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Endoscopic Retrograde Cholangiopancreatography-Related Acute Pancreatitis – Identification, Prophylaxis and Treatment

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1. Introduction

Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP) [1–4]. The reported incidence ranges from 1.8% to 7.2% in most prospective series [5–9] but can be up to 30%, depending on the criteria used to diagnose pancreatitis, the type and duration of patient follow-up, and the type of case mix [10]. More commonly, hyperamylasemia occurs in up to 30% of patients undergoing ERCP [11].

As the indications for ERCP have increased, a greater focus on recognizing and preventing complications has emerged. The recognized complications of ERCP include asymptomatic hyperamylasemia, cardiopulmonary depression, hypoxia, aspiration, intestinal perforation, bleeding, cholangitis, adverse medication reactions, sepsis, acute pancreatitis, and death. Post-ERCP pancreatitis (PEP) remains the leading cause of morbidity and mortality after the procedure and is the focus of studies designed to improve procedural outcomes [12,13]. Some studies have suggested that the rates of PEP can be reduced, but the incidence of pancreatitis remains high particularly in at-risk patient populations. Pancreatitis continues to be the major cause of postprocedure morbidity and mortality [14–17].

2. Diagnosis of PEP

PEP was defined initially as the presence of new pancreatic-type abdominal pain associated with at least a threefold increase in serum amylase concentration occurring 24 h after an ERCP, with pain severe enough to require admission to the hospital or to extend an
admitted patient’s length of stay. This definition was developed in 1991 based upon approximately 15,000 procedures evaluated during a consensus workshop. The severity of PEP was defined according to the length of stay (mild pancreatitis 2–3 d, moderate pancreatitis 4–10 d, and severe pancreatitis >10 d, or intensive care admission or local complications secondary to pancreatitis) [18]. This consensus definition has not been adopted uniformly and many studies published after 1991 have used different criteria to define PEP and to classify its severity. Several studies have challenged the serum amylase threshold of three times the upper limit of normal, arguing that this definition is not always consistent with the clinical and morphological features of pancreatitis [19–25]. Other criteria for serum amylase elevation include twice [23–26], four times [6,27,28] and five times [20,21,28–30] the upper normal limit.

There is also heterogeneity in the criteria used to classify the severity of PEP in published studies. Some authors have used the Atlanta criteria published in 1993 to define severity [31–33]. The Atlanta criteria incorporate systemic complications of PEP by integrating the Acute Physiologic and Chronic Health Evaluation (APACHE) II classification and Ranson’s criteria to define the severity [33–35]. An APACHE II score of >8 or a Ranson’s score of ≥3 of 11 criteria are defined as severe PEP. Some studies have used the APACHE II classification alone to grade the severity of PEP [36]. Other studies have used combinations of criteria to define the presence and severity of PEP or have established unique definitions [26,31,37–40]. The heterogeneity of criteria in the literature on PEP hinders direct comparison of the published clinical trials.

3. Pathophysiology of PEP

The pathophysiology of PEP is not well understood. Mechanical, hydrostatic, chemical, enzymatic, allergic, thermal, cytokine, oxidative, and microbiological factors have all been proposed as causes [32,41–46]. Many studies suggest that PEP results from mechanical trauma, causing injury to the papilla or pancreatic sphincter and subsequent swelling of the pancreatic duct and obstruction to the flow of pancreatic enzymes. This hypothesis remains controversial, and no consensus about the pathogenesis of PEP has been established.

The cascade of events leading to acute pancreatitis is characterized by three phases. The first phase is characterized by premature activation of trypsin within the pancreatic acinar cells [47]. The second phase is characterized by intrapancreatic inflammation. The third phase is characterized by extrapancreatic inflammation [47]. Inflammation in the second and third phases has been described as a four-step process: (1) activation of inflammatory cells; (2) chemoattraction of activated inflammatory cells; (3) activation of adhesion molecules causing binding of inflammatory cells to the endothelium; and (4) migration of activated inflammatory cells into areas of inflammation [47]. Recent studies have evaluated proinflammatory markers (TNF, interleukin-1 (IL-1), IL-6, PAF, and IL-10) in the setting of PEP [48–51]. Although three randomized controlled trials (RCTs) suggested a protective effect of low- or high-dose (4 μg/kg or 20 μg/kg) IL-10 given intravenously 15–30 min before ERCP [52], subsequent studies using similar IL-10 protocols did not support these findings [53,54]. Although not demonstrated at present, modulation of proinflammatory pathways might be an appealing goal for studies evaluating PEP and the systemic inflammatory response.
4. Procedural-related factors associated with PEP

Although the triggers of the inflammatory cascade are not well understood, procedural- and patient-related factors have been clearly associated with the incidence of PEP. ERCP is the most technically difficult endoscopic procedure performed by trainees and experienced endoscopists in both inpatient and outpatient settings. Whereas trauma to the duodenum or papilla during endoscopy without cannulation rarely causes pancreatitis [55], cannulation of the papilla, especially in moderate to difficult cases, is associated with high rates of PEP. Procedures involving multiple (>1–4) or failed attempts at cannulation, multiple pancreatic injections (≥2–5), pancreatic acinarization, and prolonged cannulation time (>10 min) are associated with PEP. The following factors have also been associated with a higher risk for developing PEP: operator experience, ampullary balloon dilation, precut access sphincterotomy, endoscopic sphincterotomy (ES), sphincter of Oddi manometry, distal common bile duct diameters of ≤1 cm, presence of a pancreatic stricture, papillectomy, and procedures not involving stone removal [45,56–59] (Table 1).

<table>
<thead>
<tr>
<th>Patient related factors</th>
<th>Procedure related factors</th>
<th>Operator/technical related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age.</td>
<td>Multiple pancreatic duct injections.</td>
<td>Inadequate training and/or experience</td>
</tr>
<tr>
<td>Female gender.</td>
<td>Difficult cannulation.</td>
<td>Trainee involvement in procedure</td>
</tr>
<tr>
<td>Prior history of post-ERCP pancreatitis.</td>
<td>Precut access.</td>
<td></td>
</tr>
<tr>
<td>Patients with normal serum bilirubin.</td>
<td>Balloon dilation.</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Factors Increasing the Risk of Post-ERCP Pancreatitis.

4.1 Operator experience

Although there is no established mandate for the procedure volume to develop competence in ERCP, a prospective study published in 1996 evaluated the number of supervised ERCPs a physician must perform to achieve procedural competence and reported that at least 180 procedures are required [60]. In the United States, the American Society for Gastrointestinal Endoscopy and the American College of Gastroenterology have published quality indicators for ERCP. Competent endoscopists are expected to be able to perform sphincterotomy, clear the common bile duct of stones, provide relief of biliary obstruction, and successfully place stents for bile leaks in ≥85% of patients [61].

Few studies have been published on operator experience in ERCP, and this issue remains controversial. A recent study in Austria showed that a case volume of >50 ERCPs per year had higher success and lower overall complication rates [62]. It is generally agreed that the case mix at high volume and in academic referral centers may include a larger proportion of
difficult and high-risk cases, which may confound the relationship between experience and complication rates. Although operator experience is felt to be critical for high-quality outcomes, many large prospective and retrospective trials have not shown consistent correlations between inexperience and PEP. Higher rates of bleeding have been reported after endoscopic sphincterotomy with a mean case volume of <1 per wk [14], and trainee involvement was associated with severe or fatal complications in a recent retrospective analysis [63]. However, a large prospective trial found that case volume had no effect on the incidence of PEP [24]. A prospective study of ERCP in the United Kingdom (UK) in 2007 based on self-reported surveys demonstrated that 15% of all credentialed endoscopists performed <50 ERCPs per year compared with 61% of those in training; 11% of deaths occurred after procedures by endoscopists who performed <50 ERCPs per year. Although the rates of PEP were low at 1.5%, the success rates for bile duct stone extraction and biliary stent placement were 62% and 73%, respectively. The authors concluded that in the UK there is a need for fewer operators and greater experience in those performing therapeutic endoscopy [64]. In the same year, a study in France showed no risk associated with operator inexperience [65].

4.2 Cannulation techniques
Cannulation techniques to access the pancreatic and biliary ducts include the use of a sphincterotome or straight or curved catheter with guide wires or contrast injection. When an initial attempt at cannulation fails, access may be achieved after placement of a pancreatic guide wire or stent to help guide the endoscopist toward the common bile duct and away from the pancreatic duct. Precut access papillotomy is used frequently in referral centers when conventional approaches fail. Rare or experimental techniques such as the use of endoscopic scissors or endoscopic dissection with a cotton swab have been reported but are used rarely in clinical practice [66]. Compared with a standard catheter, the use of a sphincterotome may decrease the number of failed attempts to obtain biliary access, the time required to cannulate the common bile duct, and the rate of PEP [67,68]. Selective sphincterotome cannulation with a guide wire may reduce the rate of PEP compared with cannulation with contrast injection [67–71]. In 2008, a large prospective controlled trial randomized 430 patients into sphincterotome plus guide wire versus conventional cannulation arms. The series demonstrated a significantly higher rate of cannulation with guide wires but failed to show a significant difference in the rate of PEP between the two approaches [72]. The authors reported an 8.8%–14.9% increased risk of PEP after >4 attempts at the papilla, highlighting the importance of cannulation with fewer attempts. These findings are consistent with those of previous studies [7,72].

4.3 Pancreatic duct injection
Multiple pancreatic duct injections (≥2–5) [6,7,15,24,58] and pancreatic acinarization [6,12,15,30] are recognized as risk factors for PEP. Differences in the osmolality and ionicity of contrast media have been studied with varying results in terms of impact on PEP [25,28,59,73–75]. A recent meta-analysis of 13 RCTs found no significant difference between high- and low-osmolality contrast media [75]. Earlier studies suggested that there is a decreased risk of PEP with the use of nonionic contrast agents [73], although this has not been demonstrated consistently [74]. One large retrospective analysis of 14 331 ERCPs suggested that less opacification of the pancreatic duct in the head than in the tail produced
significantly lower rates of PEP [59]. Despite the variable findings, clinical trial data suggest that hydrostatic pressure may play a role in the development of pancreatitis.

4.4 Pancreatic duct stenting
The theory that PEP is caused by pancreatic duct obstruction is supported by most RCTs, which show a decreased incidence of pancreatitis in high-risk patients after placement of a pancreatic duct stent [76–84]. The three largest published studies to evaluate the rate of pancreatitis with pancreatic duct stent placement reported significant decreases, by 10.4%, 14.8%, and 52.3%, in the rates of PEP in patients treated with stent placement versus those without stent placement [78,79,85]. Although pancreatic duct stenting decreases the risk of PEP, it has not been shown to prevent it. Despite stent placement, pancreatitis occurs in 2.0%–14% of patients [78,79,81,83,84], and some studies have failed to demonstrate a significant protective effect [59,83,84]. Eight RCTs, multiple prospective uncontrolled studies, and five meta-analyses have compared the rates of pancreatitis after ERCP with and without prophylactic pancreatic stent placement [86–90]. Prophylactic stent placement reduces the incidence of PEP, particularly in high-risk patients, and virtually eliminates the risk of severe pancreatitis.

Many studies have criticized the absence of intent-to-treat analysis (i.e., patients with attempted but unsuccessful stent placement were excluded). However, a meta-analysis showed that the four RCTs used intent-to-treat principles by assuming that PEP developed in patients in whom the attempted prophylactic pancreatic stent placement failed, even when the clinical outcome was not stated in the original study. Despite the use of this approach, the odds ratio in the stent group was 0.44 compared with the controls and differed significantly in favor of stent placement [86]. On the basis of these results, prophylactic stent placement can be considered as the single most important advance in the past 15 years for the prevention of PEP in high-risk patients. Despite these findings, questions remain about when to place a prophylactic pancreatic stent, the type of stent to place, and the optimal follow-up period to ensure adequate removal. The incidence of adverse events associated with pancreatic stent placement is around 4% and must be considered in the decision-making process for the placement of a stent [86,91].

4.5 Biliary stone extraction
In the setting of choledocholithiasis, endoscopic papillary balloon dilatation (EPBD), ES, and mechanical lithotripsy are techniques used to extract obstructing stones. Many studies have shown an increased rate of PEP with EPBD; the rates range from 4.9–20% with EPBD versus 0.42–10% with ES [92–95]. Prospective trials support this observation, although it is difficult to generalize the findings given the many factors that contribute to procedural complications [96–100]. Balloon dilation may also be required in some clinical settings. If a patient has had a prior sphincterotomy and has limited remaining tissue for incision, balloon dilation may be necessary to enlarge the bile duct insertion and enable stone extraction.

5. Patient-related risk factors associated with PEP
Given the high risk of PEP in certain populations, identifying a clear indication is critical for reducing the complication rate. ERCP is riskiest in patients who need it the least [101,102].
Large prospective trials have demonstrated that being female, being younger than 60–70 years, and having suspected sphincter of Oddi dysfunction (SOD) or a recurrent or prior PEP are associated with a higher risk of PEP [6,9,15,24,45,87,103,104] (Table 1). However, there is some variability between studies. For example, one smaller trial suggested an age of <50 years as a significant risk factor [104]. A recent large retrospective study of 16,855 patients reported that the highest rates of PEP occurred in patients with SOD, but the rate was not significantly higher in younger patients or in women [63]. Alternatively, a meta-analysis evaluating five patient-related risk factors demonstrated relative risks of SOD of 4.09 (95% CI, 1.93–3.12; P<0.001) and of being female of 2.23 (95% CI, 1.75–2.84; P<0.001) [87]. One study demonstrated a 10-fold increase in the risk of PEP in patients with SOD [105]. Some factors may be protective as well. The absence of chronic pancreatitis [57], presence of obesity [106], older age (>80 years) [107], and a history of alcohol consumption or cigarette smoking may be associated with a lower risk of PEP [108]. Proper patient selection and identification of patients at higher risk are the most effective means for reducing the incidence of PEP.

6. Pharmacological agents evaluated for the prevention or reduction of PEP

The effects of pharmacological agents on PEP have attracted much interest. Preventing cellular injury and pancreatic tissue auto-digestion may involve blocking the premature activation of proteolytic enzymes within the acinar cells [14,45,109–116]. Although conceptually straightforward, the goal of blocking this activation has been difficult to achieve. Multiple trials have been performed with the goal of reducing the incidence or severity of PEP. About 34 pharmacological agents and procedures (e.g., topical application of pharmacological agents injected or sprayed onto the papilla) have been evaluated for their potential to prevent PEP in controlled trials. Most clinical trials have been disappointing, and only a minority of studies has demonstrated benefit (Table 2-5) [26,29,37,39,40,53,54,58,87,117–175].

In two of five prospective trials, allopurinol was shown to decrease the incidence of PEP [119,120]. In these trials showing benefits, allopurinol was given in 300 mg or 600 mg doses 15 h and 3 h before ERCP. When reviewing other studies of allopurinol, these effects were not significant in patients dosed on different 4 h and 1 h regimens and with varying dose concentrations of allopurinol [121–123]. This suggests that both the dose and timing of allopurinol administration are important in reducing the risk of PEP. Three meta-analyses have been published using data obtained from four prospective, randomized, placebo-controlled studies that compared rectally administered diclofenac or indomethacin at a dose of 100 mg versus placebo [124–126]. No statistical heterogeneity was detected between the studies. Two RCTs evaluated the effect of rectal administration of 100 mg diclofenac immediately after the procedure [39,143], and the other two evaluated rectal administration of 100 mg indomethacin immediately before the procedure [144,145]. Both sets of studies showed similar results. Patients who were considered to be at high risk for PEP were included in both studies. Overall, PEP occurred in 20/456 (4.4%) patients in the treatment groups versus 57/456 (12.5%) patients in the placebo groups. The estimated pooled relative risk was 0.36 (95% CI, 0.22–0.60), and the number needed to treat to prevent one episode of PEP was 15. The administration of nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with a similar decrease in the incidence of PEP regardless of risk. No adverse event attributable to NSAIDs has been reported. A trial evaluating diclofenac 50
<table>
<thead>
<tr>
<th>Agent</th>
<th>Author</th>
<th>Factor studied</th>
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<th>Overall</th>
<th>Control</th>
<th>Intervention</th>
<th>Pvalue</th>
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<td>Hydrocortisone</td>
<td>Krzysztyn et al.</td>
<td>Hydrocortisone 100 mg IV at 1 h before ERCP</td>
<td>120</td>
<td>6.67</td>
<td>11.86</td>
<td>1.64</td>
<td>0.031</td>
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<td>Mantel et al. [20]</td>
<td>Hydrocortisone 100 mg IV at 30 min before ERCP</td>
<td>340</td>
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<td>13.60</td>
<td>7.10</td>
<td>0.380</td>
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<td></td>
<td>De Palma et al.</td>
<td>Hydrocortisone 100 mg IV immediately before ERCP</td>
<td>329</td>
<td>3.30</td>
<td>4.90</td>
<td>5.70</td>
<td>NS</td>
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<td>Prednisone</td>
<td>Sherman et al. [20]</td>
<td>Prednisone 40 mg PO at 15 h and at 3 h before ERCP</td>
<td>1115</td>
<td>25.07</td>
<td>33.60</td>
<td>16.60</td>
<td>0.130</td>
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<td></td>
<td></td>
<td>Prednisone 40 mg at 15 h 40 min before and at 4 h before ERCP</td>
<td>207</td>
<td>16.40</td>
<td>16.70</td>
<td>16.20</td>
<td>NS</td>
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<td>Methylprednisolone</td>
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<td>Methylprednisolone 125 mg IV immediately before ERCP</td>
<td>298</td>
<td>8.70</td>
<td>12.40</td>
<td>3.40</td>
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<td>Diclofenac</td>
<td>Khoshneshin et al.</td>
<td>Diclofenac 100 mg PR immediately after ERCP</td>
<td>100</td>
<td>15.00</td>
<td>26.00</td>
<td>4.00</td>
<td>&lt; 0.010</td>
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<td></td>
<td>Chen et al. [20]</td>
<td>Diclofenac 50 mg PO at 30-60 min before and at 4-6 h after ERCP</td>
<td>327</td>
<td>18.40</td>
<td>16.70</td>
<td>16.30</td>
<td>NS</td>
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<td>Murali et al. [20]</td>
<td>Diclofenac 100 mg PR immediately after ERCP</td>
<td>220</td>
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<td>15.45</td>
<td>6.36</td>
<td>0.049</td>
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<td></td>
<td>Sen et al. [20]</td>
<td>Diclofenac 75 mg IV immediately after ERCP</td>
<td>80</td>
<td>12.5</td>
<td>17.5</td>
<td>7.5</td>
<td>0.176</td>
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<td>Indomethacin</td>
<td>Settnes et al. [20]</td>
<td>Indomethacin 100 mg PR before ERCP</td>
<td>442</td>
<td>4.98</td>
<td>6.78</td>
<td>3.16</td>
<td>OR 0.4 (0.2 - 1.1)</td>
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<td></td>
<td>Menon et al. [20]</td>
<td>Indomethacin 100 mg PR before ERCP</td>
<td>150</td>
<td>10.6</td>
<td>16</td>
<td>5.3</td>
<td>0.034</td>
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<td>Allopurinol</td>
<td>Martinez-Torre et al.</td>
<td>Allopurinol 300 mg PO at 15 h 300 mg PO at 3 h before ERCP</td>
<td>170</td>
<td>6.47</td>
<td>9.40</td>
<td>2.30</td>
<td>0.049</td>
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<td></td>
<td>Bettencourt et al.</td>
<td>Allopurinol 300 mg PO at 3 h before ERCP</td>
<td>386</td>
<td>5.82</td>
<td>4.13</td>
<td>5.50</td>
<td>0.442</td>
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<td></td>
<td>Ketaminsa et al.</td>
<td>Allopurinol 600 mg PO at 15 h 600 mg PO at 3 h before ERCP</td>
<td>243</td>
<td>10.20</td>
<td>17.80</td>
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<td>&lt; 0.01</td>
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<td></td>
<td>Maier et al. [20]</td>
<td>Allopurinol 600 mg PO at 4 h 300 mg PO at 1 h before ERCP</td>
<td>346</td>
<td>22.55</td>
<td>12.14</td>
<td>12.96</td>
<td>0.520</td>
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<td></td>
<td>Bzylinski et al.</td>
<td>Allopurinol 200 mg PO at 3 h 200 mg PO at 3 h before ERCP</td>
<td>320</td>
<td>10.70</td>
<td>7.50</td>
<td>12.10</td>
<td>&lt; 0.020</td>
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<td>N-acetylcysteine</td>
<td></td>
<td>NAC 600 mg IV BED + 2 d after ERCP</td>
<td>106</td>
<td>9.43</td>
<td>11.76</td>
<td>7.27</td>
<td>NS</td>
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<td></td>
<td>Katzenstein et al.</td>
<td>NAC 70 mg/kg 2 h before and 35 mg/kg 4 h intervals for 24 h after procedure</td>
<td>249</td>
<td>10.80</td>
<td>9.60</td>
<td>12.10</td>
<td>&lt; 0.020</td>
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<td>Cefpodoxime</td>
<td>AKS et al.</td>
<td>Cefpodoxime 2g IV 30 min before ERCP</td>
<td>301</td>
<td>9.36</td>
<td>2.58</td>
<td>0.039</td>
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<td>Interleukin-10</td>
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<tr>
<td>Sherman et al.</td>
<td></td>
<td>IL-10 8 μg/kg IV 15-30 min before ERCP</td>
<td>305</td>
<td>17.38</td>
<td>14.30</td>
<td>15.40</td>
<td>0.830</td>
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<td></td>
<td>IL-10 6 μg/kg IV 15-30 min before ERCP</td>
<td>303</td>
<td>21.60</td>
<td>22.00</td>
<td>1.40</td>
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<tr>
<td>Devlin et al.</td>
<td></td>
<td>IL-10 4 μg/kg IV 30 min before ERCP</td>
<td>144</td>
<td>29.90</td>
<td>24.60</td>
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<td>0.046</td>
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<td></td>
<td></td>
<td>IL-10 3 μg/kg IV 30 min before ERCP</td>
<td>100</td>
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<td>0.17</td>
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<td>Dumo et al.</td>
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<td>IL-10 3 μg/kg IV 15 min before ERCP</td>
<td>200</td>
<td>30.00</td>
<td>9.10</td>
<td>13.90</td>
<td>0.650</td>
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</tbody>
</table>

**PEP:** Post-ERCP pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography; IL-10: Interleukin-10; NAC: N-acetylcysteine; NS: Not significant; NR: Not reportable due to scarce primary data from publication; MC: Multi-centred.
Table 3. Randomized controlled trials of drugs that interrupt the activity of proteases evaluated for reduction or prevention of post-ERCP pancreatitis.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Author</th>
<th>Factor studied</th>
<th>Rate of post-ERCP pancreatitis (%)</th>
<th>n</th>
<th>Overall</th>
<th>Control</th>
<th>Intervention</th>
<th>P value</th>
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<td>Heparin</td>
<td>Barkay[39]</td>
<td>Unfractionated heparin 5000 IU SC 20-30 min before ERCP</td>
<td>106</td>
<td>NR</td>
<td>7.40</td>
<td>7.80</td>
<td>NS</td>
<td></td>
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<tr>
<td></td>
<td>Rabenstein[38]</td>
<td>Low molecular weight heparin Certoparin 3000 IU SC the day before ERCP</td>
<td>448</td>
<td>8.50</td>
<td>8.81</td>
<td>8.14</td>
<td>0.870</td>
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<td>Gabexate</td>
<td>Licci[40]</td>
<td>Gabexate 600 mg IV 60-90 min before and 22 h after ERCP</td>
<td>68</td>
<td>2.90</td>
<td>NR</td>
<td>2.90</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Manes[29]</td>
<td>Gabexate mesylate 500 mg within 1 h before ERCP</td>
<td>608</td>
<td>5.60</td>
<td>9.40</td>
<td>3.90</td>
<td>&lt; 0.01</td>
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<tr>
<td></td>
<td></td>
<td>Gabexate mesylate 500 mg within 1 h after ERCP</td>
<td>608</td>
<td>5.60</td>
<td>9.40</td>
<td>3.90</td>
<td>&lt; 0.01</td>
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<tr>
<td></td>
<td>Xiong[41]</td>
<td>Gabexate 300 mg IV 30 min before gtt until 4 h after ERCP</td>
<td>200</td>
<td>6.70</td>
<td>10.50</td>
<td>3.10</td>
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<tr>
<td></td>
<td>Fujishiro[42]</td>
<td>Gabexate 900 mg/1500 mL gtt for 13 h; beginning 1 h before ERCP</td>
<td>139</td>
<td>NR</td>
<td>NR</td>
<td>4.30</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Andriulli[29]</td>
<td>Gabexate 500 mg 30 min before gtt until 6 h after ERCP</td>
<td>1127</td>
<td>5.60</td>
<td>4.80</td>
<td>5.80</td>
<td>NS</td>
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</tr>
<tr>
<td></td>
<td>Masci[29]</td>
<td>Gabexate 500 mg IV 30 min before gtt until 6.5 h after ERCP and 1 g IV for 13 h after ERCP</td>
<td>434</td>
<td>1.80</td>
<td>2.20</td>
<td>1.40</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Andriulli[29]</td>
<td>Gabexate 500 mg IV 30 min before and 2 h after ERCP</td>
<td>579</td>
<td>8.60</td>
<td>6.50</td>
<td>8.10</td>
<td>NS</td>
<td></td>
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<tr>
<td></td>
<td>Cavallini[29]</td>
<td>Gabexate 1 g IV 30-90 min before gtt until 12 h after ERCP</td>
<td>415</td>
<td>5.00</td>
<td>8.00</td>
<td>2.00</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Ulinastatin</td>
<td>Yoo[43]</td>
<td>Ulinastatin 100 000 U gtt after ERCP for 5.5 h</td>
<td>227</td>
<td>6.20</td>
<td>5.60</td>
<td>6.70</td>
<td>0.715</td>
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</tr>
<tr>
<td></td>
<td>Licci[40]</td>
<td>Ulinastatin 150 000 units 60-90 min before &amp; for 22 h after ERCP</td>
<td>68</td>
<td>2.90</td>
<td>2.90</td>
<td>2.90</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fujishiro[42]</td>
<td>Ulinastatin 150 000 units 1 h before, during; 11 h after ERCP</td>
<td>650</td>
<td>6.50</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Ulinastatin 50 000 units</td>
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</tr>
<tr>
<td></td>
<td>Tsuji[29]</td>
<td>Ulinastatin 150 000 U gtt 10 min before ERCP</td>
<td>406</td>
<td>5.17</td>
<td>7.40</td>
<td>2.90</td>
<td>0.041</td>
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</table>

PEP: Post-ERCP pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography; NS: Not significant; NR: Not reported/unable to acquire primary data from publication; MC: Multi-centered.
Table 4. Randomized controlled trials of inhibitors of pancreatic secretion evaluated for reduction or prevention of post-ERCP pancreatitis.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Author</th>
<th>Factor studied</th>
<th>n</th>
<th>Overall</th>
<th>Control</th>
<th>Intervention</th>
<th>P-value</th>
</tr>
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<tr>
<td><strong>Beta-carotene</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lavy[72]</td>
<td></td>
<td>Natural beta-carotene 2 g at 12 h before ERCP</td>
<td>321</td>
<td>9.60</td>
<td>9.60</td>
<td>10.00</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Octreotide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kiss[54]</td>
<td></td>
<td>Octreotide 0.1 mg gtt 60 min before ERCP and continued during and after ERCP</td>
<td>120</td>
<td>NR</td>
<td>11.49</td>
<td>15.15</td>
<td>NS</td>
</tr>
<tr>
<td>LE[54]</td>
<td></td>
<td>Octreotide 0.3 mg gtt 1 h before; 6 h after ERCP; then 0.1 mg SC; 12 h later 0.1 mg SC</td>
<td>832</td>
<td>3.85</td>
<td>5.26</td>
<td>2.42</td>
<td>0.046</td>
</tr>
<tr>
<td>Themopoulos[51]</td>
<td></td>
<td>Octreotide 500 µg TID starting 24 h before ERCP</td>
<td>201</td>
<td>10.89</td>
<td>8.90</td>
<td>2.00</td>
<td>0.03</td>
</tr>
<tr>
<td>Testolin[28]</td>
<td></td>
<td>Octreotide 200 µg TID × 24 h before ERCP</td>
<td>114</td>
<td>NR</td>
<td>14.30</td>
<td>12.00</td>
<td>NS</td>
</tr>
<tr>
<td>Hard[71]</td>
<td></td>
<td>Octreotide 200 µg SC the night before ERCP</td>
<td>94</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td>Dzierska[60]</td>
<td></td>
<td>Octreotide 0.5 mg SC 60 min before ERCP</td>
<td>209</td>
<td>NR</td>
<td>9.32</td>
<td>3.83</td>
<td>NS</td>
</tr>
<tr>
<td>Arvanitidis[58]</td>
<td></td>
<td>Octreotide 0.1 mg SC 30 min before; 8 h and 16 h after ERCP</td>
<td>73</td>
<td>10.95</td>
<td>11.11</td>
<td>10.81</td>
<td>NS</td>
</tr>
<tr>
<td>Tulassay[56]</td>
<td></td>
<td>Octreotide 0.1 mg SC 45 min after ERCP</td>
<td>1199</td>
<td>7.84</td>
<td>6.00</td>
<td>5.90</td>
<td>NS</td>
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<tr>
<td>Arcidiacono[29]</td>
<td></td>
<td>Octreotide 0.1 mg SC 150 and 30 min before; 4 h after ERCP</td>
<td>151</td>
<td>6.62</td>
<td>NR</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td>Baidazzi[39]</td>
<td></td>
<td>Octreotide 0.1 mg SC 45 min before; 6 h after ERCP</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td>Testolin[38]</td>
<td></td>
<td>Octreotide 0.2 mg SC before ERCP</td>
<td>60</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Somatostatin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee[17]</td>
<td></td>
<td>Somatostatin 3 mg in 500 ml NS gtt 12 h starting 30 min before ERCP</td>
<td>391</td>
<td>6.65</td>
<td>9.60</td>
<td>3.60</td>
<td>0.02</td>
</tr>
<tr>
<td>Andruzzi[30]</td>
<td></td>
<td>Somatostatin 750 µg IV 30 min before and continued for 6 h after ERCP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arvanitidis[72]</td>
<td></td>
<td>Somatostatin 4 µg/kg gtt 12 h on identification of the papilla and before introduction of the catheter</td>
<td>372</td>
<td>NR</td>
<td>9.80</td>
<td>1.70</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Poore[71]</td>
<td></td>
<td>Somatostatin 3 mg gtt 12 h on identification of the papilla and before introduction of the catheter</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Poore[71]</td>
<td></td>
<td>Somatostatin 250 mg IV bolus immediately after ERCP</td>
<td>270</td>
<td>NR</td>
<td>13.30</td>
<td>4.40</td>
<td>0.01</td>
</tr>
<tr>
<td>Andruzzi[30]</td>
<td></td>
<td>Somatostatin 750 µg IV 30 min before and 2 h after ERCP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poore[71]</td>
<td></td>
<td>Somatostatin 3 mg in 500 ml NS gtt for 12 h starting 30 min before ERCP</td>
<td>220</td>
<td>5.95</td>
<td>10.00</td>
<td>3.00</td>
<td>0.03</td>
</tr>
<tr>
<td>Bordas[17]</td>
<td></td>
<td>Natural somatostatin 4 mg/kg IV on identification of the papilla and before introduction of the catheter</td>
<td>160</td>
<td>NR</td>
<td>10.00</td>
<td>2.50</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

PEP: Post-ERCP pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography; NS: Not significant; NR: Not reported/unable to acquire primary data from publication; MC: Multi-centered
Table 5. Randomized controlled trials of drugs that decrease Sphincter of Oddi Pressure and miscellaneous drugs evaluated for reduction or prevention of post-ERCP pancreatitis.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Author</th>
<th>Factor studied</th>
<th>n</th>
<th>Overall</th>
<th>Control</th>
<th>Intervention</th>
<th>Pvalue</th>
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</thead>
<tbody>
<tr>
<td><strong>Injected Botulinum toxin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gorelick[28]</td>
<td>Botulinum toxin injection after biliary sphincterotomy</td>
<td>26</td>
<td>NR</td>
<td>43.00</td>
<td>25.00</td>
<td>0.340</td>
<td></td>
</tr>
<tr>
<td><strong>Nifedipine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Prat[29]</td>
<td>Nifedipine 20 mg PO 3-6 h before ERCP</td>
<td>159</td>
<td>15.50</td>
<td>17.70</td>
<td>13.20</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Sand[30]</td>
<td>Nifedipine 20 mg PO q 8 h the day of ERCP</td>
<td>166</td>
<td>3.61</td>
<td>4.00</td>
<td>4.00</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td><strong>Nitroglycerin</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Hao[31]</td>
<td>Glyceryl trinitrate 5 mg IV and 100 mg vitamin C 5 min before ERCP maneuvers</td>
<td>74</td>
<td>16.20</td>
<td>25.00</td>
<td>7.90</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Beauchamp[32/33/MC]</td>
<td>Nitroglycerin bolus of 0.1 mg, then 35 μg/kg/min IV for 6 h after ERCP</td>
<td>208</td>
<td>12.00</td>
<td>15.00</td>
<td>10.00</td>
<td>0.260</td>
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</tr>
<tr>
<td>Kaffee[34]</td>
<td>Transternal glyceryl trinitrate patch (15 mg) precordial area 30-40 min before ERCP</td>
<td>318</td>
<td>NR</td>
<td>7.40</td>
<td>7.70</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Moret[35]</td>
<td>Transternal glyceryl trinitrate patch (15 mg) precordial area 30-40 min before ERCP</td>
<td>144</td>
<td>9.00</td>
<td>15.00</td>
<td>4.00</td>
<td>0.030</td>
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<tr>
<td>Tsuji[36/37/38/39]</td>
<td>Glyceryl trinitrate 2 mg SL 5 min before ERCP</td>
<td>186</td>
<td>13.00</td>
<td>19.00</td>
<td>8.00</td>
<td>&lt; 0.000</td>
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</tr>
<tr>
<td><strong>Nafamostat mesylate</strong></td>
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<td></td>
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<tr>
<td>Chou[40]</td>
<td>Nafamostat mesylate 20 mg gtt 1 h before and for 24 h after ERCP</td>
<td>704</td>
<td>5.40</td>
<td>7.40</td>
<td>3.30</td>
<td>0.018</td>
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<tr>
<td><strong>Pentoxifylline</strong></td>
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<tr>
<td>Kapetanakis[41]</td>
<td>Pentoxifylline 400 mg PO TID before ERCP</td>
<td>320</td>
<td>4.38</td>
<td>5.00</td>
<td>5.60</td>
<td>0.28</td>
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<td><strong>Recombinant PAF acetylhydrolase</strong></td>
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</tr>
<tr>
<td>Sherman[42/43/MC]</td>
<td>Recombinant PAF acetylhydrolase (rPAF-AH)</td>
<td>60</td>
<td>17.60</td>
<td>19.60</td>
<td>17.50</td>
<td>0.59</td>
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</tr>
<tr>
<td></td>
<td>1 mg/kg gtt&lt; 1 h before ERCP</td>
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</tr>
<tr>
<td></td>
<td>Recombinant PAF acetylhydrolase (rPAF-AH)</td>
<td>60</td>
<td>17.60</td>
<td>19.60</td>
<td>17.50</td>
<td>0.59</td>
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<tr>
<td></td>
<td>5 mg/kg gtt&lt; 1 h before ERCP</td>
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<tr>
<td><strong>Semapimod</strong></td>
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<td></td>
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<tr>
<td>van Westerloo[44]</td>
<td>Semapimod IV 50 mg/100 mL glucose gtt 1 h</td>
<td>242</td>
<td>11.98</td>
<td>14.88</td>
<td>9.09</td>
<td>0.117</td>
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<tr>
<td>before ERCP</td>
<td></td>
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<td></td>
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<tr>
<td><strong>Sprayed Epinephrine</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Matsuhashi[45]</td>
<td>Epinephrine (10 mL of 0.02%) sprayed on papilla before cannulation</td>
<td>370</td>
<td>1.10</td>
<td>2.16</td>
<td>0.00</td>
<td>0.00 0.123</td>
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</tr>
<tr>
<td><strong>Sprayed Lidocaine</strong></td>
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</tr>
<tr>
<td>Schwartz[46]</td>
<td>Lidocaine (10 mL of 1.%) sprayed on the major papilla before cannulation</td>
<td>294</td>
<td>4.08</td>
<td>3.04</td>
<td>4.32</td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>

ERCP: Endoscopic retrograde cholangiopancreatography; NS: Not significant; NR: Not reported/unable to acquire primary data from publication; MC: Multi-centered.
mg by mouth given 30–90 min before ERCP and up to 4–6 h after ERCP showed no decrease in the incidence of PEP [146]. A small clinical trial by Senol and colleagues found no significant difference in the incidence of PEP in patients given ERCP with the use of 75 mg of diclofenac by the intramuscular route plus intravenous (IV) hydration versus those given placebo and IV solutions [147]. According to the European Society of Gastrointestinal Endoscopy, no other drug prophylaxis has been proven to be effective against PEP as rectal NSAIDs [148].

Glyceryl trinitrate [141], hydrocortisone [130], and IL-10 [52] were shown to be beneficial in one RCT. However, studies with larger numbers of patients [26,54,140] found no significant effects of these treatments. Gabexate [160,161,163], octreotide [150,151], somatostatin [171,174], and ulinastatin [167] have all been reported to reduce the incidence of PEP. However, studies evaluating each of these agents using similar designs have reported no significant reduction in the incidence of PEP. These differences might be explained by differences in the selection and number of patients, clinical presentation, and timing of administration or dosage of the agents under investigation.

7. Management of PEP

Not all patients with pain and hyperamylasemia following ERCP have acute pancreatitis, and clinicians may have difficulty establishing the diagnosis. As a result, some patients with severe post-ERCP pancreatitis may not be identified in the early stages of their illness when aggressive hydration is most important. Some endoscopists may have difficulty acknowledging that post-ERCP pancreatitis has occurred, as this requires accepting that there has been a complication. A sense of guilt on the part of the clinician performing the procedure is understandable. However, delay in either the diagnosis or treatment of post-ERCP pancreatitis may lead to adverse consequences.

Post-ERCP pancreatitis should be managed as for other causes of acute pancreatitis. This is sometimes complicated by the difficulty distinguishing mild from severe disease in the early stages. The elevations in serum amylase and lipase levels do not always correlate with disease severity.

Mild and moderate PEP usually resolve quickly with conservative therapy. Although there are no specific guidelines for the treatment of PEP, a recent study found that a protocol-based management strategy was associated with less severe pancreatitis, shorter length of hospital stay, the need for fewer imaging studies, and less use of antibiotics [109,177]. Practice guidelines for acute pancreatitis treatment are available and may be applicable to PEP as well [47]. In patients with persistent or severe PEP, two important markers of severity are multisystem organ failure and pancreatic necrosis, both of which require aggressive management [18]. Early identification of organ failure, pancreatic necrosis, perforation (especially in the setting of endoscopic sphincterotomy), biliary damage/leak and pancreatic fluid collections are important clinical branch points that may require more intensive intervention. Checking the levels of serum transaminases, amylase, and lipase is not routinely recommended after ERCP, but if assessed, postprocedure elevations occur often. These elevations are likely to be secondary to intermittent biliary, pancreatic, or papillary obstruction. In a recent study, 46% of patients had elevated liver test results after ERCP, but only 5.4% had PEP [110]. Asymptomatic elevation of liver markers is not an indication for a change in management and a repeat ERCP should be performed only with a clear indication. Although the use of enteral feeding during treatment of acute pancreatitis is
controversial, patients who are unlikely to resume oral nutrition within 5 days require nutritional support, which can be provided via total parenteral nutrition or enteral routes [177]. There appear to be some advantages to enteral feeding. A recent study found that initiating oral nutrition after mild acute pancreatitis with a low-fat soft diet appeared to be safe but did not shorten the length of hospitalization [111].

8. Conclusion

Acute pancreatitis is a well-recognized and frequent complication that can occur in 1%–15% of patients undergoing ERCP. Clinical research to prevent PEP using depurate endoscopic techniques and pharmacological prophylaxis is intense and so far indicates that the use of NSAIDs and pancreatic stenting, coupled with appropriate selection of eligible patients and performed by an experienced endoscopist are the most effective preventive measures to reduce the incidence and severity this complication.

9. References

[27] Sherman S, Ruffolo TA, Hawes RH, Leeman GA. Complications of endoscopic sphincterotomy. A prospective series with emphasis on the increased risk


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Endoscopic Retrograde Cholangiopancreatography-Related Acute Pancreatitis – Identification, Prophylaxis and Treatment


[137] Sand J, Nordback I. Prospective randomized trial of the effect of nifedipine on pancreatic irritation after endoscopic retrograde cholangiopancreatography Digestion. 1993;54(2):105-11.


Acute Pancreatitis (AP) in approximately 80% of cases, occurs as a secondary complication related to gallstone disease and alcohol misuse. However, there are several other different causes that produce it such as metabolism, genetics, autoimmunity, post-ERCP, and trauma for example. This disease is commonly associated with the sudden onset of upper abdominal pain that is usually severe enough to warrant the patient seeking urgent medical attention. Overall, 10-25% of AP episodes are classified as severe. This leads to an associated mortality rate of 7-30% that has not changed in recent years. Treatment is conservative and generally performed by experienced teams often in ICUs. Although most cases of acute pancreatitis are uncomplicated and resolve spontaneously, the presence of complications has a significant prognostic importance. Necrosis, hemorrhage, and infection convey up to 25%, 50%, and 80% mortality, respectively. Other complications such as pseudocyst formation, pseudo-aneurysm formation, or venous thrombosis, increase morbidity and mortality to a lesser degree. The presence of pancreatic infection must be avoided.

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