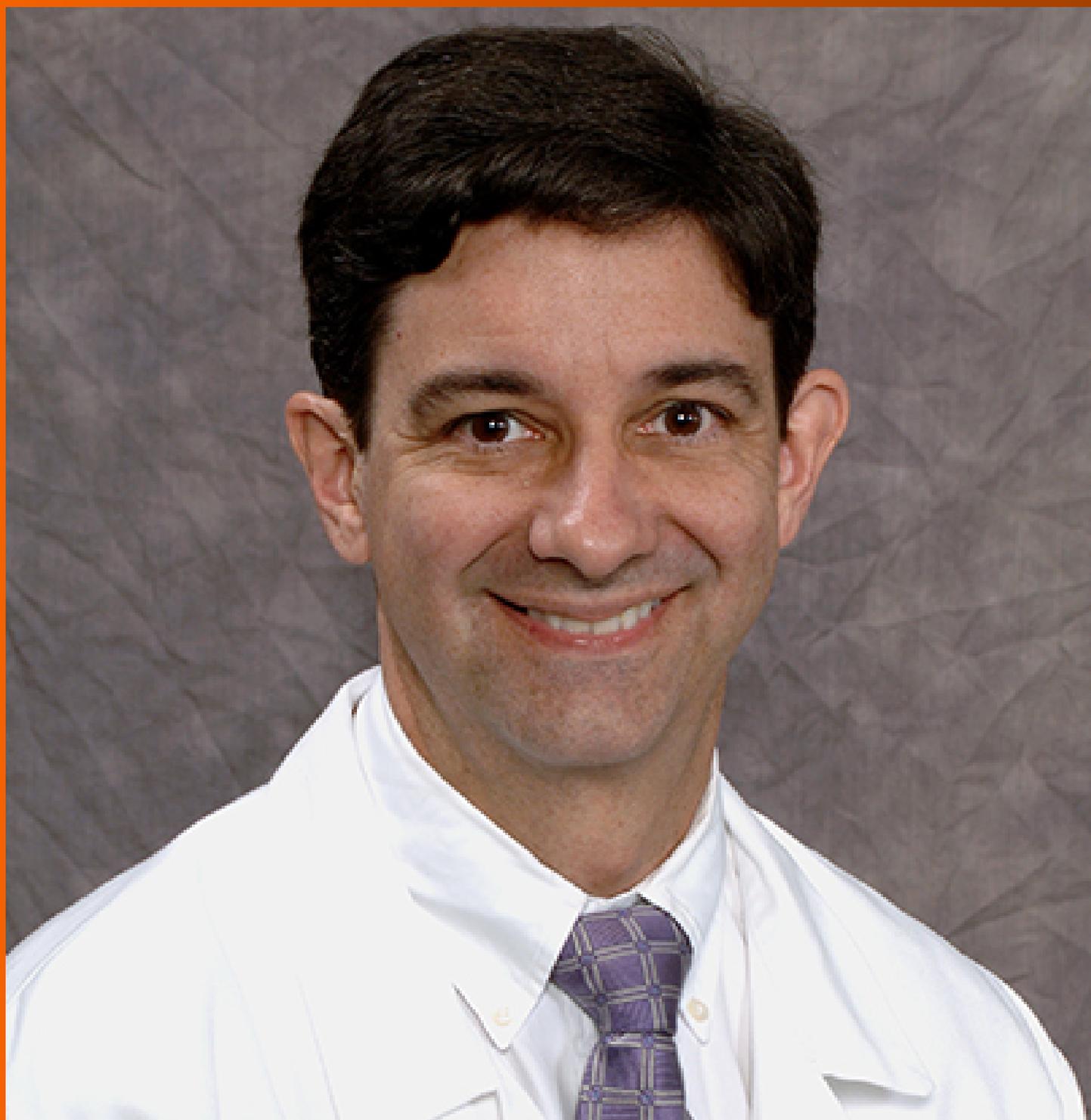


# World Journal of *Gastroenterology*

*World J Gastroenterol* 2021 May 28; 27(20): 2434-2663



**REVIEW**

- 2434 Role of modern radiotherapy in managing patients with hepatocellular carcinoma  
*Chen LC, Lin HY, Hung SK, Chiou WY, Lee MS*
- 2458 Open reading frame 3 protein of hepatitis E virus: Multi-function protein with endless potential  
*Yang YL, Nan YC*
- 2474 Breakthroughs and challenges in the management of pediatric viral hepatitis  
*Nicastro E, Norsa L, Di Giorgio A, Indolfi G, D'Antiga L*

**MINIREVIEWS**

- 2495 Pancreatitis after endoscopic retrograde cholangiopancreatography: A narrative review  
*Ribeiro IB, do Monte Junior ES, Miranda Neto AA, Proença IM, de Moura DTH, Minata MK, Ide E, dos Santos MEL, Luz GO, Matuguma SE, Cheng S, Baracat R, de Moura EGH*
- 2507 RON in hepatobiliary and pancreatic cancers: Pathogenesis and potential therapeutic targets  
*Chen SL, Wang GP, Shi DR, Yao SH, Chen KD, Yao HP*
- 2521 Evolving role of endoscopy in inflammatory bowel disease: Going beyond diagnosis  
*Núñez F P, Krugliak Cleveland N, Quera R, Rubin DT*
- 2531 Deep learning for diagnosis of precancerous lesions in upper gastrointestinal endoscopy: A review  
*Yan T, Wong PK, Qin YY*
- 2545 State of machine and deep learning in histopathological applications in digestive diseases  
*Kobayashi S, Saltz JH, Yang VW*
- 2576 COVID-19 in normal, diseased and transplanted liver  
*Signorello A, Lenci I, Milana M, Grassi G, Baiocchi L*

**ORIGINAL ARTICLE****Basic Study**

- 2586 Upregulation of long noncoding RNA W42 promotes tumor development by binding with DBN1 in hepatocellular carcinoma  
*Lei GL, Niu Y, Cheng SJ, Li YY, Bai ZF, Yu LX, Hong ZX, Liu H, Liu HH, Yan J, Gao Y, Zhang SG, Chen Z, Li RS, Yang PH*

**Retrospective Cohort Study**

- 2603 Understanding celiac disease monitoring patterns and outcomes after diagnosis: A multinational, retrospective chart review study  
*Lundin KEA, Kelly CP, Sanders DS, Chen K, Kayaniyil S, Wang S, Wani RJ, Barrett C, Yoosuf S, Petersen ES, Sambrook R, Leffler DA*

- 2615** Development and validation of a prognostic model for patients with hepatorenal syndrome: A retrospective cohort study

*Sheng XY, Lin FY, Wu J, Cao HC*

**Observational Study**

- 2630** Inflammatory bowel disease in Tuzla Canton, Bosnia-Herzegovina: A prospective 10-year follow-up

*Tulumović E, Salkić N, Tulumović D*

**META-ANALYSIS**

- 2643** Association between oral contraceptive use and pancreatic cancer risk: A systematic review and meta-analysis

*Ilic M, Milicic B, Ilic I*

**CASE REPORT**

- 2657** Cyclophosphamide-associated enteritis presenting with severe protein-losing enteropathy in granulomatosis with polyangiitis: A case report

*Sato H, Shirai T, Fujii H, Ishii T, Harigae H*

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## Pancreatitis after endoscopic retrograde cholangiopancreatography: A narrative review

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### Abstract

Acute post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is a feared and potentially fatal complication that can be as high as up to 30% in high-risk patients. Pre-examination measures, during the examination and after the examination are the key to technical and clinical success with a decrease in adverse events. Several studies have debated on the subject, however, numerous topics remain controversial, such as the effectiveness of prophylactic medications and the amylase dosage time. This review was designed to provide an update on the current scientific evidence regarding PEP available in the literature.

**Key Words:** Endoscopic retrograde cholangiopancreatography; Pan-creatitis; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Adverse events; Pancreatitis; Prevention

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**Core Tip:** Acute post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is a feared and potentially fatal complication. Early diagnosis remains the key to the clinical success of these patients. Unfortunately, several topics remain controversial, especially early diagnosis with hyperamylasemia still being mistaken for PEP.

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The purpose of this review is to demonstrate the evidence in the current literature on PEP.

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## INTRODUCTION

Starting in 1968, endoscopic retrograde cholangiopancreatography (ERCP) was a watershed in the diagnosis and treatment of biliopancreatic diseases. Since then, an accurate indication for this examination is very important given the potential adverse effects associated with the procedure[1].

Early recognition and proper management of potential adverse events are essential to reduce associated morbidity and mortality.

As in other endoscopic procedures, there are safety determinants for ERCP, in addition to the precise indication, the clinical condition of the patient, age, sex, the type of sedation used, what type of therapeutic procedure performed, the appropriate use of accessories and the training of the endoscopist and assistants are taken into consideration[2].

Acute pancreatitis is the most common serious complication after ERCP[3,4], often confused with an increase in serum amylase concentration that occurs in up to 75% of patients[5,6].

Acute clinical pancreatitis itself, defined as a clinical syndrome of abdominal pain and hyperamylasemia which requires hospitalization, is much less common than it appears. There are still some controversies in the literature on the subject. The purpose of this review is to provide an update on post-ERCP pancreatitis and its prevention.

## PATHOGENESIS

The determinants of the inflammatory process in the pancreas are multifactorial. Several proposed factors can act independently or in combination to induce post-ERCP pancreatitis (PEP). The two most important are mechanical injury due to instrumentation in the pancreatic duct and hydrostatic injury due to contrast injection[7].

During ERCP and sphincterotomy, the pancreas is exposed to various forms of trauma: mechanical, chemical, hydrostatic, thermal, and even allergic[8].

It is also known that prolonged manipulation around the papillary orifice, inadvertent cannulation of the pancreatic duct and multiple injections into the pancreatic duct are common when selective cannulation of the bile duct is difficult[9,10]. This can result in mechanical damage to the duct or ampoule. Thermal injury to the electrocautery current can also produce edema of the pancreatic orifice, leading to obstruction of the duct, impairing the emptying of pancreatic secretions[11].

Hydrostatic injury due to excessive injection of contrast into the pancreatic duct is probably an important cause of PEP[12].

Either by allergy or chemical injury, contrast agents can lead to injuries. In a study by George *et al*[13], there was no statistically significant difference between the types of contrast in the analysis of randomized studies.

## EPIDEMIOLOGY AND RISK FACTORS

### Incidence

The incidence of pancreatitis post-ERCP can vary from 1% to 10%, reaching an alarming 30% in high-risk patients[14,15]. Stratification of the degree of post-examination pancreatitis shows incidence rates of 3.6% to 4% for mild acute pancre-

atitis, 1.8% to 2.8% for moderate acute pancreatitis, and 0.3% to 0.5% for severe acute pancreatitis[16,17] with a mortality rate of 0.2%[18]. Higher rates are observed in patients undergoing evaluation for possible sphincter of Oddi dysfunction[19].

### **Risk factors**

According to the guidelines of the European Society for Gastrointestinal Endoscopy (ESGE)[20] and the American Society for Gastrointestinal Endoscopy (ASGE)[2]: History of pancreatitis, suspected sphincter of Oddi dysfunction, female gender, and young age are definitely “patient-related risk factors” for PEP. On the other hand, difficult cannulation, pancreatic injection, and pre-cut sphincterotomy are “risk factors related to the procedure”[3,4].

### **Patient-related factors**

There are several factors related to the patient, the most common factors are female gender, normal levels of bilirubin, young adults, history of recurrent pancreatitis, and patients with suspected sphincter of Oddi dysfunction. Patients with a history of chronic pancreatitis have a protective effect against PEP[2].

Unfortunately, risk factors are additive[7,21,22]. For example, the combination of female gender, patients with suspected sphincter of Oddi dysfunction, young age, difficult cannulation, bilirubin within the acceptable standard, and absence of bile duct stones are associated with a risk of the pancreatitis of more than 40%.

### **Operator-related factors**

These are the most subjective factors. It is believed that the experience of the endoscopist, the presence of fellows and multiple operators is an independent risk factor for PEP[23,24].

### **Procedure-related factors**

The factors related to the procedure are the best studied and discussed in the literature. Pre-cut sphincterotomy, often used in difficult ERCP, time and number of cannulation times, trauma, and edema of the major duodenal papillae due to the number of attempts are independent factors for PEP[25].

In a systematic review with a meta-analysis that included 25 randomized controlled trials (RCTs) evaluating the incidence of PEP in patients undergoing sphincterotomy, ballooning dilation of the major duodenal papilla without sphincterotomy and patients undergoing both procedures, it was concluded that the incidence of PEP was similar between the groups[26].

The risk factors can be divided into three groups and are shown in [Table 1](#)[7,27-29].

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## **CLINICAL MANIFESTATIONS**

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The clinical manifestations of PEP are the same as those seen in patients with acute pancreatitis due to other causes.

These include epigastric or upper right quadrant pain, abdominal tenderness and high levels of amylase and lipase.

Post-ERCP acute pancreatitis can be classified as mild, moderate or severe based on the American Gastroenterology Association[30] and the American College of Gastroenterology[31]: (1) mild-amylase levels 24 h after the examination, remaining above up to three times the reference value with necessary hospitalization; (2) moderate-need for hospitalization of 4 to 10 d; and (3) severe-need for hospitalization over 10 d or need for invasive therapeutic intervention.

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## **DIAGNOSIS**

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Most patients with PEP have an acute onset of severe and persistent epigastric abdominal pain and in approximately 50% of patients, the pain radiates to the back. Approximately 90% of patients experience nausea and vomiting that can persist for several hours[32].

Patients with severe acute pancreatitis may have dyspnea due to diaphragmatic inflammation secondary to pancreatitis, pleural effusions, or acute respiratory distress syndrome, and 5% to 10% of patients with severe acute pancreatitis may have painless disease and unexplained hypotension[33].

**Table 1 Risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis related to the operator and the procedure**

Operator related	Factors related to the procedure
Inadequate training	Extended procedure time ( $\geq 30$ min)
Lack of experience	Difficult cannulation ( $\geq 15$ min)
<b>Patient-related risk factors</b>	Injection of contrast into the pancreatic duct
Young age	Sphincter of Oddi manometry
Women	Pancreatic sphincterotomy
Normal serum bilirubin	Small papillary sphincterotomy
Recurrent pancreatitis	Biliary balloon sphincteroplasty
Previous ERCP-induced pancreatitis	Endoscopic papillectomy with loop
Sphincter of Oddi dysfunction	Pancreatic intraductal ultrasound
	Precut sphincterotomy

ERCP: Endoscopic retrograde cholangiopancreatography.

For diagnostic confirmation, radiological evidence with computed tomography may be necessary[34] but biochemical tests are more commonly used, as they are inexpensive and sensitive[35].

Early diagnosis of PEP is crucial as late diagnosis can be fatal[36,37].

### **Pancreatic enzymes**

The diagnosis of PEP can be complicated, since elevations in pancreatic enzymes are common after the examination, but are generally not associated with clinical pancreatitis.

There is no consensus in the literature on the ideal time after examination to request serum amylase levels and their real meaning. Two prospective studies including 263 and 886 patients found that the 4-h post-ERCP amylase level proved useful in predicting PEP[38,39]. We suggest that the patient should fast for the next 12 h and amylase analysis should be requested for all patients.

In patients with suspected pancreatitis, the degree and speed of elevations in pancreatic enzymes may be a way of differentiating patients with PEP from those in pain due to other causes. Some studies state that patients with PEP often have serum amylase levels more than five times the upper limit of normal[40,41].

Patients undergoing a contrast study of the main pancreatic duct should be admitted if the 4-h amylase level is greater than 2.5 times the upper reference limit. Patients who have not undergone a contrast study should be admitted if the 4-h amylase level is greater than five times the upper limit of normal[38]. The 4-h post-ERCP amylase level was useful in predicting PEP in two prospective studies including 263 and 886 patients, respectively[38,39].

## **DIFFERENTIAL DIAGNOSIS**

Not all patients with pain after ERCP have pancreatitis. Other causes of abdominal pain after ERCP include discomfort due to air insufflation[42-44] and perforation.

In patients with discomfort due to air insufflation, the pain is generally not as severe as that seen with PEP, and pancreatic enzyme levels may be normal or elevated, as pancreatic enzymes are elevated in most patients after ERCP[5].

If serum lipase is less than three times the upper limit of normal, pancreatitis is unlikely (specificity of 85 to 98%). However, it should be borne in mind that amylase and lipase start to increase several hours after the onset of pancreatitis; thus, blood tests taken soon after ERCP can show false negative results.

If the clinical suspicion of pancreatitis is high, tests should be repeated at least 4-6 h after ERCP. Perforated patients may experience diffuse abdominal pain, bloating, tachycardia, fever, and leukocytosis.

Symptoms can be immediate after the examination or hours later[45]. Many of the perforation symptoms overlap with those of acute pancreatitis and, if perforation is

suspected, an abdominal tomography should be performed immediately for intraperitoneal and retroperitoneal evaluation[46].

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## TREATMENT

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Most of the patients who develop PEP requiring hospitalization are classified as mild. In severe cases, admission to an intensive care unit may be necessary[30-31]. Initial treatment should focus on the following:

### **Pain control**

This usually manifests as abdominal pain and must be one of the main pillars in the treatment, since its non-control can lead to hemodynamic instability. There is still a lot of controversy in the use of opioids such as morphine as it has been shown to increase pressure in the sphincter of Oddi, but without clinical data that this has resulted in worsening of pancreatitis. Indicated: Meperidine, fentanyl, and morphine[47].

Particular attention should be given to patients who are dehydrated or who have not received an adequate amount of fluids since hypovolemia and hemoconcentration can cause ischemic pain and increased lactic acidosis.

### **Fluid replacement**

Fluid replacement is one of the main items in the treatment of patients with PEP. The use of crystalloid solutions, mainly Ringer Lactate, from 5 to 10 mL/kg/h is recommended in patients without restrictions. In critically ill patients, with hemodynamic instability, 20 mL/kg is recommended in 30 min followed by 3 mL/kg/h in the next 8 to 12 h[48,49].

### **Monitoring**

As these patients' condition may worsen in the next 24 h, it is recommended that they be monitored for at least 48 h. This surveillance includes vital signs, urine volume, electrolytes, and blood glucose[48].

### **Antibiotics**

Prophylactic antibiotics are not recommended in patients with PEP regardless of the type or severity of the disease. Antibiotics should only be used in about 20% of patients who develop extrapancreatic infections[48,50].

### **Nutrition**

Fasting is recommended for all patients with PEP. The time for restarting oral feeding is dependent on the severity of pancreatitis[51].

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## PREVENTION

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Certain measures can reduce the incidence of PEP[7]: (1) adequate training and experience of endoscopists and assistants; (2) use of wire-guided techniques for biliary cannulation; (3) minimizing the number of cannulation attempts; (4) placement of a prophylactic pancreatic stent in patients at high risk of developing PEP; (5) placement of prophylactic pancreatic stents in patients who require the assistance of a pancreatic guidewire for biliary cannulation (double guidewire technique); (6) selective cannulation of the bile duct if an assessment of the pancreatic duct is not necessary; (7) minimizing the volume of contrast medium injected into the pancreatic duct, if necessary; (8) careful use of the electrocautery current during sphincterotomy; (9) high-risk patients should undergo ERCP in specialized centers; and (10) use of carbon dioxide for luminal insufflation to decrease post-procedure abdominal pain that can be mistaken for pancreatitis.

### **Effectiveness of preventive measures**

**Endoscopic techniques:** The endoscopic technique is an important factor in the development of PEP. Cannulation guided by a hydrophilic-coated wire, careful use of electrocautery during sphincterotomy, and placement of a prophylactic pancreatic stent should be undertaken in patients at high risk of developing PEP.

**Cannulation techniques:** Various instruments such as guidewires are available and can decrease the risk of PEP as suggested by the ASGE and ESGE[52-55].

A systematic review that included only randomized trials, evaluating a total of 3450 patients, demonstrated that cannulation guided by a guidewire was superior to contrast-assisted cannulation technique[56]. Cannulation rates were higher for the wire-guided technique, and the risk of PEP was halved.

In a multicenter RCT, including 274 patients with naïve papilla undergoing ERCP using wire-guided cannulation in whom the guidewire was inadvertently inserted into the main pancreatic duct, the patients were randomized to undergo the double guidewire technique or a new cannulation attempt with a single wire. Conversion to the double guidewire technique did not facilitate selective bile duct cannulation and did not decrease the incidence of PEP compared to the new single guidewire cannulation attempt. However, double guidewire cannulation was more effective in patients with malignant biliary stenosis[57].

**Electrocautery:** In a recent systematic review evaluating 11 randomized studies involving 1791 patients, it was found that the performance of sphincterotomy with electrocautery in pure cut mode leads to a higher incidence of mild bleeding compared to endocut and blend. However, this modality may have a lower incidence of pancreatitis. Monopolar mode causes higher rates of pancreatitis compared to bipolar mode[11].

**Pancreatic stent:** Pancreatic stent placement can be performed as prophylaxis for PEP mainly in high-risk patients. We suggest the use in patients undergoing pancreatic sphincterotomy, a contrasting study of the main pancreatic duct when it is necessary to use the double guidewire technique, in patients with suspected sphincter of Oddi dysfunction, and in patients undergoing pre-cut sphincterotomy[7].

The possible benefit is believed to be related to a reduction in pancreatic intraductal pressure of papillary edema.

Studies have shown that in special situations, the passage of a pancreatic stent in the DPP may be necessary to prevent the evolution of pancreatitis after ERCP. This procedure must be performed 8 to 20 h after the start of PEP[58-60].

Pancreatic stents should be short (less than 5 cm and small in diameter (5 French), plastic, and not have flanges distally[7]. Non-flanged stents can lead to spontaneous migration to the gastrointestinal tract, which occurs in 95% of cases within 10 d[55]. If radiographs show evidence of persistent stent within 1 wk, a high endoscopy should be performed to remove the stent[55].

**Intravenous hydration:** ASGE guidelines suggest the use of periprocedural intravenous hydration with lactated Ringer to decrease the risk of PEP[2].

In a RCT of 150 patients, the PEP rate was lower in patients who received aggressive intravenous hydration compared to standard therapy[61].

In patients with contraindications to rectal non-steroidal anti-inflammatory drugs (NSAIDs), who are not at risk of fluid overload and a pancreatic stent has not been placed, the suggested alternative is aggressive hydration with lactated Ringer's solution (3 mL/kg/h during ERCP, 20 mL/kg bolus after ERCP and 3 mL/kg/h for 8 h after the examination)[25].

### **Chemoprevention**

Since 1977, more than 35 different drugs have been evaluated for the prevention of PEP with variable results[62,63]. The available options are discussed below:

#### **NSAIDs**

**Rectal NSAIDs:** The ASGE and the ESGE recommend the administration of NSAIDs to reduce the incidence and severity of PEP (for example, 100 mg of indomethacin or diclofenac rectally immediately before or after ERCP)[2,20].

A systematic review with meta-analysis evaluating 21 RCTs with a total of 6854 patients, found that the rectal administration of NSAIDs in all patients adequately reduced the incidence of PEP and that mild pancreatitis was the only preventable result. In this context, both diclofenac and indomethacin are considered effective[64].

Rectal NSAIDs were also compared indirectly with stenting of the pancreatic duct. A meta-analysis showed that rectal NSAIDs were superior to pancreatic duct stenting for the prevention of PEP (OR 0.48, 95%CI: 0.26-0.87)[65].

**Non-rectal NSAIDs:** There are no data in the current literature to support the prophylactic use of any NSAIDs administered by any non-rectal route or in combination with

other agents.

In a multicenter study with 430 patients, oral diclofenac (50 mg) before and after ERCP showed no benefit compared to placebo[66].

**Other agents in the prevention of PEP:** There are several drugs potentially useful for the prevention of PEP although some drugs are difficult to access and few are used for this purpose.

#### **Topical adrenaline**

A systematic review with meta-analysis evaluating 6 randomized and 2 observational studies including 4123 patients found that topical adrenaline does not provide any additional advantage in combination with rectal indomethacin in the prevention of PEP in patients who underwent ERCP. However, topical adrenaline alone is associated with a lower risk of PEP compared to placebo and can be considered if rectal indomethacin is not available or if the patient has any contraindications to its use[67].

#### **Nitrates**

In a systematic review with 2000 patients, the use of nitroglycerin was compared to placebo and it was found that the intervention group demonstrated a 10% reduction in the development of PEP[68].

These data suggest that nitrates combined with rectal NSAIDs may provide more benefits than NSAIDs alone[69,70]. In a randomized trial including 886 patients undergoing ERCP, the risk of PEP was lower in patients treated with diclofenac suppositories and sublingual isosorbide dinitrate compared to patients receiving diclofenac suppositories alone (RR: 0.59, 95%CI: 0.37-0.95)[70].

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## **PANCREATIC SECRETION INHIBITORS**

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#### **Somatostatin**

Somatostatin leads to a reduction in pancreatic exocrine secretion of basal origin and also when stimulated. A meta-analysis that included 9 studies concluded that somatostatin was ineffective in preventing PEP when administered in the short-term (< 6 h) or long-term (≥ 12 h)[71]. Another meta-analysis, which included 11 RCTs with a total of 2869 patients, found no benefit when somatostatin was administered as a short-term infusion, but showed a benefit when administered as a single bolus or as a long-term infusion[72].

#### **Octreotide**

Two systematic reviews with meta-analyses found no benefit of octreotide use in PEP prophylaxis[73,74].

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## **INHIBITORS OF PROTEASE ACTIVATION**

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The most studied protease inhibitors include gabexate mesylate, nafamostat mesylate, and ulinastatin. As the activation of proteolytic enzymes can contribute to PEP, protease inhibitors have been investigated in the prevention of PEP. In a meta-analysis of 18 studies involving 4966 patients, there was a small benefit with the use of protease inhibitors[75].

#### **Gabexate mesylate**

Although controversial results have been observed, a meta-analysis of five studies concluded that gabexate mesylate was ineffective in reducing pancreatitis and post-ERCP pain[71].

#### **Nafamostat mesylate**

Although controversial results have been observed, a meta-analysis that included 7 RCTs with 2956 patients found that the incidence of PEP was reduced by 53% compared to patients in the control groups (RR: 0.47, 95%CI: 0.34-0.63)[76].

Another meta-analysis which included 26 studies, found that unlike gabexate mesylate and ulinastatin, nafamostat mesylate and NSAIDs were associated with decreased risk of PEP[77].

### Ulinastatin

A systematic review with a meta-analysis that included 7 RCTs comparing ulinastatin with placebo or gabexate demonstrated a decreased risk of PEP in patients receiving ulinastatin[77].

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## MONITORING CARE AFTER ERCP

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Many complications of ERCP are apparent during the first 6 h after the procedure, and others may take days to manifest. We suggest the following recommendations: (1) Serum amylase: Studies have shown that the 4-h serum amylase level is a useful measure in predicting PEP; (2) Clinical monitoring: The immediate post-examination period is critical and the patient must be monitored for signs and symptoms of adverse events; and (3) Diet: We recommend fasting the patient for 6 to 12 h after the examination and discharge only after the serum amylase results and clinical reassessment (patient without complaints of abdominal pain, for example).

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## CONCLUSION

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Pancreatitis after ERCP is a feared, potentially fatal, and not entirely preventable complication. The correct and early diagnosis is a turning point in the outcome of the disease. Pre-examination measures such as a correct indication for the procedure, use of rectal NSAIDs, and well-trained staff are necessary. During the examination: Hyperhydration, examination with precision and speed with the correct technique and appropriate material, and prophylactic use of a pancreatic stent. After the examination, maintaining fasting and the appropriate amylase dosage are essential for the clinical and technical success of the procedure.

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