitis • Evidence based medicine • Review • Guidelines • Management • Diagnostic imaging • Treatment*

1. Introduction

Until now the management of pancreatitis has been largely governed by American, Japanese and British clinical guidelines. However, a number of innovations have emerged recently, the most important ones being: those related to its definition and classification; and changes in its surgical treatment. Our goal is to conduct a review of the most recent literature and analyze the changes that have taken place since the last guidelines were published.

2. Methods

Guidelines and review articles for acute pancreatitis were identified by electronic searches of PubMed, Medline and the Cochrane Library. The terms used for this search were: “pancreatitis”, “acute pancreatitis”, “guidelines”, “practice guidelines”, “management”, “classification”, “diagnosis” and “treatment”.

3. Results

3.1. Definition

Acute cases of pancreatitis (AP) have been classified in accordance with the Atlanta Classification (1992) [1], which recommended a clinically-based system. However, due to broad variations in the interpretation of radiological criteria, this classification system has not been applied strictly. In this context, Banks published a review that proposed three categories for classifying AP (mild, moderately severe, and severe), integrated new physiological and pathological concepts, and provided detailed definitions of local complications occurring in AP [2].

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In parallel, following an international consensus-based meeting in December 2012, a classification emerged that was based on determinants of severity, i.e., those factors which are causally associated with the severity of AP. The two principal factors identified as determinants of severity were: systemic complications centered on organ failure (absent, present and persistent) and local complications centered on necrosis (peripancreatic or pancreatic; sterile or infected) [3,4]. Table 1 presents a summary of those differences.

3.2. Clinical Diagnosis and Initial Presentation

- Key steps include: obtaining an etiological diagnosis and determining the seriousness of its presentation. In that regard, both American and Japanese guidelines agree on all points:
- • Clinical data, such as abdominal pain and vomiting, are as important in reaching a diagnosis as are elevations in pancreatic enzymes due to pancreatic necrosis (amylase and lipase). Almost all clinical guidelines prefer lipase because of its elevated sensitivity, thus, making it the most recommended for establishing a diagnosis (grade A recommendation) [5]. In the studies conducted, lipase's negative predictive value (NPV) oscillates between 94 and 100%; this assumes that while amylase may be normal in some cases, normal lipase values are next to impossible in the context of pancreatitis [6]. Studies are also being done with: serum and urinary trypsinogen-1, -2 and -3, phospholipase A2, pancreatic elastase, procalcitonin, trypsinogen activated protein, activation peptide of carboxypeptidase B, trypsin-2-alpha1 antitrypsin complex and circulating DNA. For many reasons, however, none of them have managed to establish themselves as a standard. One reason involves their inferiority to current diagnostic methods [7].

Table 1. Differences among classification criteria.

	ATALANTA CLASIFICATION (Bradley, 1993)	**WORKING GROUP** (Banks, 2012)	**DETERMINANT-BASED CLASSIFICATION** (Dellinger, 2012)
SEVERITY ASSESSMENT			
	Organ Failure: Shock, pulmonary insufficiency, renal failure or gastrointestinal bleeding	**Organ failure** (score of ≥2 in modified Marshall scoring system): • **Transient**: Organ failure in the same organ system for <48 hours • **Persistent**: Organ failure in the same organ system for ≥ 48 hours	**Systemic determinants**: Organ failure (score of ≥ 2 in SOFA): • **Transient**: Organ failure in the same organ system for <48 hours. • **Persistent**: Organ failure in the same organ system for ≥ 48 hours
	Systemic complications: DIC, severe metabolic disturbance (calcium ≤7.5 mg/dl)	**Systemic complications:** Exacerbations of underlying co-morbidities related to acute pancreatitis	
	Local complications: Necrosis, abscess, pseudocyst	**Local complications:** (peri) pancreatic fluid collections	**Local determinants:** (peri) pancreatic necrosis: • **Sterile** • **Infected**
	Prognostic signs: Ranson´s score ≥3, Apache II ≥8		
CLASSIFICATION OF SEVERITY			
	Mild: Minimal organ dysfunction, uneven recovery	**Mild:** No organ failure, no local or systemic complications	**Mild:** No (peri)pancreatic necrosis and no organ failure
		Moderately Severe: Transient organ failure and/or local or systemic complications without persistent organ failure	**Moderate:** Sterile (peri)pancreatic necrosis and/or transient organ failure
	Severe: Organ failure and/or local complications	**Severe:** Persistent organ failure (single or multiple)	**Severe:** Infected (peri)pancreatic necrosis or persistent organ failure
			Critical: Infected (peri)pancreatic necrosis and persistent organ failure

SOFA: Sepsis-Related Organ Failure Assessment; DIC: Disseminated Intravascular Coagulation

- An etiological diagnosis should be made within the first 48 hours, and attempts made to ensure that only 20% of the cases be classified as idiopathic (recommendation C) [5].
- Ultrasound findings are a good way to begin evaluating the biliary origin of the process (Grade C recommendation). However, a contrast-enhanced computerized axial tomography (CAT) is the test of choice when serious doubts exist regarding a case's clinical origin. Furthermore, in the most severe cases it's recommended that contrast-enhanced CAT scans be done during the first 48-72 hours from the onset of symptoms to evaluate the extent of pancreatic necrosis. This should be followed by another one if, over 6-10 days following admission, the patient presents persistent organ failure, signs of sepsis or clinical deterioration (grade B recommendation) [5].

3.3. Evaluating Risk

Performing a risk evaluation at the very beginning is essential to establishing appropriate treatment (grade A recommendation) [8]. Since no single method on its own is sufficiently sensitive and specific, risk evaluations must combine scoring scales, clinical assessment, and imaging tests (particularly contrast-enhanced TAC).

Scoring systems appear to have reached their maximum efficacy in predicting persistent organ failure in AP. A sophisticated array of combinations exists to predict it, but they are unwieldy and thus of limited utility. Therefore, unless new diagnostic approaches emerge [9,10], no improvements are expected regarding the capacity to predict a case's severity. American, Japanese and British guidelines all coincide in the use of APACHE II (Acute Physiology and Chronic Health Evaluation), which has a grade A recommendation. Even beyond that, recommendations include following the evolution of C-reactive protein (CRP) during the first 48 hours following admission (grade A recommendation) [8,11].

3.4. Transfer to ICU or Specialist Care

This is always indicated in the event of severe illness and for patients with extensive necrosis or other complications requiring follow-up in an intensive care unit; also for patients requiring interventional radiology, endoscopic or surgical (grade B recommendation) [8].

3.5. Image Testing

The reason for performing these tests is essentially practical: mild pancreatitis responds well to support treatment, while more severe cases require intensive monitoring and specific therapies, leading to a more complex prognosis. Contrast-enhanced TACs and Magnetic Resonance Imaging (MRI) are essential for determining risk (grade A recommendation). The classification system proposed by Balthazar [12] (Table 2) should be used (grade B recommendation) [8,13]. This scale focuses on the presence and degree of inflammation and necrosis. However, it does have its limitations. First: it doesn't always correlate with possible organ failure or with extrapancreatic parenchymal changes and/or vascular complications. Moreover, no differences are found in morbility and mortality between patients with 30-50% necrosis and those with over 50%. These are some of the reasons why other criteria, such as those of Mortelé [14], are proposed (see Table 3). They can be used to determine: the presence and number of collections and extent of necrosis, in addition to other extrapancreatic findings, such as pleural hemorrhage, ascites, extraparenquimatosic pancreatic anomalies (infarct, hemorrhage, or subcapsular collection), vascular complications (venous thrombosis, arterial hemorrhage or the formation of pseudo aneurisms), and the gastrointestinal system's involvement (inflammation, perforation, or intramural collection). Another proposed classification system is the EPIC scale (Extra-Pancreatic Inflammation on Computed Tomography) (Table 4). The goal of this scale is soley to assess the presence of systemic signs of inflammation (pleural hemorrhage, ascites, and retroperitonal inflammation) and use them to reach a prognosis. The EPIC score can be easily

Table 2. CT grading of severity. Modified from the International Association of Pancreatology and based on the paper of Blathazar et al [8].

a. CT grades

CT grade	Points
(A) Normal pancreas	0
(B) Edematous pancreatitis	1
(C) B plus mild extrapancreatic changes	2
(D) Severe extrapancreatic changes, including one fluid collection	3
(E) Multiple or extensive extrapancreatic collections	4
Necrosis	
None	0
Less than one third	2
Greater than one third or less than one half	4
Greater than one half	6

b. CT severity index (CT grade + necrosis score)

Severity index	Complications
0-3	8%
4-6	35%
7-10	92%
Deaths	
0-3	3%
4-6	6%
7-10	17%

Table 3. CT severity index and patient outcomes using a modified CT severity index. [8]

PROGNOSTIC INDICATOR	POINTS
Pancreatic inflammation	
Normal pancreas	0
Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat	2
Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis	4
Pancreatic necrosis	
None	0
≤30%	2
>30%	4
Extrapancreatic complications (one or more of the following: pleural effusion, ascites, vascular complications, parenchymal complications or gastro-intestinal tract involvement)	2

Table 4. The Extra-Pancreatic Inflammation on Computed Tomography (EPIC) score [8].

SIGNS OF EXTRAPANCREATIC INFLAMMATION	POINTS
Pleural effusion	
None	0
Unilateral	1
Bilateral	2
Ascites in any of these locations: perisplenic, perihepatic, interloop, pelvis	
None	0
One location	1
More than one location	2
Retroperitoneal inflammation	
None	0
Unilateral	1
Bilateral	2
Mesenteric inflammation	
Absent	0
Present	1

calculated without the need for post-processing analysis, thus making it more suitable for use by non-radiologists. Since it doesn't require the administration of intravenous contrast, it can also be used in patients at risk for or with acute kidney damage. The EPIC score evaluates the extent of the inflammation and probably, indirectly, the degree of injury to the patient, which is linked to the extent of multi-organ dysfunction.

3.6. Nutrition

Severe cases of pancreatitis can become complicated with a Systemic Inflammatory Response Syndrome (SYRS) and infectious syndromes. SYRS can provoke hypermetabolism and thus a catabolic state that can lead to malnutrition and an increased risk of developing sepsis and multi-organ failure. The goal is to guarantee sufficient caloric intake and reduce exocrine pancreatic secretion. Fasting can easily cause mucosal atrophy and facilitate bacterial translocation through the wall, conversely enteral feeding may be protective. This is why enteral nutrition (EN) should begin within the first 24-48 hours following admission, once the initial resuscitation phase has passed (grade A recommendation). Most clinical guidelines agree that nutrition support therapy (NST) is generally not needed for mild to moderate disease; NST is needed for severe disease; EN is preferred over parenteral nutrition (PN) (grade A recommendation); and they recommend using PN when EN is contraindicated or not feasible [5,13,15,16]. In severe acute pancreatitis it is also possible to combine PN and EN when adequate caloric support cannot be obtained by the enteral route alone (grade C recommendation) [8]. The recommendation to reinitiate feeding with a low-fat, solid diet applies when pain disappears; in fact, in mild acute pancreatitis immediate oral feeding is feasible and safe and may accelerate recovery without adverse gastrointestinal events [8].

3.7. Antiobiotic Prophylaxis

The use of antibiotic prophylaxis remains controversial and leading clinical guidelines differ in their recommendations. Currently available studies are inconclusive, although some of them do show certain benefits in the prophylactic use of antibiotics. The problem in establishing overall recommendations is that studies use different antibiotics, different selection criteria, different definitions for severe AP and different treatment cycles. This makes meta-analyses less reliable and requires a greater number of double blind, randomized, controlled trials. British guidelines, in those cases when antibiotics are given, recommend their maintenance for a maximum of 14 days (grade B recommendation); American guidelines don't recommend them and the Japanese consider it useful to employ broad-spectrum antibiotics in acute severe pancreatitis (grade A recommendation) [5,13,16]. Studies conducted following the publication of these guidelines, which included several meta analyses [18,19], don't provide any clear recommendations.

3.8. Actions on the Biliary Tract

All guidelines concur on the need to perform an endoscopic retrograde cholangio-pancreatography (ERCP) in AP cases of biliary origin with cholangitis or obstruction of the biliary pathway (grade A recommendation) [8]. This is confirmed in later reviews, which point out that a routine ERCP performed early does not affect mortality, nor local or systemic complications, independently of estimated severity [20,21].

3.9. Surgical Treatment

• Cholecystectomy: Laparoscopic cholecystectomy, or open, if necessary, should be done during the same hospital stay. Choledochotomy and common bile duct clearance should be performed as required (grade B recommendation). Laparoscopic cholecystectomy in mild gallstone-associated acute pancreatitis should be performed as soon as the patient has recovered and during the same hospital admission (grade B recommendation). In severe gallstone-associated acute pancreatitis, cholecystectomy should be delayed until there is sufficient resolution of the inflammatory response and clinical recovery (grade B recommendation) [8]. Later articles maintain this same stance [21,22].

• Necrosectomy: Ample recommendations have been made for the management of necrotizing pancreatitis, but no published guidelines have incorporated the many recent developments in minimally invasive techniques for necrosectomy. Most recent guidelines propose that once infected necrosis is confirmed in patients with signs and symptoms of sepsis, surgery or percutaneous drainage of the collection (radiological drainage) should be indicated (grade B recommendation). It is recommended that the definitive diagnosis of infected pancreatic necrosis be made with a fine needle aspiration in the presence of well-demarcated necrosis or combined with a minimally invasive surgical approach in selected cases (grade B recommendation). It is suggested that necrosectomy be done 14 days following the onset of pancreatitis, or in patients presenting with compartimental abdominal syndrome (grade B recommendation), and all the guidelines agree that necrosectomy is the best intervention (grade A recommendation). They also provide indications when the case presents sterile pancreatic necrosis: the patient should be managed conservatively and only be intervened in carefully selected situations in which the patient shows multi organ failure and no improvement despite maximal therapy in the intensive care unit (grade B recommendation) [8]. However, the optimal management of necrotizing pancreatitis continues to evolve. The question of the most appropriate surgical technique for the treatment of pancreatic necrosis remains unsettled. Developments in interventional radiology and other minimal access interventions have revolutionized the management of necrotizing pancreatitis. It is precisely here where most changes are appearing with regard to previous guidelines. Various types of minimally invasive interventions are described: endoscopic, radiology-assisted percutaneous drainage, and laparoscopic or retroperitoneal surgical techniques. And these interventions are beginning to be considered not only as measures that can delay a necrosectomy, but as alternative treatments that have led to better results in recent randomized controlled trials.

• In the Dutch group's most recent consensus meeting [23], the following recommendations were made: intervention is primarily indicated for infected necrosis, less often for symptomatic sterile necrosis, and should ideally be delayed as long as possible, preferably 4 weeks or longer after the onset of disease for better demarcation and liquefaction of the necrosis. They also note that a step-up approach, using percutaneous drainage followed by minimally invasive video-assisted retroperitoneal debridement and per-oral endoscopic necrosectomy, have been shown to have superior outcomes to traditional open necrosectomy with respect to short- and long-term morbidity, and are emerging treatments of choice [23-26]. Regardless, it is important to emphasize the need for better designed randomized studies; this will be one of the points with most changes over the next few years.

• Pancreatic abscesses: These are treated through surgery or percutaneous drainage (grade C recommendation). If clinical findings of a pancreatic abscess do not improve with percutaneous drainage, surgical drainage should be performed immediately (Recommendation B) [8].

4. Discussion

The most important changes that have appeared over recent years in the management of pancreatitis are those related to the definition of a case's severity, especially in its therapeutic management. The use of better definitions is important because existing ones have led to differences in patient classification and, consequently, make it more difficult to compare results across those studies that have been done. Insofar as treatment is concerned, the development of interventionist radiology and minimally invasive techniques have unleashed a revolution in the management of the most severe cases, delaying, and even avoiding, the need to perform necrosectomies.

Conflict of interest statement

Authors state no conflict of interest.

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