

# ERCP-related adverse events: European Society of Gastrointestinal Endoscopy (ESGE) Guideline



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## MAIN RECOMMENDATIONS

### Prophylaxis

**1** ESGE recommends routine rectal administration of 100 mg of diclofenac or indomethacin immediately before endoscopic retrograde cholangiopancreatography (ERCP) in all patients without contraindications to nonsteroidal anti-inflammatory drug administration.  
Strong recommendation, moderate quality evidence.

**2** ESGE recommends prophylactic pancreatic stenting in selected patients at high risk for post-ERCP pancreatitis (inadvertent guidewire insertion/opacification of the pancreatic duct, double-guidewire cannulation).  
Strong recommendation, moderate quality evidence.

**3** ESGE suggests against routine endoscopic biliary sphincterotomy before the insertion of a single plastic stent or an uncovered/partially covered self-expandable metal stent for relief of biliary obstruction.  
Weak recommendation, moderate quality evidence.

**4** ESGE recommends against the routine use of antibiotic prophylaxis before ERCP.

Strong recommendation, moderate quality evidence.

**5** ESGE suggests antibiotic prophylaxis before ERCP in the case of anticipated incomplete biliary drainage, for severely immunocompromised patients, and when performing cholangioscopy.

Weak recommendation, moderate quality evidence.

**6** ESGE suggests tests of coagulation are not routinely required prior to ERCP for patients who are not on anti-coagulants and not jaundiced.

Weak recommendation, low quality evidence.

## Treatment

**7** ESGE suggests against salvage pancreatic stenting in patients with post-ERCP pancreatitis.

Weak recommendation, low quality evidence.

**8** ESGE suggests temporary placement of a biliary fully covered self-expandable metal stent for post-sphincterotomy bleeding refractory to standard hemostatic modalities.

Weak recommendation, low quality evidence.

**9** ESGE suggests to evaluate patients with post-ERCP cholangitis by abdominal ultrasonography or computed tomography (CT) scan and, in the absence of improvement with conservative therapy, to consider repeat ERCP. A bile sample should be collected for microbiological examination during repeat ERCP.

Weak recommendation, low quality evidence.

## SOURCE AND SCOPE

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE), reviewing the definitions, epidemiology, risk factors, prophylaxis measures, and management of adverse events related to ERCP.

## 1 Introduction

The range and incidence of adverse events (AEs) related to endoscopic retrograde cholangiopancreatography (ERCP) differ substantially from those related to other endoscopic procedures. Familiarity with these AEs is critical for providing patient information during the consent phase as well as for prophylaxis and management. Adverse events related to sedation, biliary stent obstruction, radiation, infection, and to the endoscopic resection of ampullary neoplasms will not be discussed as they are included in other Guidelines from the European Society of Gastrointestinal Endoscopy (ESGE) [1–4].

## 2 Methods

ESGE commissioned this Guideline (Guideline Committee Chair, J.v.H) and appointed a Guideline leader (J.M.D.) who invited the listed authors to participate in the project development. The key questions were prepared by the Guideline leader and then approved by the other members. The coordinating team formed task force subgroups, each with its own leader, who was assigned key questions (see **Appendix 1s**, online-only Supplementary Material).

Each task force performed a systematic literature search to prepare evidence-based and well-balanced statements on their assigned key questions. The literature search was performed in MEDLINE and Embase published in English, focusing on meta-analyses and fully published prospective studies, particularly

randomized controlled trials (RCTs), performed in humans. Retrospective analyses and pilot studies were also included if they addressed topics not covered in the prospective studies. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was adopted to define the strength of recommendation and the quality of evidence [5]. Each task force proposed statements on their assigned key questions which were discussed during a meeting in Munich, June 2019. Literature searches were re-run in September 2019. This time-point should be the starting point in the search for

## ABBREVIATIONS

<b>AE</b>	adverse event
<b>ASGE</b>	American Society of Gastrointestinal Endoscopy
<b>BSG</b>	British Society of Gastroenterology
<b>CBD</b>	common bile duct
<b>CI</b>	confidence interval
<b>CT</b>	computed tomography
<b>DGW</b>	double-guidewire
<b>ERCP</b>	endoscopic retrograde cholangiopancreatography
<b>ESGE</b>	European Society of Gastrointestinal Endoscopy
<b>INR</b>	International Normalized Ratio
<b>LRS</b>	lactated Ringer's solution
<b>NNT</b>	number needed to treat
<b>NS</b>	not significant
<b>NSAID</b>	nonsteroidal anti-inflammatory drug
<b>OR</b>	odds ratio
<b>PEC</b>	post-ERCP cholangitis
<b>PEP</b>	post-ERCP pancreatitis
<b>PSB</b>	post-sphincterotomy bleeding
<b>RCT</b>	randomized controlled trial
<b>RR</b>	relative risk
<b>SEMS</b>	self-expandable metal stent

new evidence for future updates to this Guideline. In September 2019, a draft prepared by J.M.D. and C.K. was sent to all group members for review. The draft was reviewed by external reviewers and then sent for further comments to the ESGE National Societies and Individual Members. After agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final revised version.

This Guideline was issued in 2020 and will be considered for review in 2024, or sooner if new and relevant evidence becomes available. Any updates to the Guideline in the interim period will be noted on the ESGE website: <https://www.esge.com/publications/guidelines/>.

### 3 Definitions and epidemiology

#### RECOMMENDATION

ESGE suggests to define (i) post-ERCP pancreatitis as new or worsened abdominal pain combined with >3 times the normal value of amylase or lipase at more than 24 hours after ERCP and requirement of admission or prolongation of a planned admission; (ii) cholecystitis according to the revised “Tokyo Guidelines 2018”; and (iii) other ERCP-related adverse events according to the 2010 lexicon of definitions proposed in 2010 for the American Society of Gastrointestinal Endoscopy (ASGE).

Weak recommendation, low quality evidence.

The proposed definition of post-ERCP pancreatitis (PEP) derives from Cotton et al. [6]; it has been used in most large clinical trials, though with small variations in the minimum duration of hospital stay [7], the time at which pancreatic enzymes are measured [8] and their minimum elevation for diagnosis [9]. The definition takes into account patients with pre-existing pain due to pancreatitis, as proposed by Freeman et al. [9]. The Atlanta definition has not been embraced so far, probably because it requires pancreas imaging [10].

Other ERCP-related AEs have been defined as follows:

- Cholangitis: new onset temperature >38 °C for more than 24 hours combined with cholestasis [8];
- Bleeding: hematemesis and/or melena or hemoglobin drop >2 g/dL [8];
- Perforation: evidence of gas or luminal contents outside of the gastrointestinal tract as determined by imaging [8];
- Hypoxemia: hemoglobin oxygen saturation <85% [8];
- Hypotension or hypertension: either a blood pressure value <90/50 or >190/130 mmHg, or a change in value down or up 20% [8];
- Cholecystitis: right upper quadrant signs of inflammation, systemic signs of inflammation, and imaging findings characteristic of acute cholecystitis, without any suggestive clinical or imaging findings prior to ERCP [11].

The incidences of the most frequent AEs are summarized in ► **Table 1**; these values were extracted from prospective studies, except where otherwise stated.

The incidence of PEP reported in meta-analyses varies from 3.5% (21 studies, 16 855 patients) [12] to 9.7% (108 RCTs, 13 296 patients) [13]; the majority of PEP is mild and only 0.1%–0.7% of patients subjected to ERCP die from PEP. These figures vary depending on patient, procedural, and endoscopist-associated risk factors. For example, a meta-analysis reported a PEP incidence of 14.7% in high-risk patients [13].

Infections, including cholecystitis and cholangitis occurred in 1.4% of ERCPs in the abovementioned meta-analysis of 2007 [12]; 20% of these were considered severe events and the mortality rate was 0.11% overall. Other studies have reported cholecystitis separately, in 0.5% and 5.2% of patients following biliary sphincterotomy and biliary self-expandable metal stent (SEMS) insertion, respectively [9, 14], with a mortality rate of 0.04% [9].

Bleeding may be immediate, mostly self-limited, or delayed, and become evident from hours to 7–10 days following ERCP [15]. The abovementioned 2007 meta-analysis showed an overall bleeding rate of 1.3%, with 71% of these being graded as moderate and 29% as severe; the mortality rate was 0.05% overall.

Perforation most frequently happens following sphincterotomy but balloon dilation, guidewire maneuvers, and the tip of the endoscope may also cause this AE. In the abovementioned 2007 meta-analysis [12], it was reported in 0.6% of cases but some perforations, particularly Stapfer type IV perforations, frequently pass unnoticed. The overall mortality rate was 0.06% (9.9% perforation-related fatality). A more recent meta-analysis (12 retrospective studies, 42 374 patients) reported an identical 0.6% overall perforation rate [16].

Recurrence of bile duct stones after endoscopic extraction is a frequent problem; it occurred in 11.3% of 46 181 patients at 4.2 years in a nationwide Korean study [17]. Furthermore, after a first recurrence of bile duct stones, second and third recurrences are even more likely [17, 18], with incidences of 23.4% and 33.4%, respectively, in the abovementioned nationwide study [17].

Sedation-related events are mostly intraprocedural, mild, and transient events that do not affect the overall management plan. A study (528 ERCPs) reported that sedation-related AEs were frequent (24.6%, mostly hypoxemia and hypotension) but rarely had consequences at 48 hours (aspiration pneumonia was reported in 0.4% of patients) [19]. A multicenter registry (20 967 ERCPs) reported a sedation-related mortality of 0.02% [20].

Finally, outbreaks of infections with multidrug-resistant bacteria, although rare, have been associated with insufficient duodenoscope disinfection [21]. The awareness of this problem has become widespread, prompting revision of reprocessing Guidelines [3] as well as instrument design modifications.

► **Table 1** Incidence, mortality and severity grading of the most common ERCP-related adverse events.

Type [reference for severity grading]	Incidence	Mortality	Severity grading		
			Mild	Moderate	Severe
Pancreatitis [10]	3.5%–9.7%	0.1%–0.7%	<ul style="list-style-type: none"> <li>No organ failure</li> <li>No local or systemic complications</li> </ul>	<ul style="list-style-type: none"> <li>Transient (&lt;48 hours) organ failure and/or</li> <li>Local or systemic complications without persistent organ failure</li> </ul>	<ul style="list-style-type: none"> <li>Persistent (48 hours) organ failure</li> </ul>
Cholangitis [25]	0.5%–3.0%	0.1%	<ul style="list-style-type: none"> <li>No criteria of moderate/severe cholangitis.</li> </ul>	Any of the following: <ul style="list-style-type: none"> <li>White blood cell count &gt;12 000 or &lt;4000/mm<sup>3</sup>,</li> <li>Fever ≥39°C,</li> <li>Age ≥75 years,</li> <li>Total bilirubin ≥5 mg/dL,</li> <li>Hypoalbuminemia</li> </ul>	Dysfunction of any one of the following (see reference for specific criteria): <ul style="list-style-type: none"> <li>Cardiovascular</li> <li>Neurological</li> <li>Respiratory</li> <li>Renal</li> <li>Hepatic, or</li> <li>Hematological system</li> </ul>
Cholecystitis [11]	0.5%–5.2%	0.04%	<ul style="list-style-type: none"> <li>No criteria of moderate/severe cholecystitis</li> </ul>	Any one of the following: <ul style="list-style-type: none"> <li>White blood cell count &gt;18 000/mm<sup>3</sup>,</li> <li>Palpable tender mass in the right upper abdominal quadrant,</li> <li>Duration of complaints &gt;72 h,</li> <li>Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)</li> </ul>	Dysfunction of any one of the following (see reference for specific criteria): <ul style="list-style-type: none"> <li>Cardiovascular</li> <li>Neurological</li> <li>Respiratory</li> <li>Renal</li> <li>Hepatic</li> <li>Hematological system</li> </ul>
Bleeding [8]	0.3%–9.6%	0.04%	Either of the following: <ul style="list-style-type: none"> <li>Abortion of procedure</li> <li>Unplanned admission &lt;4 nights</li> </ul>	Any one of the following: <ul style="list-style-type: none"> <li>Unplanned admission 4–10 nights</li> <li>ICU admission 1 night</li> <li>Need for transfusion</li> <li>Repeat endoscopy or interventional radiology</li> <li>Intervention for integument injuries</li> </ul>	Any one of the following: <ul style="list-style-type: none"> <li>Unplanned admission &gt;10 nights</li> <li>ICU admission &gt;1 night</li> <li>Need for surgery</li> <li>Permanent disability</li> </ul>
Perforation [8]	0.08%–0.6%	0.06%	Identical to bleeding	Identical to bleeding	Identical to bleeding
Sedation-related AEs [8]	24.6%	0.02%	Identical to bleeding	Identical to bleeding	Identical to bleeding

ERCP, endoscopic retrograde cholangiopancreatography; AE, adverse event; ICU, intensive care unit.

### RECOMMENDATION

ESGE suggests to grade the severity of ERCP-related adverse events according to the Atlanta classification for pancreatitis, the revised Tokyo Guidelines 2018 for cholangitis and cholecystitis, and the 2010 ASGE lexicon for other ERCP-related adverse events.

Weak recommendation, low quality evidence.

The 2010 ASGE lexicon proposed a severity grading usable for all AEs [8]. At the core of this system was the consequence of AEs in terms of admission to hospital and/or intensive care

unit, the type of treatment applied, and death or permanent disability outcomes. This system is useful for research and comparison purposes but for some AEs, more specific classification systems are available:

- Pancreatitis:** the revised Atlanta classification of severity [10] is a better predictor for PEP-related mortality than a system based on hospital duration as shown in a multicenter comparison with the 1991 consensus criteria (retrospective study of 387 patients with PEP) [22]. The determinant-based classification is accurate but has not been compared with alternatives in the setting of PEP [23, 24]
- Cholangitis and cholecystitis:** the revised Tokyo severity grading systems may offer more accurate predictive power than the generic alternatives; they are presented in a

simplified form in ► **Table 1** (a smartphone app is available for easy use) [11, 25]

- Perforation: in addition to severity grading, the type of perforation according to the Stapfer classification (► **Table 2**) should be stated [26].

## 4 Risk factors for AEs

► **Table 3** summarizes risk factors for ERCP-related AEs while **Table 1s** (**Appendix 2s**, available online-only in Supplementary Material), more completely details the odds ratios (ORs) reported by various studies for each risk factor.

### 4.1 Risk factors for post-ERCP pancreatitis

#### RECOMMENDATION

ESGE suggests that patients should be considered to be at high risk for post-ERCP pancreatitis when at least one definite or two likely patient-related or procedure-related risk factors are present (► **Table 3**).

Weak recommendation, low quality evidence.

Some definite patient-related risk factors for PEP, i.e., suspected sphincter of Oddi dysfunction, female sex, and previous pancreatitis [27], have been confirmed by two recent systematic reviews (32 381 and 54 889 patients, 12 and 28 studies) [28, 29]. Both studies also found that previous PEP is an independent risk factor (OR 2.90 and 3.23, 95% confidence interval [CI] 1.87–4.48). Of note, younger age could not be confirmed as a risk factor in one of the recent systematic reviews [29] and was not studied in the other one [28]. However, in a more recent prospective study (996 patients), age less than 35 years was an independent risk factor for PEP (OR 0.035) [30].

With respect to definite procedure-related risk factors for PEP, difficult cannulation and pancreatic injection have been confirmed in the abovementioned meta-analysis that studied these factors [29]. Sphincterotomy, including biliary and pancreatic endoscopic sphincterotomy, was identified as a risk factor in both meta-analyses [28,29]. Pancreatic endoscopic

► **Table 2** Types of ERCP-related perforation according to Stapfer et al [26].

Type	Description	Frequency [16]
I	Duodenal wall perforation (by the endoscope)	18 %
II	Periampullary perforation (by sphincterotomy/precut)	58 %
III	Biliary or pancreatic duct perforation (by intraductal instrumentation)	13 %
IV	Retroperitoneal gas alone	11 %

ERCP, endoscopic retrograde cholangiopancreatography.

► **Table 3** Risk factors for post-ERCP pancreatitis (PEP), bleeding and cholangitis.

Risk factors for adverse events	Odds ratios
<b>Risk factors for post-ERCP pancreatitis</b>	
<i>Patient-related definite risk factors</i>	
▪ Suspected SOD	2.04–4.37
▪ Female sex	1.40–2.23
▪ Previous pancreatitis	2.00–2.90
▪ Previous PEP	3.23–8.7
<i>Procedure-related definite risk factors</i>	
▪ Difficult cannulation	1.76–14.9
▪ Pancreatic guidewire passages > 1	2.1–2.77
▪ Pancreatic injection	1.58–2.72
<i>Patient-related likely risk factors</i>	
▪ Younger age	1.59–2.87
▪ Nondilated extrahepatic bile duct	3.8
▪ Absence of chronic pancreatitis	1.87
▪ Normal serum bilirubin	1.89
▪ End-stage renal disease	1.7
<i>Procedure-related likely risk factors</i>	
▪ Precut sphincterotomy	2.11–3.1
▪ Pancreatic sphincterotomy	1.23–3.07
▪ Biliary balloon sphincter dilation	4.51
▪ Failure to clear bile duct stones	4.51
▪ Intraductal ultrasound	2.41
<b>Risk factors for bleeding</b>	
▪ Anticoagulants	4.39
▪ Platelets <50 000/mm <sup>3</sup>	35.30
▪ Cirrhosis	2.05–2.85
▪ End-stage renal disease	1.86–13.30
▪ Intraprocedural bleeding	4.28
▪ Low endoscopist experience	1.44
▪ Unsuccessful cannulation with precut sphincterotomy	3.09
<b>Risk factors for cholangitis</b>	
▪ Incomplete biliary drainage	
▪ Hilar obstruction	2.59
▪ History of previous of ERCP	2.48
▪ Age >60 years	1.98
▪ Cholangioscopy	4.98

ERCP, endoscopic retrograde cholangiopancreatography; SOD, sphincter of Oddi dysfunction.

sphincterotomy was also an independent risk factor in a population-based study of 381 288 patients [31]. New data confirmed that the impact of precut sphincterotomy depends on timing: both meta-analyses reported that precut sphincterotomy is associated with a twofold increase in the risk of PEP [28, 29] while two additional meta-analyses (999 and 523 patients, 7 and 5 RCTs) found that, in patients with difficult biliary access, early precut is associated with a lower risk of PEP compared with persistent cannulation attempts, especially when the procedure is performed by qualified endoscopists (relative risk [RR], 0.43 and 0.29) [32, 33].

With respect to volume, a meta-analysis (13 studies, 59 437 patients) found that AEs were less frequent when ERCPs were performed by high-volume endoscopists (OR 0.7, 95%CI 0.5–0.8) but not in high-volume centers; only three studies reported PEP specifically (8289 procedures); there was no association between endoscopist's volume (<25 to <156/year) and PEP [34]. A more recent multicenter study (1191 patients) identified less experienced endoscopists (<200 ERCP procedures) as an independent risk factor for PEP (OR 1.63, 95%CI 1.05–2.53) [35].

End-stage renal disease may be associated with PEP as the incidence was increased in two retrospective studies, but the difference was statistically significant only in the largest study (OR 1.7, 95%CI 1.4–2.1) (452 771 hospitalizations) [36, 37].

No new data have become available regarding the role of intraductal ultrasound or the synergistic effect of risk factors for PEP. As risk factors for PEP have been shown to be independent by multivariate analysis, they are considered to have a cumulative effect.

## 4.2 Risk factors for post-sphincterotomy bleeding

### RECOMMENDATION

ESGE suggests that patients should be considered to be at increased risk for post-sphincterotomy bleeding if at least one of the following factors is present: anticoagulant intake, platelet count <50 000/mm<sup>3</sup>, cirrhosis, dialysis for end-stage renal disease, intraprocedural bleeding, low endoscopist experience.

Weak recommendation, low quality evidence.

Post-ERCP bleeding is most frequently seen after biliary endoscopic sphincterotomy. The latter can be avoided in most cases when biliary stenting is performed [4] and, for the extraction of biliary stones, by performing endoscopic papillary balloon dilation. However, according to a meta-analysis of 25 RCTs (3726 patients), when balloon dilation alone is performed, mechanical lithotripsy is more frequently required and the overall success of stone removal is lower (no significant difference in PEP) [38].

With respect to post-sphincterotomy bleeding (PSB), risk factors mentioned in the above recommendation are independent and were evidenced in at least two of 10 studies summarized in **Table 2s**. Cirrhosis was confirmed as a risk factor in a

meta-analysis (6 studies, 5526 patients) [39] and in a more recent matched cohort retrospective study (331 patients) [40]. Dialysis for end-stage renal disease was associated with PSB in all four case–control studies (7508 cases vs. 450 246 controls) on the topic (OR 1.4, 95%CI 1.2–1.6 in the largest study) [36, 37, 41, 42], and particularly year-long hemodialysis [43]. Furthermore, bleeding episodes are more severe than in patients without renal disease [41] and occur with a similar incidence following endoscopic papillary balloon dilation (8.7%) or sphincterotomy (8.3%) [42]. The role of precut is controversial: in two meta-analyses (6 and 7 RCTs, 966 and 999 patients), early precut sphincterotomy in difficult biliary access did not increase the rate of post-ERCP bleeding compared with persistent cannulation attempts [32, 33, 44].

With respect to antiplatelet agents other than aspirin, six controlled studies have become available since the publication of the British Society of Gastroenterology (BSG)/ESGE Guidelines [41, 45–50]; five of them reported a significant association between antithrombotic agents and post-ERCP bleeding in univariate analysis [41, 45–47, 49] but the association became nonsignificant in multivariate analysis in all but one study [49]. All studies were retrospective with no power calculation and antiplatelet agents were generally withheld before ERCP.

For difficult biliary stones, endoscopic sphincterotomy associated with balloon dilation is recommended [51]. Bleeding was less frequent with this technique vs. endoscopic sphincterotomy alone in several [52, 53], but not all [54, 55] meta-analyses; it may depend on the extent of the endoscopic sphincterotomy [56].

With respect to the technique of endoscopic sphincterotomy, an *in vitro* dissection study concluded that the papilla should be incised in the 10–11 o'clock region because this contains only 10% of all papillary arteries [57]. Blended current, as opposed to pure cutting current, is recommended as it reduces the incidence of bleeding without increasing the risk of PEP [58, 59]; a meta-analysis (3 RCTs, 594 patients) suggested that bleeding was less frequent when Endocut was used compared to other blended current modes but this is of doubtful clinical significance as all bleeding was minor [60].

## 4.3 Risk factors for post-ERCP cholangitis

### RECOMMENDATION

ESGE suggests that patients should be considered to be at high risk for post-ERCP cholangitis when there is incomplete biliary drainage, including hilar obstruction and primary sclerosing cholangitis, and when cholangioscopy is performed.

Weak recommendation, very low quality evidence.

Only two studies have analyzed independent risk factors for post-ERCP cholangitis (PEC) in unselected patients [61, 62]. Hilar obstruction, age ≥60 years, and a history of previous ERCP were independent risk factors in the most recent, retrospective, study (4324 patients) while the complete extraction of

biliary stones was protective [62]. Incomplete biliary drainage is a well-accepted risk factor for PEC [63] even if controlled studies have mostly focused on septicemia, a surrogate marker of cholangitis [64]. Primary sclerosing cholangitis and hilar obstruction both predispose to incomplete biliary drainage and are believed to be associated with PEC although no controlled study is available [65]. Cholangioscopy increased the risk of PEC in a retrospective study (4214 ERCPs) [66]; more recently, bacteremia was suggested to be specifically related to cholangioscopy in 13.9% of 72 patients, based on serial blood samplings [67], and to be associated with biopsy sampling and strictures [68].

Some factors do not seem to influence the risk of developing PEC: cirrhosis (meta-analysis of 6 studies, 5526 patients) [38]; operator experience <200 ERCPs (prospective study, 1191 patients) [34]; or the presence of a periampullary diverticulum (meta-analysis of 4 studies, 778 cases and 3886 controls) [69].

#### 4.4 Risk factors for perforation

##### RECOMMENDATION

ESGE suggests that patients should be considered to be at increased risk for perforation in the setting of surgically altered anatomy, the presence of a papillary lesion, sphincterotomy, biliary stricture dilation, a dilated common bile duct, sphincter of Oddi dysfunction, and precut sphincterotomy.

Weak recommendation, low quality evidence.

Only a few monocentric studies have reported on the risk factors for post-ERCP perforation. The abovementioned independent risk factors have been identified in two case-control studies (70 perforations, 681 controls) [70, 71], except for altered surgical anatomy, which was shown to be a risk factor in another study [72]. A more recent retrospective study showed that looping of the endoscope during ERCP in patients with Billroth II anatomy was associated with perforation [73].

#### 4.5 Risk factors for stone recurrence

##### RECOMMENDATION

ESGE suggests advising patients to return if symptoms recur after the extraction of common bile duct (CBD) stones, in particular if these were themselves recurrent CBD stones.

Weak recommendation, low quality evidence.

The risk of stone recurrence after endoscopic extraction sharply increases to 23.4% after a first recurrence and 33.4% after a second recurrence [17, 18]. This can partly be prevented by cholecystectomy in patients with a gallbladder in situ and cholelithiasis, as shown in a meta-analysis of 7 RCTs (RR of recurrent jaundice or cholangitis, 2.16, 95%CI 1.14–4.07) [74].

This is particularly the case for younger patients: the RR for patients with vs. without a gallbladder in situ is 3.20 at age <50 as opposed to 1.26 at age ≥70 years [17]. This is against a background of more frequent stone recurrence with increasing age [17]. Other risk factors for stone recurrence are mostly nonremediable [18].

#### 4.6 Consent

##### RECOMMENDATION

ESGE recommends that both oral and written informed consent should be obtained prior to ERCP. The consent process should take into account individual and procedure-related risks, correct indication, and urgency of ERCP, as well as national practice.

Strong recommendation, low quality evidence.

Legal consequences such as malpractice claims or lawsuits related to AEs are not uncommon [75, 76]. A well-documented, oral and written, patient-informed consent is preferred before the procedure, because of patients' rights and because of ethical considerations. Patients should be made aware of the procedural indication, specific benefits to them, individual and procedure-related risks on the basis of available scientific data, and alternatives [77]. The length of time that consent is obtained prior to ERCP varies according to national and institutional practice and legislation. Informed consent should be a dynamic process rather than a single event and should at some point involve the performing endoscopist [77]. The patient must be given the possibility and the time to change his/her mind and to withdraw consent.

### 5 Prevention of post-ERCP pancreatitis

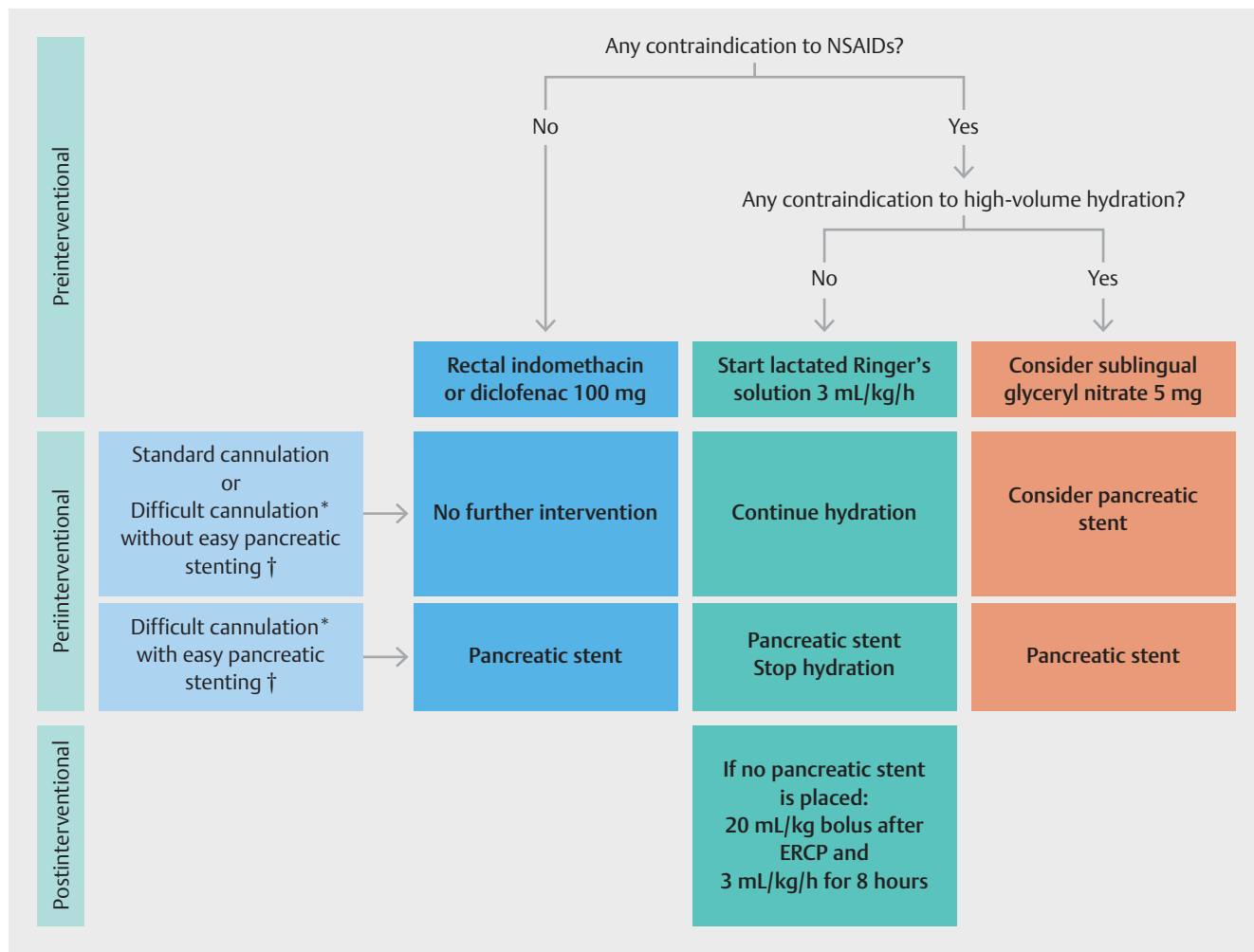
#### 5.1 Nonsteroidal anti-inflammatory drugs (NSAIDs)

##### RECOMMENDATION

ESGE recommends routine rectal administration of 100mg of diclofenac or indomethacin immediately before ERCP in all patients without contraindications to nonsteroidal anti-inflammatory drug administration.

Strong recommendation, moderate quality evidence.

Rectal nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of PEP prophylaxis as presented in the ESGE algorithm for PEP prophylaxis (► Fig. 1). Table 3s summarizes 28 meta-analyses (3 to 21 RCTs, 912 to 6854 patients) that assessed the efficacy of NSAIDs for the prevention of PEP. All but one of the meta-analyses reported an overall reduction in the incidence of PEP with NSAIDs, with an OR ranging from 0.24 to 0.63. The single meta-analysis that reported no risk reduction included only placebo-controlled RCTs of rectal indomethacin which enrolled consecutive patients in order to address the ef-



► **Fig. 1** Algorithm for prophylaxis against post-ERCP pancreatitis. \*Difficult cannulation: >5 contacts with the papilla or >5 minutes of cannulation attempts or >1 unintended pancreatic duct cannulation. †Easy pancreatic stenting: pancreatic guidewire assisted biliary cannulation, transpancreatic sphincterotomy, repeated inadvertent main pancreatic duct (MPD) cannulation. NSAIDs, nonsteroidal anti-inflammatory drugs.

ficacy of NSAIDs in average-risk patients [78]. Indeed, among 14 meta-analyses which analyzed the effect of NSAIDs in average-risk patients, 11 found a significantly lower and three a nonsignificant trend for a lower incidence of PEP with NSAIDs. Risk stratification for PEP varied across studies: procedures were classified as average-risk if they did not meet high-risk criteria [78–85] and high-risk was usually defined by the presence of one major criterion or two minor criteria. Unselected patients were defined as all patients undergoing ERCP [86] or those in studies where risk factors were not a criterion for inclusion [87]. The RCT by Levenick et al. that did not demonstrate a beneficial effect of NSAIDs in consecutive patients undergoing ERCP [88] has received many comments and criticisms. Four of the most recent meta-analyses confirmed that this study is an outlier among the RCTs that assessed the effect of NSAIDs in patients at average risk for PEP [79, 80, 89, 90]. Therefore, also considering logistical reasons as well as the benefit of pre-ERCP as compared with post-ERCP administration of NSAIDs (see

below), and the fact that patients may become at high risk for PEP during ERCP, we recommend routine administration of NSAIDs.

With respect to the severity of PEP, the incidence of mild and of moderate-to-severe PEP was decreased with NSAIDs in 7 of 8 and in 15 of 16 meta-analyses, respectively, that reported on this item. NSAID use also reduced death in the single meta-analysis that specifically analyzed that outcome [91]. The number needed to treat (NNT) to prevent one episode of PEP ranged from 8 to 21; to prevent one episode of moderate to severe PEP it ranged from 33 to 39 [87, 92].

The effects of diclofenac and of indomethacin were assessed separately in 14 meta-analyses; 13 of them found that both drugs were effective. The most frequent dosage was 100 mg for both drugs in the RCTs included in the largest meta-analyses [89, 93]. Five meta-analyses assessed separately various routes of NSAID administration; all of them reported that only the rectal route was effective.



Pre-ERCP and post-ERCP administrations of NSAIDs were compared in a single head-to-head study [94]; 2600 patients were randomly allocated to receive rectal indomethacin either before ERCP routinely or after ERCP selectively, i. e., if they were at high risk for PEP. In the subgroup of 586 patients who were at high risk (all patients therefore received rectal indomethacin), PEP developed in 6% vs. 12% in the pre- vs. post-ERCP group, respectively (RR 0.47, 95%CI 0.27–0.82). This suggests that pre-ERCP administration is the most effective timing. On the other hand, meta-analyses that suggested a higher efficacy of pre- or of post-ERCP NSAIDs based their conclusions on the comparison of RRs in subgroup analyses of different studies, but these findings are affected by factors other than drug efficacy, such as the numbers of studies [83, 90].

The overall AE rate was assessed in a meta-analysis; it reported a nonsignificant trend for a lower risk of overall AEs in the NSAIDs vs. control groups (RR 0.80, 95%CI 0.47–1.36) [83]. Other meta-analyses that looked into specific AEs (e. g., bleeding, renal failure) found no difference [83, 86, 92, 95–100].

#### RECOMMENDATION

ESGE recommends against administration of NSAIDs for PEP prophylaxis in pregnant women at  $\geq 30$ -week gestation and in patients as well as first-degree relatives with a history of Stevens–Johnson or Lyell’s syndromes attributed to NSAIDs.

Strong recommendation, low quality evidence.

NSAIDs may cause allergic and pseudoallergic reactions such as NSAID-exacerbated respiratory disease or skin disease. Among these, Stevens–Johnson and Lyell’s syndromes present the highest mortality (5%–50%); both syndromes are extremely rare but ibuprofen and diclofenac have been implicated [101]. If NSAIDs are suspected to have caused one of these syndromes, they should be avoided in survivors and first-degree relatives [102]. In other patients with allergic and pseudoallergic reactions, decisions should be individualized [103].

With respect to pregnancy, indomethacin and diclofenac are considered safe until 30 weeks of gestation [104]; NSAIDs are then contraindicated because of the fetal risks of complications including premature closure of the ductus arteriosus [105].

Caution is advised in patients with impaired renal function, particularly those taking antihypertensive drugs [106]. Finally, a single dose of ibuprofen is thought to have no effect on low-dose aspirin taken as an antithrombotic agent [107] and on the healing of gastroduodenal ulcers [108]. A single dose of 100 mg indomethacin does not increase the risk of post-sphincterotomy bleeding in patients taking aspirin or clopidogrel [109].

## 5.2 Aggressive hydration with lactated Ringer’s solution

#### RECOMMENDATION

ESGE recommends aggressive hydration with lactated Ringer’s solution (3 mL/kg/hour during ERCP, 20 mL/kg bolus after ERCP, 3 mL/kg/hour for 8 hours after ERCP) in patients with contraindication to NSAIDs, provided that they are not at risk of fluid overload and that a prophylactic pancreatic duct stent is not placed.

Strong recommendation, moderate quality evidence.

Two meta-analyses assessed the efficacy of aggressive vs. standard intravenous hydration with lactated Ringer’s solution (LRS) for the prevention of PEP [110, 111]; they included 3–7 RCTs that are detailed in **Table 4s**. The total amount of fluid used for aggressive hydration was 35–45 mL/kg administered over 8–10 hours depending on the protocol. It was associated with a lower incidence of PEP (OR [95%CI], 0.29 [0.16–0.53] and 0.47 [0.30–0.72]) [110, 111] and moderate to severe PEP (OR 0.16, 95%CI 0.03–0.96) [110] with no difference in AE rates [111]. A more recent RCT (395 patients) reported that overall PEP was less frequent with aggressive hydration vs. standard hydration, both using LRS (3.0% vs. 11.6%,  $P=0.03$ ), while PEP rates were similar for standard hydration using LRS and aggressive hydration using normal serum saline [112].

Although the overall incidence of AEs was similar in the aggressive hydration and control groups [111], fluid overload has been reported in an RCT despite the exclusion of patients at increased risk for this complication [112]. Caution is also advised in older patients, because of the higher risk of undiagnosed comorbidities of heart and kidney disease. PEP prophylaxis with aggressive hydration is not applicable when ERCP is performed as an outpatient procedure, and it is unknown whether admitting patients at low risk for PEP who present a contraindication to NSAIDs in order to administer aggressive hydration is clinically appropriate, cost-effective, or practical.

## 5.3 Roles of sublingual nitrates

#### RECOMMENDATION

ESGE suggests administration of 5 mg sublingual glyceryl trinitrate before ERCP in patients with a contraindication to NSAIDs or to aggressive hydration for the prevention of PEP.

Weak recommendation, moderate quality evidence.

An updated meta-analysis (11 RCTs, 2095 patients) showed that glyceryl trinitrate reduces the overall incidence of PEP (RR 0.67, 95%CI 0.52–0.87) but not that of moderate to severe PEP. Subgroup analyses revealed that sublingual administration (2–5 mg before ERCP) was superior to transdermal and topical

administration [113]. These results were consistent with those reported in four previously published meta-analyses (**Table 5s**) [114–117]. The only RCT that evaluated intravenous nitroglycerin was terminated prematurely because of a concerning incidence of AEs (hypotension and headache) [118].

More recently, a single-center RCT showed that, in mostly high-risk patients, the combination of 5 mg sublingual isosorbide dinitrate and 100 mg rectal indomethacin given before ERCP was more effective than indomethacin alone in reducing the incidence of PEP (6.7% vs. 15.3%,  $P=0.016$ ) [119]. The superiority of this association was confirmed in a multicenter RCT ( $n=886$ ): the combination of 5 mg sublingual isosorbide dinitrate 5 minutes before ERCP with 50 mg rectal diclofenac immediately after ERCP was more effective than diclofenac alone to reduce the overall incidence of PEP (5.6% vs. 9.5%,  $P=0.03$ ; NNT 26). The incidence of moderate to severe PEP was similar between groups. Transient hypotension occurred in 8% of patients in the combination group [120].

#### 5.4 Somatostatin and octreotide

ESGE has no recommendation about the use of somatostatin. It was associated with an overall reduction in the incidence of PEP in all but one of six meta-analyses (7–15 RCTs, 2190–4943 patients) [121–126] (**Table 6s**), but this reduction was of limited benefit with the upper value of the 95%CI being close to 1 despite the high numbers of patients. Subgroup analyses suggested that either long-term infusion of high doses (typically 3 mg over 12 hours) or a single bolus of 250 µg were both effective in preventing PEP. The benefit of bolus administration was consistent across all meta-analyses.

A recent large-scale, multicenter RCT (900 patients) confirmed that the periprocedural use of somatostatin (250 µg intravenous bolus before ERCP followed by 250 µg/hour for 11 hours) reduced the incidence of PEP in both the overall population (7.5% vs. 4.4%,  $P=0.03$ ) and in the high-risk subgroup (7.3% vs. 4.2%,  $P=0.06$ ), with no drug-related serious AEs [127]. With respect to bolus administration, although meta-analyses are encouraging, studies evaluating this regimen are few, biased by small sample size, and with conflicting results [128–132].

Octreotide, a somatostatin analogue with a longer half-life, has yielded conflicting results for prevention of PEP. The most up-to-date meta-analysis (17 RCTs, 2784 patients) found no significant difference in PEP incidence between octreotide and placebo. However, doses of octreotide  $\geq 0.5$  mg reduced the incidence of PEP in a subgroup analysis of six studies (RR 0.45, 95%CI 0.28–0.73; NNT 25) [133].

#### 5.5 Protease inhibitors and epinephrine

##### RECOMMENDATION

ESGE does not recommend protease inhibitors and topically administered epinephrine onto the papilla for PEP prophylaxis.

Strong recommendation, moderate quality evidence.

Protease inhibitors could inhibit the activation of proteolytic enzymes that play an important role in the pathogenesis of PEP. Meta-analyses of RCTs on gabexate mesilate [121, 126, 134–138] and ulinastatin [134, 139] administration for PEP prevention were inconclusive. Furthermore, two subgroup analyses revealed that in six high quality studies gabexate mesilate and ulinastatin had no effect on PEP [135].

Nafamostat, a more potent protease inhibitor with a longer half-life, reduced the overall risk of PEP by approximately 50% in four out of five RCTs and in two meta-analyses [134, 140–144] (**Table 7s**). Low-dose (20 mg) nafamostat is not inferior to high-dose (50 mg) [142], and 2–6 hours' administration is as effective as longer administration [145]. No AEs related to nafamostat were reported in any study. Major concerns related to its use are the apparent absence of benefit in high-risk cases, even at high dose [142], and high costs. At present, nafamostat is extensively used in Eastern countries for preventing PEP, but it is not available in Europe.

Epinephrine spraying onto the papilla has been proposed as a simple measure to reduce papillary edema and PEP (**Table 8s**). Conflicting results were reported in two RCTs that compared epinephrine vs. saline [146, 147] but the pooled results showed that topical epinephrine reduced PEP (RR 0.25, 95%CI 0.006–0.65; NNT 15) [148]. Of note, the study reporting positive results was limited by an atypical definition of PEP.

#### 5.6 Prophylactic pancreatic stenting

##### RECOMMENDATION

ESGE recommends prophylactic pancreatic stenting in selected patients at high risk for PEP (inadvertent guidewire insertion/opacification of the pancreatic duct, double-guidewire cannulation).

Strong recommendation, moderate quality evidence.

All of the eight meta-analyses published between 2011 and 2019 (8–14 RCTs, 656–1541 patients) reported that prophylactic pancreatic stenting was associated with a decrease in the incidence of PEP (OR 0.22 to 0.39) [85, 149–155] (**Table 9s**). Among the RCTs included, all but two of them only enrolled patients at high risk for PEP. Three meta-analyses reported results separately according to the patients' risk stratification for PEP: prophylactic pancreatic stenting was beneficial in unselected (RR 0.23, 95%CI 0.08–0.66) [152] as well as average-risk (OR 0.21 and 0.25) [85, 149, 152] and high-risk patients (OR ranging from 0.27 to 0.41) [85, 149, 152]. In a more recent RCT (167 patients), prophylactic pancreatic stenting was beneficial in unselected patients when there was inadvertent cannulation of the pancreatic duct [156]. With respect to the severe form of PEP, prophylactic pancreatic stenting markedly decreased its incidence (OR ranging from 0.22 to 0.26) in all of the seven meta-analyses that assessed this outcome, although the difference did not reach statistical significance in the smallest study [149–155]. In a meta-analysis where 62% of patients

were at high risk, the NNT was 8 [154]. Another meta-analysis reported a NNT of 7 (95%CI 6–9) [149].

The benefit of prophylactic pancreatic stenting in patients with intraductal papillary mucinous neoplasm may be questionable. A multicenter retrospective study (414 high-risk patients who had received prophylactic pancreatic stenting) showed that the only risk factor for PEP was intraductal papillary mucinous neoplasm (OR 3.1, 95%CI 1.2–7.8), particularly in the absence of main pancreatic duct dilation in the head of the pancreas [157]. This could be related to stent occlusion by mucin.

A cost-effectiveness analysis has shown that limiting the use of prophylactic pancreatic stenting to high-risk patients was the most cost-effective strategy [158]. This was partly because of the higher risk of PEP after a failed attempt at stent placement. On the other hand, repeated inadvertent guidewire insertion into the duct of Wirsung during attempts at biliary cannulation increases the risk of PEP and makes pancreatic stent insertion particularly easy.

Another argument against routine prophylactic pancreatic stenting is that the removal of retained prophylactic pancreatic stents may cause mild or moderate acute pancreatitis, thus delaying rather than eliminating the occurrence of PEP [159]. However this is very uncommon, especially if the removal is done correctly with a side-viewing scope and a gentle atraumatic withdrawal along the axis of the pancreatic duct.

#### RECOMMENDATION

For prophylactic pancreatic stenting, ESGE suggests the use of a short 5-Fr pancreatic stent with no internal flange but having a flange or a pigtail on the duodenal side; passage of the stent from the pancreatic duct should be evaluated within 5 to 10 days of placement and retained stents should be removed endoscopically. Weak recommendation, low quality evidence.

Stents of 5-Fr diameter were found to be more likely to be efficacious than 3-Fr stents (96.9% vs. 3.1%) in a network meta-analysis of six RCTs [160]. These results are consistent with two head-to-head RCTs which concluded that, compared with 3-Fr stents, 5-Fr stents were more effective in the prevention of PEP, required fewer guidewires, and decreased the need for endoscopic stent removal (one study each) [161, 162]. ESGE recommends the stent be devoid of an internal flange to facilitate spontaneous elimination [163] but should have a duodenal pigtail or flange to prevent intraductal migration, as the removal of internally migrated stents is very challenging [164]. With respect to stent length, an RCT (240 patients) found a lower PEP rate with 5-Fr stents of 3 cm vs. 5 cm in length (2.0% vs. 8.8%,  $P=0.035$ ) [165]; however the difference was not significant in intention-to-treat analysis and other authors have reported different conclusions [166].

It is believed that stents need to remain in place for a minimum of 12–24 hours to provide benefit, since removal at the

end of ERCP negates the protection from PEP [167]. On the other hand, stents still retained at 2 weeks were associated with delayed PEP in an RCT [161] but not in a large retrospective study [168]. The authors of the latter study suggested that an x-ray can be avoided in patients who require a follow-up endoscopic procedure shortly after stent insertion.

## 5.7 Combination of NSAIDs with other measures

#### RECOMMENDATION

ESGE does not suggest the routine combination of rectal NSAIDs with other measures to prevent PEP. Weak recommendation, low quality evidence.

With respect to the combination of rectal NSAIDs with other measures:

- Prophylactic pancreatic stenting: a post hoc analysis of a pivotal RCT found no difference in PEP rates between patients who had received rectal indomethacin alone or associated with prophylactic pancreatic stenting (7.8% vs. 9.4% after adjustment for PEP risk factors) [169]. Furthermore, the cost-benefit analysis found that indomethacin monotherapy saved US\$793 (95%CI 112–1619) and US\$1472 (95%CI 491–2804) per patient over the combination of indomethacin plus prophylactic pancreatic stenting and prophylactic pancreatic stenting alone, respectively. In a sensitivity analysis, no adjustment resulted in indomethacin monotherapy becoming costlier than either pancreatic stent-based strategy. A retrospective study (777 patients) found a similar PEP incidence in patients who had received rectal indomethacin alone vs. combined with prophylactic pancreatic stenting (5.1% vs. 6.1%) [170]. Similarly, a network meta-analysis found that rectal NSAIDs alone prevented PEP more effectively than prophylactic pancreatic stenting alone (OR 0.48, 95%CI 0.26–0.87), and that the combination of NSAIDs with stenting was not more effective than either approach alone [85]. Finally, there was no difference between pharmacoprophylaxis alone or combined with pancreatic stenting in a recent RCT (414 high-risk patients) [171].
- Peri-ERCP hydration: the combination of aggressive hydration with rectal NSAIDs has been found to be superior to rectal NSAIDs alone in one of two RCTs, with the positive RCT using normal serum saline instead of LRS [172]; a third RCT found similar PEP rates if rectal indomethacin was associated with a bolus of 1 L LRS vs. with 1 L normal serum saline before ERCP [173] (Table 10s).
- Topical epinephrine: two large, high quality, RCTs compared the efficacy of rectal indomethacin combined with topical epinephrine vs. indomethacin alone. One RCT found no difference between groups in terms of overall as well as severe PEP [174] while the other RCT was prematurely terminated for safety concerns and futility as the combination strategy was associated with a higher risk of PEP compared with indomethacin alone (8.5% vs. 5.3%; RR 1.60, 95%CI 1.03–2.47) [175].

- Sublingual nitrate: an RCT showed that the combination of 5 mg sublingual isosorbide dinitrate with rectal diclofenac was superior to rectal diclofenac alone in reducing the overall incidence of PEP, but the diclofenac was given at low dose (50 mg), and after the procedure in one group and before in the other group. Furthermore, side effects (in particular hypotension) were more common in the combination group, and the incidence of moderate to severe PEP was similar between the two arms [120].

## 6 Other measures for the prevention of adverse events

### 6.1 Primary biliary cannulation

For primary biliary cannulation, the guidewire-assisted technique is recommended [176]. No new evidence justifying a change in this recommendation has emerged. Four recent RCTs comparing different types of guidewire or techniques of cannulation found no differences in AE rates, particularly for PEP [177–180]. In one of these RCTs, higher rates of successful cannulation were obtained with guidewires with highly flexible tips [178].

### 6.2 Difficult biliary cannulation

Difficult biliary cannulation has been defined as (i) >5 contacts with the papilla or >5 minutes of cannulation attempts, or (ii) >1 unintended pancreatic duct cannulation/opacification [176]. In these cases, ESGE recommends, respectively, (i) early needle-knife precut sphincterotomy, or (ii) double-guidewire (DGW) technique with prophylactic pancreatic stenting.

Early needle-knife precutting was again associated with a lower rate of PEP compared to persistent cannulation attempts in two additional meta-analyses (6 and 7 RCTs; RR 0.49 and 0.57) published after the ESGE Guideline [32, 181]; one meta-analysis also assessed the overall AE rates and these were similar with both techniques [181].

The DGW technique [182] was associated with a higher rate of PEP, similar rates for other AEs, and similar success of cannulation compared to persistent cannulation attempts, precut, or pancreatic stent placement in a meta-analysis (7 RCTs, 577 patients) [183]. The higher PEP rate might reflect the design of most studies: pancreatic guidewire insertion was required for enrolment in only two studies (in the five other studies, attempts at pancreatic cannulation may indeed have increased PEP) and pancreatic stenting was not performed in most studies. Indeed an RCT published in 2010 has shown that prophylactic pancreatic stenting following the DGW technique reduces the PEP rate [184] and the efficacy of this measure was confirmed in a recent RCT that suggested superiority of the DGW technique in terms of successful biliary cannulation [185].

Transpancreatic sphincterotomy should be considered after failure of the DGW technique [176]. A meta-analysis (14 studies including 5 RCTs) found no differences in AEs and a higher success rate of transpancreatic sphincterotomy compared with the DGW technique (OR 2.72, 95%CI 1.30–5.69). However, the difference became nonsignificant when the analysis was restricted

to RCTs, and the long-term safety of the technique has not been established [186].

### 6.3 Biliary stenting

#### RECOMMENDATION

ESGE suggests against routine endoscopic biliary sphincterotomy before the insertion of a single plastic stent or an uncovered/partially covered SEMs for relief of biliary obstruction.

Weak recommendation, moderate quality evidence.

For biliary stenting, ESGE suggests against routine biliary endoscopic sphincterotomy when placed for biliary obstruction [4]. This recommendation is further supported by two recent meta-analyses which showed a lower bleeding rate if no biliary endoscopic sphincterotomy was performed before insertion of either: (i) a SEMs for a malignant biliary obstruction (OR 0.36, 95%CI 0.13–1.00) (7 studies, 870 patients) [187]; or (ii) a nasobiliary drain/stent in patients with severe cholangitis (RR 0.12, 95%CI 0.03–0.49) (4 studies, 392 patients) [188]. This translated into a lower overall AE rate in the study that reported that outcome [187]; no differences in other outcomes were reported. It is uncertain whether PEP risk is increased in the case of fully covered SEMs. A recent retrospective study reported a PEP incidence of 50% after biliary fully covered SEMs insertion without endoscopic sphincterotomy in patients with post-liver transplantation biliary strictures [189].

### 6.4 Contrast-free ERCP techniques

Contrast-free deep cannulation into the ductal systems to be drained has been proposed to prevent PEC, a frequent AE after injection of obstructed ducts that are not subsequently drained, in patients with hilar biliary obstruction. This technique is inaccurate for the detection of CBD stones according to a pilot study [190] and, with regard to biliary stenting, no new evidence has become available since the technique was reviewed in another ESGE Guideline [4]. In patients with primary sclerosing cholangitis, some authors have proposed bile aspiration prior to contrast injection, and balloon dilation of dominant strictures [191]. The level of evidence is insufficient to make a recommendation.

### 6.5 CBD stone extraction

#### RECOMMENDATION

ESGE suggests intraoperative rendezvous ERCP for CBD stone extraction in patients scheduled for cholecystectomy.

Weak recommendation, high quality evidence.

In patients scheduled for cholecystectomy and who require CBD stone extraction, ESGE has made no recommendation with respect to the two main approaches, that is, surgery alone or combined with ERCP, because of the lack of clear-cut evidence and concerns about the availability of local surgical expertise [51]. A meta-analysis (20 RCTs, 2489 patients) found that for these patients laparoscopic cholecystectomy with intraoperative ERCP had the highest success rate, lowest morbidity, and shortest length of hospital stay (the rendezvous technique was used in many RCTs of intraoperative ERCP) [192]. Other strategies analyzed were laparoscopic CBD exploration, preoperative ERCP, and postoperative ERCP. ESGE recognizes that organizing intraoperative ERCP may be challenging. For further details on biliary stone extraction see the abovementioned ESGE Guideline [51].

## 6.6 Antibiotic prophylaxis

### RECOMMENDATION

ESGE recommends against the routine use of antibiotic prophylaxis before ERCP.  
Strong recommendation, moderate quality evidence.

### RECOMMENDATION

ESGE suggests antibiotic prophylaxis before ERCP in the case of anticipated incomplete biliary drainage, for severely immunocompromised patients, and when performing cholangioscopy. The antibiotic agent used should be active against Gram-negative bacteria and adapted as much as possible to local epidemiology.  
Weak recommendation, moderate quality evidence.

The role of antibiotic prophylaxis in reducing the PEC rate has been evaluated in three meta-analyses [193–195]; the most recent one (9 RCTs, 1573 patients) found a lower cholangitis rate following elective ERCP if prophylactic antibiotics were administered. However, in the subgroup of patients with the bile ducts drained at the first ERCP, there was no significant benefit in using antibiotic prophylaxis to prevent cholangitis (**Table 11s**) [195]. Subsequent studies have reported no decrease in the incidence of PEC when antibiotic prophylaxis was used, except a large Swedish cohort study that reported a difference in a subgroup of patients with obstructive jaundice [196].

Some factors that predispose to PEC or that may increase its severity are accepted indications for antibiotic prophylaxis, such as primary sclerosing cholangitis, hilar obstruction, and peroral cholangioscopy.

The addition of antimicrobial agents to ERCP contrast media has been poorly evaluated and results are conflicting. A case-control study (84 patients, 75% of them with sclerosing cholangitis) reported fewer episodes of post-ERCP infection if gentamicin, vancomycin, plus fluconazole were added to the contrast

medium [197]. On the other hand no difference was observed in an RCT whether gentamicin or distilled water was added to the contrast medium, in 114 patients mostly treated for bile duct tumors [198].

Antibiotic resistance is an increasing concern: a Chinese study found that a majority of bacteria isolated from blood after ERCP were resistant to ciprofloxacin and ceftriaxone [199]. Similarly, a U.S. study reported that 53% of bacteria isolated from blood in 78 patients who had cholangitis following  $\geq 2$  ERCPs were resistant to conventional antibiotics used for prophylaxis [200]. Antibiotic prophylaxis for ERCP may increase the proportion of bacteria isolated from bile that are resistant to antibiotics (29.3% vs. 5.7% in a retrospective study of 93 patients who respectively had or had not received antibiotic prophylaxis) [201].

## 6.7 Coagulation tests

### RECOMMENDATION

ESGE suggests tests of coagulation are not routinely required prior to ERCP for patients who are not on anti-coagulants and not jaundiced.  
Weak recommendation, low quality evidence.

For patients on warfarin, BSG/ESGE Guidelines recommend that warfarin should be discontinued for 5 days to allow the International Normalized Ratio (INR) to reduce to  $< 1.5$  in order to perform endoscopic sphincterotomy [48]. For patients on direct oral anticoagulants, the standard tests of coagulation such as INR or activated partial thromboplastin time (aPTT) are unreliable indicators of the level of anticoagulation. Although INR was designed to test this level in patients on anticoagulants, it is an unreliable indicator in some situations [202], including ERCP [203]. In patients with abnormal coagulation associated with liver disease, INR is an unreliable predictor of bleeding risk [204–206] and this has been confirmed in the context of ERCP [207]. Nevertheless, it is common to routinely check INR in patients prior to ERCP; it is however rarely significantly abnormal in patients who are not on anticoagulants, or in those without a raised bilirubin [208]. Presumably, those patients with deep jaundice have had a prolonged period of vitamin K malabsorption, and thus prolonged INR. Patients who have unsuspected disorders of coagulation may be detected by a directed patient history including family history and bleeding tendency.

## 6.8 Management of anticoagulants and antiplatelet agents for ERCP

Detailed advice on the management of anticoagulants and antiplatelet agents in the context of ERCP is available in the BSG/ESGE Guidelines and summarized in ► **Table 4** [48]. For the purposes of the present Guideline update, no new studies have been published that alter the advice published in 2016. The underlying principles of management depend on a balance between the risk of hemorrhage due to the procedure if

► **Table 4** Management of antithrombotics in patients undergoing ERCP. Adapted from British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) 2016 Guidelines [48].

		<b>Low-risk procedure</b> <b>Biliary stenting with-</b> <b>out sphincterotomy</b> <b>Cholangioscopy</b>	<b>High-risk procedure</b> <b>ERCP with sphincterotomy</b> <b>ERCP with sphincteroplasty</b> <b>Ampullectomy</b>
<b>Aspirin</b>	Primary or secondary prophylaxis	Continue aspirin	Consider stopping aspirin 5 days prior to ampullectomy depending on thrombotic risk, and restarting 48–72 hours post procedure. Continue aspirin for other procedures.
<b>P2Y12 inhibitors</b> Clopidogrel Prasugrel Ticagrelor	<i>Low-risk indication (usually monotherapy)</i> Ischemic heart disease without coronary stent Peripheral vascular disease Cerebrovascular disease	Continue therapy	Stop drug 5 days before procedure. Continue aspirin if already prescribed. Restart P2Y12 inhibitor 24–48 hours post procedure. <sup>2</sup>
	<i>High-risk indication (usually dual antiplatelet therapy [DAPT])</i> Coronary stents: Drug-eluting stent < 12 months Bare metal stent < 1 month	Continue therapy	Liaise with cardiologist. Consider stopping therapy if: Drug-eluting stent > 12 months Bare metal stent > 1 month. Continue aspirin. Restart DAPT 24–48 hours post procedure.
<b>Warfarin</b>	<i>Low-risk indication</i> Prosthetic metal aortic heart valve Xenograft heart valve Atrial fibrillation without valvular disease > 3 months after venous thromboembolism Thrombophilia syndromes <sup>1</sup>	Continue warfarin Ensure INR in therapeutic range prior to procedure	Stop warfarin 5 days before procedure. Ensure INR < 1.5. Restart warfarin on evening of procedure at usual daily dose. <sup>2</sup>
	<i>High-risk indication</i> Prosthetic metal mitral heart valve Prosthetic heart valve and atrial fibrillation Atrial fibrillation and mitral stenosis < 3 months after venous thromboembolism	Continue warfarin Ensure INR in therapeutic range prior to procedure	Stop warfarin 5 days before procedure. Commence low molecular weight heparin (LMWH) 3 days before procedure, and omit on day of procedure. Restart warfarin on evening of procedure at usual daily dose. <sup>2</sup> Continue LMWH until INR in therapeutic range.
<b>Direct oral anticoagulant (DOAC)</b> Dabigatran Rivaroxaban Apixaban Edoxaban	<i>Indications</i> Atrial fibrillation + additional risk factors Prevention or treatment of venous thromboembolism	Omit DOAC on morning of procedure	Take last dose of DOAC > 48 hours before procedure (except dabigatran with creatinine clearance 30–50 mL/min: take last dose 72 hours before procedure). Seek hematology advice for any DOAC in a patient with evolving renal failure. Restart DOAC 24–48 hours post procedure. <sup>2</sup>

INR, International Normalized Ratio.

<sup>1</sup> Most thrombophilia syndromes will not require heparin bridging if warfarin is temporarily discontinued, but a hematology opinion should be sought in each instance.

<sup>2</sup> Consider delaying restart of therapy for up to 7 days if there is a high risk of post-procedure bleeding.

antithrombotics are continued vs. the risk of thrombosis if antithrombotic therapy is modified or interrupted.

The optimal timing for restarting antithrombotic therapy after ERCP will depend on the perceived risk of post-procedural bleeding and of thrombosis. Patients who experience significant intraprocedural bleeding are at increased risk of delayed bleeding [209], and the interval for reinstatement may be prolonged accordingly. It is important that a management plan for reinstatement of antithrombotic therapy is documented in all cases, and also that patients are made aware of the risk of delayed hemorrhage once that therapy is reinstated.

## 6.9 Role of proton pump inhibitors

No large observational study evaluating risk factors for post-endoscopic sphincterotomy bleeding has ever demonstrated a protective role of proton pump inhibitors [12, 72, 210–213]. In a recent open-label RCT (125 patients), high-dose esomeprazole starting 4 hours before ERCP and prolonged for 10 days did not reduce the risk of either intraprocedural or delayed bleeding [214].

## 7 Management of adverse events

### 7.1 Post-ERCP pancreatitis

#### RECOMMENDATION

ESGE suggests testing serum amylase and/or lipase 2–6 hours after ERCP in patients with post-procedural abdominal pain who are to be discharged on the day of ERCP. Patients with serum amylase and lipase values less than 1.5 and 4 times the upper normal limit, respectively, can be discharged without concerns about development of post-ERCP pancreatitis.

Weak recommendation, low quality evidence.

The recommendation is similar to that stated in the previous ESGE Guideline [27] and is backed by seven studies [215–221]. Four more recent studies (1820 ERCP procedures) confirmed that a low value of amylase and/or lipase had a negative predictive value of >99% for PEP [222–225]. Another simple predictive parameter that was recently proposed is serum phosphate level [226].

#### RECOMMENDATION

ESGE suggests against salvage pancreatic stenting in patients with post-ERCP pancreatitis.

Weak recommendation, low quality evidence.

PEP should be managed according to existing Guidelines. Salvage pancreatic stenting has been proposed for highly selected patients with PEP (severe pain, more than 10-fold elevation of serum amylase, rise of white blood cells and C-reactive protein values); results in two uncontrolled studies (20 patients) were promising in spite of challenging pancreatic stenting because of duodenal edema [227,228]. These data should be considered very carefully until large RCTs are available. An RCT was prematurely interrupted because of a higher rate of infected necrosis in the salvage pancreatic stent group compared with the conservative treatment group, in patients with acute necrotizing pancreatitis not related to ERCP [229].

### 7.2 Post-sphincterotomy bleeding

#### RECOMMENDATION

ESGE suggests treatment of persistent or delayed post-sphincterotomy bleeding by local injection of epinephrine (1:10000), possibly combined with thermal or mechanical therapy when injection alone fails.

Weak recommendation, low quality evidence.

In the case of PSB, general management should be similar to that of any other cause of upper gastrointestinal bleeding [230]. Injection of dilute epinephrine (1:10 000) has been used in most studies as first-line treatment, after tamponade if available. A prospective study reported 100% success without complication in 79 cases but most of these were of minor bleeding (PSB rate 14%) [231]. Spray irrigation with diluted epinephrine, alone or mixed with dextrose, may also be effective for minor bleeding [232]. A comparative study with a more typical PSB rate (1.37%) reported a 95% hemostasis rate and no re-bleeding in 19 patients treated with epinephrine, as compared with 82% hemostasis rate and 23% re-bleeding in 22 patients treated with the heater probe [233]. In the case of delayed PSB, a retrospective study (59 patients) comparing epinephrine injection alone or combined with thermotherapy described similar rates of initial hemostasis (96% vs. 100%) and of re-bleeding (16% vs. 12%) [234].

After failed epinephrine therapy, hemostatic clips may be used, delivered through a cap-fitted forward-viewing endoscope or a duodenoscope (the elevator often makes clip delivery challenging). In two studies (67 patients with persistent PSB), clips provided hemostasis in 90%–100% of the cases [235, 236]. New clips designed for delivery using the duodenoscope may also be used [237]. A small prospective series reported PSB control by monopolar coagulation with the tip of a snare in 11 cases where epinephrine injection failed [238]. Mechanical or thermal therapies should not be applied in the close vicinity of the pancreatic orifice, as this could result in pancreatitis. Adherent clots should be removed in order to treat the underlying area.

Finally, as cholangitis is more frequent in patients who present PSB [49], some experts suggest insertion of a nasobiliary drain following hemostasis of PSB, to prevent bile duct obstruction from intrabiliary clots.

#### RECOMMENDATION

ESGE suggests temporary placement of a biliary fully covered self-expandable metal stent for post-sphincterotomy bleeding refractory to standard hemostatic modalities.

Weak recommendation, low quality evidence.

PSB refractory to conventional endoscopic hemostasis can require arterial embolization or even surgery [239]. Placement of a fully covered SEMS is an effective second-line modality before resorting to embolization or surgery. A retrospective study (67 patients) found that, after failure of primary endoscopic interventions, placement of a fully covered SEMS significantly reduced the bleeding rate at 72 hours and resulted in less of a decrease in hemoglobin level than conventional methods [240]. Nevertheless, this study was limited by unclear criteria for treatment, heterogeneous groups, and the high (10%) PSB rate. The removal of fully covered SEMS within 4–8 weeks is recommended, using a recall system to avoid AEs related to long-term indwelling stents.

Hemostatic powder and fibrin glue are other possible rescue therapies, but reported experience is extremely limited [241, 242] and they cannot be routinely recommended.

Re-bleeding occurs in 5%–22% of patients following successful endoscopic hemostasis for PSB [243, 244]. Initial moderate/severe bleeding and serum bilirubin levels >10 mg/dL were identified as independent risk factors in a retrospective study of 161 patients with delayed PSB; moderate/severe initial bleeding was defined as the need for transfusion or angiographic/surgical intervention [243]. No studies analyzed the role of second-look endoscopy for PSB.

### 7.3 Perforation

The management of perforations is detailed in a Guideline [245] that is being updated at the time of writing (November 2019).

### 7.4 Post-ERCP cholangitis

#### RECOMMENDATION

ESGE suggests to evaluate patients with post-ERCP cholangitis by abdominal ultrasonography or CT scan and, in the absence of improvement with conservative therapy, to consider repeat ERCP. A bile sample should be collected for microbiological examination during repeat ERCP. Weak recommendation, low quality evidence.

In patients with PEC and no obvious cause (e.g., incomplete drainage of hilar obstruction), imaging should be obtained to assess bile duct patency [64]. Abdominal ultrasonography may be useful to rapidly assess the biliary tree and stent patency as well as to assess the gallbladder and the liver for possible abscesses [246]; however it presents some limitations in the immediate post-ERCP setting [247]. Contrast-enhanced CT scan, and magnetic resonance imaging with cholangiopancreatography when available, are the imaging modalities of choice [247, 248]. They may show signs of cholangitis, the level of biliary obstruction, and the presence of stents, stones, or pneumobilia. Of note, the assessment of pneumobilia by CT scan has only a 62% sensitivity to detect stent dysfunction [249]. Therefore, ERCP may be indicated in dubious cases.

Cultures of bile obtained during ERCP in patients with cholangitis are much more often positive for microorganisms than blood cultures (97% vs. 32% in a retrospective study of 93 patients) [250]. In a study where bile culture was performed routinely, it allowed initiation of the appropriate antibiotic or refinement of a specific antibiotic treatment for 67% of 27 ERCPs which were complicated by cholangitis [251].

### Disclaimer

ESGE Guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply to all situations and should be interpreted in the setting of specific clinical situations and resource availability. They

are intended to be an educational tool to provide information that may support endoscopists in providing care to patients. They are not rules and should not be utilized to establish a legal standard of care.

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