Objectives

• Review the risk factors for post-ERCP pancreatitis (PEP)

• Discuss endoscopic and pharmacologic interventions for the prevention of PEP
Endoscopic Retrograde Cholangiopancreatography

- ‘Name’ is diagnostic
- Usually aiming at either bile duct or pancreatic duct
- Predominantly therapeutic

Complications of ERCP

- ERCP is an INVASIVE test

- Pancreatitis 3.5% (severe in 11%, death in 3%)
- Bleeding 2%
- Cholangitis ≤ 1%
- Perforation 0.5%
- Related to Sedation 1%
- Cholecystitis 0.5%
- Death 0.3%
- Failure 5 - 10%

ASGE Standards of Practice Committee. GIE 2012
Andriulli et al AJG 2007
**Consensus Definition of Post-ERCP Pancreatitis (PEP)**

**Definition** requires all 3:
- New or worsened abdominal pain
- Amylase 3x ULN > 24 hrs post-ERCP
- Requiring ≥ 2 d hospitalization

**Severity:**
- Mild: < 4 d hospitalization
- Moderate: 4 – 10 d hospitalization
- Severe: > 10 d hospitalization, need for intervention

*Cotton et al. GIE 1991*

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**Mechanisms of Post-ERCP Pancreatitis (PEP)**

- Mechanical injury
- Thermal injury
- Chemical / Hydrostatic injury
- Microbiological injury
Risk Factors for Post-ERCP Pancreatitis

**Patient-related**
- Age < 60
- Female
- Normal bilirubin
- Normal ducts
- History of PEP
- Suspected SOD

**Procedure-related**
- Difficult cannulation
- Multiple injections of the PD
- Precut sphincterotomy
- Pancreatic sphincterotomy
- Balloon dilatation of biliary sphincter

**Endoscopist-related**
- Trainee involvement
- Case volume / experience

Freeman et al. GIE 2001

---

1. Appropriate Patient Selection

"ERCP is most dangerous for people who need it least" (Cotton 2001)

---

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>30 (6 deaths)</td>
<td></td>
</tr>
<tr>
<td>Sphincterotomy perforation</td>
<td>16 (3 deaths)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>10 (6 deaths)</td>
<td></td>
</tr>
<tr>
<td>Esophageal perforation</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lost stent</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>59 (15 deaths)</strong></td>
<td></td>
</tr>
</tbody>
</table>

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Analysis of 79 ERCP cases: mainly about indications...
ERCP should be done

- For accepted indications
- By appropriately trained and experienced endoscopists
- With all the necessary support staff and equipment
- Only after detailed informed consent
- Communication before and after the procedure

1. ASGE guideline. GIE 2005.

Accepted Indications for ERCP

**Biliary Diseases**
- CBD stones
- Biliary strictures
- Post-op complications
- Post-op bile leaks
- Selected patients with SOD

**Pancreatic Diseases**
- Recurrent acute pancreatitis
- Strictures associated with chronic pancreatitis
- Symptomatic PD stones
- PD disruptions / leaks
- Symptomatic pancreatic pseudocysts / benign pancreatic fluid collections

**Ampullary Diseases**
- Ampullary adenomas / malignancy
**Biliary Indications**

**CBD Stones (proven or strongly suspected)**
- Demonstrated with other imaging
- Strong clinical suspicion based on clinical predictors
  - Age > 55 yrs
  - Total Bilirubin > 30umol/L
  - CBD > 6mm on US
  - Suspected CBD stone on US

**Probability of CBDS varies between 18% if none present and 94% if all 4 predictors present**


**Low**

- IOC Negative
- Lap Choly

**Intermediate**

- IOC Positive
- Pre-op EUS or MRCP
- LCBD

**High**

- IOC Positive
- Post-op ERCP
- ERCP

**ASGE guideline 2010. Modified from Tse et al**

**ERCP in Acute Gallstone Pancreatitis**

Clinical predictors of persistent CBD stones:
- Progressive increases in LFTs
- Persistent dilatation of the CBD

Consider urgent ERCP only in patients with cholangitis or persistent biliary obstruction.

**Current Guidelines**

- **Consensus:**
  - Early ERCP is not indicated in patients with mild AGP
  - Concomitant cholangitis or biliary obstruction is an indication for urgent / early ERCP

- **No Consensus:**
  - The early use of ERCP in severe AGP without cholangitis or biliary obstruction

---

**Severity of Pancreatitis**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Favors early ERCP</th>
<th>Favors conservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted severe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Subgroup Analysis**

- Tse F et al. Cochrane Database Syst Rev 2012 May

<table>
<thead>
<tr>
<th>Predicted mild</th>
<th>Predicted severe</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.1</td>
<td>NA</td>
</tr>
<tr>
<td>0.01</td>
<td>0.1</td>
<td>41%</td>
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<td>0.1</td>
<td>0%</td>
</tr>
<tr>
<td>0.01</td>
<td>0.1</td>
<td>15%</td>
</tr>
</tbody>
</table>

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**Favors Favors Outcomes early ERCP conservative Mortality**

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<tr>
<th>Predicted mild</th>
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- Tse F et al. Cochrane Database Syst Rev 2012 May
### Severity of Pancreatitis

Tse F et al. Cochrane Database Syst Rev 2012 May

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<td></td>
<td></td>
</tr>
<tr>
<td>Predicted severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic complications</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Predicted severe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Mortality**
  - Predicted mild: $P = NA$
  - Predicted severe: $P = 41\%$

- **Local complications**
  - Predicted mild: $P = 15\%$
  - Predicted severe: $P = 55\%$

### Cholangitis

Tse F et al. Cochrane Database Syst Rev 2012 May

<table>
<thead>
<tr>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Mortality</td>
<td></td>
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</tr>
<tr>
<td>Included Cholangitis</td>
<td></td>
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</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Excluded Cholangitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Mortality**
  - Included Cholangitis: $NNT = 20$, $P = 0\%$
  - Excluded Cholangitis: $NNT = 13$, $P = 0\%$

- **Local complications**
  - Included Cholangitis: $NNT = 11$, $P = 0\%$

- **Systemic complications**
  - Included Cholangitis: $NNT = 20$, $P = NA$
Subgroup Analysis

Biliary Obstruction
Tse F et al. Cochrane Database Syst Rev 2012 May

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<th>Outcomes</th>
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<td></td>
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<tr>
<td>Included Obstruction</td>
<td></td>
<td>P = 11%</td>
</tr>
<tr>
<td>Local complications</td>
<td></td>
<td>P = 0%</td>
</tr>
<tr>
<td>Systemic complications</td>
<td></td>
<td>P = 10%</td>
</tr>
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</table>

Subgroup Analysis

Biliary Obstruction
Tse F et al. Cochrane Database Syst Rev 2012 May

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<tbody>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Included Obstruction</td>
<td></td>
<td>P = 11%</td>
</tr>
<tr>
<td>Excluded Obstruction</td>
<td></td>
<td>P = 48%</td>
</tr>
<tr>
<td>Local complications</td>
<td></td>
<td>P = 0%</td>
</tr>
<tr>
<td>Excluded Obstruction</td>
<td></td>
<td>P = 4%</td>
</tr>
<tr>
<td>Systemic complications</td>
<td></td>
<td>P = 10%</td>
</tr>
<tr>
<td>Excluded Obstruction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Implications for Practice

• Early conservative management with selective use of ERCP should be considered for patients with acute gallstone pancreatitis regardless of the severity of pancreatitis.

• Potential benefit of early routine ERCP strategy in cholangitis or biliary obstruction.

• Timing of ERCP (urgent < 24 hours vs. early < 72 hours) should depend on the level of suspicion, the condition of the patient, and response to initial conservative management.
Early Conservative Management Unless Cholangitis or Biliary Obstruction

Waiting is good. It means you're not going to die. The person you need to feel sorry for is the one who gets rushed into the ER and treated first.

2. Endoscopic Interventions Used to Reduce the Risk of PEP

- Guidewire-assisted cannulation technique
- Pancreatic duct stenting
- Early Precut Sphincterotomy
- Double Guidewire Technique
Guidewire-assisted Cannulation

- Guidewire technique significantly reduced PEP compared to contrast technique.
- Guidewire technique is associated with greater cannulation success, less precut sphincterotomy, and no increase in ERCP-related complications.
- Guidewire technique appears to be the most appropriate first line primary cannulation technique.

Implications for Practice

1. Guidewire-assisted Cannulation - PEP
   - Non-crossover studies: P = 0%
     - Subtotal: RR 0.22
     - 95% CI: 0.12 to 0.42
     - NNT = 31
   - Crossover studies: P = 0%
     - Subtotal: RR 0.85
     - 95% CI: 0.58 to 1.23
     - RR 0.51 (0.32 - 0.82)

   - RR (random)
Pancreatic Duct Stent

Pancreatic duct stenting may reduce post-ERCP pancreatitis in select patients

Prophylactic PD Stenting - PEP

Mild-moderate pancreatitis
- I² = 0%
- RR 0.45 (0.32 - 0.62)

Severe pancreatitis
- I² = 5%
- Subtotal: RR 0.26 (0.09 - 0.76)
- RR 0.39 (0.29 - 0.53)
- NNT = 9

Implications for Practice

- PD stenting for high risk cases:
  - SOD, pancreatic sphincterotomy, ampullectomy
  - Prior post-ERCP pancreatitis, precut sphincterotomy, difficult cannulation
- No agreement on stent size / length
- Successful placement: 80-90%
- Spontaneous stent passage: 70-85%

Mazaki J. Gastroenterol 2014

Freeman ML. Clin Gastroenterol Hepatol 2007
Precut Sphincterotomy

- Needle knife papillotomy
- Precut fistulotomy
- Transpancreatic precut sphincterotomy

Early Precut Sphincterotomy

- Often used as a rescue technique when conventional techniques fail to gain selective biliary access
  - Freeman et al. GIE 2005
- Independent risk factor for post-ERCP complications
  - Masci et al. Endoscopy 2003
- Controversial whether the increased risk is due to the precut itself or to the prolonged cannulation attempts prior to the precut
- Early use of precut has been postulated to improve cannulation success and reduce the risk of PEP

Favoring Early Precut

- Incidence of PEP (unweighted): 4.6% early precut vs. 7.5% persistent cannulation

RR 0.62 (0.38 - 1.01)

I² = 0%
Implications for Practice

• In patients with difficult biliary cannulation, early use of precut sphincterotomy by experienced endoscopists compared to persistent attempts with conventional cannulation:
  – Increases primary cannulation success
  – Does not increase post-ERCP complications
  – May reduce the risk of PEP

• Further RCTs are needed to confirm these findings, and to explore the optimal timing and technique of precut

Double Guidewire Technique

Double Guidewire Technique - PEP

<table>
<thead>
<tr>
<th>Comparison</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DGT vs. Conventional Cannulation</td>
<td>1.58</td>
<td>(0.83 - 3.01)</td>
</tr>
<tr>
<td>Subtotal:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DGT vs. Precut</td>
<td>2.92</td>
<td>(1.24 - 6.88)</td>
</tr>
<tr>
<td>P = 76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DGT vs. PG stent</td>
<td>1.75</td>
<td>(0.08 - 37.50)</td>
</tr>
<tr>
<td>P = 76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR 1.98 (1.14 - 3.42)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tse F et al. DDW 2013
Implications for Practice

- In patients with difficult cannulation, DGT technique appears to be associated with an increased risk of PEP compared to persistent conventional cannulation, precut or PD stent placement.
- Sole use of DGT technique should be discouraged.
- PD stenting after the use of DGT may reduce the risk of PEP, but requires further assessment.

3. Pharmacological Prophylaxis of Post-ERCP Pancreatitis

Pharmacologic agents RCT showed benefit:
- Allopurinol
- Ceftazidime
- Diclofenac
- Gabexate
- Glyceryl trinitrate
- Hydrocortisone
- Nafamostat mesylate
- Octreotide
- Somatostatin
- Ulinastatin

Pharmacologic agents RCT that failed to show benefit:
- Anticholinergic drugs
- Aprotinin
- Botulinum toxin
- Calcitonin
- Epinephrine
- Fresh frozen plasma
- Glucagon
- H-2 Blocker
- Heparin
- Lidocaine
- Methylprednisolone
- N-acetyl cysteine (NAC)
- Natural beta-carotene
- Nifedipine
- Nitroglycerin
- Parenteral nutrition
- Pentoxifylline
- Prednisone
- Recombinant PAF acetylhydrolase (rPAF-AH)
- Selenium
- Semapimod

Prophylactic NSAIDS - PEP

Ding X et al. Gastrointest Endosc 2012

Risk Ratio

M-M, Random, 95% CI

NNT = 17

RR 0.57 (0.38–0.86)
**Prophylactic Rectal Indomethacin - PEP**

Yaghoobi et al. APT 2013

![Odds Ratio](image)

M & H, Fixed, 95% CI

Favors Indomethacin

Favors Placebo

OR 0.49 (0.34 – 0.71)

NNT = 20

**Rectal NSAIDS for All or High Risk Patients??**

- **ESGE Guidelines** (Dumonceau et al. Endoscopy 2010):
  - Routine administration of 100mg of indomethacin or diclofenac PR immediately before or after ERCP is recommended
  
  Recommendation: Grade A

- **ACG Guidelines** (Tenner et al. AJG 2013):  
  - Rectal NSAIDS should be considered in high risk patients  
  - Rectal NSAIDS do not replace the need for PD stenting
  
Conditional recommendation
Moderate quality of evidence

**Conclusion**

- PEP is the most common complication
- Patient-related and procedural-related risk factors are major determinants of risk
- ERCP associated risks can be minimized by:
  - Careful patient selection
  - Appropriate use of techniques
    - Use wire-guided cannulation techniques
    - Use early precut in difficult cannulation (experts only)
    - Consider PD stenting in high risk patients
  - Rectal NSAIDS for all patients or high risk patients
Questions