Post-ERCP pancreatitis

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INTRODUCTION
Definition of PEP requires (1) evidence of clinical pancreatitis, (2) serum amylase or lipase 3 times the upper limit of normal 24 hours after the procedure, and (3) hospitalization (or prolongation of existing hospitalization) of at least 2 days.
Regardless of the etiology, the criteria for the diagnosis of acute pancreatitis requires two of the three following criteria:

- 1) abdominal pain (symptoms) consistent with the diagnosis;
- 2) a serum amylase and/or lipase greater than 3 times the upper limit of normal; and/or
- 3) cross-sectional imaging (CT and/or MRI) consistent with the diagnosis.

Although using two of the three criteria will accurately lead to a diagnosis of acute pancreatitis in most patients, the criteria are not always accurate in patients following ERCP. Many post-ERCP patients have two of these criteria (pain and an elevation of amylase/lipase) in the absence of acute pancreatitis.
Diagnosis

- The pain of pancreatitis is typically epigastric, persistent and radiating to the back and lasting for hours if not days. Episodic and fleeting pain is not related to pancreatitis.

- Some patients have pain following ERCP due to the large volume of air insufflated during the procedure. This results in bowel distention and painful spasm.
Diagnosis

- In addition to pain, asymptomatic elevations in the amylase and/or lipase often occur following ERCP, with no clinical sequelae.
- Inappropriate labeling of patients with abdominal pain and mild, transient elevation of serum amylase and/or lipase as having post ERCP pancreatitis may explain why the reported incidence of post ERCP pancreatitis varies greatly, from 4% to 31% among studies.
Diagnosis

- Post-ERCP pancreatitis should be suspected in any patient who develops pain within 6 hours of the procedure. It is much less likely to develop after 12 hours from the procedure.
- Post-ERCP pain with marked elevation of serum amylase and/or lipase; especially when the values are greater than 1,000 IU/L, it is strongly suggestive of pancreatitis.
Due to the lack of specificity of pain and elevations of the amylase/lipase in patients who have undergone ERCP, imaging becomes the most important criterion in determining the diagnosis of post-ERCP pancreatitis.
### Details of complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total %</th>
<th>Score %</th>
<th>Death %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>3.5</td>
<td>0.4</td>
<td>0.11</td>
</tr>
<tr>
<td>Infection</td>
<td>1.4</td>
<td>0.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.3</td>
<td>0.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Perforation</td>
<td>0.6</td>
<td>NA</td>
<td>0.06</td>
</tr>
<tr>
<td>Other</td>
<td>1.3</td>
<td>NA</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7.9</strong></td>
<td><strong>NA</strong></td>
<td><strong>0.4</strong></td>
</tr>
</tbody>
</table>

Data available for 14 studies

Andriulli et al Am J Gastroe 2007
Incidence, risk factors, and severity of PEP

- Pancreatitits is the most common complication of ERCP and carries a high morbidity and mortality.
- There is a 3%-5% incidence of this complication occurring, as shown in various large clinical studies.
Incidence, risk factors, and severity of PEP

- Based upon data from studies that have included unselected patients, PEP is mild, moderate, and severe in 45%, 44%, and 11% of cases, respectively.
- Death occurs in 3% of cases of PEP (95 %CI 1.65%–4.51 %)
<table>
<thead>
<tr>
<th>Severity of pancreatitis</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Clinical pancreatitis, amylase at least 3 × normal &gt; 24 h after procedure, requiring unplanned admission or prolongation of planned admission to 2-3 d</td>
</tr>
<tr>
<td>Moderate</td>
<td>Hospitalisation of 4-10 d</td>
</tr>
<tr>
<td>Severe</td>
<td>Hospitalisation of &gt; 10 d, haemorrhagic pancreatitis, pancreatic necrosis or pseudocyst, or need for intervention (percutaneous drainage or surgery)</td>
</tr>
<tr>
<td>Patient-related risk factors</td>
<td>Adjusted odds ratios (95% confidence intervals in parentheses except where indicated otherwise)</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Definite risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Suspected sphincter of Oddi dysfunction (SOD)</td>
<td>1.91 (1.37 – 2.65)</td>
</tr>
<tr>
<td>Female gender</td>
<td>3.5 (1.1 – 10.6)</td>
</tr>
<tr>
<td>Previous pancreatitis</td>
<td>2.46 (1.93 – 3.12)</td>
</tr>
<tr>
<td><strong>Likely risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Previous PEP</td>
<td>8.7 (3.2 – 23.86)</td>
</tr>
<tr>
<td>Younger age</td>
<td>Range of odds ratios: 1.09 – 2.87</td>
</tr>
<tr>
<td>Nondilated extrahepatic bile ducts</td>
<td></td>
</tr>
<tr>
<td>Absence of chronic pancreatitis</td>
<td>1.87 (1.00 – 3.48)</td>
</tr>
<tr>
<td>Normal serum bilirubin</td>
<td>1.89 (1.22 – 2.93)</td>
</tr>
<tr>
<td><strong>Procedure-related risk factors</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Definite risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Cannulation attempts duration &gt;10 minutes$^2$</td>
<td>1.76 (1.13 – 2.74)</td>
</tr>
<tr>
<td>Pancreatic guidewire passages &gt;1</td>
<td>2.77 (1.79 – 4.30)</td>
</tr>
<tr>
<td>Pancreatic injection</td>
<td>2.2 (1.60 – 3.01)</td>
</tr>
<tr>
<td><strong>Likely risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Precut sphincterotomy$^3$</td>
<td>2.3 (1.4 – 3.7)</td>
</tr>
<tr>
<td>Pancreatic sphincterotomy</td>
<td>3.07 (1.64 – 5.75)</td>
</tr>
<tr>
<td>Biliary balloon sphincter dilation</td>
<td>4.51 (1.51 – 13.46)</td>
</tr>
<tr>
<td>Failure to clear bile duct stones</td>
<td>3.35 (1.33 – 9.10)</td>
</tr>
<tr>
<td>Intraductal ultrasound (IDUS)$^4$</td>
<td>2.41 (1.33 – 4.39)</td>
</tr>
</tbody>
</table>

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$^1$ For definite or likely risk factors, adjusted odds ratios are reproduced either from Masci et al. [20] or from included studies that identified the characteristic as an independent risk factor. Pooled incidences were calculated using figures available in all of the included studies that provided sufficient data for calculation [6, 16, 17, 19, 21, 22, 25 – 27, 115, 116, 177]. (See text for details about included studies)

$^2$ Cannulation attempts of duration >5 minutes may already increase the incidence of PEP as shown by Halttunen et al. (11.7% vs. 2.7% for cannulation attempts ≥5 minutes vs. <5 minutes, respectively) [115].

$^3$ Evidence is growing that precut sphincterotomy is not a definite risk factor for PEP by itself, the increased risk of PEP being related to cannulation efforts that preceded precut [28].
• The list was not exhaustive because not all potential risk factors had been analyzed.
• For example, ampullectomy is generally considered to be a definitive risk factor for PEP on the basis of several small prospective studies.
<table>
<thead>
<tr>
<th>Risk factors for post ERCP pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient-related factors</strong></td>
</tr>
<tr>
<td>Younger age</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Normal serum bilirubin</td>
</tr>
<tr>
<td>Recurrent pancreatitis</td>
</tr>
<tr>
<td>Prior ERCP-induced pancreatitis</td>
</tr>
<tr>
<td>Sphincter of Oddi dysfunction</td>
</tr>
<tr>
<td><strong>Endoscopist-related factors</strong></td>
</tr>
<tr>
<td>Difficult cannulation</td>
</tr>
<tr>
<td>Pancreatic duct injection</td>
</tr>
<tr>
<td>Sphincter of Oddi manometry</td>
</tr>
<tr>
<td>Precut sphincteterotomy</td>
</tr>
<tr>
<td>Pancreatic sphincterotomy</td>
</tr>
<tr>
<td>Minor papilla sphincterotomy</td>
</tr>
<tr>
<td><strong>Procedure-related factors</strong></td>
</tr>
<tr>
<td>Trainee involvement in procedure</td>
</tr>
</tbody>
</table>
## Risk stratification

Independent risk factors for post-ERCP pancreatitis

<table>
<thead>
<tr>
<th>Patient-related factors</th>
<th>Procedure-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected sphincter of Oddi dysfunction (SOD)</td>
<td>Difficult cannulation</td>
</tr>
<tr>
<td>Prior post-ERCP pancreatitis</td>
<td>Precut (access) sphincterotomy</td>
</tr>
<tr>
<td>Normal bilirubin</td>
<td>Pancreatic sphincterotomy</td>
</tr>
<tr>
<td>Younger age</td>
<td>Ampullectomy</td>
</tr>
<tr>
<td>Female gender</td>
<td>Repeated or aggressive pancreatography</td>
</tr>
<tr>
<td>History of recurrent pancreatitis</td>
<td>Balloon dilation of an intact biliary sphincter</td>
</tr>
</tbody>
</table>
Method related

- Difficult canulation
- Ampullectomy
- Precut
- Panc endoscopic sphincterotomy
- Mode of cutting
- Number of contrast
- Balloon sphincteroplasty
- Sphincter of Oddi manometry
Metallic biliary stents

the odds of PEP from SEMS placement increased to 6.8 (95% CI, 2.2, 21.4). However, the frequency of PEP was similar between covered (6.9%) and uncovered (7.5%) SEMSs (OR 0.9 [CI, 0.3-2.4]).

Coté GA. Gastrointest Endosc. 2010;72:748-54
Smoking, liver disease are protective

- In a case-control design, 6505 patients had 8264 ERCPs, 211 patients had PEP
- Multivariate analysis identified seven independent variables for PEP, three protective (current smoking, chronic liver disease, cld + transplant/hepatectomy complications) and 4 predictive (younger age, suspected SOD, pancreatic sphincterotomy, difficult cannulation)

As risk factors for PEP were shown to be independent by multivariate analysis, they might have a cumulative effect.

Freeman et al. calculated the adjusted odds ratio (OR) for various combinations of risk factors by using data prospectively collected from about 2000 ERCPs: the highest risk of PEP (42%) was found for female patients with a normal serum bilirubin level, suspected sphincter of Oddi dysfunction (SOD), and difficult biliary cannulation.
Recently, in a Swedish case–control study of 12,718 ERCP procedures, independent risk factors were young age, female gender, prolonged procedure time, and elective ERCP; whereas rendezvous procedures reduced the risk of PEP. Needle-knife sphincterotomy was found not to be an independent risk factor for PEP.

### Patient related independent risk factors

<table>
<thead>
<tr>
<th>MRCP, EUS</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite</strong></td>
<td></td>
</tr>
<tr>
<td>• Suspected SOD</td>
<td>4.1 (3.4-5)</td>
</tr>
<tr>
<td>• Female gender</td>
<td>2.2 (1.8-2.8)</td>
</tr>
<tr>
<td>• Previous pancreatitis</td>
<td>2.5 (1.9-3.1)</td>
</tr>
<tr>
<td><strong>Likely</strong></td>
<td></td>
</tr>
<tr>
<td>• Younger age</td>
<td>1.1-2.9</td>
</tr>
<tr>
<td>• Non-dilated extrahepatic BD</td>
<td>NR</td>
</tr>
<tr>
<td>• Absence of CP</td>
<td>1.9 (1.0-3.5)</td>
</tr>
<tr>
<td>• Normal serum bilirubin</td>
<td>1.9 (1.2-2.9)</td>
</tr>
<tr>
<td>40% of PEP</td>
<td></td>
</tr>
</tbody>
</table>
In general, the more likely a patient is to have an abnormal common bile duct and/or pancreatic duct, the less likely the patient will develop post-ERCP pancreatitis.

Mehta et al. showed that the patient most at risk of developing post-ERCP pancreatitis was a woman with suspected choledocholithiasis, non-dilated common bile duct, but normal serum bilirubin, which undergoes a biliary sphincterotomy and no stone was found. In this patient population, more than a quarter of patients (27%) developed post-ERCP pancreatitis.
Pathogenesis

- Result from several factors
  1) Mechanical injury
  2) Hydrostatic injury from over injection of PD
  3) Chemical / allergic injury
  4) Enzymatic injury – activation of proteolytic enzyme
  5) Infection – From contaminated scope / accessory
  6) Thermal injury
Prediction of PEP

Statement 2010:

- Serum amylase values less than 1.5 times the ULN, obtained at 2–4 hours post-ERCP, almost exclude PEP; values more than 3 or 5 times the ULN at 4–6 hours post-ERCP have increasing positive predictive values for PEP (Evidence level 2+).

- It is recommended that serum amylase be determined in patients to be discharged on the day of ERCP; patients with amylase values less than 1.5 times the ULN can be discharged without concern about risk of PEP (Recommendation grade B).
Prediction of PEP

**Statement 2014:**

- Serum amylase or lipase values less than 1.5 and 4 times the ULN, respectively, obtained at 2–4 hours post-ERCP have a very high negative predictive value for PEP (Evidence level 2+).

- ESGE suggests testing *serum amylase or lipase 2–6 hours after ERCP in patients presenting with pain and who are to be discharged on the day of ERCP*; patients with amylase or lipase values less than 1.5 and 4 times the ULN, respectively, can be discharged without concern about risk of PEP (Recommendation grade B).
Prediction of PEP

- A prospective study from Brazil that included 300 patients showed that serum hyperamylasemia <1.5 times the ULN at 4 hours and <2 times the ULN at 12 hours had a negative predictive value of 94% for the development of PEP.

- *Serum hyperamylasemia following ERCP had a poor positive predictive value for PEP.*
Medical agents for PEP prophylaxis
Pharmaceutical agents evaluated for the prevention of post-ERCP amylase elevation and/or pancreatitis

<table>
<thead>
<tr>
<th>Postulated mechanism of action</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of pancreatic secretion</td>
<td>Somatostatin</td>
</tr>
<tr>
<td></td>
<td>Octreotide</td>
</tr>
<tr>
<td></td>
<td>Glucagon</td>
</tr>
<tr>
<td></td>
<td>Calcitonin</td>
</tr>
<tr>
<td>Stimulation of pancreatic secretion and reduction of sphincter tone</td>
<td>Secretin</td>
</tr>
<tr>
<td>Reduction of sphincter tone</td>
<td>Nifedipine</td>
</tr>
<tr>
<td></td>
<td>Glyceryl trinitrate</td>
</tr>
<tr>
<td></td>
<td>Botulinum toxin</td>
</tr>
<tr>
<td></td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Inhibition of protease activation</td>
<td>Aprotinin</td>
</tr>
<tr>
<td></td>
<td>Gabaexate mesilate</td>
</tr>
<tr>
<td></td>
<td>C1-esterase inhibitor</td>
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<tr>
<td></td>
<td>Heparins</td>
</tr>
<tr>
<td></td>
<td>Ulinastatin</td>
</tr>
<tr>
<td>Antimicrobial agents</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Anti-inflammatory agents</td>
<td>Allopurinol</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
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<tr>
<td></td>
<td>Interleukin-10</td>
</tr>
<tr>
<td></td>
<td>Diclofenac</td>
</tr>
<tr>
<td>Anti-oxidants</td>
<td>Beta-carotene</td>
</tr>
<tr>
<td></td>
<td>N-acetyl cysteine</td>
</tr>
</tbody>
</table>

Courtesy of Silvano Loperfido, MD.
<table>
<thead>
<tr>
<th>Research class</th>
<th>Agent</th>
<th>Evidence</th>
<th>Benefit</th>
<th>Safety profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rectally administered NSAIDs</td>
<td>Very strong</td>
<td>Moderate</td>
<td>Very favorable</td>
</tr>
<tr>
<td>2</td>
<td>Nitroglycerin</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Favorable when administered sublingually</td>
</tr>
<tr>
<td>2</td>
<td>Bolus-administered somatostatin</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Favorable</td>
</tr>
<tr>
<td>2</td>
<td>Nafamostat</td>
<td>Strong</td>
<td>Moderate-high</td>
<td>Favorable</td>
</tr>
<tr>
<td>3</td>
<td>Topical epinephrine</td>
<td>Weak</td>
<td>Moderate-high</td>
<td>Very favorable</td>
</tr>
<tr>
<td>3</td>
<td>Aggressive intravenous lactated Ringers</td>
<td>Weak</td>
<td>Moderate-high</td>
<td>Moderate; favorable in young, healthy adults</td>
</tr>
<tr>
<td>3</td>
<td>Gabexate</td>
<td>Moderate</td>
<td>Unclear</td>
<td>Favorable</td>
</tr>
<tr>
<td>3</td>
<td>Ulinastatin</td>
<td>Moderate</td>
<td>Moderate-high</td>
<td>Favorable</td>
</tr>
<tr>
<td>3</td>
<td>Secretin</td>
<td>Weak</td>
<td>Moderate</td>
<td>Favorable</td>
</tr>
<tr>
<td>3</td>
<td>Antibiotics</td>
<td>Weak</td>
<td>Moderate-high</td>
<td>Favorable</td>
</tr>
</tbody>
</table>
Rectally administered nonsteroidal anti-inflammatory drugs.

- Four studies evaluating the protective effects of single-dose rectal indomethacin or diclofenac were reported between 2003 and 2008 and demonstrated conflicting but generally encouraging results.

- A meta-analysis of these RCTs, involving 912 patients, demonstrated a robust 64% reduction in PEP associated with rectal NSAIDs (relative risk, 0.36; 95% confidence interval, 0.22–0.60) and no increase in associated adverse events.
Agents Appropriate for Clinical Use

- A large-scale, multicenter, methodologically rigorous RCT was conducted to definitively evaluate the efficacy of prophylactic rectal indomethacin for preventing PEP in high-risk cases.
- In this study, rectal indomethacin was associated with 7.7% absolute risk reduction (number needed to treat=13) and 46% relative risk reduction in PEP (P= .005). Additional RCTs of low-dose rectal diclofenac, the combination of rectal diclofenac plus infusion somatostatin, and the combination of indomethacin plus sublingual nitroglycerin also demonstrated benefit.

Agents Appropriate for Clinical Use

- On the basis of available data, rectal NSAIDs (100 mg diclofenac or indomethacin immediately before or after ERCP) can be recommended for patients undergoing high-risk ERCP.
- Controversy remains regarding the role of NSAIDs in low-risk cases.
In light of the very low cost of a single dose of NSAIDs, the highly favorable safety profile, and prior meta-analyses suggesting that it is equally effective in low-risk cases, the time and resources necessary to conduct a definitive RCT may not be justified.

The European Society of Gastrointestinal Endoscopy recommends rectal indomethacin or diclofenac for almost all patients undergoing ERCP as a grade A recommendation.
Agents Appropriate for Clinical Use

▶ Statement 2014:

- NSAIDs reduce the incidence of PEP in patients at high as well as low risk for PEP; effective PEP prophylaxis has only been demonstrated using diclofenac or indomethacin administered rectally (Evidence level 1++).

- ESGE recommends routine rectal administration of 100mg of diclofenac or indomethacin immediately before or after ERCP in all patients without contraindication.
Agents Appropriate for Clinical Use

- An RCT of oral diclofenac, an underpowered study of intramuscular diclofenac, and a trial of intravascular valdecoxib did not demonstrate prophylactic benefit.
- As such, there are no existing data to support administration of prophylactic NSAIDs via any nonrectal route.
Nitroglycerin

- Nitroglycerin is a smooth muscle relaxant that may lower sphincter of Oddi (SO) pressure and increase pancreatic parenchymal blood flow.
- Seven placebo-controlled RCTs have examined the effect of nitroglycerin on PEP. Three of these studies demonstrated a significant reduction in PEP, whereas the remaining showed no benefit.
Promising Agents for Which There Is High Priority for Additional Research

- Five meta-analyses have demonstrated approximately 30%–40% reduction in risk associated with the use of nitroglycerin in the prevention of PEP.
- Because nitroglycerin is postulated to work by reducing SO pressure, it is unclear whether it would provide incremental benefit over pancreatic stent placement.
- Nevertheless, sublingual nitroglycerin may have a role in lower-risk cases, in resource-limited environments, or in place of pancreatic stent insertion.
Promising Agents for Which There Is High Priority for Additional Research

- **Transdermal administration** of nitroglycerin has yielded conflicting results, with RCTs showing no benefit and 1 achieving a positive outcome.

- One RCT evaluating the role of intravenous nitroglycerin in preventing PEP in moderate- to high-risk cases was terminated prematurely because of an interim analysis suggesting futility and a concerning frequency of adverse hemodynamic events.
A recent small comparative effectiveness RCT demonstrated that the combination of sublingual nitroglycerin plus rectal indomethacin was more effective than indomethacin alone in a study sample that largely did not receive a pancreatic stent.
Another methodologically rigorous large-scale multicenter RCT is warranted to confirm the effectiveness of combined sublingual nitroglycerin and rectal indomethacin in the appropriate patient population (high-risk cases in environments where stenting is not widely available).

In the interim, *sublingual nitroglycerin may be reasonable to consider in patients with an NSAID allergy or as an adjunct to rectal NSAIDs in high-risk cases that do not receive a prophylactic pancreatic stent.*
Statement 2010:

- Nitroglycerin reduces the incidence of PEP; however, when administered transdermally, it is ineffective (Evidence grade 1++). Side effects such as transient hypotension and headache may occur.
- We do not recommend the routine use of nitroglycerin for prophylaxis of PEP (Recommendation grade A).
Promising Agents for Which There Is High Priority for Additional Research

Statement 2014:
- Glyceryl trinitrate (GTN) may be effective in preventing PEP when administered sublingually.
- ESGE does not recommend the routine use of GTN for PEP prophylaxis.
Bolus-administered somatostatin.

- Somatostatin is a potent inhibitor of pancreatic exocrine function and may therefore prevent or mitigate the pathophysiological processes that lead to pancreatic inflammation.
- Five of the 11 RCTs comparing somatostatin with placebo have yielded positive results.
Benefit has been demonstrated more consistently with bolus administration (3 of 5 published studies positive) than with infusion (3 of 8 published studies positive).

All 4 published meta-analyses have suggested benefit associated with somatostatin, especially when delivered as a bolus, with a number needed to treat of approximately 12.

In addition, an RCT of somatostatin in combination with diclofenac demonstrated benefit.
In summary, somatostatin is not appropriate for clinical use; a confirmatory RCT of bolus somatostatin is necessary.
Promising Agents for Which There Is High Priority for Additional Research

Statement 2010:

- Octreotide administration did not affect the overall incidence of PEP when data from eight high quality trials were pooled (Evidence level 1+++).

- **Prophylaxis with octreotide is not recommended** (Recommendation grade A). In future studies the efficacy of prophylactic administration of octreotidte should be evaluated using a dose greater than or equal to 0.5mg.
A meta-analysis that compared octreotide vs. placebo (18 RCTs, 3171 patients) found no significant difference in PEP incidence (OR 0.77; 95%CI 0.56–1.05).

However, at post hoc subgroup analysis, dosage seemed to have an impact: when the compound was given at a dose≥0.5mg (6 RCTs; 1470 patients) the OR for developing PEP dropped to 0.45 (95%CI 0.28–0.73; NNT=25), whereas the agent proved ineffective at a dosage<0.5mg.
A second meta-analysis assessed the effect of somatostatin (10 RCTs) and of octreotide (7 RCTs) in a total of 3818 patients.

Overall, somatostatin reduced the risk of PEP (RR 0.52; 95%CI 0.30–0.90), while octreotide was not effective (RR 0.86; 95%CI 0.45–1.63).
Subgroup analyses suggested that higher doses of somatostatin (3mg given as an infusion over 12 hours) or lower doses (250μg) given as bolus injection may be most efficacious, especially for the subgroup of patients at relatively higher risk for PEP, i.e., those undergoing pancreatic duct injection (OR 0.35; 95%CI 0.15–0.82) and biliary sphincterotomy (OR 0.33; 95%CI 0.16–0.70).

With regard to octreotide, subgroup analysis showed a protective effect when administered at high dose (OR 0.42; 95%CI 0.20–0.90).
Promising Agents for Which There Is High Priority for Additional Research

**Nafamostat**

- Nafamostat mesylate is a low-molecular-weight protease inhibitor that inhibits trypsin, a proteolytic enzyme considered to play an initial role in the pathogenesis of pancreatitis.
- Nafamostat has a half-life that is 20 times longer and a potency 10–100 times greater than gabexate mesylate, another protease inhibitor that has been the focus of much prior research and has been used in clinical practice in parts of the world.
Three RCTs have identified a significant reduction in PEP associated with nafamostat: Yoo et al, n=266 (2.8% vs 9.1% in the nafamostat group vs control group, P = .03), Choi et al, n= 704 (3.3% vs 7.4% in the nafamostat vs control group, P = .018), and Park et al, n= 608 (three arms: 13.0% in control group vs 4.0% in 20-mg nafamostat group vs 5.1% in 50-mg nafamostat group, P < .0001).
Promising Agents for Which There Is High Priority for Additional Research

- A recent meta-analysis demonstrated approximately 60% benefit associated with nafamostat (relative risk, 0.41; 95% confidence interval, 0.28–0.59).
- Major concerns related to the use of nafamostat are its high cost, need for a prolonged intravenous infusion (7–25 hours), and apparent absence of benefit in high-risk cases.
Statement 2014:

A novel protease inhibitor, nafamostat, is likely effective for preventing PEP in patients at low risk of PEP but not in high risk patients.
Topical epinephrine

- Epinephrine sprayed directly on the papilla at the time of ERCP has been postulated to prevent PEP through direct relaxation of the SO and reduction of papillary edema by decreasing capillary permeability.
- Two RCTs have been published with conflicting results.
• On the basis of available data, topical epinephrine is not appropriate for clinical use.

• Additional exploratory research is necessary, but a large-scale methodologically rigorous RCT in an appropriate patient population may be warranted.
Statement 2010:

There is no evidence that drugs reducing sphincter of Oddi pressure (other than nitroglycerin) [namely, botulinum toxin, epinephrine, lidocaine, and nifedipine] reduce the incidence of PEP.
Statement 2014:

- **ESGE does not recommend the routine use of epinephrine for PEP prophylaxis.**
- No changes concerning botulinum toxin, lidocaine, and nifedipine.
Intravenous fluid resuscitation

- Aggressive intravenous fluid resuscitation with lactated Ringer’s solution (which attenuates the acidosis that appears to promote zymogen activation and pancreatic inflammation) may be an effective intervention for PEP by favorably affecting physiologic (pH) and microanatomic (pancreatic parenchymal perfusion) parameters.
Research Class 3: Additional Exploratory Research Necessary to Justify a Confirmatory Randomized Controlled Trial

- Only 1 small hypothesis-generating RCT has demonstrated benefit, although intravenous fluid resuscitation has a well-established role in treating non-ERCP pancreatitis.

- On the basis of available RCT data pertaining to PEP, aggressive intravenous fluid is not appropriate for clinical use but may be reasonable to use in clinical practice on the basis of non-ERCP pancreatitis data, safety profile, and widespread availability.
Research Class 3: Additional Exploratory Research Necessary to Justify a Confirmatory Randomized Controlled Trial

- Based on a pilot study in 62 patients, intensive hydration in the periprocedural period with intravenous lactated Ringer’s solution appears to reduce PEP incidence.
- None of the patients who received aggressive hydration developed PEP, compared with 17% of patients who received standard hydration (P = 0.016). No patients had evidence of volume overload.
- Two observational studies support this strategy of hydration for attenuating the severity of PEP.
Statement 2014:

- In a pilot study, intensive hydration seemed to effectively prevent PEP.
- Large-scale RCTs to establish an evidence-based approach to intensive hydration are needed.
Gabexate mesylate

- Gabexate mesylate is a protease inhibitor with a short half-life that may prevent PEP by inhibiting the activation of trypsin, an important initial component in the inflammatory cascade that leads to pancreatitis.
- RCT data are conflicting, but 6 of 7 meta-analyses published after 2006 have failed to demonstrate prophylactic benefit.
On this basis, gabexate is not appropriate for clinical use.

Additional exploratory research is necessary but is of lower priority than research on nafamostat and several other class 3 agents (epinephrine, intravenous fluids, and antibiotics).
Statement 2010:

- Prophylaxis with **gabexate or ulinastatin** does not reduce the incidence of PEP (Evidence 1++).
- **Neither drug is recommended for prophylaxis of PEP** (Recommendation grade A).
Statement 2014:

- Some meta-analytical results seem to support the benefit of gabexate and ulinastatin at high doses for averting PEP but *their clinical use cannot be recommended* owing to the discordance of the data.
Secretin

- A dose of intravenous secretin administered immediately before ERCP (with a second dose administered selectively during ERCP) was found to reduce the risk of PEP by approximately 40% in a mixed population of patients in a large single-center RCT.

- However, the definition of PEP did not include measurement of serum lipase or amylase and was primarily based on postprocedural pain.
Research Class 3: Additional Exploratory Research Necessary to Justify a Confirmatory Randomized Controlled Trial

- Furthermore, the study predated routine prophylactic stent placement and did not use an intention-to-treat analysis.
- On this basis, the results remain hypothesis-generating, and *secretin is not appropriate for clinical use*. Additional exploratory research is necessary.
Antibiotics

- For antibiotics, a single, small RCT of low methodological quality demonstrated that 2 g ceftazidime administered intravenously 30 minutes before ERCP reduced the risk of PEP.
- Because an infectious etiology for PEP is biologically plausible, additional exploratory research is necessary.
- *On the basis of available data, antibiotics are not appropriate for clinical use to prevent PEP.*
Statement 2010:
- Ceftazidime reduced the incidence of PEP in a single study (Evidence grade 1—). Further data are needed before recommending ceftazidime for the prophylaxis of PEP (Recommendation grade C).

Statement 2014:
- Antibiotics have not been proven effective in PEP prophylaxis; further data are needed (Recommendation grade C).
Research Class 4: Lowest Research Priority at This Time—Agent Unlikely to Be Effective or There Are Inadequate Data to Determine Status

- This agents have been minimally studied and/or have demonstrated predominantly negative results.
- **Agents with predominantly negative results in both RCTs and meta-analyses include allopurinol, antioxidants and corticosteroids.**
**Research Class 4:** Lowest Research Priority at This Time—Agent Unlikely to Be Effective or There Are Inadequate Data to Determine Status

▶ *Statement 2010, 2014:*

- There is no evidence that glucocorticoids, antioxidants, heparin, interleukin-10, or some anti-inflammatory drugs (other than diclofenac and indomethacin), such as pentoxifylline, semapimod, and the recombinant platelet-activating factor acetylhydrolase, reduce the incidence of PEP (Evidence levels from 1–to 1++).

- None of these drugs is recommended for PEP prophylaxis (Recommendation grade A).
The efficacy of glucocorticoids for PEP prophylaxis was evaluated in two meta-analyses that included 6 RCTs; the incidence of PEP was not significantly different in the glucocorticoids vs. the control group (11.8% vs. 10.6%, respectively).

Three RCTs that evaluated interleukin-10 have yielded contradictory results.
Subcutaneous **heparin** was not found to reduce PEP incidence in 2 RCTs.

Drugs potentially reducing the sphincter of Oddi pressure (other than GTN and topical epinephrine), including **botulinum toxin, lidocaine, and nifedipine, have not been found to reduce PEP incidence in RCTs**
• Oxygen-derived free radicals contribute to the pathogenesis of acute pancreatitis by inducing capillary-endothelial injury, which leads to an increase in capillary permeability.

• Drugs that prevent the generation of, and/or inactivate, free radicals include **allopurinol and n-acetylcysteine**, respectively.
Research Class 4: Lowest Research Priority at This Time—Agent Unlikely to Be Effective or There Are Inadequate Data to Determine Status

- Three antioxidant agents, namely allopurinol, N-acetylcysteine, and natural beta-carotene were not found to be effective in preventing PEP in 5 RCTs and one meta-analysis
Pancreatic stent placement for PEP prophylaxis
Pancreatic sphincter hypertension is a significant risk factor for post-ERCP pancreatitis, which may explain the high risk of pancreatitis in patients with sphincter of Oddi dysfunction.

There is prolonged alleviation of ductal obstruction when pancreatic stents are placed. Typically, 3-5 French (Fr) gauge, unflanged, plastic pancreatic stents are used.
Statement 2010:

- Prophylactic pancreatic stent placement is recommended to prevent PEP in patients who are at high risk for development of PEP. Short, 5-Fr diameter, plastic pancreatic stents are currently recommended.

- Passage of the stent from the pancreatic duct should be evaluated within 5 to 10 days of placement and retained stents should be promptly removed endoscopically (Evidence level 1+; Recommendation grade A).
Statement 2014:

- Prophylactic pancreatic stenting decreases the risk of PEP in high risk and mixed-case groups; *it nearly eliminates the risk of severe PEP.* 5-Fr pancreatic stents are more efficacious than 3-Fr stents in preventing PEP.
- ESGE recommends the placement of 5-Fr pancreatic stents in cases at high risk of PEP.
Chahal et al compared the outcomes of a short straight 5 French stent without an inner flange with an unflanged long single pigtail 3 French stent.

They found a significantly higher placement failure rate in the 3 French group (8.3% vs 0%, \( P = 0.0003 \)), a higher spontaneous dislodgement rate in the 5 French group (98% vs 88% for 3 Fr, \( P = 0.0001 \)) and a non-significant higher pancreatitis rate (14% vs 9%, \( P = 0.3 \)).
Two meta-analyses have demonstrated that, in patients at high risk of PEP, prophylactic pancreatic stent placement significantly reduces the incidence of PEP.

The OR was 0.44 (95 %CI 0.24–0.81), with an absolute risk reduction of 12.0% (95 %CI 3.0–21.0).
A multicenter RCT (201 patients) showed a decreased incidence of PEP when prophylactic pancreatic stent placement was performed, regardless of the concomitant occurrence of other known risk factors for PEP (PEP incidence in the stent vs. no-stent group, 3.2% vs. 13.6%, respectively; P=0.019).

In these studies, the risk of severe PEP was nearly eliminated following successful placement of a prophylactic pancreatic stent. *Pancreatic stent placement was shown to be cost-effective only in patients at high risk for PEP.*
Ameta-analysis of 14 RCTs with a total of 1541 patients showed a significant reduction in the incidence and the severity of PEP when prophylactic pancreatic stenting was used.

In addition, subgroup analysis showed that pancreatic stenting reduced the risk of PEP in high risk and mixed-case groups.
In a network meta-analysis, prophylactic pancreatic stenting alone was shown to be less effective than NSAIDs alone, and the combination of NSAIDs with prophylactic pancreatic stenting did not further reduce the risk of PEP.

• The ideal stent characteristics for PEP prophylaxis and the optimal duration of stent placement are not definitively known.

• However, a network meta-analysis showed that the probabilities of 5-Fr and 3-Fr stents being ranked as the most efficacious for the prevention of PEP were 96.8% vs. 3.1%, respectively, with 5-Fr single-pigtail, unflanged stents and 5-Fr straight, flanged stents producing similar results.

Afghani E, Akshintala VS, Khashab MA et al. 5-Fr vs. 3-Fr pancreatic stents for the prevention of post-ERCP pancreatitis in high-risk patients: a systematic review and network meta-analysis. Endoscopy 2014; 46: 173–80
Furthermore, placement of 5-Fr stents requires fewer guidewires and is easier than that of 3-Fr stents.

It is believed that stents need to remain in place for a minimum of 12–24 hours to provide benefit, since removal at the end of ERCP negates the protection from PEP and early outward migration may also result in PEP.
Adverse events related to attempted prophylactic pancreatic stenting include PEP, stent-induced pancreatic ductal damage, and inward migration.

Removal of proximally migrated small-diameter stents can be technically challenging, if not impossible.
Although prophylactic pancreatic duct stenting is a cost-effective strategy for the prevention of post-ERCP pancreatitis for high-risk patients, higher incidence of severe pancreatitis has been reported in patients with failed pancreatic duct stenting.

Also, pancreatic duct stenting is not always technically feasible with reported failure rate ranging from 4 to 10%.
When should a pancreatic stent be placed to prevent PEP

- Before precut (access) papillotomy
- Before/after biliary sphx for SOD
- Pancreatic spincterotomy
- Endoscopic papillotomy
- After manometry of pancreatic instrumentation for suspected SOD
- Pancreatic brush cytology
- After difficult cannulation or repeated panc duct injection in point with **risk factors**

*Freeman and guda, Gastroint endos 2004*
ERCP techniques
Statement 2010, 2014:

- There is no evidence that the incidence of PEP is influenced by patient position during ERCP (Evidence level 2++).
- Therefore, no recommendation is made regarding patient position.
Cannulation attempts

- Trauma resulting from repeated attempts at biliary cannulation has been proven to be a risk factor for the development of PEP (Evidence level 2++).
- ESGE recommends keeping the number of cannulation attempts as low as possible (Recommendation grade B).
Cannulation attempts

- The rendezvous technique allows cannulation trauma to be minimized, and has been used in most studies that evaluated intraoperative endoscopic sphincterotomy.
- A meta-analysis assessed 5 RCTs that compared preoperative vs. intraoperative endoscopic sphincterotomy; PEP was less frequent (2.2% compare to 3.6%) with the latter approach while the incidence of other ERCP-related complications was similar with both techniques.
Contrast medium

▶ *Statement 2010, 2014:*
- Injection of contrast medium into the pancreatic duct is an independent predictor of PEP (Evidence level 1+).
- If pancreatic duct injection occurs incidentally or is required, the number of injections and volume of contrast medium injected into the pancreatic duct should be kept as low as possible (Recommendation grade B).
Contrast medium

- Compared with traditional, high-osmolality contrast agents, low-osmolality contrast agents are costlier but are not associated with reduction in the rates of PEP (Evidence level 1–). The routine use of these agents for ERCP is not recommended (Recommendation grade B).

- The hypothesis that low-osmolality contrast agents would be less harmful than high-osmolality contrast agents because of less important fluid shifts in the pancreas was invalidated in a meta-analysis of 13 RCTs that involved 3381 patients.
Use of carbon dioxide (CO2) as a replacement for air for luminal insufflation during ERCP does not influence the incidence of PEP but decreases the incidence and severity of post-procedural abdominal pain (Evidence level 1+).

Carbon dioxide is recommended for insufflation, and might be particularly useful for outpatient ERCPs, to reduce post-procedural abdominal pain and to avoid confusion with PEP (Recommendation grade B).
Carbon dioxide

- Because of its higher solubility in water compared with nitrogen and oxygen, the main components of air, carbon dioxide is cleared from the bowel following endoscopy much faster than air (through the bloodstream and respiration).
Cannulation techniques

▶ **Statement 2010, 2014:**

- For deep biliary cannulation, the wire-guided technique reduces the risk of PEP and increases the success rate of primary cannulation when compared with the standard contrast-assisted method (Evidence level 1++).
- The wire-guided technique is recommended for deep biliary cannulation (Recommendation grade A).
Statement 2010, 2014:

- The incidence of post-sphincterotomy pancreatitis is not influenced by the type of electrosurgical current used (whether pure-cut or blended) (Evidence level 1+).

- Blended current is recommended for biliary sphincterotomy, particularly in patients at high risk of bleeding (Recommendation grade A).
Electrosurgical current

- As pure-cut current produces less edema than blended current, it was hypothesized that it might reduce the incidence of PEP after biliary sphincterotomy.
- A meta-analysis of four RCTs that included 804 patients found no significant difference in the incidence of PEP following the use of pure vs. blended current. However, the incidence of bleeding was significantly higher when pure-cut current was used.
Difficult biliary cannulation: definition

Statement 2014:

- ESGE recommends that future studies define difficult biliary cannulation in an intact papilla as any of the following: cannulation attempts of duration >5 minutes, >5 attempts, or 2 pancreatic guidewire passages.

- Any of the following factors was associated with a PEP incidence of >10% during wire-guided cannulation of a native papilla: cannulation attempts of duration >5 minutes, >5 attempts, or 2 pancreatic guidewire passages.
Statement 2010:

Pancreatic guide wire assistance (the so-called “double guidewire” (DGW) technique) may facilitate biliary cannulation mostly in the case of inadvertent but repeated cannulation of the pancreatic duct; if this method is used, a pancreatic stent should be placed for PEP prophylaxis (Recommendation grade B).
**Statement 2014:**

- In cases of difficult biliary cannulation, pancreatic guidewire (PGW) placement allows biliary cannulation in a proportion of cases similar to persistence in attempting cannulation with standard cannulation techniques (or precut if it is used as a backup technique), but the risk of PEP is likely higher.

- In such circumstances, PEP is effectively prevented by prophylactic pancreatic stenting (Evidence level 1—).
Difficult biliary cannulation: Pancreatic guidewire-assisted technique

- In the PGW-assisted technique, a guidewire is inserted in the main pancreatic duct to facilitate deep biliary cannulation by straightening the papillary anatomy and to prevent repeated cannulation of the pancreatic duct.

- *ESGE suggests restricting the use of a PGW as a backup technique to cases with repeated inadvertent cannulation of the pancreatic duct;*
Difficult biliary cannulation: Pancreatic guidewire-assisted technique

- In two RCTs that compared the PGW vs. the precut techniques, success rates of biliary cannulation were similar but, in one of the RCTs, the PGW technique was plagued by a higher incidence of PEP.
- Another RCT showed that prophylactic pancreatic stenting significantly decreased the incidence of PEP after the PGW technique had been used.
- In a retrospective study that included 146 patients, prophylactic pancreatic stenting was always attempted after the PGW technique had been used, and failed prophylactic pancreatic stenting was the only independent predictor of PEP.
Difficult biliary cannulation: Precut biliary sphincterotomy

▶ Statement 2014:
- In cases of difficult biliary cannulation, early precut is associated with a lower PEP incidence than persistent attempts using the standard approach but the overall success and complication rates are similar with both approaches.
- Needle-knife fistulotomy seems to be associated with fewer complications, including PEP, compared with other precut techniques.
Difficult biliary cannulation: Precut biliary sphincterotomy

- Precut biliary sphincterotomy can be done by different techniques: needle-knife precut starting at the orifice of the papilla (conventional precut), needle-knife above the orifice (fistulotomy), transpancreatic sphincterotomy (septotomy) and needleknife over a pancreatic stent.
Difficult biliary cannulation: Precut biliary sphincterotomy

- In a retrospective study comparing different precut techniques, the risk of PEP was significantly lower after fistulotomy (2.6 %) compared with conventional precut (20.9 %) and pancreatic septotomy (22.4 %); the overall complication rate was also significantly lower after fistulotomy vs. other precut techniques.
Difficult biliary cannulation: Precut biliary sphincterotomy

- In another retrospective study of needle-knife fistulotomy performed in 204 patients, complications (mostly PEP) progressively increased with decreasing common bile duct (CBD) diameter, up to 14% in patients with a CBD diameter <4mm.
- Two retrospective studies compared transpancreatic septotomy and needle-knife precut (with pancreatic stenting or not) for biliary access; they found no significant differences in terms of PEP, overall complication and overall success rates.
Difficult biliary cannulation: Precut biliary sphincterotomy

- Needle-knife precut assisted by pancreatic stenting has been proposed for reducing PEP.
- One RCT found that, compared with stent removal at the end of the procedure, leaving the stent for 7–10 days reduces the incidence and severity of PEP (P<0.05 for both comparisons).
Difficult biliary cannulation: Precut biliary sphincterotomy

- ESGE suggests that needle-knife fistulotomy should be the preferred precut technique in patients with a bile duct dilated down to the papilla.

- Conventional precut and transpancreatic sphincterotomy present similar success and complication rates; if conventional precut is elected and pancreatic cannulation is easily obtained, ESGE suggests attempting to place a small-diameter (3-Fr or 5-Fr) pancreatic stent to guide the cut and leaving the pancreatic stent in place at the end of ERCP for a minimum of 12–24 hours (Recommendation grade B).
Statement 2010:

- Compared with endoscopic sphincterotomy, endoscopic papillary balloon dilation (EPBD) using small-caliber balloons (≤10 mm) is associated with a significantly higher incidence of PEP and significantly less bleeding (Evidence level 1+++).
- EPBD is not recommended as an alternative to sphincterotomy in routine ERCP but may be useful in patients with coagulopathy and altered anatomy (e.g. Billroth II) (Recommendation grade A).
- If balloon dilation is performed in young patients, the placement of a prophylactic pancreatic stent should be strongly considered (Evidence level 4; Recommendation grade D).
Statement 2014:

ESGE does not recommend endoscopic papillary balloon dilation as an alternative to sphincterotomy in routine ERCP, but it may be advantageous in selected patients; if this technique is used, the duration of dilation should be longer than 1 minute (Recommendation grade A).
The use of EPBD may be advantageous compared with endoscopic sphincterotomy, by decreasing clinically significant bleeding in patients with coagulopathy, for preserving sphincter of Oddi function in younger patients, and in patients with altered anatomy (Billroth II) where sphincterotomy is technically difficult.

In two meta-analyses, the use of EPBD resulted in a lower success rate than endoscopic sphincterotomy for the initial removal of biliary stones, with a significantly higher incidence of PEP and significantly lower incidence of bleeding.
A meta-analysis that included 12 RCTs (1649 patients) indicated that duration of EPBD is inversely associated with the incidence of PEP: short (≤1 minute) EPBD was associated with a higher risk of PEP (OR 3.87; 95%CI 1.08–13.84) compared with endoscopic sphincterotomy (4 RCTs), but long EPBD inflation time (>1 minute) was not (OR 1.14; 95%CI 0.56–2.35) (6 RCTs).
A lower risk of PEP after long EPBD was also reported in the single RCT that compared long (5-minute) vs. short (1-minute) EPBD (RR 0.32; 95%CI 0.11–0.93).

The authors suggested that the increased risk of PEP after short EPBD might be related to inadequate balloon expansion resulting in a worsened compression of the pancreatic duct.
A meta-analysis that included 3 RCTs (496 patients) with a follow-up longer than 1 year showed that stone recurrence was less frequent after EPBD vs. endoscopic sphincterotomy (OR 0.48; 95% CI 0.26–0.90).

Another RCT that was not included in this meta-analysis and included 474 patients also reported that, in patients with biliary stones ≤8 mm, overall late complications and stone recurrence were less frequent after EPBD than after endoscopic sphincterotomy (5.3% vs. 17.3%, P=0.009; 4.4% vs. 12.7%, P=0.048, respectively) (mean follow-up, 55 months); the difference was not significant for patients with stones >8 mm.
Balloon dilation as a substitute for endoscopic sphincterotomy

- A retrospective cohort study with a median followup of 92 months also showed a lower incidence of common bile duct stone recurrence after EPBD vs. endoscopic sphincterotomy.
Statement 2014:

- For the extraction of difficult biliary stones, endoscopic sphincterotomy plus large-balloon dilation presents a risk of PEP similar to that of endoscopic sphincterotomy alone; it presents a lower bleeding risk and, possibly, lower overall morbidity and requires less use of mechanical lithotripsy.

- ESGE suggests performing endoscopic sphincterotomy plus large-balloon dilation in place of endoscopic sphincterotomy alone for the extraction of selected difficult biliary stones (Recommendation grade B).
In patients with a tapered distal bile duct or large biliary stones, endoscopic sphincterotomy followed by biliary dilation using a large-diameter (12–20mm) balloon has been proposed to facilitate stone extraction.
Statement 2014:

- ESGE recommends that all patients undergoing ERCP for known or suspected sphincter of Oddi dysfunction (SOD) receive rectal NSAIDs combined with pancreatic stenting.
- Pancreatic sphincter of Oddi manometry should be done using a modified triple-lumen perfusion catheter with simultaneous aspiration or a microtransducer catheter (non-water-perfused) (Recommendation grade B).
It is well documented that patients undergoing ERCP for known or suspected SOD are at high risk of PEP, regardless of whether sphincter of Oddi manometry (SOM) is performed.

Biliary SOM does not appear to increase the risk of PEP; pancreatic SOM is associated with an increased risk of PEP depending on the technique used.
Sphincter of Oddi manometry

- When water-perfused catheters are used to measure pancreatic sphincter pressure, continuous aspiration of fluid from the main pancreatic duct through one of the three manometry ports prevents overfilling of the duct, a known risk factor for PEP.
- The use of solid state manometry catheters decreases the risk of PEP as there is no perfusion or filling of the pancreatic duct.
The results of SOM should not influence the decision of whether to institute measures for prevention of PEP. As mentioned, all patients with known or suspected SOD are at high risk for PEP and should receive PEP prophylaxis.

Indeed one study showed that pancreatic stent placement reduced PEP in patients with an intact papilla undergoing SOM and when the manometry results were normal.
Recent data suggest that rectal NSAIDs are at least as effective as pancreatic stents in patients with SOD. However, the most evidence-based approach for preventing PEP in high risk cases remains the combination of rectal NSAIDs and prophylactic pancreatic stenting.

In the RCT mentioned above, patients who received rectal indomethacin and a pancreatic stent (n=247) had a PEP rate of 9.7% compared with 16.1% in those who received a stent alone (n=249) (P=0.04)
Sphincter of Oddi manometry

- To date, there are no clinical trial data examining whether rectal NSAIDs are effective when administered instead of prophylactic pancreatic stenting. The data apply mainly to the initial SOM or in patients with SOD and intact papillae.

- One exception to routine PEP prophylaxis might be in patients with SOD who have had dual sphincterotomy and continued pain who undergo repeat ERCP with re-evaluation.
Sphincter of Oddi manometry

- If both sphincters are found to be patent and/or only the biliary sphincter is studied, one might consider not placing a pancreatic stent.
- However, the risk of administration of one dose of rectal NSAIDS is so small that its use outweighs the risk of avoiding them.
Selection of measures for PEP prophylaxis
- **Statement 2010:**
  - For low-risk ERCPs, periprocedural rectal administration of nonsteroidal anti-inflammatory drugs (NSAIDs) is recommended.
  - For high risk ERCPs, prophylactic pancreatic stent placement should be strongly considered (Evidence level 1+; Recommendation grade A).
Statement 2014:

- ESGE recommends routine rectal administration of 100mg of diclofenac or indomethacin immediately before or after ERCP in all patients without contraindication.

- In addition to this, in cases at high risk for PEP, the placement of a 5-Fr prophylactic pancreatic stent should be strongly considered.
Sublingually administered GTN or 250μg somatostatin given in bolus injection might be considered as an option in high risk cases if NSAIDs are contraindicated and if prophylactic pancreatic stenting is not possible or successful (Recommendation grade A).
The following conditions are considered to represent **high risk** for PEP: endoscopic ampullectomy, known or suspected SOD, pancreatic sphincterotomy, precut biliary sphincterotomy, pancreatic guidewire-assisted biliary cannulation, endoscopic balloon sphincteroplasty, and presence of more than three of the risk factors listed in Table1 (definite or likely).

Procedures and patient conditions that do not fulfill these criteria are considered to represent low risk for PEP.
Patient-related risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected sphincter of Oddi dysfunction (SOD)</td>
<td>1.91 (1.37 - 2.65)</td>
<td>8.6% vs. 2.5%</td>
</tr>
<tr>
<td>Female gender</td>
<td>3.5 (1.1 - 10.6)</td>
<td>4.0% vs. 2.1%*</td>
</tr>
<tr>
<td>Previous pancreatitis</td>
<td>2.46 (1.93 - 3.12)</td>
<td>6.7% vs. 3.8%</td>
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<tr>
<td><strong>Likely risk factors</strong></td>
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<td></td>
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<tr>
<td>Previous PEP</td>
<td>8.7 (3.2 - 23.86)</td>
<td>30% vs. 3.5%</td>
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<tr>
<td>Younger age</td>
<td>Range of odds ratios: 1.09 - 2.87</td>
<td>6.2% vs. 2.6%</td>
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<tr>
<td>Nondilated extrahepatic bile ducts</td>
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<tr>
<td>Absence of chronic pancreatitis</td>
<td>1.87 (1.00 - 3.48)</td>
<td>4.0% vs. 3.1%</td>
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<tr>
<td>Normal serum bilirubin</td>
<td>1.89 (1.22 - 2.93)</td>
<td>4.15% vs. 1.43%</td>
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</tbody>
</table>

Procedure-related risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>Comparison</th>
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</thead>
<tbody>
<tr>
<td><strong>Definite risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannulation attempts duration &gt; 10 minutes²</td>
<td>1.76 (1.13 - 2.74)</td>
<td>3.8% vs. 10.8%</td>
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<tr>
<td>Pancreatic guidewire passages &gt; 1</td>
<td>2.77 (1.79 - 4.30)</td>
<td>2.9% vs. 9.5%</td>
</tr>
<tr>
<td>Pancreatic injection</td>
<td>2.2 (1.60 - 3.01)</td>
<td>3.3% vs. 1.7%</td>
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<tr>
<td><strong>Likely risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precut sphincterotomy³</td>
<td>2.3 (1.4 - 3.7)</td>
<td>5.3% vs. 3.1%</td>
</tr>
<tr>
<td>Pancreatic sphincterotomy</td>
<td>3.07 (1.64 - 5.75)</td>
<td>2.6% vs. 2.3%</td>
</tr>
<tr>
<td>Biliary balloon sphincter dilation</td>
<td>4.51 (1.51 - 13.46)</td>
<td>9.3% vs. 2.6%</td>
</tr>
<tr>
<td>Failure to clear bile ductal stones</td>
<td>3.35 (1.33 - 9.10)</td>
<td>1.7% vs. 1.6%</td>
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<tr>
<td>Intraductal ultrasound (IDUS)³⁴²</td>
<td>2.41 (1.33 - 4.39)</td>
<td>8.37% vs. 2.76%</td>
</tr>
</tbody>
</table>