Chapter 14
Post-ERCP Pancreatitis

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Case Presentation

A 36-year-old woman presents with a history of recurrent acute pancreatitis. She has had three episodes of documented acute pancreatitis confirmed by the revised Atlanta classification. She does not drink alcohol or smoke cigarettes and has normal serum triglyceride levels and liver enzymes. She has a history of obesity, hypertension, and gastroesophageal reflux disease – treated with amlodipine and pantoprazole, respectively. She has no family history of pancreatitis.

During her prior admissions, the episodes of pancreatitis were uncomplicated and resolved with supportive care. CT examinations demonstrated peripancreatic fat stranding without biliary dilation or pancreatic fluid collections. MRCP demonstrated no anatomic ductal variants.

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She undergoes an endoscopic ultrasound (EUS) at an outside hospital facility, which identifies a small, 2 mm stone that is seen in a 4 mm main pancreatic duct. Thought to be contributing to her symptoms, she undergoes ERCP for removal of this stone. Rectal indomethacin is administered for pharmacoprophylaxis of post-ERCP pancreatitis. During the ERCP, the ventral pancreatic duct is deeply cannulated, contrast is injected, and a single stone is seen. A ventral pancreatic sphincterotomy is made using electrocautery. The ventral pancreatic duct is swept with an 8.5 mm balloon, and a 5 Fr by 5 cm plastic pancreatic stent is placed into the ventral pancreatic duct. After the procedure, the patient has significant epigastric pain with an elevated serum lipase and is admitted for post-ERCP pancreatitis. She is managed with aggressive intravenous hydration, nutritional support, and pain control and is discharged home after 3 days.

She transfers care to our institution for further assessment and management of her recurrent acute pancreatitis. Abdominal X-ray confirms retained pancreatic duct stent, and she undergoes endoscopy for pancreatic duct stent removal. During the endoscopy, her stent is removed, and she is noted to have a mildly prominent ampulla. Biopsies are performed and are consistent with a villous adenoma.

The ampullary adenoma is determined to be the likely cause of her recurrent acute pancreatitis, and the patient returns for ERCP and endoscopic ampullectomy (Video 14.1). Upon initial inspection, a 12 mm villous mass is seen at the major papilla. A 0.025 inch guidewire is passed into the biliary tree, and a sphincterotome is passed over the guidewire to deeply cannulate the bile duct, contrast is injected, and a sphincterotomy is made with electrocautery. Next, the 0.025 guidewire is passed into the ventral pancreatic duct. This is also deeply cannulated with the sphincterotome, and contrast is injected. Using a 15 mm snare, the major papilla is grasped and then resected using electrocautery. A small villous area is noted at the pancreatic duct orifice and is biopsied. After resection, a guidewire is again passed into the ventral pancreatic duct, and a 5 Fr by 3 cm plastic pancreatic

stent with a full external pigtail and a single internal flap is placed. Similarly, a guidewire is passed into the bile duct, and a 7 Fr by 7 cm plastic biliary stent with a single external flap and a single internal flap is placed with fluid flowing through both stents. Pathologic analysis confirms a diagnosis of ampullary adenoma but unfortunately with residual adenoma at the pancreatic duct orifice. The patient is initially discharged home after 24-hour observation but admitted 2 days later for another episode of post-ERCP pancreatitis. Abdominal radiograph confirms premature pancreatic duct stent migration. She receives supportive care and is discharged home 2 days later.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) provides the ability to detect, classify, and provide therapy for diseases involving the pancreaticobiliary system. Despite being introduced in the late 1960s, it remains one of the most technically challenging and high-risk endoscopic procedures performed. Complications arising from ERCP can include post-ERCP pancreatitis (PEP), bleeding, perforation, cholecystitis, and cholangitis. Of these complications, PEP is the most frequent and can lead to significant morbidity and occasionally mortality.

Due in part to the risk of complications and the advancements in EUS and cross-sectional radiologic imaging techniques, namely, magnetic resonance cholangiopancreatography (MRCP), ERCP has transitioned primarily to pancreatobiliary therapeutics. However, advances in technology built on the scaffold of ERCP, including intraductal ultrasound, direct cholangioscopy, and pancreatoscopy, have secured ERCP as an obligate endoscopic procedure for clinical problems involving the pancreatic duct and hepatobiliary system. Therefore, understanding the definition, patient and procedural risk factors, and preventative management strategies for PEP are critical for any therapeutic endoscopist practicing ERCP.

Diagnosis/Assessment

Incidence and Definition

Post-ERCP pancreatitis (PEP) is the most common complication of ERCP (Table 14.1). Prospective, multicenter studies have examined the frequency of PEP and found incidence rates ranging from 3% to 15% for the average-risk population with approximately 5% of patients developing a severe course [1–9]. In high-risk stratified cohorts, the risk of PEP has been reported to range from 15% to 25%.

Two recent large cohort studies evaluate the incidence of PEP in which the reported incidence rate of PEP has been estimated to be 3.5% and 9.7%. Andriulli et al. [10] conducted a systematic review of 21 prospective studies, including 16,855 ERCPs for PEP incidence, and found that post-procedural pancreatitis occurred in 3.5% of all patients undergoing ERCP with approximately 90% being mild or moderate in severity (Table 14.1). This was followed in 2015 by Kochal et al. who conducted a systematic review of the control groups (placebo or no-stent arms) of 108 randomized, controlled trials (RCTs) to determine the incidence, severity, and mortality of PEP [11]. Evaluating 13,296 control patients that underwent ERCP for both diagnostic and therapeutic purpose, the overall rate of PEP was 9.7%, with a mortality rate of 0.7% and incidence of severe PEP of 0.5%.

The definition of PEP includes the consensus PEP-specific diagnostic and grading severity criteria, proposed by Cotton et al. in 1991 [12], and the revised 2012 Atlanta international classification [13]. The proposed consensus PEP-specific diagnostic criteria includes new or increased abdominal pain

Table 14.1 Incidence and mortality of ERCP complications

Complication	Pancreatitis	Bleeding	Perforation	Infection
Incidence (%)	3.47	1.34	0.60	1.43
Mortality (%)	0.11	0.05	0.06	0.11

Adapted from Andriulli et al. [10]

characteristic of pancreatitis, serum amylase ≥3 times the upper limit of normal at ≥24 hours after ERCP, and requirement of hospital admission or a prolongation of planned admission of at least two nights. Cotton et al. [12] also propose a PEP severity grading system to differentiate between mild, moderate, and severe PEP (Table 14.2). While providing a standardized reporting method of PEP, this criterion is limited by the decreased use of serum amylase and subjective nature of defining post-procedure pain and requirement for hospitalization. To address these limitations, Freeman et al. have proposed modifying the criteria to include serum lipase and defining clinical pancreatitis as "new or worsened abdominal pain."

Although not designed specifically for PEP, the revised Atlanta classification provides a clear classification for acute pancreatitis that can be extrapolated for use in diagnosing PEP. According to the revised Atlanta classification, acute pancreatitis can be diagnosed if two of the following three criteria are present: (1) abdominal pain consistent with acute pancreatitis (epigastric, radiating to the back), (2) serum amylase and/or lipase ≥3 times the upper limit of normal, and (3) CT or MRI findings characteristic of acute pancreatitis [11]. The revised Atlanta classification system is limited for PEP evaluation in that the utility of contrast-enhanced cross-section imaging in the PEP setting has not been extensively studied.

Table 14.2 Grading system for severity of post-ERCP pancreatitis

Criteria	Mild	Moderate	Severe
Length of hospitalization (days)	2–3	4–10	>10
Other complications	None	None	Hemorrhagic pancreatitis Phlegmon Pseudocyst Percutaneous drainage Surgery

Adapted from Cotton et al. [12]

Case Discussion

In the case presented above, the patient met criteria for acute pancreatitis as she had characteristic abdominal pain and lipase ≥3 times the upper limit of normal. Demonstrating the limitations of the consensus criteria for PEP, she cannot be evaluated by the criteria proposed by Cotton et al. [12] as our institution does not routinely test serum amylase to diagnose acute pancreatitis. The recommendation by multiple societies [14–18] to preferentially use serum lipase over serum amylase in the diagnosis of acute pancreatitis may be a barrier to widespread use of the Cotton et al. [12] criteria, as it was in our case. By the Cotton et al. [12] grading system, our patient met criteria for mild PEP given that she was hospitalized for 3 days and had no other complications.

Risk Factors for Post-ERCP Pancreatitis

The mechanism through which ERCP causes pancreatitis is multifactorial. Most evidence points to increased hydrostatic pressure and mechanical obstruction due to post-procedural papillary edema as the primary mechanisms. However, the risk for PEP can be influenced by multiple patient, procedural, and operator characteristics, and the key factor to preventing PEP is pre-procedural careful selection of patients and identification of high-risk patients. Identification of these factors is necessary for risk-stratification, informed consent, and implementation of preventative measure to reduce the incidence and severity of PEP.

Patient-Related Risk Factors

Patient characteristics associated with an increased risk of PEP include sphincter of Oddi dysfunction, female gender, younger age, history of recurrent pancreatitis, prior history of PEP, normal serum bilirubin, non-dilated bile ducts, and absence of common bile duct stones.

Patients with sphincter of Oddi dysfunction are unequivocally at higher risk for PEP, though the mechanism is unknown. Prospective, multicenter studies have found odds ratio (OR) for PEP of 5.0 [2] and 2.6 [1]. A meta-analysis of 15 prospective studies found an OR of 4.1 [19]. These patients also tend to have more severe PEP [2]. Female sex, for unknown reasons, is an independent risk factor for PEP (OR 2.5) [2]. Younger age is a PEP risk factor. One prospective, multicenter study found that a 30-year-old has an OR of 2.1 of PEP compared to a 70-year-old [3]. Another prospective, multicenter study found that patients age <60 have an OR of 2.1 compared to patients age >0 [20]. Patients with a history of recurrent pancreatitis had PEP at a rate of 16% versus 6% for those without it [21]. Another study found an OR of 2.5 [19]. Prior history of PEP strongly predicts future risk of PEP (OR 5.3) [2]. Normal serum bilirubin doubles the risk of PEP [2]. Absence of common bile duct stones is also a risk factor [22].

Procedural-Related Risk Factors

The methods utilized in attempting selective cannulation can have a significant impact on the risk of developing PEP. Cannulation techniques (guidewire assisted vs. contrast assisted), pancreatic duct contrast injection (OR 1.4–2.7), difficult cannulation (OR 2.4–14.9), pancreatic sphincterotomy (OR 1.7–3.1), minor papillotomy (Video 14.2), failed pancreatic stenting, balloon dilation of an intact sphincter, advanced cannulation techniques, and self-expanding metal biliary stent placement (Fig. 14.1) have all been associated with increased risk of PEP [23, 24].

Difficult cannulation, frequently referred to as the failure to obtain selective deep access of the duct of interest using standard cannulation techniques, has been demonstrated to be one of the strongest independent risk factors for PEP (OR 2.4–14.9) [23]. Repeated (>5) attempts at cannulation carry a 11.9% risk of PEP as opposed to a 0.6% risk with a single cannulation attempt [23]. Therefore in the case of difficult cannulation, typically defined as >5 attempts or >10 minutes of

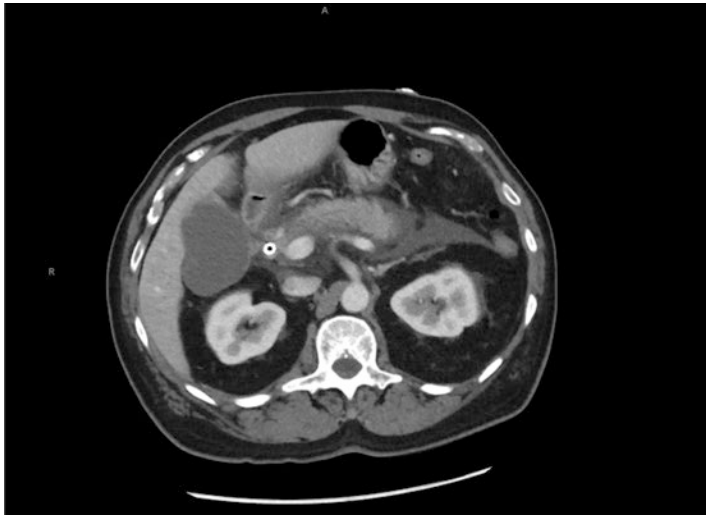

Figure 14.1 CT scan showing changes of post-ERCP pancreatitis (PEP) after self-expandable metal stent placement. After placement of an 8 mm × 8 cm uncovered metal biliary stent for the treatment of cholangiocarcinoma, the patient developed acute interstitial pancreatitis. CT examination revealed new marked peripancreatic stranding and fluid. Extending in the mesenteric root and bilateral anterior pararenal space. Rectal indomethacin and aggressive fluid hydration were administered during ERCP as part of routine practice. The pancreatic duct was neither cannulated nor injected during the ERCP

attempting to cannulate (OR 1.76) [8] a native papilla, some experts advocate early utilization (after 2–3 attempts) of advanced access techniques, consideration for repeat attempt in 24–48 hours, or referral to another endoscopist [25]. The advanced techniques commonly include the double-wire technique (Fig. 14.2), biliary cannulation adjacent to a pancreatic duct stent, needle-knife precut sphincterotomy (+/− over a pancreatic duct stent) (Video 14.3), transpancreatic septotomy, and biliary fistulotomy. While these advanced techniques may increase the likelihood of achieving biliary access, they can also increase the risk of PEP. Precut sphincterotomy has been associated with a higher risk of pancreatitis (OR 3.6) [3], though this risk can be mitigated with pancreatic duct stenting

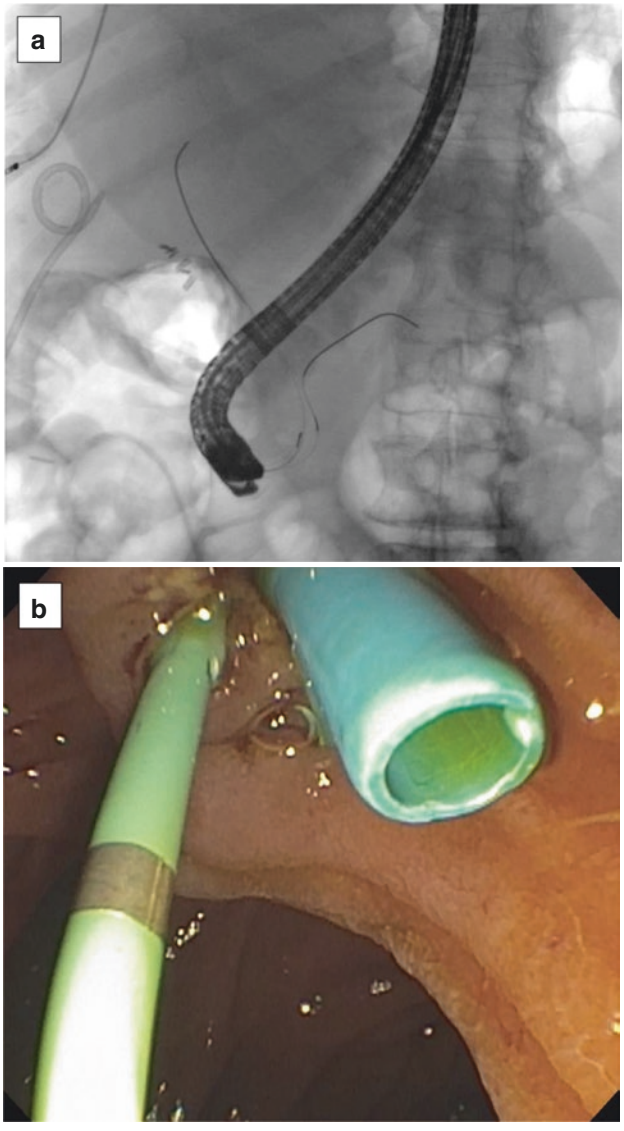

FIGURE 14.2 Double-wire technique to aid biliary cannulation. (**a**) Guidewire placement in the PD can help aid in subsequent cannulation of the common bile duct (CBD) and (**b**) can then be used for PD stent placement to prevent PEP

[26], and it is possible that some of the risk attributed to precut sphincterotomy is confounded by the PEP risk of difficult cannulation. Precut sphincterotomy is usually used after failed cannulation, at which point the papilla may have been sufficiently traumatized to cause PEP.

Operator-Related Risk Factors

Some evidence points to experience, as determined by case volume, to influence PEP risk [3]. Loperfido et al. [5] found that centers performing <200 ERCPs per year had increased rates of PEP. However, other studies have not found a significant difference [2, 27]. It is likely that endoscopists with lower case volumes choose to perform fewer risky cases than high-volume endoscopists, confounding complication rates for each group [27]. There is mixed evidence on effect of trainee involvement on PEP risk. Cheng et al. found increased risk when trainees participated in the case (OR 1.5) [1]. However, Schulman et al. showed that PEP risk does not vary throughout the year at academic institutions, suggesting that trainee experience, at least, does not influence risk [28] and Freeman et al. [3] did not find increased risk with trainee involvement.

One important finding regarding PEP risk factors is that the risk is not simply additive but rather synergistic. For example, Freeman et al. [2] found that a woman with normal serum bilirubin, suspected sphincter of Oddi dysfunction, and a difficult cannulation would have a PEP risk greater than 40%.

Diagnostic Evaluation: Clinical Assessment

Although patients are most frequently identified as having clinical findings suspicious for PEP in the post-procedure recovery unit, the diagnostic consideration and evaluation for PEP should begin prior to the procedure, be maintained throughout the duration of the procedure, and continued until discharged. Even before the procedure is initiated, the indication for the procedure, determination of independent patient and procedure-related risk factors for PEP, and

consideration for procedural techniques and pharmacologic intervention should be assessed.

Early recognition of possible PEP is important to initiate the appropriate medical management. Throughout the duration of the ERCP, patient vital signs should be continuously monitored for acute changes. New-onset tachycardia intraoperatively, while under anesthesia, should raise concern for possible impending or developing complication including PEP. In our practice, if these changes are identified in the setting of difficult biliary cannulation, inadvertent pancreatic duct cannulation, and/or contrast injection, we initiate therapeutic maneuvers including intensifying IV hydration with Lactated Ringer's solution, ensuring placement of prophylactic pancreatic stents and delivering rectal NSAIDs (if not already given).

Given the diagnosis of acute pancreatitis can be confounded with benign etiologies of abdominal discomfort such as insufflation-related discomfort and there is significant morbidity for delay in initiation of therapy, the treatment team should have a very low threshold for considering PEP. In our clinical practice, when patients have post-ERCP abdominal pain, we routinely look for objective signs to supplement subjective reports of abdominal pain including changes in vital signs and laboratory testing. Use of radiologic imaging, including plain films or cross-sectional imaging, is not routinely performed in the immediate (2–4 hour post-procedure) period for assessment of PEP and, however, should be considered in cases of suspected perforation.

Similar to the intraoperative assessment, post-procedure vital signs changes including tachycardia in the setting of new or worsening abdominal pain increase our suspicion for PEP. However, while assessing the vital signs, it is important to review the medical record for use of any heart rate controlling agents such as beta-blockers or calcium channel blockers which may provide a false-negative assessment for possible inflammatory conditions such as PEP.

In addition to observing vital signs, it is our practice to obtain a serum amylase and lipase level 2–4 hours post-procedure on patients with post-ERCP abdominal pain. Although studies have primarily evaluated the predictive value of amy-

lase for PEP, including a recent study from Brazil that identified negative predictive value of 94% with an amylase level <1.5 times the ULN at 4 hours [29], a single study evaluating lipase identified a level of <4 times the ULN was associated with a negative predictive value for PEP of 99% [30]. As recommended by the European Society for Gastrointestinal Endoscopy (ESGE), if a serum amylase level is less than 1.5 times the ULN or serum lipase level is less than 4 times the ULN obtained 2–4 hours, the PEP risk is sufficiently low to safely discharge the patient without risk for PEP [31].

Case Discussion

The patient in this case was at very high risk for post-ERCP pancreatitis with multiple patient and procedural risk factors that likely acted in a synergistic manner. Regarding patient risk factors, our patient (1) was a woman (2) of young age (3) with a history of recurrent pancreatitis and (4) a history of prior PEP and (5) normal liver function tests and non-dilated bile ducts. There were also procedural technical factors that contributed to an increased risk of PEP including pancreatic duct contrast injection. Further the procedure itself, an ampullectomy, is associated with an increased risk of PEP (~15%) [26].

Treatment/Management

The management of PEP is not different than that of acute pancreatitis from other causes and consists of early, aggressive intravenous fluid resuscitation, pain control, early implementation of enteral nutrition, and monitoring for severe complications such as necrosis or cholangitis [3, 16, 32].

Prevention Strategies

There is strong interest in developing preventive measures for PEP, and these can be divided into procedural interventions and chemopreventive interventions.

Procedural Prevention Strategies

Guidewire-Assisted Cannulation

Conventional contrast-assisted bile duct cannulation consists of inserting a cannula or papillotome into the papilla and advanced into the bile duct using contrast injection for confirmation. Guidewire cannulation is thought to potentially prevent PEP by decreasing papillary trauma and contrast injections into the pancreatic duct in comparison to conventional cannulation (Fig. 14.3). In this technique, the tip of a dual-lumen catheter is inserted 2–3 mm into the ampulla, and a guidewire, usually 0.035 or 0.025 inches in diameter, is advanced under fluoroscopy into the bile duct and the catheter then advanced over the guidewire with contrast injection used for confirmation [33]. If the guidewire is inadvertently inserted into the pancreatic duct, it can be withdrawn and redirected – though repeated guidewire insertion into the pancreatic duct is associated with increased of PEP (OR 2.25) [34].

In cases of difficult bile duct cannulation, a guidewire can also be inserted into the pancreatic duct first; this alters the anatomy in a way that facilitates insertion of a second guidewire into the bile duct. In one study, this technique led to successful selective cannulation of the bile duct in 73% of patients in which a 15-minute attempt at conventional cannulation had been unsuccessful [35]. A meta-analysis of 12 RCTs found that guidewire cannulation of the bile duct decreased incidence of PEP by 49% (NNT = 31) and improved cannulation success (84% vs. 77%) without increased complications when compared to conventional cannulation [36]. Based on this data, guidewire cannulation is considered standard of care for PEP prevention and recommended by both the ASGE and ESGE [31, 37].

Prophylactic Pancreatic Duct Stent Placement

Placement of prophylactic pancreatic stents is another technique that has been successful in preventing PEP. As discussed earlier in this chapter, mechanical outflow obstruction of pancreatic secretions due to papillary edema and injury due

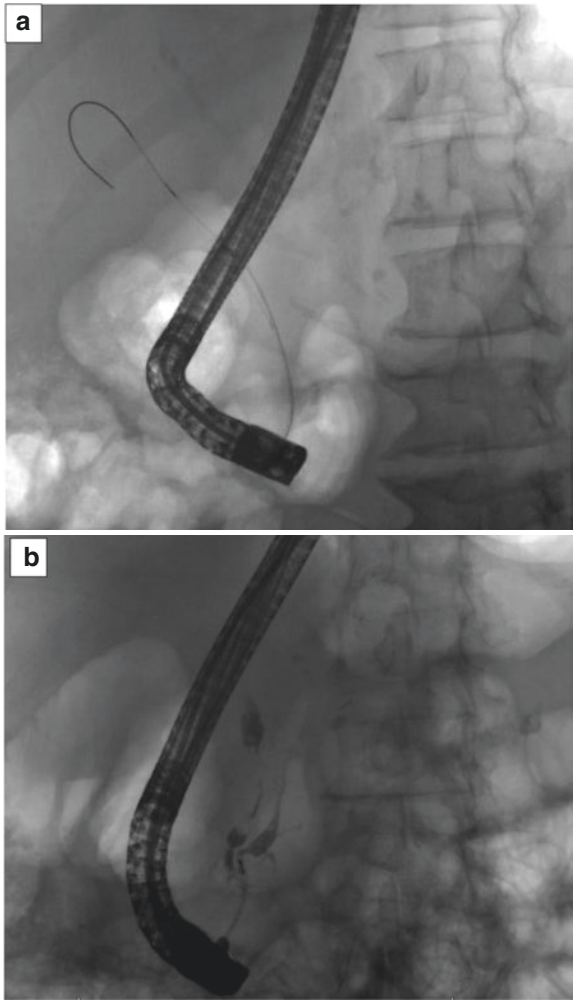

FIGURE 14.3 Guidewire-assisted cannulation vs. contrast-assisted cannulation. **(a)** Guidewire cannulation is thought to potentially prevent PEP by decreasing papillary trauma and contrast injections into the pancreatic duct and is considered standard of care for PEP prevention. (**b**) Contrast-assisted cannulation may be beneficial in cases of difficult cannulation; however repeated injection of the pancreatic duct can increase the risk of PEP

to increased hydrostatic pressure are thought to be the most important mechanisms in the pathogenesis of PEP. Placement of pancreatic duct stents in theory should lead to appropriate drainage and decompression of the duct even in the setting of papillary edema. A recent meta-analysis of 14 RCTs pooling 1541 patients found that prophylactic pancreatic stent placement after ERCP decreased the risk of pancreatitis by 61% (NNT = 8) [38]. The benefit was seen in both mild to moderate PEP and severe PEP (55% and 74% relative risk reduction, respectively). Given the strong benefit seen in these trials, prophylactic pancreatic stent placement after ERCP for PEP prevention is recommended by the ASGE and ESGE [42, 43]. There is little evidence regarding optimal stent choice. Chahal et al. showed no difference in PEP or stent dislodgement between long 3 Fr and short 5 Fr stents in an RCT [39]. One expert reports using 4-Fr, 11-cm, soft, unflanged, single-pigtail stent in cases when the guidewire can easily be passed to the pancreatic tail and a 5-Fr, double-inner and double-outer flanged, ultrasoft stent if the wire does not pass beyond the genu [40]. Spontaneous stent passage can be assessed with an abdominal radiograph 2–3 weeks post-procedure; if a stent does not pass spontaneously, it should be endoscopically removed. There is some evidence that if a patient who underwent prophylactic pancreatic duct stent placement develops severe PEP, it may be due to premature stent migration, and outcomes may improve with prompt replacement of the stent. Similarly, if a patient did not have a prophylactic pancreatic stent placed and subsequently develops severe PEP, prompt placement of a stent may improve outcomes [41].

Pharmacologic Prevention Strategies

Rectal Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most effective PEP chemopreventive agents to date. Elmunzer et al. [42] demonstrated, in a meta-analysis pooling 912 patients from four RCTs, that prophylactic administration of rectal NSAIDs decreased the incidence of PEP by

64% and of moderate or severe PEP by 90%. This study was followed by a multicenter, double-blind RCT [43] that tested rectal indomethacin versus placebo in 602 patients, showing that patients who received indomethacin were 46% less likely to develop pancreatitis (NNT = 13) and 50% less likely to develop moderate or severe pancreatitis (NNT = 23). Despite these strongly positive results, there is conflicting evidence. Levenick et al. [44] conducted a single-center RCT also administering 100 mg of rectal indomethacin or a placebo suppository and found no difference between the two groups in the incidence or severity of PEP. Of note, this trial contained more patients of average-risk, as opposed to high-risk patients than prior RCTs. This suggested that perhaps NSAID chemoprevention was only effective in high-risk patient populations. However, a subgroup meta-analysis pooling 2450 average-risk patients from five RCTs (including the Levenick et al. [44] study) still found a relative PEP risk reduction of 28% [45]. As of the time of this writing, both the American Society for Gastrointestinal Endoscopy (ASGE) and the European Society of Gastrointestinal Endoscopy (ESGE) recommend rectal NSAID administration (100 mg of indomethacin or diclofenac) for PEP prophylaxis [31, 37].

In regard to the timing of the delivery of rectal NSAIDs, Yu et al. performed a meta-analysis which showed effectiveness prior to ERCP as well as after ERCP [46]. Additional experts have supported delivering the rectal NSAIDs prior to the procedure, as the initiation of the inflammatory cascade of pancreatitis may be early in the procedure [23, 47]. In our practice, we deliver rectal NSAIDs to all of our patients prior to the beginning of the ERCP unless there is a documented allergy.

Protease Inhibitors

Protease inhibitors are another class of drugs that may have a role in PEP chemoprevention. Like NSAIDs, protease inhibitors attempt to interrupt the inflammatory reaction that leads to PEP but in this case through inhibition of

trypsin activation as opposed to inhibition of prostaglandin and phospholipase A-2 signaling. Nafamostat mesylate has been the most promising protease inhibitor thus far. In a meta-analysis, pooling 2956 patients from 7 RCTs showed a 53% decrease in PEP incidence compared to controls [48], though it is likely more helpful for low-risk rather than high-risk patients [49]. Despite this significant chemopreventive effect, nafamostat mesylate is not widely used due to high costs and the logistical inconvenience of needing to administer a lengthy intravenous infusion, sometimes lasting up to 24 hours, and is not recommended in the ASGE or ESGE guidelines [31, 37]. Two other protease inhibitors have been thoroughly studied, gabexate and ulinastatin, but have overall been less effective and more cumbersome than nafamostat mesylate [50–52]. Other drug classes are also being investigated with mixed results to date, as shown on Table 14.3.

Table 14.3 Classes of chemopreventive agents under investigation and recommendation status in society guidelines [31, 37]

PEP chemopreventive agents under investigation		
Drug class	**Mechanism**	**ASGE or ESGE recommendation**
Rectal NSAIDs [42–45]	Anti-inflammatory effect through prostaglandin and phospholipase A-2 inhibition	Yes
Protease inhibitors [48, 49]	Trypsin activation inhibition	No
Sublingual nitroglycerin [62]	Sphincter of Oddi relaxation	No
Topical epinephrine [63–65]	Papillary edema reduction through vasoconstriction	No
Somatostatin and analogues [66]	Inhibition of pancreatic exocrine secretion	No

Somatostatin and Nitroglycerin

Somatostatin and nitroglycerin have been investigated as potential pharmacological interventions to prevent PEP. Somatostatin, a suppressor of pancreatic exocrine function, has been studied for PEP prevention in at least 15 RCTs. A meta-analysis of these trials found that somatostatin significantly decreased the incidence of PEP in high-risk patients when administered as a long-term infusion (0.25 mg/h intravenously for >10 hours) initiated 0–60 minutes prior to ERCP; unfortunately no preventive effect was seen with less burdensome delivery regimens or in patients who were not at high risk [53]. However, this long-term delivery is not practical for outpatient ERCP procedures. Another meta-analysis found the evidence for somatostatin to be inconclusive [54].

Nitroglycerin may prevent PEP by promoting relaxation of the sphincter of Oddi and outflow of pancreatic secretions; however the published data to date has been conflicting. Four RCTs – two using transdermal nitroglycerin, one intravenous, and one sublingual – were examined in a meta-analysis; this study suggested some reduction in PEP but did not achieve statistical significance [55]. However, three additional placebo-controlled RCTs have demonstrated a significant reduction in PEP [56–58]. Further, a double-blind RCT combination study by Sotoudehmanesh et al. [59] reported that the rates of PEP were significantly decreased in patients who received combination indomethacin-nitroglycerin therapy compared with the indomethacin-placebo cohort (6.7% vs. 15.3%).

Therefore, while somatostatin and nitroglycerin both show some promise as agents for pharmacological prevention of PEP and can be considered in certain cases, current data remains inconclusive, and larger trials are necessary before widespread clinical adoption.

Aggressive Periprocedural Lactated Ringer's Solution

Early aggressive intravenous hydration provides support to the microcirculation of the pancreas, reducing tissue ischemia, and thereby aids in the prevention of severe pancreatitis.

Lactated Ringer's (LR) solution is currently the favored crystalloid solution for fluid resuscitation as it reduced the likelihood for metabolic acidosis and has been found to decrease systemic inflammation and serum C-reactive protein levels in patients with acute pancreatitis more effectively than normal saline (NS). In addition to the treatment of acute pancreatitis, LR can also be used as a preventive measure against PEP. Two RCTs demonstrated that aggressive LR administration resulted in lower incidence of PEP when compared to standard LR administration (defined as 1.5 ml/kg/hr. during and 8 hours post-ERCP) [60, 61]. The optimal LR administration strategy for PEP prevention is unknown; both a regimen of 10 ml/kg bolus pre-ERCP, 3 ml/kg/hr. during, and 8 hours post-ERCP and a regimen of 3 ml/kg/hr. during, 20 ml/kg bolus post-ERCP, and 3 ml/kg/hr. for 8 hours post-ERCP were found to significantly decrease rates of PEP compared to the standard regimen without causing volume overload.

Case Discussion

Despite identifying the patient in this case to be high risk for PEP and undertaking maneuvers to reduce the likelihood of PEP, the patient still developed PEP on two different occasions. In the two instances that this patient developed PEP, she received standard of care PEP prevention measures discussed above, including administration of rectal indomethacin, guidewire cannulation, and prophylactic pancreatic stent placement.

Although these cases are challenging, acknowledgment of the patient's risk factors allows for a thorough, pre-procedure informed consent process prior to completing the ampullectomy. It also raises the question whether or not combination therapy to target different components of the pancreatitis inflammatory cascade should be considered. In addition to the aforementioned RCT demonstrating superior PEP prevention in patients receiving rectal indomethacin and sublingual nitroglycerine, a recently published RCT compared combination therapies of different IV crystalloid fluids and rectal

indomethacin. In this study, Mok et al. [67] reported that the combination of LR and rectal indomethacin was associated with a lower rate of PEP than NS and placebo (6% vs. 21%). However, there was no statistical difference between LR alone and LR with rectal indomethacin. Some experts have questioned whether rectal indomethacin can decrease the need for pancreatic duct stenting, as one post hoc analysis demonstrated that after adjusting for risk using two different logistic regression models, rectal indomethacin alone appeared to be more cost-effective and possibly more clinically effective for preventing PEP than a pancreatic duct stent alone and the combination of indomethacin and a pancreatic duct stent [68]. A comparative effectiveness, multicenter, randomized, double-blind, non-inferiority study of rectal indomethacin alone versus the combination of rectal indomethacin and pancreatic stenting for preventing PEP in high-risk cases is ongoing [69].

Her recurrent episode of PEP after the ampullectomy and noted premature/early passage (48 hours) of the short 5 Fr × 3 cm pancreatic duct stent also warrants discussion. There is limited data on (1) the optimal stent size and length for prophylactic pancreatic duct stenting or (2) the optimal duration required for effective prophylaxis.

Of the available data published on pancreatic duct stents, larger stents (5 Fr stents) have been demonstrated to have higher rate of successful placement and in theory may better facilitate pancreatic pressure reduction, but also a higher rate of pancreatic duct injury when compared to smaller stents (3 or 4 Fr stents) [39, 70]. There is limited data available on optimal stent length. Chahal et al. reported no particular advantage of long (>8 cm) 3 Fr stents over short (3 cm) 5 Fr stents, including no difference in PEP incidence, increased rate of spontaneous dislodgement with short 5 Fr stents, and increased rate of stent placement failure in the long, 3 Fr cohort [39]. This suggests that the added manipulation required for deep guidewire cannulation into the pancreatic tail is not necessarily warranted to place a long stent. In our practice, we favor placing short, 3 cm stents (occasionally with

the inner flange removed) to facilitate this passage and decrease the need for repeat endoscopy for removal.

Although most stents pass spontaneously on their own within a few weeks of placement, there remains minimal data regarding optimal duration of pancreatic duct stenting for prophylaxis. Some experts have hypothesized that early salvage ERCP to replace prematurely migrated pancreatic stents might reduce the severity of PEP. In a study of 3216 ERCPs, Kerdsirichairat et al. [41] performed urgent salvage ERCP to place or replace a pancreatic stent in 14/57 patients with PEP, including 7 with premature pancreatic duct stent migration. In this small cohort, very early outward stent migration was temporally associated with moderately delayed onset PEP, and stent reinsertion improved the severity of pancreatitis. Further investigation is required before recommending salvage ERCP for stent replacement in cases of early migration and delayed onset PEP.

In our patient, given (1) the nature of increased thermal injury to the pancreatic sphincter from the ampullectomy and (2) the synergistic high-risk patient risk factors for PEP, a more prolonged duration of prophylactic stenting with a longer, more stable stent may have been a better choice to ensure complete pancreatic duct decompression until the trauma and edema of the ampullectomy had resolved.

Outcomes

Despite PEP being the most frequent complication of ERCP, the majority of patients will have a mild to moderate course with approximately 5% of patients developing a severe course requiring prolonged hospitalization or additional interventions [11]. Early identification and management with aggressive intravenous fluid resuscitation, pain control, early implementation of enteral nutrition, and monitoring for severe complications are required to limit the severity of PEP.

Case Discussion

Six weeks after her ampullectomy, the patient presented for an EGD for biliary stent removal. A small pancreatic orifice lesion is again seen, concerning for recurrent adenoma; this is confirmed through pathologic analysis. The patient is further evaluated with an EUS, which demonstrated a 4 mm frond-like projection into the main pancreatic duct suspicious for tissue in-growth from external papillary adenoma. Given her young age, intraductal extension of her adenoma, and recurrent pancreatitis history, she is referred to a pancreatic surgeon who recommended elective pancreaticoduodenectomy (Whipple) procedure to prevent further episodes of pancreatitis or malignant transformation of adenoma. The patient underwent the Whipple procedure and has not had any further episodes of acute pancreatitis.

Pearls and Pitfalls

- Pancreatitis is the most common complication of ERCP (3–15% of patients) and results in significant cost, morbidity, and occasionally mortality.
- Post-ERCP pancreatitis occurs as an inflammatory reaction and is activated by increased hydrostatic pressure in the pancreatic duct and/or outflow obstruction of pancreatic juices due to post-procedural papillary edema.
- A complete understanding of patient- and procedural-related risk factors for PEP informs pre-, mid-, and post-procedural management strategies, including informed consent and use of procedural and pharmacotherapy prevention strategies.
- The patient- and procedural-related risk factors for PEP may have a synergistic effect.
- The most important factor in preventing post-ERCP pancreatitis is careful and appropriate selection of patients with adherence to the evidence-based indications for ERCP.

- In addition to new-onset abdominal pain, new-onset vital sign changes, particularly intra-procedure or post-procedure tachycardia, should raise suspicion of possible PEP. Watch for false negatives in patients on beta-blockers.
- After >10 minutes or >3 attempts, if standard cannulation techniques remain unsuccessful at selective biliary cannulation, consider alternative more advanced cannulation techniques.
- Guidewire cannulation, rectal NSAID administration, and prophylactic pancreatic duct stent placement are all standard of care measures to prevent PEP in high-risk cases and should be considered in average-risk patients.
- In our practice, unless a documented allergy, we give rectal NSAIDs to all patients undergoing ERCP.
- Aggressive, liberal delivery of intravenous hydration with lactated Ringer's solution (1 liter in pre-op, 150 mL/hour after) should be considered for patients undergoing ERCP.
- Pancreatic duct stents (typically short, 5 Fr soft stents) placed for PEP prevention must be documented to spontaneously have passed (abdominal X-ray) or be removed endoscopically.

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