POST ERCP PANCREATITIS

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Chief of Gastroenterology Division, Zahraa University Hospital
Lebanese University, Lebanese American University
Questions for the audience

- Women + normal bil = 5%? 10%? 15%?
- Women + normal bil + difficult cannulation = 11%? 16%? 22%?
- Women + normal bil + difficult cannulation + SOD = 22%? 32%? 42%?
ERCP procedural safety depend

- Indication for ERCP
- Sedation and monitoring practice
- Patient age and clinical condition
- Diagnostic or therapeutic
- Setting and equip of Endoscopy Unit
- Training and competence of endoscopist and team
ERCP should be done

- Good indication
- By trained endoscopist
- Using standard techniques
- Informed consent
NIH 2002 statement regarding ERCP indication

- Choledocholithiasis
- Jaundice
- Dilated CBD
- Acute pancreatitis
- Cholangitis
- Patient with pancreatic or biliary cancer – palliation
- Tissue sampling in patient with pancreatic or biliary cancer – in patient not going for surgery
NIH 2002 statement regarding ERCP indication

- ERCP has no role in the diagnosis of AP except when biliary pancreatitis is suspected. Early ERCP ↓ mortality 
morbidity
- Patient with sphincter of Oddi, dysfunction
- In selected patient with P. pseudocyst
Guideline of ASGE (2005) Regarding ERCP

- ERCP is primarily a therapeutic procedure for managing pan/bil disorder (C)
- Diagnostic ERCP should not be done in the absence of objective finding on other studies (B)
- Diagnostic ERCP before L.C. should not be performed (B)
- First line of management of biliary leaks and strictures (B)
- Effective for palliation of malignant biliary obstruction (B)
Guideline of ASGE (2005) Regarding ERCP

- ERCP has important role in patient with recurrent acute pancreatitis and can identify and treat underlying cause (B)
- Is effective in treating symptomatic strictures of Ch. Panc (B)
- Diagnose and treat symptomatic pancreatic stones (B)
- Pancreatic duct leak – can be effectively treated by stent (B)
ERCP – related complications

A) General – common to all endoscopic procedure
   • Medication reaction
   • O2 desaturation
   • Cardio pul. accident
   • Haemorrhage and perforation induce by instrument passage
B) Selective – to pancreatic biliary manipulation

- Pancreatitis
- Sepsis
- Hemorrhage
- Perforation
## Details of complications

<table>
<thead>
<tr>
<th></th>
<th>Total %</th>
<th>Score %</th>
<th>Death %</th>
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<tbody>
<tr>
<td>Pancreatitis</td>
<td>3.5</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Bleeding</td>
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<tr>
<td>Perforation</td>
<td>0.6</td>
<td>NA</td>
<td>0.06</td>
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<tr>
<td>Other</td>
<td>1.3</td>
<td>NA</td>
<td>0.07</td>
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<tr>
<td>Total</td>
<td>7.9</td>
<td>NA</td>
<td>0.4</td>
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</tbody>
</table>

Data available for 14 studies

Andriulli et al Am J Gastroe 2007
# Overall complications of endoscopic sphincterotomy and related mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Patients</th>
<th>Pancreatitis</th>
<th>Bleeding</th>
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<tr>
<td>Rabenstein et al 1998</td>
<td>Prospective monocenter study</td>
<td>746</td>
<td>148</td>
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<td>Freeman et al 1996</td>
<td>Prospective multicenter study</td>
<td>2347</td>
<td>127</td>
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<td>35</td>
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<tr>
<td>Cotton et al 1991</td>
<td>Retrospective multicenter review</td>
<td>7729</td>
<td>148</td>
<td>234</td>
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<th></th>
<th>Number</th>
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<tr>
<td>Pancreatitis</td>
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<tr>
<td>Number</td>
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<td>4.7</td>
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<tr>
<td>Percent</td>
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<tr>
<td>Bleeding</td>
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<td>Sepsis</td>
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<td>35</td>
<td>1.5</td>
<td>10</td>
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<td>Percent</td>
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</tbody>
</table>
Post ERCP Pancreatitis
Definition-pathogenesis
Pathogenesis

• Result from several factors
  1) Mechanical injury
  2) Hydrostatic injury from over injection of PD
  3) Chemical / allergic injury
  4) Enzymatic injury – activation of proteolytic enzyme
  5) Infection – From contaminated scope / accessory
  6) Thermal injury
Post ERCP Pancreatitis

- Abdominal pain (symptoms) consistent
- Serum amylase and/or lipase greater than 3 times the upper limit of normal
- Cross-sectional imaging (CT and/or MRI) consistent with the diagnosis
**PEP**

- Incidence of PEP: 3.5-5% all

*ESGE Guidelines 2010*

- PEP is often self-limited

- BUT procedures might also result in severe necrotic pancreatitis and even death caused by multi-organ failure due to fulminante pancreatitis

*Andriulli Am j Gastroenterol 2007*

**ERCP has considerable risks**

**Know how to avoid or at least minimize risks**
Risk factors of PEP
ESGE Guideline: Prophylaxis of post-ERCP pancreatitis

<table>
<thead>
<tr>
<th>Patient-related risk factors</th>
<th>Adjusted odds ratios (95% CI in parentheses except where indicated otherwise)</th>
<th>Pooled incidence of PEP in patients with vs. those without risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected SOD</td>
<td>4.09 (3.37 – 4.96)</td>
<td>10.3% vs. 3.9%</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.23 (1.75 – 2.84)</td>
<td>4.0% vs. 2.1%</td>
</tr>
<tr>
<td>Previous pancreatitis</td>
<td>2.46 (1.93 – 3.12)</td>
<td>6.7% vs. 3.8%</td>
</tr>
<tr>
<td><strong>Likely risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger age</td>
<td>1.09 – 2.87 (range 1.09 – 6.68)</td>
<td>6.1% vs. 2.4%</td>
</tr>
<tr>
<td>Non-dilated extrahepatic bile ducts</td>
<td>NR</td>
<td>6.5% vs. 6.7%</td>
</tr>
<tr>
<td>Absence of chronic pancreatitis</td>
<td>1.87 (1.00 – 3.48)</td>
<td>4.0% vs. 3.1%</td>
</tr>
<tr>
<td>Normal serum bilirubin</td>
<td>1.89 (1.22 – 2.93)</td>
<td>10.0% vs. 4.2%</td>
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<tr>
<td><strong>Procedure-related risk factors</strong></td>
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<td></td>
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<tr>
<td><strong>Definite risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precut sphincterotomy</td>
<td>2.71 (2.02 – 3.63)</td>
<td>5.3% vs. 3.1%</td>
</tr>
<tr>
<td>Pancreatic injection</td>
<td>2.2 (1.60 – 3.01)</td>
<td>3.3% vs. 1.7%</td>
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<tr>
<td><strong>Likely risk factors</strong></td>
<td></td>
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<tr>
<td>High number of cannulation attempts†</td>
<td>2.40 – 3.41 (range 1.07 – 5.67)</td>
<td>3.7% vs. 2.3%</td>
</tr>
<tr>
<td>Pancreatic sphincterotomy</td>
<td>3.07 (1.64 – 5.75)</td>
<td>2.6% vs. 2.3%</td>
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<tr>
<td>Biliary balloon sphincter dilation</td>
<td>4.51 (1.51 – 13.46)</td>
<td>9.3% vs. 1.9%</td>
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<tr>
<td>Failure to clear bile duct stones</td>
<td>3.35 (1.33 – 9.10)</td>
<td>1.7% vs. 1.6%</td>
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</table>
### Risk factors for PEP identified by multivariate analysis in prospective studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Object of the study</th>
<th>Number of patients</th>
<th>Post-procedure pancreatitis rate</th>
<th>Independent risk factors</th>
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<tr>
<td>Freeman et al 2001</td>
<td>Multicenter study</td>
<td>Diagnostic and therapeutic ERCP</td>
<td>1963</td>
<td>6.7 percent</td>
<td>Prior ERCP pancreatitis</td>
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<td>Suspected dysfunction of sphincter of Oddi</td>
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<td>Female sex</td>
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<td>Normal serum bilirubin</td>
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<td>Absence of chronic pancreatitis</td>
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<td>Biliary sphincter balloon dilation</td>
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<td>Difficult cannulation</td>
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<td>Pancreatic sphincterotomy</td>
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<td>1 or more injections of contrast into the pancreatic duct</td>
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<td>Vandervoort et al 2002</td>
<td>Monocenter study</td>
<td>Diagnostic and therapeutic ERCP</td>
<td>1223</td>
<td>7.2 percent</td>
<td>Recurrent pancreatitis</td>
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<td>Prior ERCP pancreatitis</td>
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<td>Difficult cannulation</td>
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<td>Pancreatic brush cytology</td>
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<td>Pain during procedure</td>
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<td>Precut sphincterotomy</td>
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<td>Christensen et al 2004</td>
<td>Monocenter study</td>
<td>Diagnostic and therapeutic ERCP</td>
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<td>3.8 percent</td>
<td>Age under 40</td>
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<td>Dilated bile duct</td>
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<td>Placement of stent</td>
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<td>Cheng et al 2006</td>
<td>Multicenter study</td>
<td>Diagnostic and therapeutic ERCP</td>
<td>1115</td>
<td>15.1 percent</td>
<td>Minor papilla sphincterotomy</td>
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<td></td>
<td>Sphincter of Oddi dysfunction</td>
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<td>Prior ERCP pancreatitis</td>
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<td>Age &lt;70</td>
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</tbody>
</table>
Operator related risk factors

"Normally I'd never prescribe this for your condition...but I'm curious."
Prevention

- Proper training of endoscopist and maintaining proficiency
- Hospital ERCP volume
- Adequate disinfection
- Avoidance of diagnostic ERCP
- Avoidance of canulation and injection of PD
- Careful use of electrocautery
Operator experience

- Perform sphincterotomy, clear CBD stones, provide relief of biliary obstruction, place a stent for biliary leak in >85%
- Few studies in regard to operator experience

- Higher rate of bleeding with a mean case of < 1/ week
- Trainee involvement associated with severe or fatal complications

*Cotton Gastrointes endoscopy 2009*

- Case volume exceeding 50 ERCP/year: higher success, lower complications rate

*Baron et al Am J gastroenterol 2006*
Patient related risk factors

IB Learner Profile: Risk-Taker
## Patient related independent risk factors

<table>
<thead>
<tr>
<th>MRCP, EUS</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td><strong>Definite</strong></td>
<td></td>
</tr>
<tr>
<td>• Suspected SOD</td>
<td>4.1 (3.4-5)</td>
</tr>
<tr>
<td>• Female gender</td>
<td>2.2 (1.8-2.8)</td>
</tr>
<tr>
<td>• Previous pancreatitis</td>
<td>2.5 (1.9-3.1)</td>
</tr>
<tr>
<td><strong>Likely</strong></td>
<td></td>
</tr>
<tr>
<td>• Younger age</td>
<td>1.1-2.9</td>
</tr>
<tr>
<td>• Non-dilated extrahepatic BD</td>
<td>NR</td>
</tr>
<tr>
<td>• Absence of CP</td>
<td>1.9 (1.0-3.5)</td>
</tr>
<tr>
<td>• Normal serum bilirubin</td>
<td>1.9 (1.2-2.9)</td>
</tr>
<tr>
<td>40% of PEP</td>
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</tbody>
</table>
Specific therapeutic techniques
Method related

- Difficult canulation
- Ampullectomy
- Precut
- Panc endoscopic sphincterotomy
- Mode of cutting
- Number of contrast
- Balloon sphincteroplasty
- Sphincter of Oddi manometry
Ampullectomy

• Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla
• 19 patients were enrolled, and 10 received pancreatic stents
• All cases occurred in the unstented group, 33% vs. 0% (stented group)

Harwood et al et al, Gastrointest Endos 2005
Precut biliary sphincterotomy

- Definition: opening papilla with needle knife or papillotome w/o deep cannulation
- Meta-analysis: increased incidence of PEP
  
  Masci et al, Endoscopy 2003

- Multiple studies showing no difference
  - Patient profile show high vs low risk
  - Pancreatic stent
  
  Fogel et al, Endoscopy 2002

- Meta-analysis- early precut
  - 6 RCT
    - Early precut vs persistence :2.5% vs 5.3%, OR 0.47%, 95% CI 0.24-0.91

  Cennamo et al, Endoscopy 2010
Balloon dilation of the biliary sphincter (balloon sphincteroplasty)

- Compared with endoscopic sphincterotomy, endoscopic papillary balloon dilation (EPBD) using small-caliber balloons (≤ 10 mm) is associated with a significantly higher incidence of PEP and significantly less bleeding.
- Potential advantages of performing large-balloon dilation in addition to endoscopic sphincterotomy.
- The incidence of PEP did not seem excessive compared with that reported in patients undergoing endoscopic sphincterotomy alone.

*Dumonceau et al. Guidelines for PEP prophylaxis Endoscopy 2010*
Sphincter of Oddi manometry

- Use of the standard perfusion catheter without an aspiration port has been shown to increase the risk of PEP (Evidence level 2++)
- Pancreatic sphincter of Oddi manometry should be done using a modified triple-lumen perfusion catheter with simultaneous aspiration or a microtransducer catheter (Recommendation grade B)

Dumonceau et al. Guidelines for PEP prophylaxis Endoscopy 2010
Prevention of Post-ERCP Pancreatitis
Prevention of PEP

• Patient selection
• Careful technique
• Pancreatic stent ducting
• Pharmacologic
Wire technique Meta-analysis

- 5 RCT
- Decreased pancreatitis: OR 0.23, CI 0.13-0.14
- Increased cannulation rate: 85.3% vs 74.9%

Fuccio et al, AJG 2009
Recommendations based on (limited) evidence but personal (practice) shared with others

- Cannulation with sphincterotome and soft hydrophilic wire
- Tip of sphincterotome is advanced 2mm beyond the papilla. The wire is gently advanced “normal papilla”
- Papilla is entered with sphincterotome and the wire is advanced “large and floppy papilla”
- Tip of wire is positionned 2mm beyond the tip of sphincterotome leading the direction “small papilla”

Bourke et al endoscopy 2009
Pancreatic stent

Pancreatitis

no Pancreatitis

Number of patients

40

2%

28%

P=0.003%

RR=10.5%

95% CI

Tamashi PR et al, Gastroenterology 1998
Pancreatic stent Metanalysis

• Singh et al, GIE 2010
  - PEP reduced 5.8 vs 15.5%, OR 3.2%, 95% CI 1.6 – 6.4 %

• Choudari et al, GIE 2011
  - 8 RCT
  - Deceased pancreatitis: OR 0.22%, 95% CI 0.12-0.38, p< 0.01

• Mazaki et al, Endoscopy 2010
  - 8 RCT
  - Decreased pancreatitis: OR 0.32%, 95% CI 0.19-0.52, p< 0.001
Why is there inconsistent adoption of PS

- Failure to place increases the risk of pancreatitis
- Inexperience with small guide wires
- Stenting requires deep placing of guidewires
- Concern about intraductal placement or migration of stent - happens only with flaps
- Fear of causing ductal changing
- Fear of misplacement (into side branch)
- Failure of stent to migrate out – pt lost to f/u
Pancreatic stent

- Must have contrast in MPD but minimum amount
- Soft tip wire or 0.018 “roadrunner” soft coil tip
- Small wire better?
- “J” formation prevent side branch penetration
- Move slowly, carefully, coordinate with assistant
- Fluoroscopic control
- Size: long 3-4 Fr, short 5Fr, no flaps or Panc side
- Match stent to duct formation
When should a pancreatic stent be placed to prevent PEP

- Before precut (access) papillotomy
- Before/after biliary sphx for SOD
- Pancreatic spincterotomy
- Endoscopic papillotomy
- After manometry of pancreatic instrumentation for suspected SOD
- Pancreatic brush cytology
- After difficult cannulation or repeated panc duct injection in point with risk factors

Freeman and guda, Gastroint endos 2004
Pharmacological agent

- Drugs that Decrease Inflammation
- Drugs that Decreases Sphincter of Oddi Pressure
- Drug that Interrupt the Activity of Proteases
- Inhibitors of Pancreatic Secretion
Drugs that Decrease Inflammation

- Antioxidants, antibiotics, steroids
- Allopurinol and n-acetylcysteine

Studies in animals demonstrated a decrease in the incidence and severity of acute pancreatitis. Subsequent human trials failed to show significant benefit.

Räty S, Sand J, J Gastrointest Surg 2001
Wiener GR, Gastrointest Endosc 1995
Mosler P, Gastrointest Endosc 2005
European Society of Gastrointestinal Endoscopy (ESGE) Guideline: Prophylaxis of post-ERCP pancreatitis

Based on an ad hoc meta-analysis of results from 10 high quality RCTs, somatostatin proved to be ineffective in preventing PEP (Evidence level 1++). We do not recommend universal administration of prophylactic somatostatin in average-risk patients undergoing ERCP. (Recommendation grade A). Administration of somatostatin might be more efficacious using specific dose schedules, but caution is needed when interpreting the results of subgroup analyses as they often exaggerate differences between treatments in RCTs.
Drugs that Decrease Inflammation

- Multicenter (at four university-affiliated medical centers in the United States)
- Randomized
- Controlled clinical trial

➢ To evaluate the efficacy of prophylactic rectal indomethacin for the prevention of post-ERCP pancreatitis in high-risk patients
Inclusion criteria

- Elevated baseline risk of post-ERCP pancreatitis:
  - If they met one or more of the following major criteria:
    - Clinical suspicion of SOD
    - Pancreatic sphincterotomy
    - Precut sphincterotomy
    - >8 cannulation attempts
    - Pneumatic dilatation of an intact biliary sphincter
    - Ampullectomy
  - If they met two or more of the following minor criteria
    - Age < 50 y
    - Female sex
    - History of recurrent pancreatitis (≥2 episodes)
    - Three or more injections of contrast agent into the pancreatic duct with at least one injection to the tail of the pancreas
    - Excessive injection of contrast agent into the pancreatic duct resulting in opacification of pancreatic acini
    - The acquisition of a cytologic specimen from the pancreatic duct with the use of a brush
Elmunzer et al NEJM 2012
Study Outcomes

The primary outcome of post-ERCP pancreatitis occurred in 79 of 602 patients

Elmunzer et al NEJM 2012
Exploratory Subgroup Analyses

- Indomethacin appeared to be protective regardless of whether patients had undergone pancreatic stenting or had a clinical suspicion of SOD
- Indomethacin was also protective in all three subtypes of SOD
Meta-analysis of rectal NSAIDS in the prevention of PEP

- 4 RCT
- 912 patients
- Patient received NSAIDS periprocedural period
- Diclofenac or indomethacin
- 64% less likely to develop PEP
- 90% less likely to develop moderate to severe PEP

B Elmunzer et al Gut 2008
European Society of Gastrointestinal Endoscopy (ESGE) Guideline: Prophylaxis of post-ERCP pancreatitis

Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the incidence of PEP; effective PEP prophylaxis has only been demonstrated using 100 mg of diclofenac or indomethacin administered rectally (Evidence level 1++). Routine rectal administration of 100 mg of diclofenac or indomethacin, immediately before or after ERCP, is recommended (Recommendation grade A)
Treatment of Post-ERCP Pancreatitis
Post-ERCP pancreatitis management

- Using clinical, hematologic and biochemical indices to predict severity
- Close monitoring for signs of organ dysfunction is paramount
- Pain control, monitoring infection and attention to nutrition
- Aggressive intensive care to prevent complications requires the early identification of severe disease
- Hydration to expand the intravascular volume (hemodilution) is imperative
ERCP in 2012

- No diagnostic procedure!
- Indication: therapy of stones and strictures
- Sphincterotomy necessary

→ Primary intubation with sphincterotome
→ Wire guided intubation
Key messages

- PEP has an incidence of 3.5-5% (for solely primary ERCP probably higher)
- The main reason for PEP is the failure to cannulate the CBD with subsequent edema of the papilla
- Cannulation of papilla can be either done after injection contrast or by advancing soft wire- preferably via sphincterotome
- At present meta-analysis showed that the wire technique appears to be most favorable for prevention of PEP if the endoscopist is familiar with such technique
Most important recommendations for PEP prophylaxis

- Periprocedural rectal NSAIDs
- Limit cannulation attempts /pancreas injections
- High risk conditions: prophylactic pancreatic stenting
  - Ampulectomy
  - Known or suspected SOD
  - Pancreatic sphincterotomy
  - Precut biliary sphincterotomy
  - Pancreatic guide-wire assisted biliary cannulation
  - Endoscopic balloon sphincteroplasty
THANK YOU

An ounce of prevention is worth a pound of cure.
## Grading system for the major complications of ERCP and endoscopic sphincterotomy

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>Amylase at least three times normal at more than 24 hours after the procedure, requiring admission or prolongation of planned admission to two to three days</td>
<td>Hospitalization of 4 to 10 days</td>
<td>Hospitalization of more than ten days, hemorrhagic pancreatitis, phlegmon or pseudocyst, or intervention (percutaneous drainage or surgery</td>
</tr>
</tbody>
</table>

## Incidence and grading of post-endoscopic sphincterotomy pancreatitis

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
</tr>
<tr>
<td>Number of patients</td>
<td>2347</td>
<td>4.1</td>
</tr>
<tr>
<td>Mild-moderate pancreatitis</td>
<td>118</td>
<td>5.0</td>
</tr>
<tr>
<td>Severe pancreatitis</td>
<td>9</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Grading:

- Mild – 53/127
- Moderate – 65/127
- Severe – 9/127

5.4%
Risk factors for Post ERCP Pancreatitis

Operator factor
  Low case volume
Patient factors –
- Young
- Female
- Normal bil.
- Prior ERCP panc.
- Sphincter of oddi dysfunction
- Small bile duct
Method related –

- Difficult canulation
- Precut
- Panc. endoscopic sphincterotomy
- Number of contrast
- Mode of cutting
- Two studies showed reduced incidence of AP with pure cut vs blended current (3.5 vs. 11.5 %) and with bipolar compared to monopolar (6% vs 12%).
However large randomized prospective study found no significant difference between the two modes (7.8 vs 6.1)
SOD multicentre study

- 19% of 272 patients develop acute pancreatitis vs 4% of 2075

- Those with small duct + SOD $\rightarrow$ 3 times more likely to develop A.P.
Diagnosis

• Clinical + Lab tests.
Prevention:

General Principles

- Proper training of endoscopist and maintaining proficiency.
- Adequate disinfection.
- Avoidance of diagnostic ERCP
- Avoidance of canulation and injection of PD.
- Careful use of electrocautery.
Specific measure:
Placement of pancreatic stent:
  4 Randomized PT
  3 found stenting ↓ the risk.

Recommendation:
  • Available evidence support prophylactic use of pancreatic stent
  • pancreatic endotherapy for 1-14 days.
Pancreatic stenting after biliary sphincterotomy for sphincter of Oddi dysfunction in patients with pancreatic sphincter hypertension

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Pancreatic, percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Stent (n=41)</td>
<td>2</td>
</tr>
<tr>
<td>No stent (n=39)</td>
<td>26*</td>
</tr>
</tbody>
</table>

* P = 0.003 (N.B. incidence of pancreatitis was 7 percent in the stent group when including two patients who developed pancreatitis after stent removal). Data from Tarnasky, PR, et al. Gastroenterology 1998; 15:1518
### Pharmaceutical agents evaluated for the prevention of post-ERCP amylase elevation and/or pancreatitis

<table>
<thead>
<tr>
<th>Postulated mechanism of action</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of pancreatic secretion</td>
<td>Somatostatin</td>
</tr>
<tr>
<td></td>
<td>Octreotide</td>
</tr>
<tr>
<td></td>
<td>Glucagon</td>
</tr>
<tr>
<td></td>
<td>Calcitonin</td>
</tr>
<tr>
<td>Stimulation of pancreatic secretion and reduction of sphincter tone</td>
<td>Secretin</td>
</tr>
<tr>
<td>Reduction of sphincter tone</td>
<td>Nifedipine</td>
</tr>
<tr>
<td></td>
<td>Glyceryl trinitrate</td>
</tr>
<tr>
<td></td>
<td>Botulinum toxin</td>
</tr>
<tr>
<td></td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Inhibition of protease activation</td>
<td>Aprotinin</td>
</tr>
<tr>
<td></td>
<td>Gabaexate mesilate</td>
</tr>
<tr>
<td></td>
<td>C1-esterase inhibitor</td>
</tr>
<tr>
<td></td>
<td>Heparins</td>
</tr>
<tr>
<td></td>
<td>Ulinastatin</td>
</tr>
<tr>
<td>Antimicrobial agents</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Anti-inflammatory agents</td>
<td>Allopurinol</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Interleukin-10</td>
</tr>
<tr>
<td></td>
<td>Diclofenac</td>
</tr>
<tr>
<td>Anti-oxidants</td>
<td>Beta-carotene</td>
</tr>
<tr>
<td></td>
<td>N-acetyl cysteine</td>
</tr>
<tr>
<td></td>
<td>Sodium selenite</td>
</tr>
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</table>

*Courtesy of Silvano Loperfido, MD.*
• Pharmacologic prophylaxis
• Antibiotic + Calcitonin + glucgon + Nifedipine ⇒ Failed to reduce complication

Allopurinol produced mixed result
• C1 – inhibitor – presented hyperamylasemia in placebo controlled trial of 40 patients.
• Secretin – No benefit in RCT.
• Unfractionated heparin – appeared to reduce pancreatitis in a large prospective study of 815 patients.
• Corticosteroids – showed no benefit in at least 3 controlled trials (both I.V. & P.O.).
• Aprotinin (antiprotrolytic agent) – uncertain
• 5 FU – added to contrast – appear to reduce pancreatitis in RT.
• Gabexate mesilate (protease inhibitor)
  R Placebo controlled study of 418
  Acute pancreatitis developed in (2 v 8%) ✔
• Another study of 193 showed similar result
In contrast

Controlled trial comparing (579 patients)

   Gabexate vs Somatostatin or Placebo showed no benefit.

   Another controlled trial of 1127 of same drugs → no benefit.
• Somatostatin and Octreotide in several prospective studies compared to Placebo showed significant statistical benefit.

• However – updated meta-analysis showed no benefit from short duration of infusion of gabexate or somastatin.
Recently

Diclofenac in P.R CT involving 220 patients vs Placebo administered post procedure → showed significant reduction (6.4 vs 15.5)

Needs further study
• Glycert Trinitrate:
  Reduces sphincter. oddi pressure
  2 controlled trials – showed benefit
  However the rate of pancreatitis was unexpectedly high in control arm:

  No benefit from a third controlled study.
Conclusion:

A. Conclusive evidence on the efficacy of
   * Pretease inhibitor
   * Antisecretory agents

Requires confirmation from large prospective trials.
B. Cost-effectiveness needs to be addressed.
C. It is possible that drugs as gabexate and somatostatin will have a role in patient at high risk.
Post ERCP bleeding

- Most feared complication incidence
  2-5% mortality 0.3%
Recent data 1-2% in prospective study.
Hge 48/2347 (2%) in prosp, multicenter series 21/1827 1%
Grading:

• Mild – Clinical evidence – no need of transfusion.
• Moderate – \( \leq 4 \) unit.
• Severe – \( \geq 5 \) unit or intervention (Surgery/Angio)
Risk factors:

- Retrospectively 3 factor independ predicted He Haemodialysis (RR 8.4)
- Prolong pT (RR 7.8)
- Observed bleeding of time of ES (RR 5.9)
Another study found (Hong Kong)

- Stone impaction
- Presence of periampullary Div.
- Extension of previous ES.
Prospective studies

Multicentre prospective study identified (2347)

- Coagulopathy
- Anticoagulant
- Presence of cholangitis
- Bleeding during procedure
- Low case volume
Risk factor identified form other study

Included -
- Precut
- Rapid cutting
- Use of needle-knife
Summary

- Risk of bleeding ~ 2%
- Patient factor – coagulopathy / RF / Liver cirrhosis.
- Cholangitis.
- Haemodialysis.
Anatomical factor
• Divert, stone impaction, stenosis of orifice

Technical factor
• Ext of previous ES
• Needle Knife
• Low case volume
• Fast/ zipper cut.
• Prevention
• Risk can be minimize by identifying patient at risk.
• Plat ≥ 80000
• INR < 1.2

Post procedure observation should be extended in high risk patient.
• Discontinuation of ASP/NSAID – Recommended although – data suggest E/S in safe in such patients.
• Warfarin discontinue 5 days and 3 days post.
• Some literature support of using Low mel heparin as bridging III
• Proper training
• Use of blend – moder of endo-cut.
• Large controlled – study →
• Pure cut – associated with significant higher rate of immediate bleeding
• However – delayed bleeding was similar
• Management
• Stops spont.
• Clinical relevant He can be managed endoscopically
• Angiography + Surgery → Rarely needed.
  e.g. 2/45 patient with bleeding required surgery. (North American study) 0.08%
  Italian study 2/21 required surgery 0.1%
• Endoscopic therapy
• Injection – Adrenaline – one study showed initial haemostasis in all.
• Rebleeding recur in 8/130
• Responded to R treated.
• Sclerosing agent can be used with extreme caution.
• Heater probe – can be used.
- Angiographic treated
- Infusion of vasopressin
- Embolization
- Data – available in source surgery.
## Risk factors for post-ERCP pancreatitis identified by multivariate analysis in prospective studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Object of the study</th>
<th>Number of patients</th>
<th>Post- procedure pancreatitis rate</th>
<th>Independent risk factors</th>
</tr>
</thead>
</table>
| Freeman et al 1996 | Multicenter study | Endoscopic biliary sphincterotomy | 2347               | percent 5.4                       | Suspected dysfunction of sphincter of Oddi  
Younger age  
Precut sphincterotomy  
Difficulty of cannulation  
Number of pancreatic contrast injections |
| Loperfido et al 1998 | Multicenter study | Therapeutic ERCP                  | 1827               | percent 1.6                       | Small bile duct  
Age under 70  
Pancreatic opacification |
| Rabenstein et al 1999 | Multicenter study | Endoscopic sphincterotomy       | 633                | percent 4.7                       | Sphincterotomy frequency of the (endoscopist (<40 per year  
Pancreas divisum  
Previous laparoscopic cholecystectomy  
Female sex |
| Masci et al 2001 | Multicenter study | Diagnostic and therapeutic ERCP | 2103               | percent 1.8                       | Age under 60  
Pre-cut sphincterotomy  
Failed clearing of biliary stones |
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<td>Freeman et al 2001</td>
<td>Multicenter study</td>
<td>Diagnostic and therapeutic ERCP</td>
<td>1963</td>
<td>6.7 percent</td>
<td>Prior ERCP pancreatitis, Suspected dysfunction of sphincter of Oddi, Female sex, Normal serum bilirubin, Absence of chronic pancreatitis, Biliary sphincter balloon dilation, Difficult cannulation, Pancreatic sphincterotomy, 1 or more injections of contrast into the pancreatic duct</td>
</tr>
<tr>
<td>Vandervoort et al 2002</td>
<td>Monocenter study</td>
<td>Diagnostic and therapeutic ERCP</td>
<td>1223</td>
<td>7.2 percent</td>
<td>Recurrent pancreatitis, Prior ERCP pancreatitis, Difficult cannulation, Pancreatic brush cytology, Pain during procedure, Precut sphincterotomy</td>
</tr>
<tr>
<td>Christensen et al 2004</td>
<td>Monocenter study</td>
<td>Diagnostic and therapeutic ERCP</td>
<td>1177</td>
<td>3.8 percent</td>
<td>Age under 40, Dilated bile duct, Placement of stent</td>
</tr>
<tr>
<td>Cheng et al 2006</td>
<td>Multicenter study</td>
<td>Diagnostic and therapeutic ERCP</td>
<td>1115</td>
<td>15.1 percent</td>
<td>Minor papilla sphincterotomy, Sphincter of Oddi dysfunction, Prior ERCP pancreatitis, Age &lt;70</td>
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Prevention:

General Principles
- Proper training of endoscopist and maintaining proficiency.
- Adequate disinfection.
- Avoidance of diagnostic ERCP
- Avoidance of canulation and injection of PD.
- Careful use of electrocautery.