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# Prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis

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## 1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is an essential modality for the diagnosis and therapy of pancreatobiliary disease. However, complications of ERCP-related procedures are also common. Post-ERCP pancreatitis (PEP), the most common and potentially serious complication of ERCP-related procedures, occurs in 1 - 9% of all procedures (1-16). Moreover, the PEP rate increases to 10 - 40% in cases with risk factors (1-16). In most cases, PEP is generally mild and requires only conservative treatment. However, substantial complications, occasionally fatal, can occur. Therefore, it is imperative to establish a strategy for preventing PEP based on medical, social, and economical circumstances. The prevention of PEP, according to various studies, is presently based on the elucidation of its underlying mechanisms, the identification of its risk factors, the administration of pharmacological drugs, and endoscopic procedures such as pancreatic stenting.

## 2. Mechanisms of post-ERCP pancreatitis

Various mechanisms of PEP have been suggested (1-25), which include obstruction of the outflow of pancreatic juice due to papillary edema or spasm of the sphincter of Oddi after ERCP procedures, chemical injury due to the injection of contrast material or leakage of intestinal juice to the pancreatic duct, mechanical injury of the pancreatic duct caused by the deep cannulation of a catheter and related devices including a guidewire, hydrostatic injury from the rise of pressure in the pancreatic duct due to repeated pancreatography with contrast agents, or the infusion of water or saline solution in manometry and pancreatic scope procedures, and thermal injury of the pancreas causing papillary edema due to radiofrequency ablation (**Table 1**). One of the most likely mechanisms is impaired drainage from the pancreatic duct caused by papillary edema or spasm of the sphincter of Oddi after ERCP procedures (10-14,19,22,25). Another is local injury of the papilla and pancreatic duct as a result of ERCP procedures, or forceful and repetitive contrast injections causing local inflammation (1-20,26). This may lead to premature intracellular activation of proteolytic enzymes, consequently causing further damage and local inflammation as indicated by

increased levels of cytokines, and possible initiation of a systemic inflammatory response with multi-organ involvement (1,10,11,13).

Papillary edema	Rise in pressure in the pancreatic duct due to retention of pancreatic juice accompanying papillary edema or spasm of the sphincter of Oddi after ERCP
Mechanical injury	Damage to the pancreatic duct due to deep cannulation with a catheter and related devices such as a guidewire
Hydrostatic injury	Rise in pressure in the pancreatic duct due to repeated pancreatography with a contrast agent or the infusion of water or saline solution in manometry and pancreatic scope procedures
Chemical injury	Injection of contrast agents and intestinal juice leakage to the pancreatic duct
Thermal injury	Inflammation of the pancreas causing papillary edema due to radiofrequency ablation

Table 1. Suggested mechanisms of post-ERCP pancreatitis

3. Risk factors of post-ERCP pancreatitis

PEP can be prevented by careful patient selection with full consideration of the risk factors for PEP. Previous researchers have reported several factors which may increase the risk of PEP (1-27). A meta-analysis of 15 prospective cohort studies and 52 retrospective cohort studies previously evaluated and elucidated the risk factors of PEP.

Freeman et al. (1,2) reported that the high risks of PEP were associated with both patient-related risk factors and procedure-related risk factors on multivariate analysis of prospective studies and meta-analyses (Table 2). In their review, they advocated special caution in performing ERCP-related procedures in patients with specific patient-related risk factors (e.g., young age, female gender, suspected sphincter of Oddi dysfunction (SOD), prior PEP, recurrent pancreatitis, and absence of chronic pancreatitis) and procedure-related risk factors (e.g., pancreatic duct injection, pancreatic sphincterotomy, balloon dilation of an intact biliary sphincter, difficult or failed cannulation, and pre-cut (access) sphincterotomy).

Young age
Female gender
Suspected sphincter of Oddi dysfunction (SOD)
Prior post-ERCP pancreatitis
Recurrent pancreatitis
Absence of chronic pancreatitis
Pancreatic duct injection
Initial pancreatography
Two or more pancreatic duct injections
Pancreatic sphincterotomy
Minor papilla sphincterotomy
Balloon dilation of intact biliary sphincter
Difficult or failed cannulation
Pre-cut (access) sphincterotomy
Procedure time ≥ 30 min
Pancreatic tissue sampling by any method
IDUS (pancreatic duct)
Trainee involvement
Non-placement of pancreatic stent after ERCP procedures

Table 2. Risk factotrs of post-ERCP pancreatitis on multivariate analysis

Cheng et al. (3) also reported the risk factors of PEP in a large prospective multivariate analysis as patient-related risk factors (e.g., suspected SOD, a history of PEP, and young age (< 60 yrs)) and procedure-related risk factors (e.g., previous minor papilla sphincterotomy, pancreatic duct injections of 2 or more, and trainee involvement).

We previously (28) identified the risk factors of PEP on multivariate analysis as procedure-related risk factors such as initial pancreatography, non-placement of a pancreatic stent (PS) after ERCP procedures, procedure time of 30 min or more, pancreatic-tissue sampling by any method, pancreatic-intraductal ultrasonography (IDUS), and difficulty of cannulation ( $\geq 15$  min). Moreover, we evaluated the correlation between the number of risk factors and PEP. We found a statistically significant association between PEP and the number of risk factors ( $P = 0.011$ ), and the frequency of PEP was statistically significant when there were more than 3 risk factors ( $P = 0.001$ ).

Special consideration should be taken for risk factors, as indicated by multivariate analysis and meta-analysis, in performing ERCP-related procedures, although these procedures also involve comparatively wide-ranging variables such as the experience of the endoscopist.

## 4. Prevention attempts

To date, there have been several attempts to prevent PEP in terms of patient selection considering the risk factors of PEP, pharmacological drug administration and endoscopic procedures.

### 4.1 Pharmacological prophylaxis

Chemoprophylaxis to reduce the synthesis and secretion of proteolytic enzymes (octreotide or somatostatin), protease inhibitors (gabexate mesilate, ulinastatin, nafamostat, or aprotinin), antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to prevent PEP (1,29-42) (Table 3). Numerous randomized controlled trials (RCTs) and several meta-analyses have been performed to evaluate the efficacy of pharmacological drugs for preventing PEP. Freeman et al. evaluated and reviewed the results of previous studies (1), and found that most of these studies failed to show clearly the efficacy of pharmacological drugs, although some promising drugs for preventing PEP were indicated. However, their results should be interpreted in consideration of a lack of unified study design, for example, the selection of high-risk cases, mixed high-risk and non-high-risk cases, and a variety of criteria to define PEP. The outcomes varied and there is as yet no consensus on whether or not chemoprophylaxis is useful for preventing PEP.

#### 4.1.1 Gabexate mesilate

Andriulli et al. (29) demonstrated that gabexate mesilate was effective for PEP evaluation. However, they found that the prophylactic use of gabexate mesilate did not prevent ERCP-related pancreatic damage, even in patients at high risk for PEP in an additional study of the same subject group. Four other meta-analyses (29-32) of RCTs clearly showed that gabexate mesilate was ineffective in preventing PEP, (odds ratio [OR], 0.67; 95% confidence interval [CI], 0.31 – 1.47) and that it was not useful in preventing severe pancreatitis, death, hyperamylasemia, or abdominal pain (30). On the other hand, another meta-analysis which

considered the administration schedule (31) showed that the incidence of PEP after long-term infusion (12 h) of gabexate mesilate was significantly decreased by 5.2% (95% CI, 1.1 – 9.4, P = 0.01), although an examination of short-term infusion (within 12 h) failed to show its usefulness in PEP.

Medication	Assessment	Meta-analyses	RCTs
Gabexate mesilate (long-term infusion)	Effective		
Nitroglycerin	Possibly effective		
Antibiotics	Possibly effective		
NSAIDs	Possibly effective	Effective	
Somatostatin (long-term infusion)	Possibly effective	Possibly effective	
Somatostatin (bolus injection)		Effective	
Gabexate mesilate (short-term infusion)	Ineffective	Ineffective	Effective
Ulinastatin			Possibly effective
Semapimod			Possibly effective
Octreotide	Ineffective	Ineffective	
Somatostatin (short-term infusion)	Ineffective	Ineffective	
Calcium inhibitors	Ineffective		
Lidocaine (local administration)	Ineffective		
Nonionic contrast medium	Ineffective		
Steroids	Ineffective	Ineffective	
PAF inhibitors	Ineffective		
IL-10	Ineffective		
Heparin	Ineffective		
Allopurinol	Ineffective	Ineffective	
N-acetylcysteine			Ineffective
RCT, randomized controlled trial; PAF, platelet activating factor; IL, interleukin; NSAIDs, nonsteroidal anti-inflammatory drugs		Refs. (1,42) with alterations	

Table 3. Pharmacological interventions to reduce risk of post-ERCP pancreatitis

4.1.2 Ulinastatin

Tsujino et al. (33) in their multicenter RCT showed that ulinastatin significantly lowered the incidence of PEP in the ulinastatin-administered group compared with the control group (2.9% vs. 7.4%, P = 0.041). Another RCT, which compared a group given a high dosage of ulinastatin (450,000 U) with a group given a low dosage of ulinastatin (150,000 U) and a group administered gabexate mesilate (900 mg) showed PEP rates of 6.5%, 8.5%, and 4.3%, respectively, indicating no significant differences among the groups (34). Ueki et al. conducted a RCT which compared a group given ulinastatin (150,000 units) and a group given gabexate mesilate (600 mg) and demonstrated a similar PEP rate in both groups, indicating no difference between the 2 groups (35). Chen at al. in their meta-analysis (36) showed that the incidence of PEP was significantly reduced by ulinastatin (OR, 0.53; 95% CI, 0.31 - 0.89; P = 0.02), as well as the incidence of hyperamylasemia (OR, 0.42; 95% CI, 0.30 - 0.59; P < 0.00001); however, subsequent sensitivity and subgroup analyses produced conflicting results. The authors concluded that ulinastatin had value in preventing PEP in average-risk patients when administered intravenously at a dose of at least 150,000 U, given immediately before ERCP.

#### 4.1.3 Somatostatin and octreotide

A meta-analysis (32) of 9 RCTs showed a PEP rate of 7.3% in control groups and 5.3% in the groups administered somatostatin and octreotide (OR, 0.73, 95% CI, 0.54 – 1.006; relative risk [RR], 0.734, 95% CI, 0.535 – 1.006), indicating no significant difference between the 2 groups. In contrast, a different meta-analysis (31) showed that in terms of the administration schedule of somatostatin, long-term infusion (12 h) was associated with a decrease in PEP rate by 7.7% (95% CI, 3.4 – 12.0;  $P < 0.0001$ ). Short-term infusion (within 12 h) of somatostatin failed to show usefulness in preventing PEP. A study with bolus injections revealed that a bolus injection of somatostatin significantly reduced the PEP rate by 8.2% (95% CI, 4.4 – 12.0;  $P < 0.0001$ ). A meta-analysis of the bolus injection groups in 3 other RCTs showed that a bolus injection of somatostatin was useful in preventing PEP (OR, 0.271, 95% CI, 0.138 – 0.536; difference in incidence 8.2%, 95% CI, 4.4 – 12.0; number needed to treat [NNT] = 12, 95% CI, 8 – 23).

A meta-analysis of 15 RCTs involving octreotide demonstrated that the overall examination of 2,621 cases failed to show the usefulness of octreotide in preventing PEP (OR, 0.78; 95% CI, 0.57 – 1.08) (38). However, when the analysis was limited to a total of 1,714 cases including the cases in 5 RCTs in which more than 200 cases were studied, it was shown that the PEP rate was significantly decreased by octreotide (OR, 0.50; 95% CI, 0.32 – 0.79;  $P = 0.003$ ; NNT, 31).

#### 4.1.4 Nonsteroidal anti-inflammatory drugs

A meta-analysis of 6 RCTs involving the administration of NSAIDs showed that the PEP rate was significantly lower in the NSAID-administered group (8.9% vs. 16.8%; OR, 0.46; 95% CI, 0.32 – 0.65;  $P < 0.0001$ ) (39). Of these 6 RCTs, a meta-analysis of 4 RCTs evaluating a rectally administered drug showed that the single use of NSAIDs just before or after ERCP was useful in preventing PEP (4.4% vs. 12.5%; RR, 0.36; 95% CI, 0.22 – 0.60; NNT, 15) (40). A subgroup analysis of the same 4 RCTs demonstrated that in the NSAID-administered group, there was a significant decrease in the PEP rate in both the low-risk group (RR, 0.29; 95% CI, 0.12 – 0.71;  $P = 0.006$ ) and the high-risk group (RR, 0.40; 95% CI, 0.23 – 0.72;  $P = 0.002$ ) (41).

Allopurinol, steroids, N-acetylcysteine, and mitogen-activated protein kinase inhibitors all failed to show a significant preventative effect in PEP (42).

#### 4.1.5 Endoscopic procedures

Careful pancreatic duct injection and avoiding cannulation trauma are essential in performing ERCP-related procedures. Moreover, the placement of a PS with internal and external flanges, or a nasopancreatic drainage tube (9,10) has been performed. To prevent PEP, some endoscopists have inserted a naso-pancreatic drainage tube into the pancreatic duct (9,10) or employed a flanged PS, apparently not considering the possible advantages of spontaneous dislodgement (10-14,19,20). A temporary PS has recently become commercially available and has been reported to be effective in preventing PEP (1,15,17-20,25). PSs are classified into those with and without flanges on the pancreatic ductal side. The former is unlikely to naturally dislodge, and endoscopic removal is often necessary. As for the latter unflanged PS, the rate of natural dislodgement within a short period is high (1,17,25), and re-insertion of an endoscope for removal is generally unnecessary.



Several, mainly non-prospective, randomized studies (9-12,14,18-21) have evaluated endoscopic drainage using a PS with flanges on both sides, unlike our pancreatic duct spontaneous dislodgement stent (PSDS), for preventing PEP in high-risk patients (Table 4). The results suggested that the frequency of PEP decreased, and the PS provided a maintained drainage route when the papilla was blocked as a result of edema, or spasm of the sphincter of Oddi, or both, after the procedure.

Recently, Freeman et al. (17) found that the insertion of a PS in high-risk patients reduced the frequency of PEP by 4 - 23%. In contrast, Smithline et al. (12) reported that PS insertion did not confer a significant beneficial effect in patients with previous biliary sphincterotomy.

Sofuni et al. conducted 3 RCTs (15,28,43) to prospectively evaluate the usefulness of PSDS for PEP prophylaxis. In a preliminary single-center RCT (15), they evaluated PEP prophylaxis using the same unflanged 5-Fr PSDS in 80 consecutive patients, including those who underwent simple ERCP and those who received additional manipulation of the papilla through several stressful examinations including manometry, IDUS, and aspiration of pure pancreatic juice (PPJ). The trial revealed that a temporary unflanged 5-Fr PS reduced the frequency of PEP.

Study (yr)	Study design	No. of patients	Procedures	Pancreatitis rate		
				Non-PD stent	PD stent	P
Smithline, 1993	RCT*	93	Precut biliary ES, SOD, small ducts	18%	14%	0.299
Sherman, 1996	RCT (abstract)	93	Precut biliary ES	21%	2%	0.036
Vandervoort, 1996	(abstract)	127	Pancreatic duct manipulation	18%	8.3%	>0.05
Tarnasky, 1998	RCT	80	Biliary ES for SOD	26%	7%	0.03
Elton, 1998	Retrospective, c.c. <sup>‡</sup>	194	Pancreatic ES for all indications	12.5%	0.7%	<0.003
Patel, 1999	RCT (abstract)	36	Pancreatic ES for SOD	33%	11%	>0.05
Vandervoort, 1999	Prospective, c.c.	42	Pancreatic brush cytology	28.1%	0%	0.08
Aizawa, 2001	Retrospective, c.c.	40	EPBD for stone removal	6%	0%	0.11
Fogel, 2002	Retrospective, c.c.	436	Biliary +/- pancreatic ES for SOD	28.2%	13.5%	<0.05
Norton, 2002	Retrospective, c.c.	28	Endoscopic ampullectomy	11.1%	20%	>0.05
Fazel, 2003	RCT	76	Difficult cannulation, ES, SOD	28%	5%	<0.05
Freeman, 2004	Prospective, c.c.	225	Pancreatic stent in high risk therapeutic ERCP	66.7%	14.4%	0.06
Catalano, 2004	Retrospective, c.c.	103	Endoscopic ampullectomy	16.7%	3.3%	0.10
Rashdan, 2004	Retrospective, c.c.	2283	SOD, divisum therapy, precut ES	N.A.	7.6-14.6**	N.A.
Tsuchiya, 2007	RCT*	64	All patients needed ERCP procedures	28.1%	6.2%	0.02
Sofuni, 2007	RCT*	201	All patients needed ERCP procedures	13.6%	3.2%	0.019
Sofuni, 2011	RCT*	426	15 risk factors for post-ERCP pancreatitis	15.2%	7.9%	0.021

\*Randomized controlled trial, <sup>‡</sup> case control; SOD, sphincter of Oddi dysfunction; ES, endoscopic sphincterotomy; EPBD, endoscopic balloon dilation; PD, pancreatic duct; N.A., not available; \*\*, evaluation of stent characteristics on the rate of post-ERCP pancreatitis

Ref. (1) with alterations

Table 4. Studies of pancreatic atent for prevention of post-ERCP pancreatitis

A multi-center RCT (43) of 6 endoscopy units based on a previous study (15) demonstrated that the insertion of PSDS significantly reduced the frequency of PEP (3.2% vs. 13.6%, P =0.019). In particular, in cases of hyperamylasemia, the placement of a PSDS significantly reduced the mean serum amylase level (767 vs. 1364 IU/l). This previous study clearly showed the efficacy of PSDS in preventing PEP.

Finally, another RCT (28) conducted in 37 large endoscopic units evaluated whether or not the placement of a PSDS would prevent pancreatitis after ERCP-related procedures in

patients with any of the risk factors for PEP, as well as identified risk factors for PEP. The results demonstrated that the placement of a PSDS significantly reduced the frequency of PEP in the analysis, excluding invalid cases (7.9% vs. 15.2%,  $P = 0.021$ ). A total of 6 risk factors for PEP were identified.

Four meta-analyses (13,44-46) for prophylactic PS placement and PEP indicated that prophylactic temporary stent placement significantly reduces the risk of PEP.

A meta-analysis by Andriulli et al. (44) showed that PEP developed in 16.5% of controls, and in 5.1% or 9.6% of the stent group on per-protocol (PP) or intention-to-treat (ITT) analyses. Analysis of 4 RCTs showed that PEP developed in 24.1% of controls, and in 6.1% or 12.0% of the stented patients on PP or ITT analyses. The risk was significantly lower in the stent group than in the controls (OR, 0.44; 95% CI, 0.24 - 0.81). The ORs for mild to moderate PEP were reduced in the stent group (OR, 0.537; 95% CI, 0.283 - 1.021), as well as those for severe PEP (OR, 0.123; 95% CI, 0.021 - 0.726). These trials indicated the benefits of pancreatic stenting in the prophylaxis of PEP; however, further randomized studies are needed before endorsing the routine use of this endoscopic procedure.

Choudhary et al. (45) have recently found that PS placement decreases the risk of PEP and hyperamylasemia in high-risk patients. They concluded in a meta-analysis of RCTs that prophylactic PS placement decreased the odds of PEP (OR, 0.22; 95% CI, 0.12 - 0.38;  $P < 0.01$ ). Stents also decreased the level of hyperamylasemia (weighted mean difference, -309.22; 95% CI, -350.95 to -267.49;  $P \leq 0.01$ ). Similar findings were also noted in other non-randomized studies.

Mazaki et al. (46) in their meta-analysis showed that PS placement after ERCP reduces the risk of PEP. They concluded that PS placement was associated with a statistically significant reduction in PEP (RR, 0.32; 95% CI, 0.19 - 0.52;  $P < 0.001$ ). Subgroup analysis with stratification according to PEP severity showed that pancreatic stenting was beneficial in patients with mild to moderate PEP (RR, 0.36; 95% CI, 0.22 - 0.60;  $p < 0.001$ ) and in patients with severe PEP (RR, 0.23; 95% CI, 0.06 - 0.91;  $P = 0.04$ ). Subgroup analysis according to patient selection demonstrated that pancreatic stenting was effective for both high-risk and mixed-case groups.

Freeman et al. (1,20) also reported that unsuccessful cases of stent placement were at higher risk of PEP. Therefore, the PS insertion method for such risk factor cases, and for those in which cannulation is difficult should involve only the insertion of a guidewire before the main procedure. Moreover, it is occasionally difficult to place a stent in anatomic deformity cases. In such cases, the careful use of the Radifocus R (Terumo, Tokyo, Japan) guidewire or a 0.025-inch guidewire will enable successful stent placement. Taken together, PS placement is a strategy for preventing PEP which has been shown to be the most effective procedure related to prevention of PEP.

Recently, to increase the success rate of primary deep biliary cannulation and reduce the risk of PEP, a wire-guided cannulation method has been proposed. However, several prospective studies (50-52) provided conflicting results as to whether the wire-guided cannulation technique reduces PEP risk compared with the standard method. Further RCTs are needed to confirm the effectiveness of this method.



#### 4.1.6 Type of stent

Stents with various diameters (3 - 7-Fr), lengths (2.0 - 12 cm), and with or without flanges have been used in previous studies of PEP. However, the optimal stent has not been determined (25,53).

An internal flange is likely to make spontaneous PS dislodgment difficult, and in such cases, generally, the PS has to be removed 7 - 14 days after placement by additional endoscopy, which may not only injure the pancreatic duct, but also be an economic burden. An unflanged stent designed to pass spontaneously from the pancreatic duct may obviate the need for a second endoscopic procedure for stent retrieval. It may also reduce the overall cost of treatment and procedures, and the pancreatic duct is less likely to be injured by an internal flange when the PS dislodges spontaneously. It has been reported that 86% of 3-Fr stents spontaneously dislodged (25).

Unflanged duodenal pigtail- and straight-type stents may spontaneously dislodge into the duodenum owing to pancreatic juice flow or friction with passing food. According to previous RCTs (15,43), unflanged duodenal pigtail- and straight-type stents spontaneously dislodge at a higher rate. The spontaneous dislodgement rates were 93.8% and 95.7%, and the durations until dislodgement were 2.7 and 2 days on average, respectively. The straight type of PS shape on the duodenal side is an important feature facilitating stent placement. Although the unflanged pigtail-type stent may be spontaneously dislodged at a higher rate due to friction with passing food and duodenal peristalsis, the handling of the short duodenal pigtail-type stent is slightly complicated, for example, the possible sudden forward movement of the stent on release, thus it requires close attention and experience. The straight-type PS with a flange on the duodenal side is easier to place than the pigtail-type PS.

Long-term PS retention is a significant risk factor with respect to chronic pancreatitis (1,25-28). Rashdan et al. (25) reported that 3 - 4-Fr stents are more effective than traditionally used stents for preventing PEP, and that 5 - 6-Fr stents cause more significant stent-induced pancreatic duct changes than 3 - 4-Fr stents. However, 3 - 4-Fr stents require a small-caliber guidewire (0.018 - 0.025 inches), and the use of a small-caliber guidewire is difficult and requires a high level of experience (1,25-27). In contrast, the 0.035-inch guidewire used with the 5-Fr PS is relatively easy to use for stent placement.

#### 5. Conclusion

PEP is the most common and potentially serious complication of ERCP-related procedures. The current optimal strategy for preventing PEP is considered to include the elucidation of its underlying mechanisms, identification of risk factors, administration of pharmacological drugs, and endoscopic procedures such as pancreatic stenting. The placement of a PS currently remains the most effective strategy for preventing PEP.

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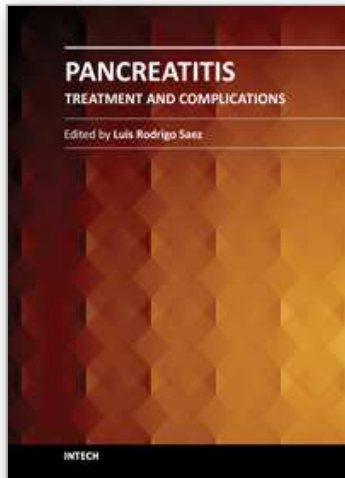
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## **Pancreatitis - Treatment and Complications**

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Pancreatitis may be acute or chronic. Although they can be caused by similar aetiologies, they tend to follow distinct natural histories. Around 80% of acute pancreatitis (AP) diagnoses occur as secondary to gallstone disease and alcohol misuse. This disease is commonly associated with the sudden onset of upper abdominal that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10 to 25% of AP episodes are classified as severe, leading to an associated mortality rate of 7 to 30%. Treatment is conservative and consists of general medical support performed by experienced teams, sometimes in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has significant prognostic importance. Necrosis, hemorrhage, and infection convey rates of up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudoaneurysm formation, or venous thrombosis increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

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