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Unresolved Issues about Post-ERCP Pancreatitis: An Overview

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Summary

Pancreatitis represents the most common and feared complication after endoscopic retrograde cholangio-pancreatography. Since the introduction of ERCP into clinical practice, many attempts have been made to identify the mechanisms and conditions that can place patients at risk of developing post-procedure pancreatitis, with conflicting and in most cases unsatisfactory results. The following questions about post-ERCP pancreatitis still remain unanswered: the knowledge of the mechanisms involved in the onset of pancreatitis, procedural factors that can induce pancreatic damage, patient conditions that can increase the risk of developing pancreatitis in the post-procedure period, criteria for predicting the occurrence of pancreatitis, and possible methods of preventing the complication. Moreover, the criteria used to define post-ERCP pancreatitis differ in various studies and, consequently, there is a wide variation in the literature of the incidence of this complication and it is still not clear what its real incidence is.
In the last six years, a significant advance in knowledge has been achieved in most of the above-mentioned fields. Four large prospective multicentre trials seemed to definitely identify patient- and technique-related risk factors that can place patients at risk of developing post-ERCP pancreatitis; clinical conditions, procedure- and patient-related factors, and laboratory tests able to predict the occurrence of post-ERCP pancreatitis in the early phase have been identified. An attempt to identify criteria for defining post-ERCP pancreatitis has also been carried out, although these proposed criteria have not been widely adopted by all Authors.

Introduction

Acute pancreatitis still represents the most frequent and feared complication after procedures involving the papilla of Vater; the overall reported incidence of this complication varies from less than 1% up to 40%, but mean rates of about 5% are reported in most studies involving non-selected patients. Although most episodes of post-ERCP pancreatitis are mild, a small percentage of patients may develop severe pancreatitis resulting in prolonged hospitalization, intensive unit care and utilization of major hospital resources; these patients have also a significant morbidity and mortality.
Since the introduction of diagnostic and therapeutic ERCP into clinical practice, many attempts have been made to understand both the aetiopathogenetic mechanisms and the risk factors leading to post-procedure pancreatitis in order to predict and possibly prevent this complication. Unsettled issues about post-ERCP pancreatitis include the comprehension of the mechanisms involved in its occurrence and the identification of possible factors or clinical conditions that may influence its incidence. Identification of factors potentially able to affect the incidence

of pancreatitis and to predict which patients go on to develop such a complication is therefore of paramount importance in clinical practice. Another unsettled issue is the definition of post-ERCP pancreatitis; the different criteria adopted and the case mix probably account "*per se*" for the different incidence rates reported in the literature.

Identification of the Mechanisms Involved in the Onset of Post-ERCP Pancreatitis

The knowledge of the mechanisms involved in the early phase of onset of acute pancreatitis plays a pivotal role in the search for both laboratory tests able to predict pancreatitis and pharmacological prophylaxis and the therapy for this complication.
In experimental models of acute pancreatitis, it has been suggested that digestive enzyme activation might occur within acinar cells and it has been shown that, in the early stages of acute pancreatitis, there is a co-localization of digestive enzymes and lysosomal hydrolases within large cytoplasm vacuoles. This co-localization mechanism might result in the activation of the digestive enzymes, mainly trypsin. When trypsinogen is converted to trypsin, trypsinogen-2, trypsinogen activation factor (TAP) and bound trypsin 2 alpha-1-antitrypisin complex (trypsin 2-AAT) are generated and released into the blood; these markers of proteolytic activation can be measured either in serum or urine and used as early predictors of pancreatic reaction. Later in the inflammatory process, various interleukins and C-reactive protein can be used as inflammatory markers to monitor the course of the pancreatitis and predict the severity of the disease. Drugs potentially able to reduce the proteolytic activation and modulate the inflammatory response of the gland have therefore been tested both in the prevention and in early treatment of post-ERCP pancreatitis.
Whether or not mechanical or chemical factors are "*per se*" able to activate the proteolytic activation is still a debated question.

Cannulation trauma to the papilla is the most common cause of sphincter of Oddi spasm and/or papillary oedema, thus creating an obstacle to the flow of pancreatic juice with subsequent acute pancreatic inflammation. The importance of this mechanism in the development of acute pancreatitis has recently been highlighted in a study [1] showing that, although the frequency of sphincterotomy-induced pancreatitis was significantly higher than that of post-ERCP pancreatitis, the frequency of severe pancreatitis within 48 hours and the worsening of pancreatitis after 48 hours was significantly lower within the group of patients who had undergone sphincterotomy; the severity of post-procedure pancreatitis is therefore mitigated by the lowering of the intraductal pressure obtained by sphincterotomy.
Other conditions that lead to a reduction or a rise of intraductal pressure, such as a patent minor papilla and dorsal duct, or high volume and pressure of injected contrast have been reported to be associated with a lower or higher incidence of post-ERCP pancreatitis, respectively. On the other hand, intraductal lesions determined by deep cannulation do not seem to be able to induce pancreatitis and opacification of the main pancreatic duct alone is associated with an incidence of hyperamylasemia similar to that induced by cholangiography alone. This suggests that mechanical trauma in the duct is a less important cause of hyperamylasemia and pancreatitis than increased intraductal pressure.
The contrast media used for pancreatography can also induce pancreatitis. The osmolarity and ionic nature of the contrast media are believed to be responsible for the occurrence of post-procedure pancreatitis. Contrast media may also activate the conversion of trypsinogen into trypsin in the pancreatic juice. However, results of previous studies comparing different contrast media have been inconclusive; of the several prospective randomized studies which have attempted to compare the frequency of pancreatic enzyme level elevation, clinical pancreatitis and the

quality of pancreatograms with low- and high-osmolarity agents, some have suggested that low-osmolarity media were safer whereas others have shown no difference between the media used.
Other possible causes of post-ERCP pancreatitis are the introduction of activated intestinal enzymes and bacteria into the pancreatic ductal system by ERCP maneuvers. If enzyme activation and bacterial infection are causes of post-ERCP pancreatitis, enzyme inhibitors and antibiotic prophylaxis might have a therapeutic role.

Predicting Post-ERCP Pancreatitis

Predicting the risk of developing pancreatitis before the procedure and its occurrence in the early phase once the procedure has been performed, is useful in adequately informing the patients about their own risk before they are asked to provide informed consent, in predisposing prolonged hospital admission if the procedure is done in an outpatient setting or in prescribing the appropriate therapy.
Since the introduction of ERCP into clinical practice, attempts have been made to identify potential conditions that place the patient at increasing risk of developing post-procedure pancreatitis. Current practice and single-centre studies, either retrospective or prospective, have identified a number of high-risk conditions, either patient- or procedure-related. In recent years, four large, prospective, multicentre studies gave important contributions in this field with partially conflicting results [2, 3, 4]. The last study by Freeman *et al*. [5] definitely identified a previous history of post-ERCP pancreatitis, suspected sphincter of Oddi dysfunction, female gender, normal serum bilirubin and normal pancreas as patient-related risk factors, and biliary sphincter balloon dilatation, difficult cannulation, pancreatic sphincterotomy and repeated injection of pancreatic ductal system as independent procedure-related risk factors at multivariate analysis. Interestingly, sphincter of Oddi manometry has not been confirmed to be "*per se*" an independent risk factor. Other suggested conditions such as patient age, small duct diameter and low case volume have been reported in some of the previous multicentre studies but need further confirmation.
In the post-procedure period, efforts have been made to try to identify those patients who will go on to develop pancreatitis. Early prediction of the occurrence of pancreatitis may be achieved by clinical assessment, laboratory tests or by a combined clinical and laboratory approach. Clinical assessment alone (i.e. pancreatic-type pain) is not useful since pain in the post-procedure period may occur for several non-pancreatitis-related reasons. As post-ERCP pancreatitis can take some hours to present clinically, the evaluation of pain alone in the first hours after the procedure is not useful "*per se*" in predicting the occurrence of the complication. The duration of pain is crucial for defining pancreatitis, since the disappearance of pain within 24 hours is unlikely to indicate pancreatitis.
Attempts have been made to investigate the role of laboratory tests as predictors of post-ERCP pancreatitis. Three categories of tests may be used: markers of pancreatic injury, proteolytic activation, and systemic inflammation.
Serum pancreatic enzymes rise in reaction to manipulations during ERCP in more than 70% of patients. In the absence of pancreatitis, serum amylase levels peak at 90 minutes to 4 hours after ERCP and return to normal levels within 24-48 hours. Although serum amylase is commonly elevated in uncomplicated ERCPs, the swiftness and degree of elevation is much more marked in patients who develop post-ERCP pancreatitis. However, serum amylase elevation can be considered predictive for acute pancreatitis only if associated with pancreatic-type pain. A 4-hour post-ERCP amylase level less than 1.5 times the upper normal level has been reported predictive in ruling out the risk of developing pancreatitis (negative predictive value 100%) whereas an amylase level greater than 3 times or more the upper normal limit should be considered a predictor of ongoing

pancreatitis [6]. Two-hour and six-hour serum amylase levels greater than six times and five times the upper normal limit, respectively, have been reported highly predictive for post-ERCP pancreatitis [7, 8]. Urine amylase has been also used to predict post-ERCP pancreatitis. The test was 79% sensitive and 89% specific for the diagnosis of pancreatitis.
Trypsinogen-2 has been found to be markedly elevated in the serum and urine of patients with acute pancreatitis. Elevated trypsinogen-2 levels were documented as early as 1 hour after ERCP; this peaked at 6 hours in patients with pancreatitis. Additionally, the rise in level seemed to correlate with the severity of the pancreatitis. A three-fold rise in trypsinogen 2 at 1 hour was reported to have a 74% sensitivity and an 87% specificity. Trypsinogen-2 levels in the urine have also been investigated as potential markers; the rapid urinary trypsinogen-2 test in the diagnosis of post-ERCP pancreatitis carried out 6 hours after the procedure, showed a 81% sensitivity and a 90% specificity. A negative urine dipstick test carried out 6 hours after the procedure seems therefore to be highly reliable for excluding pancreatitis. On the other hand, the bound trypsin 2-alpha-1-antitrypsin complex (trypsin 2-AAT) did not show a clear rise until 24 hours after ERCP. Trypsinogen activation peptide (TAP) is generated in the pancreas when trypsinogen is converted to its active form, trypsin. Plasma and urine levels of TAP have been found to be elevated and predictive of the development of acute pancreatitis; however, in a study specifically involving post-ERCP patients, urinary TAP 4 hours after the procedure was not found to be useful in predicting mild pancreatitis.
A drawback of using these markers is the lack of specificity, as many other conditions including biliary and pancreatic malignancies, pseudocysts and cholangitis can cause elevations. Moreover, laboratory markers have been shown to be predictive for post-ERCP pancreatitis only 6 hours after the procedure; at the same time, clinical and laboratory evaluation have also been found to adequately predict the risk of pancreatitis. For these reasons, proteolytic markers are not widely used in clinical practice in most centers.
C-reactive protein is an acute phase reactant synthesized by hepatocytes. It has been shown to be elevated in patients with acute pancreatitis, but serum levels have been shown to be greatly elevated only at 48 hours post procedure. C-reactive protein accurately predicts disease severity, but it appears to be a late marker. Serum Interleukin (IL-6, IL-10) levels seem to be indicative of the degree of pancreatic injury and inflammation, but few studies are currently available and these markers have been used only for investigational purposes.
In conclusion, we have sufficient data to believe that, at present, the risk of pancreatitis can be predicted in a large proportion of cases on the basis of either well-known patient- and procedure-related conditions or 4 to 6-hour combined clinical and laboratory approaches.

Definition of Post-ERCP Pancreatitis

The definition of post-procedure pancreatitis still remains a controversial issue in the field of post-ERCP/sphincterotomy complications, due to the different parameters and criteria adopted. This leads to a varying incidence of pancreatitis in published series. The varying incidence of post-procedure pancreatitis may reflect, on the one hand, differences in patient populations, indications and endoscopic expertise and, on the other, different definitions of pancreatitis and methods of data collection. However, apart from studies in selected series of high-risk patients for post-procedure pancreatitis, most studies involve a variety of patients (at either higher or standard risk of developing post-procedure pancreatitis – mostly the latter) and are done by skilled endoscopists. Therefore, differences in data collection methods or in the definition of pancreatitis likely play a large part in the figures for post-ERCP pancreatitis.
Attempts were made a few years ago to establish reliable criteria for defining this complication, leading to a consensus statement based on more than 15,000

procedures [9]; 24-hour persisting pancreatic-type pain associated with a three-fold increase above the normal serum amylase levels were proposed to be consistent for post-ERCP pancreatitis. Length of hospitalization and occurrence of local or systemic complications were used as criteria for establishing the severity of the disease; pancreatitis was defined mild or moderate when no complications occurred and when less than three days or between three and ten days of hospitalization were required, respectively; severe when either local or systemic complications occurred and more than ten days of hospitalization were required. However, the criteria proposed have not been widely adopted since then, even in some of the largest series published.

The continuing search for reliable criteria for defining pancreatitis probably reflects endoscopists' difficulty in establishing which parameters fulfil the need of identifying cases with real pancreatic damage, in practice.

It is generally agreed that epigastric pain irradiating to the back in the post-procedure period is a reliable indicator of some pancreatic involvement, whereas the amplitude of the serum enzymatic rise, whether associated or not with pain, is still a more questionable issue. However, problems related to the role of pancreatic pain and high enzyme levels as indicators of acute pancreatitis are their duration and entity. It has been proposed that epigastric pain, as an indicator of pancreatitis in the postprocedure period, must persist for at least 24-48 hours, or should require a hospital stay of more than 48 hours. The duration of pain is crucial for defining post-procedure pancreatitis, since pain disappearing within 24 hours is unlikely to indicate clinical pancreatitis, and is more probably due to some transient pancreatic reaction or other causes, such as intolerance to air inflation during the procedure. Moreover, pain persisting for 24 hours, but disappearing within the subsequent 12-24 hours and not requiring a prolonged hospital stay, still does not fulfil the criteria for defining pancreatitis.

Severity of pain could also be a parameter in the classification of pancreatitis. However, in most reports, it has neither been graded nor standardized and its reliability remains uncertain since subjective evaluation makes it difficult to define the degree. One aspect could be the need for narcotics whose request is again patient-dependent.

The amplitude and duration of postprocedure serum enzymatic rise associated with pancreatic pain are further points in the definition and grading of a pancreatic reaction. Hyperamylasemia "*per se*" cannot be considered a complication, unless the patient also has pain and other signs of pancreatitis. The rise in serum enzyme levels may vary considerably, without clinical significance. Serum amylasemia more than five times the upper normal limit lasting for 24 hours after the endoscopic procedure, although suggesting some pancreatic involvement, may occur without clinical symptoms in about one-third of patients, whereas only in about one-third of these cases is there also evidence of computed tomography (CT) scan-confirmed pancreatitis. Patients with 4 to 6-hour hyperamylasemia greater than three times the upper normal limit are generally carefully monitored with a prolonged hospital stay in many centers, independent of the occurrence of a true pancreatitis. This aspect further contributes another confusing factor in the definition and evaluation of pancreatitis and confirms how difficult it is to interpret the wide variability in serum enzymatic rises, when there is no typical pancreatic pain or when patients report only mild 24-hour discomfort, without confirmation of the pancreatitis by imaging techniques.

Procedure-related hospital stay has also been considered in defining the occurrence and severity of pancreatitis; prolongation of planned admission by 2-3 days is generally considered an indicator of postprocedure pancreatitis, and its severity is based on the duration of the hospital stay. On the other hand, the Atlanta classification for pancreatitis severity classifies such a

complication as mild or severe on the basis of the absence or presence of local (documented by CT scan) or systemic complications, independently of the duration of the hospital stay [10]. The different modalities of follow-up for patients or the different clinical significance attributed to pain and severe hyperamylasemia could account for variable prolongation of the hospital stay and therefore for differences in the incidence of cases considered to have pancreatitis.

Key words Acute Disease; Acute-Phase Proteins; Cholangiopancreatography, Endoscopic Retrograde; Enzymes; Pancreatitis; Pancreatitis, Acute Necrotizing; Risk Factors; Sphincterotomy, Endoscopic

Abbreviations 2-AAT: 2 alpha-1-antitrypisin; CT: computed tomography; IL: interleukin; TAP: trypsinogen activation peptide

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