Outline of Possible ERCP COMPLICATIONS

Mohamad Husseini Saeid Mohamed Zidan [1], Emad Fawzy Hamed [1], Samir Abdel Azim Morsy Afifi [1], Mohamed Abdel Azim Abdel Azim Abu Taleb [1], Hesham Radwan Abdelaziz[2]

1 Department of Internal Medicine, Faculty of Medicine, Zagazig University, Egypt.

2 Department of Pathology, Faculty of Medicine, Zagazig University, Egypt

Corresponding author: Mohamad Husseini Saeid Mohamed Zidan

E-mail: Mh.said22@medicine.zu.edu.eg, muhamedzidan95@gmail.com

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Abstract

Biliary endoscopic sphincterotomy (EST) is associated with several complications both in the short term and long term. These complications are inevitable due to the invasive nature of ERCP and observed in a variable ratio of patients, depending on some patient and procedure related factors. Early identification and appropriate management of complications is essential to reduce mortality and morbidity. The short-term complications of EST are bleeding, perforation, pancreatitis and cholangitis. They have an incidence between 2.5% and 11.8%.

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Introduction

Biliary endoscopic sphincterotomy (EST) is associated with several complications both in the short term and long term. These complications are inevitable due to the invasive nature of ERCP and observed in a variable ratio of patients, depending on some patient and procedure related factors. Early identification and appropriate management of complications is essential to reduce mortality and morbidity. The short-term complications of EST are bleeding, perforation, pancreatitis and cholangitis. They have an incidence between 2.5% and 11.8% [1].

Pancreatitis;

The incidence and pathophysiology;

• Post-ERCP pancreatitis (PEP) is the most common serious ERCP complication [2].

• Post- ERCP Pancreatitis (PEP) is the most common complication of ERCP. The incidence depends on some patient and procedure-related factors. Biliary EST is not an independent risk factor for PEP [3].

• The incidence of PEP ranges from 3.5 to 9.7%, and 0.1–0.7% of patients die from PEP [4].

• Although, whilst the final pathogenic mechanisms of pancreatic damage are similar regardless of the causative factor, it has been suggested that non-ERCP-induced acute pancreatitis and PEP are different clinical entities with different outcomes in both mild and severe forms [5].

• Post-ERCP pancreatitis (PEP), which is closely related to difficult biliary cannulation, has been identified as the most common and serious post-ERCP complication, with an incidence rate of 3%–10% [4].

• The consensus definition of PEP consists of the following criteria: serum amylase at least 3 times above the upper limit of normal 24 h post-procedure level accompanied by new abdominal pain consistent with pancreatitis and symptoms severe enough to require a hospital stay or to extend the length of stay of already hospitalized patients, and/or abdominal computer tomography scan (CT) consistent with the diagnosis of acute pancreatitis [6].

• The 2020 ESGE guideline on ERCP-related adverse events defines PEP as a condition that is associated with new or worsened abdominal pain combined with elevated pancreatic enzymes (amylase or lipase $\geq$ 3 times upper limit of normal), thus prolonging a planned hospital admission or necessitating hospitalization after an ERCP [4].

• In ICU patients, altered mental status and/or deep sedation interferes with the patient's ability to communicate symptoms and limits the sensitivity of physical examination. For study purposes, PEP was defined as lipase >3 times normal limit within 24 hours after ERCP (according to the revised European Society of Gastrointestinal Endoscopy (ESGE) guidelines published in 2014) [7].

• Post-ERCP pancreatitis (PEP) is thought to result from an interplay of mechanical obstruction and/or hydrostatic injury, which causes early activation of pancreatic enzymes, leading to local and potentially systemic inflammation [8].

• Obstruction can be caused by oedema or trauma to the papilla most often through over-manipulation. Thus, it is crucial to recognize this and to consider alternative cannulation techniques when standard attempts fail. Hydrostatic injuries can be induced by pancreatic duct (PD) injection with the use of contrast agents or water, especially in the case of acinarization. Further causes for injuries include perforation of the pancreatic duct side branch with guidewire, use of electrocautery and possibly allergic reaction to the contrast agent [9].

• Post-ERCP pancreatitis (PEP) normally is diagnosed when patients develop symptoms of acute pancreatitis (ie, abdominal pain) in addition to elevation of pancreatic enzymes in serum [9].

The severity of attack was graded by the proposed classification of mild, moderate and severe based on needed duration of hospital stay, presence of local or systemic complications, which may be also estimated using the revised Atlanta classification consensus [10].

• Testoni et al., 2010 concluded that the level of serum amylase measured 4 h after endoscopic sphincterotomy was a sufficiently reliable indicator of PEP, as more than two-thirds of the cases involving pancreatitis occurred among the patients whose 4-h amylase level was higher than 5 times the normal upper limit [11].

• Ito et al., 2007 has stressed the importance of a dynamic rise of serum amylase between 3 and 6 h post procedure in the diagnosis of PEP [12].

He suggested that when hyperamylasemia (higher than 2 times the normal upper limit) is observed at 3 h after ERCP, serum amylase concentration should be measured at 6 h after the procedure. A decrease in serum amylase level at 6 h after ERCP indicates the absence of PEP. Gottlieb et al. proposed ruling out the diagnosis of PEP in accordance with 2-h serum amylase and lipase values [13].

With regards to post-procedural prediction of PEP, ESGE suggest testing serum amylase or lipase 2–6 h after ERCP in patients presenting with pain and those who are to be discharged on the day of ERCP. It is reported that patients with amylase or lipase values less than 1.5 and 4 times the upper normal limit, respectively, can be discharged without concern about the risk of PEP [7].

Chronic pancreatitis has been demonstrated to be protective against PEP, possibly because of decreased enzymatic exocrine function and pancreatic atrophy.

The presence of pancreas divisum is not an independent risk factor for PEP, but dorsal duct manipulation and minor papilla sphincterotomy increases the rate of PEP. Risk factors for PEP are synergistic; therefore, the risk of PEP is additive for each risk factor that an individual has. The rate of PEP has been reported to be as high as 40% in patients with multiple risk factors [14].

The pathophysiology of PEP is not entirely clear with a multi-factorial concept being held. This involves a combination of chemical, thermal, mechanic, hydrostatic, enzymatic, allergic, and microbiological insults that result from papillary instrumentation and/or hydrostatic injury from the overfilling of the pancreatic duct with contrast material. The influence of these factors leads to a cascade of events resulting in premature intracellular activation of pancreatic proteolytic enzymes, autodigestion, and the release of inflammatory cytokines that produce both local and systemic effects [15].

Among pathogenic factors of PEP, cannulation trauma to the papilla is the most common cause of sphincter of Oddi spasm and/or edema of the papilla. It creates an obstacle to the flow of pancreatic juice, and subsequently determines an acute pancreatic inflammation [16].

Another important factor is the contrast media used with its osmolarity and ionic nature believed to be the major factors responsible [3].The role of intestinal enzymes refluxed into the pancreatic ductal system by ERCP maneuvers has been suggested as another possible trigger [17].

It has also been suggested that bacteria may play a role in the induction of PEP, where bacterial-specific enzymes, toxins or activators of bacterial origin may initiate cytokine release from immune cells which will subsequently initiate pancreatic cell damage [18].

Finally, genetic abnormalities should be noted as a risk factors as well. Homozygous alpha-1-anti trypsin deficiency causing increased rates of hemorrhagic PEP compared to the general cohort is a known example [3].

A widely used consensus definition for post ERCP pancreatitis (PEP) is (1) new or worsened abdominal pain, (2) new or prolongation of hospitalization for at least 2 days, and (3) serum

amylase 3 times or more the upper limit of normal, measured more than 24 hours after the procedure [6].

Stents are used in ERCP to relieve biliary obstructions caused by malignant and benign lesions [19].

These stents, which are commonly made of metal (stainless steel or metal alloy) or plastic (polyethylene, polyurethane or Teflon), are available in a range of different lengths and diameters.Self-expanding metallic stents (SEMS) may be uncovered or covered with materials such as polytetrafluoroethylene for ease in repositioning, removal and maximizing patency [20].

ERCP is a commonly performed procedure and Post-ERCP pancreatitis (PEP) is the most common serious adverse event. The pathophysiology of PEP is not entirely clear with etiology likely involving a combination of chemical, thermal, mechanical, hydrostatic, enzymatic, allergic, and microbiological insults that result from papillary instrumentation and/or hydrostatic injury from the overfilling of the pancreatic duct with contrast material [8].

A consensus paper in 1991 defined PEP as “clinical evidence of pancreatitis” after ERCP associated with a three-fold increase of serum amylase at ≥24 h and necessitating hospital admission or prolonged hospital stay [6].Thereafter, in 1996, Freeman added pain (i.e., new or worsening abdominal pain) as a further criterion to the PEP definition [3].

Risk Factors

Multiple patient- and procedure-related factors have been identified that can affect the rate of post-ERCP pancreatitis (PEP) [21].

Patient-related factors

• Patient-related factors include female gender, alcohol and cocaine use, previous pancreatitis, previous PEP and suspicion of Sphincter of Oddi dysfunction (SOD), younger age, non-dilated common bile duct, normal bilirubin obesity, congestive heart failure and end stage renal disease [4].

• Risk factors for developing Post-ERCP pancreatitis (PEP) have been investigated in many studies for years and a meta-analysis defined risk factors for PEP as : female gender, young age, non-extrahepatic bile duct dilation, prior post-ERCP pancreatitis, normal serum bilirubin, previous pancreatitis history , Sphincter of Oddi dysfunction, intraductal papillary mucinous neoplasm, absence of chronic pancreatitis and difficult cannulation [22].

Operator-related factors

• Operator-related risk factors, including prior experience, case volume, and trainee participation, have been hypothesized to influence the risk of PEP but have been difficult to evaluate because of confounding variables including the complexity of ERCP at high-volume centers versus low-volume centers [5].

• Procedure-related independent risk factors include difficult or failed cannulation, precut sphincterotomy, pancreatic sphincterotomy, pancreatic tissue sampling, repetitive pancreatic

guidewire cannulation, pancreatic duct injection, balloon dilation of the intact biliary sphincter and endoscopic papillectomy [7].

• A prospective multicenter study with >1,000 patients identified endoscopists with <200 endoscopic retrograde cholangio-pancreatographies (ERCP) to represent an independent risk factor for Post-ERCP pancreatitis (PEP) development [23].

• Atraumatic cannulation with a guidewire cannulation technique, early precut sphincterotomy in patients with difficult biliary access, combining papillary balloon dilation with endoscopic sphincterotomy and pancreatic stenting, particularly in patients with a high risk of PEP, may reduce the risk of pancreatitis [24].

Historically, precut (access) sphincterotomy has been attributed to be a risk factor for PEP. In these studies, precut sphincterotomy was primarily used after difficult cannulation. In 1 study, 64% of patients underwent a precut sphincterotomy only after prolonged attempts at cannulation (>15 attempts) [3].

It is likely that this increased rate of PEP attributed to precut sphincterotomy is actually related to ampullary trauma from prior attempts with a difficult cannulation rather than the precut sphincterotomy itself. Using a strategy of early precut sphincterotomy for cases with difficult biliary access is associated with similar if not improved rates of cannulation compared with standard techniques and appears to reduce the risk of pancreatitis [24].

A comparison of ESGE and ASGE guidelines in ERCP-related adverse events showed similar patient- and procedure-related factors [4].

ESGE further classifies patient- and procedural-related factors into “definite” and “likely” groups. An ERCP can be considered as high-risk for PEP if one definite factor (either patient- or procedure-related) or two likely factors are fulfilled.

Methods Of Reducing Post-Ercp Pancreatitis

• Patient selection

Appropriate patient selection is instrumental in reducing the incidence of PEP. EUS and MRCP are equivalent to ERCP for the detection of some pancreaticobiliary disorders such as choledocholithiasis but lack the risk of pancreatitis associated with ERCP. Therefore, ERCP is now largely reserved for indications in which the likelihood of therapeutic intervention is high [25].

Irrespective of the endoscopist’s experience, prophylactic measures can be taken based on an individual assessment to reduce the likelihood of PEP development. The 2020 ESGE guideline on ERCP-related adverse events [4].

• IV hydration

Aggressive hydration with lactated Ringer’s solution (3 mL/kg/h) should be started before ERCP whenever contraindications for NSAID are present and contraindication for high volume hydration are absent. Continuing hydration post int erventionally with 20 mL/kg bolus followed by 3 mL/kg/h for 8 h is recommend in patients without pancreatic duct (PD) stent placement,

while PD stent placement should result in a stop of high-volume therapy post interventionally [4].

• Pharmacologic prophylaxis

Pharmacologic prophylaxis includes rectal NSAID administration either before or immediately after ERCP and periprocedural aggressive intravenous hydration [26].

Therefore, the European Society of Gastrointestinal Endoscopy strongly recommends to use rectally administered indomethacin or diclofenac in every patient undergoing ERCP to reduce the risk of PEP [7].

Since most meta-analyses found a significant reduction of PEP risk when administer 100 mg of rectal indomethacin or diclofenac pre- interventionally in every patient without contraindications to nonsteroidal anti-inflammatory drugs (NSAID) [27].

Due to the lack of solid data, the ESGE does not suggest the routine combination of NSAID with other PEP prevention methods [4].

The best way of preventing PEP is by avoiding unnecessary ERCP. There should be measures in place to ensure appropriate referrals and case selection, with access to multidisciplinary team review, to ensure that ERCP is absolutely indicated for strategic planning of complex cases and to ensure that cases are appropriate for the endoscopist's skill set [28].

• Guidewire cannulation

Cannulation techniques that minimize ampullary trauma reduce the risk of PEP. Data on the risk of PEP with wire-guided versus contrast material–assisted techniques from primary studies have been mixed [11].

Wire-guided cannulation also reduces the risk of PEP in cases of inadvertent pancreatic duct (PD) manipulation. However, the differences in rates of PEP were only observed in studies that did not allow crossover to another technique. When additional techniques or rescue approaches were used, including precut sphincterotomy or PD stent placement, there were no differences in PEP rates between the 2 initial cannulation techniques [29].

• Pancreatic duct stents

Several randomized, controlled trials and meta-analyses have proven a significantly reduced incidence and severity of PEP with prophylactic pancreatic duct stenting [30].

placement of a prophylactic pancreatic duct stent should be considered in patients with risk factors for PEP or repeated unintended pancreatic duct cannulation, although there is only limited evidence for such recommendation [31].

Furthermore, in those patients with unintended pancreatic duct guidewire insertion, pancreatic duct opacification, or double-guidewire cannulation, a short 5F PD stent should be placed ("difficult cannulation with easy pancreatic stenting") [4].

Perforation

Perforation rates with ERCP range from 0.1% to 0.6% [14].

Three distinct types of perforation have been described: guidewire-induced perforation, periampullary perforation during sphincterotomy, and luminal perforation at a site remote from the papilla [32].

Cotton et al., 1991 categorized the severity of perforations into 3 groups:

mild (possible or only slight leak of fluid or contrast, treated by fluids and suction for 3 d or less), moderate (definite perforation treated medically for 4-10 d) and severe (medical treatment for more than 10 d or need for percutaneous or surgical intervention) [6].

ERCP-ASSOCIATED perforations can be divided into three types: guide wire perforation, papillary perforation, and duodenal perforation [32].

Perforation during ERCP transpires by several mechanisms: (1) luminal perforation by the endoscope, typically resulting in intraperitoneal perforation; (2) extension of a sphincterotomy incision beyond the intramural segment of the bile duct or pancreatic duct with retroperitoneal leakage; and (3) extramural passage of guidewires or migration of stents. The incidence of duodenal perforations during ERCP is approximately 0.08% to 0.6% [33].

Perforations must be promptly diagnosed and treated, because delayed therapy may result in sepsis and multiple organ failure, which are associated with an 8% to 23% mortality rate [34].

Risk factors for perforation

Patient-related and procedure-related risk factors for perforation during ERCP have been described. Patient- related factors include suspected Sphincter of Oddi dysfunction (SOD), female sex, older patient age, and surgical or altered anatomy (ie, situs inversus or Billroth II gastrectomy) [35].

Procedure-related factors include difficult cannulation, intramural injection of contrast material, longer duration of procedure, sphincterotomy and precut papillotomy, biliary stricture dilation, procedure performed by lesser experienced operators and EPLBD [35].

Although endoscopic sphincterotomy with EPLBD and complete endoscopic sphincterotomy alone are risk factors for ERCP-related perforation, there is a lower rate of perforation with the former approach [36].

Risk factors for perforation determined in a large retrospective study included the performance of a sphincterotomy, Billroth II anatomy, the intramural injection of contrast, prolonged duration of procedure, biliary stricture dilation, and Sphincter of Oddi dysfunction (SOD) [37].

However, in a more recent multicenter prospective study, only malignancy and precut access were associated with an increased risk of perforation [38].

Biliary Endoscopic Sphincterotomy is the most common cause of ERCP related perforation [39].

The incidence of sphincterotomy related perforation, also named Type 2 duodenal perforation, is between 0% and 1.8% [1].

Extensions of sphincterotomy beyond the intraduodenal segment of the bile duct and towards the wrong direction are the most frequent mechanisms. Perforation risk increases after needle knife precutting and in patients with sphincter of Oddi dysfunction [3].

Stapfer et al., 2000 classified perforations into 4 types in decreasing order of severity with the goal of correlating the mechanism of injury and the anatomic location of perforation as predictors of outcomes and the need for surgery. Type I perforations are perforations of the duodenal wall caused by the duodenoscope. Type II perforations are periampullary perforations of the medial wall of the duodenum that typically result from biliary or pancreatic sphincterotomy or precut papillotomy and are variable in their severity. Type III perforations are bile duct or pancreatic duct injuries caused by instrumentation (guidewires), stone extraction and/or stenting. Type IV perforations are diminutive retroperitoneal perforations of no clinical significance that result from excessive insufflation during endoscopy together with sphincter manipulation [40].

An alternate classification has also been proposed: duodenal perforation, papillary perforation, bile duct perforation, and retroperitoneal emphysema [40].

Overview Of Management Concepts

Symptoms and signs suggestive of duodenal perforation are severe epigastric and back pain, epigastric tenderness progressing to generalized abdominal wall rigidity, subcutaneous emphysema, fever and tachycardia [41]. Signs of peritonitis often develop after 4 to 6 hours when duodenal contents extravasate into the peritoneal cavity. The presence of a systemic inflammatory response is often present 12 hours or more following endoscopy [42].

A majority of bile duct perforations and papillary perforations can be treated conservatively; however, most duodenal perforations require surgical treatment [40].

Prompt recognition of periampullary perforation and treatment with aggressive biliary and duodenal drainage (by means of naso-biliary and nasogastric tubes) coupled with broad spectrum antibiotics can result in clinical resolution without the need for operative intervention in as many as 86% of patients [37].

Management based on type of perforation

If duodenal perforation is suspected, fasting, intravenous fluids, and intravenous antibiotics should be commenced while the diagnosis is being confirmed. After initial resuscitation and establishment of diagnosis, the first step in management is to determine whether the patient should be managed medically or surgically. This is determined by the patient's condition (presence of peritoneal signs, systemic inflammatory response), the mechanism of injury, anatomical location, and degree of leakage [43]. Despite high-quality imaging, it may be impossible to precisely define the location of perforation [44].

A-Duodenal wall perforation

Duodenal wall perforations traditionally have been managed with immediate surgical repair. Because iatrogenic perforation has a lower risk of bacterial contamination with patients in the fasting state, patients potentially can be treated endoscopically [45].

Successful intraprocedural closure of duodenal perforations has been reported with the use of endoclips, the over-the-scope clip, and endoscopic suturing de- vices [43]. Closure of large, luminal defects may be difficult with the earlier-mentioned techniques, but the combination of endoclips and a detachable plastic snare (PolyLoop; Olympus Inc, Center Valley, Pa) has been successful in some cases [46].

B- Periampullary perforations

Sphincterotomy accounts for the majority of recognized ERCP-related perforations. The incidence can be minimized by limiting the length of cutting wire in contact with the tissue and performing stepwise cutting. The optimal management of perforations related to sphincterotomy, precut papillotomy, or EPLBD is debated. However, if a peri-ampullary perforation is recognized during the procedure, immediate endoscopic therapy should be attempted if feasible [45].

The deployment of an FCSEMS to seal the perforation and divert biliary contents is a simple and effective first-line treatment [47].The optimal duration of stent dwell is unknown, but the stent can likely be removed safely after 2 weeks. For large perforations, a nasoduodenal decompression tube may be placed. Alternatively, a naso-biliary tube may be placed to decompress and divert bile directly from the biliary tree. Additionally, endoclips have been successfully used to close these perforations [43].

C-Instrument-related perforations

To reduce the risk of guidewire perforations, it is important to monitor the wire frequently and advance the wire only under fluoroscopic guidance. These perforations tend to be small, contained, and likely to heal spontaneously, and hence are almost always managed without surgery. Additionally, it is often challenging to identify the site of perforation during surgical exploration. Placement of biliary or pancreatic stents allows appropriate diversion of fluid away from the area of perforation. Asymptomatic patients with retroperitoneal free gas alone detected intra-procedural or afterward should be managed with observation alone [44].

D- Stent-induced perforation

Luminal perforation has been reported following migration of plastic and metal stents and no particular stent is considered higher risk than another. The treatment for stent-induced perforation is endoscopic removal and endoscopic closure of the perforation if the patient does not have clinical features of peritonitis. Surgical management is appropriate for patients with peritonitis or a retro-peritoneal fluid collection [48].

Bleeding:

The incidence of bleeding after therapeutic ERCP is from 0.3 % to 2 %. Post-ERCP bleeding is classified by the European Society of Gastrointestinal Endoscopy (ESGE), according to its severity, as mild, moderate or severe, considering different factors, such as the need for transfusion or the admission to hospital or Intensive Care Unit [4].

Hemorrhage secondary to ERCP is defined as hematemesis and/or melena or a drop in hemoglobin of over 2 g/dl [14].

Delayed bleeding occurs from a few hours up to 2 weeks after the procedure [9]. It is more significant and frequently requires therapeutic interventions [14].

Clinically significant bleeding is defined as the presence of hematemesis and/or melena, hemoglobin drop > 2 g/ dL or requirement for interventions, such as transfusion or endoscopy. It has an estimated incidence between 0.1% and 2% [14].

Cotton et al., 2009, categorized the severity of clinically significant bleeding into 4 groups based on the number of transfusions and requirement for interventions: mild (hemoglobin drop < 3 g/dL and no need for blood transfusions), moderate (blood transfusion ≤ 4 units), severe (requiring angiographic or surgical treatment or blood transfusion ≥ 5 units) and fatal [14].

Risk factors:

The ESGE considers the following risk factors for post-ERCP bleeding: use of anticoagulants, platelets < 50,000/mm3, cirrhosis, end-stage renal disease, intra-procedural bleeding, low endoscopist experience and unsuccessful cannulation with precut sphincterotomy [4].

Endoscopic sphincterotomy (EST) bleeding is classified as immediate or delayed depending on the timing of presentation. Immediate bleeding occurs during or immediately after EST. It is seen in up to 30% of patients and self-limiting in most of the time [4].

In a cornerstone study, multivariable analysis identified 5 independent risk factors for bleeding: the presence of any coagulopathy or thrombocytopenia, active cholangitis, anticoagulant therapy within 3 d after ERCP, endoscopist's low case volume and occurrence of any observed bleeding during ERCP [3].

ERCP-associated bleeding is seldom encountered in normal ERCP cases. Papillary treatments such as endoscopic sphincterotomy (EST), endoscopic papillary balloon dilation (EPBD), and endoscopic papillectomy are the primary causes of bleeding. Although a majority of the cases of bleeding are minor and bleeding may spontaneously stop during treatment [49], it sometimes may obscure the field of view. Patient-related risk factors of post-EST bleeding include the presence of coagulopathy, undergoing anticoagulant therapy within 3 days of ERCP, and active cholangitis [50].

Other possible risk factors are cirrhosis, dilated common bile duct, periampullary diverticulum, precut sphincterotomy, uncontrolled cutting (zipper cut) and am-pullary stone impaction [9].

Longer sphincterotomy incision and use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) do not seem to increase risk of bleeding [3].

Most ERCP-associated bleeding is intraluminal, although intraductal bleeding can occur and hematomas (hepatic, splenic and intra-abdominal) have been reported. Hemorrhage is primarily a complication related to sphincterotomy rather than diagnostic ERCP [51].

Although sphincterotomy alone is a risk factor for hemorrhage, other factors identified in multivariate analysis include coagulopathy, the use of anticoagulants within 72 hours of sphincterotomy, the presence of acute cholangitis or papillary stenosis, the use of precut

sphincterotomy, and low case volume of the endoscopist (ie, 1 sphincterotomy per week or less) [52].

Anticoagulants and antiplatelet agents (APA) are associated with post-ERCP bleeding, and the American Society for Gastrointestinal Endoscopy suggests refraining from APA when undergoing ERCP [3]. Alternatively, aspirin use is considered safe and has not been reported to increase the risk of post-ERCP bleeding [53].

Prevention and management

The risk of post-ERCP bleeding is minimized by avoiding unnecessary sphincterotomy, especially in patients with 1 or more risk factors for bleeding. However, if sphincterotomy is required, a number of factors may be used to prevent post- procedure bleeding [54].

First, Endoscopic papillary large-balloon dilation of an intact sphincter (EPLBD) has been studied as an alternative to endoscopic sphincterotomy in patients with coagulopathy at high risk for bleeding after sphincterotomy. Therefore, EPLBD without endoscopic sphincterotomy is best reserved for patients with coagulopathy who are at significantly increased risk for post sphincterotomy bleeding [55].

Second, the use of blended rather than pure-cutting current and use of a microprocessor-controlled generator may decrease the risk of post-sphincterotomy bleeding. Third, a randomized trial of 120 patients found that prophylactic injection of hypertonic saline-epinephrine proximal to the papilla significantly reduced the risk of post-sphincterotomy bleeding [55].

Initial management of post-sphincterotomy bleeding includes adequate fluid resuscitation, reversal of coagulopathy, and blood transfusion, as needed. Endoscopic management is indicated for significant procedural bleeding or clinically significant delayed bleeding. The most commonly used treatment is injection of dilute epinephrine into and around the sphincterotomy site, which is effective in most cases.The volume of injectate varies between studies but typically is 0.5 mL to 4 mL [56].

Thermal therapies such as multipolar electrocautery and argon plasma coagulation also may be used alone or in combination with epinephrine injection [57].

Balloon tamponade of the sphincterotomy site also may be used to treat intraprocedural bleeding [9].

Placement of through the scope clips onto the bleeding site (typically at the apex) by using a duodenoscope is challenging but may be facilitated by use of a forward viewing endoscope with a cap [58].

Care must be taken to avoid the pancreatic orifice during thermal and mechanical applications. Several recent studies of refractory post-sphincterotomy bleeding have reported excel- lent outcomes with the use of fully covered self-expandable metal stents (FCSEMSs) for refractory post-sphincterotomy bleeding with excellent outcomes in the vast majority (100% in most series). FCSEMSs also can be used to tamponade bleeding originating from deep within the ampulla or mid/distal common bile duct [59].

Angiographic embolization and surgery are equally effective therapies for refractory bleeding. Angio- graphic interventions successfully control bleeding in 83% to 100% of patients in reported series and should be considered before surgery [60].

Cholangitis

ERCP is the endoscopic modality of choice for the treatment of acute cholangitis. Cholangitis and sepsis also are known adverse events associated with ERCP, occurring in up to 0.5% to 3% of cases. Patients typically present with fever, jaundice, and abdominal pain, but hypotension and altered mental status can ensue in severe cases [61].

The risk of post-ERCP cholangitis is highest in patients with incomplete biliary drainage (ie, hilar cholangiocarcinoma and primary sclerosing cholangitis) and prior history of liver transplantation. Therefore, periprocedural antibiotics and meticulous biliary drainage techniques are essential in these patients [62].

Current guidelines recommend antibiotic prophylaxis before ERCP in patients who have had liver transplantation or when patients with known or suspected biliary obstruction may be incompletely drained, and these guidelines discourage the routine use of antibiotic prophylaxis before ERCP when complete biliary drainage is anticipated or for cases in which biliary obstruction is not suspected. Antibiotics that cover biliary flora such as enteric gram negative organisms and enterococci should be used and continued after the procedure if biliary drainage is incomplete [63].

Proper ERCP techniques should be used to minimize risk of post-ERCP cholangitis. In cases of hilar obstruction, cholangitis can occur if only unilateral drainage is accomplished after bilateral contrast material opacification. Therefore, it is recommended to use noninvasive imaging (MRCP) to format a “roadmap” before ERCP [64].

Incomplete biliary drainage leading to cholangitis also may occur in patients with choledocholithiasis and incomplete stone clearance. Retained stone fragments may occur following mechanical lithotripsy, and the risk of cholangitis in these patients has been reported to be as high as 10%. A biliary stent should be placed when complete stone extraction has not been accomplished. An alternative technique to avoid retained stone fragments is to perform EPLBD, which facilitates large stone removal and obviates the need for lithotripsy [65].

Cholangitis can also be a delayed adverse event with ERCP when a plastic or metallic stent has been placed previously, although the risk is small after placement of metal stents [66].

Stents may become obstructed because of stone fragments, bacterial biofilm, sludge, tumor, tissue ingrowth and overgrowth occluding the stent lumen. In addition, cholangitis can occur because of stent migration in the setting of an obstructed bile duct. Appropriate choice of stent (plastic vs metal) may help minimize these adverse events. Factors that should be taken into consideration include stricture etiology, stricture location, response to prior therapy, local expertise, stent availability, cost of stents, and expected patient survival. Plastic stents are typically exchanged at scheduled intervals (eg, every 3 months) or at the first sign, symptom, or laboratory anomaly suggesting stent occlusion. Placement of multiple plastic stents may aid in avoiding early stent occlusion and cholangitis [67].

The rate of post-ERCP cholangitis is 1% or less [3]. Risk factors identified as significant include the use of combined percutaneous endoscopic procedures, stent placement in malignant strictures, the presence of jaundice especially caused by malignancy, primary sclerosing cholangitis, low case volume, incomplete or failed biliary drainage and inexperience of the endoscopist [3].

In the case of malignant hilar obstruction (ie, Klatskin tumor), it is suggested that endoscopists avoid filling all intrahepatic segments and drain all intrahepatic segments that are filled with contrast. Unilateral endoscopic biliary stent placement directed by previous imaging (eg, MRCP) has been shown to offer palliation of jaundice equal to bilateral placement but with less risk of cholangitis [68].

Long-term complications Long-term complications

Endoscopic sphincterotomy include recurrent common bile duct stone, cholecystitis, cholangitis, hepatic abscess, papillary stenosis and biliary stricture. Recurrent common bile duct stone is the most common complication. It can be seen in up to 17% of patients. Large diameter of the common bile duct, presence of a periampullary diverticulum, gallstones and the use of mechanical lithotripsy during previous stone extraction increase the risk of recurrence [1].

SOD and ischemia of the ampulla due to previous complicated endoscopic procedures, such as injection and heater probe for the treatment of bleeding, are the risk factors for papillary stenosis. In sphincterotomy associated biliary stricture, the stricture extends over the intraduodenal segment of the bile duct to the distal part of extra duodenal common bile duct. It develops in 1% of patients [69].

Cholecystitis

Cholecystitis complicates approximately 0.2% to 0.5% of ERCPs [3].

The risk appears to be correlated with the presence of stones in the gallbladder and possibly filling of the gallbladder with contrast during the examination [3].

Post-ERCP cholecystitis is an uncommon adverse event but should be recognized early and not be mistaken for acute cholangitis. Patients may present with fever, abdominal pain, leukocytosis, and a positive Murphy's sign. Diagnosis should be confirmed by imaging findings. Pathogenesis is believed to be related to gallbladder contamination by nonsterile contrast material in the context of gallbladder dyskinesia or outflow (cystic duct) obstruction. Therefore, it is believed that the presence of cholelithiasis increases the risk of post-ERCP cholecystitis Acute cholecystitis following biliary FCSEMS placement occurs in 1.9% to 12% of cases and is believed to result from cystic duct obstruction [70]. Tumor involvement of the cystic duct orifice appears to be a major risk factor for acute cholecystitis in this setting [71].

The role of prophylactic periprocedural intravenous antibiotics to prevent cholecystitis has not been studied. Treatment of post-ERCP cholecystitis traditionally includes surgery or percutaneous cholecystostomy. However, trans-papillary and EUS-guided gallbladder drainage may be considered, especially in patients who are not surgical candidates (eg, inoperable periampullary carcinoma) [72].

Successful management of acute cholecystitis after covered SEMS placement with stent removal and replacement with either uncovered stents or plastic stents has been reported [70].

Additionally, placement of self-expandable metal stents may increase the risk of cholecystitis, particularly if the stent is covered and the cystic duct is obstructed [73].Acute cholecystitis is a complication that may occur after metallic stent placement [74].

The risk is particularly high in cases where a tumor extends to the cystic duct and where the cystic duct is obstructed by a covered metallic stent. Furthermore, the risk has been reported with the presence of stones in the gallbladder and the filling of the gallbladder with contrast during the examination [3].; adequate attention should be taken to prevent excessive contrast. If there is no improvement with conservative therapy, percutaneous transhepatic gallbladder aspiration or percutaneous transhepatic gallbladder drainage should be considered. In the case of cholecystitis due to a covered metallic stent, removal of the stent and replacing with a plastic stent or uncovered metallic stent should be considered [3].

Cholecystitis complicates approximately 0.2% to 0.5% of ERCPs. The risk appears to be correlated with the presence of stones in the gallbladder and possibly filling of the gallbladder with contrast during the examination [3].

Additionally, placement of self-expandable metal stents may increase the risk of cholecystitis, particularly if the stent is covered and the cystic duct is obstructed [73].

ASGE guidelines currently recommend that antibiotic prophylaxis should be considered before an ERCP in patients with known or suspected biliary obstruction in which there

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is a possibility that complete drainage may not be achieved at the ERCP, such as in patients with a hilar stricture and primary sclerosing cholangitis [75].

Antibiotic prophylaxis is not recommended before an ERCP when obstructive biliary tract disease is not suspected. Antibiotic prophylaxis is recommended before an ERCP in patients with communicating pancreatic cysts or pseudocysts and before trans papillary or transmural drainage of pseudocysts. Some advocate use of peri-procedure antibiotics for immunocompromised patients undergoing ERCP [62].

Stent-Related Adverse Events

Numerous stent-related adverse events have been described, including stent occlusion, bowel wall perforation, and injury to the biliary or pancreatic duct. Unintended migration of plastic biliary or pancreatic stents has been reported in 5% to 6% of patients [76].

Pancreatic duct stenting has been associated with the development of ductal irregularity, side branch dilation, and stricture formation, the appearance of which can mimic changes seen with chronic pancreatitis [3].

Modifications in stent design without an internal flange may reduce the risk of these ductal changes. Internally migrated biliary or pancreatic stents should be removed, because these can result in jaundice, cholangitis, pancreatitis, or perforation. Various techniques for removal of a proximally migrated stent have been described, including the use of stent retrieval devices, forceps, snares, or retrieval balloons. Rarely, patients may require surgery to remove these migrated stents [77].

Migration of plastic stents into the bile duct has been observed. Proximal stent migration was reported in approximately 5% of cases in an initial report. Malignant strictures, larger diameter stents, and shorter stents were significantly associated with proximal biliary stent migration [76].

Miscellaneous Complications

A wide variety of additional complications have been reported. These include ileus, antibiotic related diarrhea, hepatic abscess formation, pneumothorax, pneumomediastinum, perforation of colonic diverticula, duodenal hematoma, portal venous air, and impaction of therapeutic devices, such as stone retrieval baskets [52].

Pseudocysts may become infected, and filling of pseudocysts in the absence of subsequent drainage should be avoided, if possible. Numerous complications of ERCP-placed stents have also been described, including stent migration, stent occlusion, perforation, liver abscess, acute cholecystitis, injury to the biliary duct or pancreatic duct and compression of adjacent organs [78].

Stent placement in the pancreatic duct has been associated with the development of ductal irregularity (36%-49%), side branch dilation (16%), and stricture development (18%-16%), all of which can mimic chronic pancreatitis [79].

Pancreatic duct stent size, composition, and duration of placement may all influence the incidence of these changes, which are not clinically relevant in all cases [80].

Subcapsular hepatic hematoma may result from guide wire perforation and laceration of small hepatic vessels and often is managed conservatively with intravenous fluids and antibiotics, because these individuals are at risk for infection from an instrumented biliary tree [81].

Adverse Reaction To Contrast Material

Although systemic absorption of contrast material has been well-documented, adverse reactions to contrast material have rarely been described with ERCP [82]. Reaction to contrast material is idiosyncratic and can range from a rash to anaphylaxis. A prospective study of 601 patients undergoing ERCP, including a subset of patients with a history of intravenous contrast material

or shellfish allergy, identified no adverse events with the use of full-strength high osmolality contrast material [83].

For individuals with a documented IV contrast allergy, some centers use non- iodinated contrast materials, whereas others premedicate with oral prednisone and diphenhydramine before the procedure, although there is lack of evidence for any benefit with pre-medication [84].

Duodenoscope-Related Transmission Of Infection

Transmission of multi drug-resistant organisms, including carbapenem- resistant Enterobacteriaceae, has been reported recently, which is not attributable to recognized breaches of standard reprocessing protocol. There is some evidence that bacterial contamination may occur in difficult to clean or even sealed portions of the duodenoscope [85].

With the recognition of this rare but serious adverse event, renewed emphasis has been placed on diligent mechanical cleaning of the duodenoscope (including the introduction of a new cleaning brush) as well as strict adherence to the manufacturer's standard protocol for high-level disinfection (HLD). In addition, 4 methods of enhanced reprocessing of duodenoscopes have been proposed: microbiological culturing, repeated HLD, gas sterilization by using ethylene oxide, or the use of a liquid chemical sterilant processing system such as peracetic acid [86].

Air Embolism

Air embolism is a rare but potentially devastating adverse event that occurs as a result of direct communication with the vasculature and an external pressure gradient (ie, from the GI tract or the bile duct) allowing the passage of air into the circulation. Mechanisms associated with air embolism include trauma or inflammation of the bile ducts from contrast administration, insufflation, or from the endoscope or ERCP accessories. Air embolism has been associated with direct cholangioscopy [87].

Venous air embolism is readily diagnosed with air in the portal vein and can be managed conservatively with IV antibiotics and decompression via nasogastric tube. The presence of portal vein gas also can be noted with perforation and intestinal ischemia and should therefore be evaluated for such in the correct clinical context. Systemic air embolism, including intracardiac and intracerebral air embolism, is highly lethal [88].

Systemic air embolism should be considered if a patient suddenly develops hypotension or hypoxia when being moved from the prone to supine position or if the patient develops new neurologic symptoms after the procedure. If intracardiac or intracerebral air embolism is suspected, the patient should be endotracheally intubated, ventilated with 100% oxygen, and positioned in the Trendelenburg and left lateral decubitus position to minimize the amount of air traveling to the brain and encourage egress of air from the right ventricular outflow tract. CT of the chest and head, and a transthoracic echocardiogram should be performed to assess for air embolism. The routine use of CO2 insufflation during ERCP or the use of water instillation to distend the biliary tree during cholangioscopy may reduce the risk of this life- threatening adverse event [88].

Cardiopulmonary Complications

Significant cardiopulmonary complications are rare, occurring in 1% of cases with an associated fatality rate of 0.07% based on a meta-analysis of 12,973 patients enrolled in 14 prospective studies [49].

Complications include cardiac arrhythmia, hypoxemia, and aspiration [89].

Cardiopulmonary problems may also arise from medications used for sedation and analgesia. Recent studies with propofol for ERCP have found this drug to have the same efficacy and safety as conventional moderate sedation medications, with fewer associated hypoxemic events. Additionally, ERCP can be safely performed without requiring universal intubation in patients receiving propofol based anesthesia. Careful pre-operative evaluation and collaboration with anesthesiologists for high risk or difficult to sedate patients may reduce complications [90].

Mortality

The overall mortality rate after diagnostic ERCP is approximately 0.2%. Death rates after therapeutic ERCP are twice as high (0.4%-0.5% in 2 large prospective studies). Death may occur from any of the complications described previously. The mortality rate must be considered in the light of the underlying indication for ERCP and patient comorbidity [49].

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