Post-ERCP Pancreatitis- Prophylactic Measures Implementation Study

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Title: Post-ERCP Pancreatitis – Prophylactic Measure Implementation Study (PEP-PROMIS)

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1 STUDY OVERVIEW

1.1 BACKGROUND/INTRODUCTION:

Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive diagnostic and therapeutic procedure associated with a risk of serious complications, the most common of which is post-ERCP pancreatitis (PEP). Despite the implementation of various prophylactic measures, as for example those issued in the guidelines of the European (ESGE) and American (ASGE) Societies of Gastrointestinal Endoscopy, the occurrence of PEP remains a clinically significant issue. The aim of this study is to assess the incidence of PEP and to analyze the implementation of prophylactic measures in routine clinical practice.

1.2 STUDY DESIGN

- **Study type**: Prospective, observational, multicenter study.
- **Duration**: The study will be terminated when the required number of patients will be reached. Estimated end of data collection is May 31, 2026
- **Location**: Selected centers within the Slovakia and Czechia. The centers selected for this study are those that expressed interest in participating based on our yet unpublished survey, conducted between January and June 2024, which aimed to assess how ERCP quality parameters were monitored and how prophylactic measures for PEP were implemented across centers. A total of 26 ERCP centers participated in the survey, including 14 from Slovakia and 12 from Czechia. Centers that expressed interest, as well as all remaining ERCP-performing centers in Slovakia and several in Czechia, were subsequently contacted by email with information about the study and invited to participate.

1.3 PRIMARY AIM

- To determine the incidence of PEP (any severity) in real clinical practice at selected ERCP centers in the Slovakia and Czechia.

1.4 SECONDARY AIMS

- To determine the incidence of PEP across different severity grades: none, mild, moderate, and severe.
- To evaluate the use of preventive measures for prevention of PEP in real clinical practice at selected ERCP centers in Slovakia and Czechia.
- To investigate association between the incidence of PEP and the use of measures of prevention.
- To assess PEP-related mortality.

2 STUDY POPULATION

2.1 INCLUSION CRITERIA

- ERCP in a patient with a native papilla (first ERCP) or repeat ERCP in a patient with previous failed cannulation attempt.
- Age at least 18 years at the time of ERCP.
- Signed informed consent.

2.2 EXCLUSION CRITERIA

- Previous papillotomy, papilla dilation, or sphincteroplasty.
- Rendez-vous cannulation technique.
- ERCP not performed due to insufficient patient cooperation.
- ERCP terminated before cannulation due to sedation/anesthesia-related complications.
- Failure to reach the Vater's or minor papilla (e.g. duodenal stenosis).
- Acute biliary pancreatitis.
- Altered anatomy that prevents reaching the papilla with a standard duodenoscope (e.g. Roux-en-Y).

3 DATA COLLECTION AND OUTCOMES

Form of collection: Paper case report forms (CRF), filled out at the time of the procedure by the attending physician.

Recording occurrence of PEP: Within 24-48 hours after the procedure.

Monitoring PEP severity: Every 7 days until hospital discharge.

3.1 PRIMARY OUTCOME

Outcome	Obtained data
Incidence of PEP	Presence/absence of PEP (any severity) in each enrolled patient.

3.2 SECONDARY OUTCOMES

Outcome	Obtained data in each enrolled patient
Incidence of different severity grades of PEP	Severity of PEP (none/mild/moderate/severe) *(as detailed below)
Rate of use of PEP preventive measures	Patients estimated risk of PEP: low/high **(as detailed below) Prophylactic Measures Considered "Adequate" per ESGE a) **Low-risk patients** • NSAID administration (preferred) • Aggressive hydration if NSAIDs contraindicated • Nitroglycerin if both NSAIDs and aggressive hydration are contraindicated + consider Prophylactic Pancreatic Stent (PPS) ***(as detailed below) b) **High-risk patients** • NSAID + PPS***(as detailed below) • Aggressive hydration + PPS***(as detailed below) if NSAIDs contraindicated • Nitroglycerin + PPS***(as detailed below) if both NSAIDs and aggressive hydration are contraindicated
Determination and/or confirmation of PEP risk factors	Age, sex, indication for ERCP, and patient-related and procedure-related risk factors according to ESGE **(as detailed below)

3.2.1 * Severity Grading of PEP (Atlanta-based criteria)

Mild PEP- without organ failure and local or systemic complications
Moderate PEP- with transient organ failure that resolved within 48 hours and/or local or systemic complications (see below)
Severe PEP- with persistent organ failure (see below)

Local complications:

- Acute peripancreatic fluid collection
- Pancreatic pseudocyst
- Acute necrotic collection
- Walled-off necrosis (WON)
- Gastric outlet dysfunction
- Portal or splenic vein thrombosis
- Necrosis of the colon

Systemic complications

- Exacerbation of chronic disease (e.g., heart failure or chronic obstructive pulmonary disease)

Organ failure

- Respiratory failure with hypoxemia
- Cardiovascular failure with hypotension
- Renal failure

3.2.2 ** Determination of PEP risk

High risk for developing PEP is defined as:

a) the presence of at least one definite risk factor (see below), or
b) the presence of two or more probable risk factors (see below).

Risk factors for the development of PEP according to ESGE:

Definite risk factors

- Suspected SOD (Sphincter of Oddi Dysfunction)
- Female sex
- History of acute pancreatitis
- History of PEP
- Difficult cannulation

Probable risk factors

- Age less than 35 years
- Normal serum bilirubin level
- Non-dilated bile ducts
- Absence of chronic pancreatitis
- End-stage kidney disease
- Precut
- Pancreatic sphincterotomy
- Papilla dilation without sphincterotomy
- Failure to completely remove stones from bile ducts

3.2.3 *** Placement of a PPS

Placement of a PPS is recommended, provided there is good access to the pancreatic duct.

4 PLANNED ANALYSES

4.1 CHARACTERISTICS OF PATIENTS AND PROCEDURES

The following characteristics of **patients** will be summarized as mean with standard deviations, medians with quartiles or as counts with percentages:

- Age
- Gender
- **Patient-related risk factors of post-ERCP pancreatitis (PEP)**
  History of acute pancreatitis
  History of PEP
  Normal bilirubin
  Nondilated bile ducts
  Dilated pancreatic duct
  Chronic pancreatitis
  Peripapillary diverticulum
  End-stage renal disease

The following characteristics of **procedures** will be summarized as mean with standard deviations, medians with quartiles or as counts with percentages:

- Difficult cannulation (more than 5 minutes, more than 5 contacts, more than 1 unintended pancreatic duct cannulation or opacification)
- Guidewire-assisted cannulation
- Contrast-assisted cannulation
- Conventional precut (starting at the upper margin of the papillary orifice)
- Precut- fistulotomy
- Dual-wire cannulation (pancreatic guidewire-assisted biliary cannulation)
- Trans-pancreatic biliary sphincterotomy
- Biliary sphincterotomy
- Pancreatic sphincterotomy
- Papillary balloon dilation (without previous sphincterotomy)
- Papillary large balloon dilation (after sphincterotomy)
- Pancreatic duct brushing cytology
- Minor papilla cannulation
- Failed cannulation (cannulation of the desired duct was not successful)
- Was the procedure effective? (Was the intended goal achieved?)
- Cholangioscopy or pancreaticoscopy
- EUS plus ERCP (during one session)
- Was a trainee involved? (Did trainee participate in the cannulation?)

4.2 PRIMARY OUTCOME

For the primary outcome, the rate of PEP will be calculated along with 95% confidence interval obtained using the Wilson method.

4.2.1 Sample size calculation

When assuming the rate of PEP being up to 15 %, the study with 950 participants will have 90 % power to provide a two-sided 95% confidence interval for the PEP rate within a 2.5 % (absolute) margin on either side of the point estimate. To account for an expected drop-out (due to data issues), the final target sample size was set to 1000 patients.

The sample size calculation was performed as follows: Since the required sample size increases with the actual rate of PEP, a simulation using the rate of 15% was performed. For a given sample size, each possible outcome was tested and the error (the larger distance from one side of the confidence interval to the point estimate) was compared to 2.5% and the result was weighted by the probability of obtaining this number of cases (taken from a binomial distribution).

4.3 SECONDARY OUTCOMES

The rates of use of different preventive measures will be listed for all patients and separated by the patients PEP risk level. Point estimates along with two-sided 95% confidence intervals will be provided.

A logistic regression model will be used to estimate the influence of preventive measures on the risk of PEP controlling for patients PEP risk.

For each risk factor, a separate logistic regression model will be used to estimate the risk of PEP. Risk factors with a statistically significant result in their single-variable model will be included into a single multi-variable model.

Additional post-hoc tests may be performed.

4.4 ALPHA LEVELS AND MULTIPLE TESTING

The study has a pre-defined primary outcome, for which the alpha error level is maintained. There are no pre-defined strategies for multiple testing corrections, and all the secondary outcomes are to be considered as exploratory.

The primary outcome will be presented as a point estimate along with a two-sided 95% confidence interval and this will be the preferred way of presentation for most of the results.