Stents, NSAIDs and fluids: how do I prevent post-ERCP pancreatitis

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Disclosure

Consultant with Salix, CalciMedica, and Shire
Overview

- Magnitude of problem
- Risk Stratification
- Endoscopic Preventive Techniques
- Pharmacologic Prevention
- Intravenous Fluids
- Ongoing, future studies
- Tips

Post-ERCP Pancreatitis (PEP)

- Most common complication of ERCP
- Incidence varies widely (2-15%)
- Expensive: $200 million/year in the US
- Substantial patient suffering & endoscopist stress

Kochar B. Gastroint Endosc 2014
El Munzer BJ. Gut 2008
**PEP**

- **Definition**
  - New or worsening upper abdominal pain
  - amylase/lipase $\geq 3 \times$ uln
  - hospitalization or prolongation for $>1$ night

- **Severity**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>Clinical pancreatitis, amylase at least $3 \times$ normal $24$ h after procedure, requiring unplanned admission or prolongation of planned admission to $2-3$ days.</td>
<td>Pancreatitis requiring hospitalization of $4-10$ d.</td>
<td>Pancreatitis requiring hospitalization $&gt;10$ d, intervention (percutaneous drainage or surgery), development of necrosis, or pseudocyst.</td>
</tr>
</tbody>
</table>

*Adapted from Cotton et al. (Reference #1).

Cotton PB. Gastroint Endosc 1991

- **PEP**
  - Mild PEP is acceptable to most informed patients with minimal impact on QOL and modest impact on health care dollars
  - Severe PEP is life threatening/life modifying with devastating impact on QOL and health care dollars, is unacceptable to all & results in law suits
Risk Reduction

- Pre-Procedure
  - Indications
  - Patient selection
  - MD selection

- Intra-Procedure
  - Technical maneuvers
  - IV hydration

- Post-Procedure
  - Pharmacologic prophylaxis
  - Recognition
  - Treatment

Patient-Related Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age</td>
<td>1.1-1.6</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.8-2.5</td>
</tr>
<tr>
<td>Normal Bilirubin Level</td>
<td>1.9</td>
</tr>
<tr>
<td>Suspected SOD</td>
<td>1.8-2.6</td>
</tr>
<tr>
<td>Prior episode of AP/PEP</td>
<td>2.0-5.4</td>
</tr>
<tr>
<td>Absence of Chronic Pancreatitis</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Freeman ML. Gastrointest Endosc 2001
Williams EJ. Endoscopy 2007
Cotton PB. Gastrointest Endosc 2001
Cheng CL. Am J Gastroenterol 2006
Wang P. Am J Gastroenterol 2009
<table>
<thead>
<tr>
<th>Procedure-Related Risk Factors</th>
<th>Odds Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult cannulation</td>
<td>1.8-3.4</td>
</tr>
<tr>
<td>PD contrast injection/guidewire</td>
<td>1.5-2.8</td>
</tr>
<tr>
<td>(Precut sphincterotomy)</td>
<td>4.3</td>
</tr>
<tr>
<td>Pancreatic sphincterotomy</td>
<td>3.1-3.8</td>
</tr>
<tr>
<td>Biliary Sphincter Balloon dilation</td>
<td>4.5</td>
</tr>
<tr>
<td>Low-volume ERCP center</td>
<td>2.4</td>
</tr>
<tr>
<td>Trainee involvement</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Risk factors are interactive & synergistic

Adjusted odds ratio:
- Female: 2.5
- Female + normal bilirubin: 4.8
- Female + normal bilirubin + SOD: 12.4
- Female + normal bilirubin + difficult cannulation: 16.2
- Female + normal bilirubin + SOD + difficult cannulation: 42.1

Freeman ML. Gastrointest Endosc 2001
Williams EJ. Endoscopy 2007
Cotton PB. Gastrointest Endosc 2001
Cheng CL. Am J Gastroenterol 2006
Wang P. Am J Gastroenterol 2009
Evaluating Predictors & Interventions in SOD

- 214 type III SOD pts randomized 2:1 to Sphincterotomy vs. Sham
- Elevated PD pressure randomized to Dual ES vs. Biliary ES
- All patients received PD stent
- Successful outcome in 22% ES vs. 36% Sham (p<0.02)
- No correlation of outcome results with manometry

Cotton PB. J Am Med Assoc 2014

Risk Stratification

- ERCP is a therapeutic procedure
- Risk-Benefit Ratio
- No benefit of ERCP for SOD type III
- Referral to Expert centers

Cotton PB. J Am Med Assoc 2014
Procedure techniques

- Wire-guided cannulation
  Meta-analysis (>3000 pts): RR 0.51

- Early implementation of alternative techniques
  double-wire, pre-cut sphincterotomy
  Meta-analysis (~1000 pts): RR 0.47

Tse F. Cochrane Database Syst Rev 2012
Cennamo et al. Endoscopy 2010

Wire-guided cannulation: CAUTION!

- Guidewire PD perforations occur
- Primary cause of severe PEP
- Apply selectively & cautiously
Prophylactic PD stent placement

- Preserves PD drainage (orifice trauma/edema)
- >20 RCTs & non-randomized studies showed benefit
- RR 0.4; NNT 8
- Profound reduction in severe PEP
- 5-Fr diameter better than 3-Fr
- Dangerous if attempted but unsuccessful
- Inconvenient & costly (KUB; EGD to remove stent in 10%)

Choudhary et al. Gastrointest Endosc 2011
Mazaki et al. Endoscopy 2010
Afghani E. Endoscopy 2014
Freeman et al. Gastrointest Endosc 2004

Pharmacoprevention

- 35 unique pharmacologic agents studied
- > 60 RCTs since 2000
- Most studies underpowered, inconsistent
Promising Pharmacologic Agents

- Protease inhibitors
  - Nafamostat (infusion)
  - Ulinastatin (bolus)
  - Gabexate

- Sphincter relaxants
  - Nitroglycerin (SL)
  - Epinephrine (topical)

- Hormones
  - Somatostatin (bolus)
  - Secretin

- Antibiotics
  - Ceftazidime 2 gm i.v.

- Anti-inflammatory
  - NSAIDS (rectally)

Kubiliun NM. Clin Gastroent Hepatol 2015

Rectal Indomethacin RCT

- 602 high-risk pts
- 82% with suspected SOD
- Randomized to 100 mg of IM PR vs. placebo immediately after ERCP
- 82% received PD stent
- No difference in adverse events

Elmunzer BJ. NEJM 2012
Rectal Indomethacin works

- Meta analysis of 4 RCT (~1500 subjects)
- PEP in 5% with IM & 10% with placebo
- OR 0.49
- NNT 20
- Average risk pts OR 0.49
- Preventing severe PEP OR 0.41

Yaghoobi et al Ail Pharm Ther 2013

Indomethacin vs. PD stenting

- Post hoc analysis of NEJM RCT
- Logistic regression adjusted for imbalances in risk factors
- Rectal indomethacin more effective in preventing PEP than no Rx, PS and PS plus IM

Elmunzer BJ. Am J Gastro 2013
Ongoing RCTs

- **Optimal dose/timing** of Indomethacin
  Indomethacin 150 mg PR + 50 mg PR 4 hours later vs. Indomethacin 100 mg PR once

- Indomethacin vs. placebo in all comers

- Indomethacin PR + *papillary epinephrine spray* vs. Indomethacin PR alone

- *Indomethacin + PD stent* vs. Indomethacin alone (SVI)
  NIH funded, multi-center, double-blind, non-inferiority

Aggressive IVF

- Small RCT (62 pts) comparing aggressive to standard LR (2:1)
- Aggressive: 3mL/kg/hr during, 20 mL/kg bolus and 3mL/kg/hr x 8hr after (n=39)
- Std = 1.5mL/kg/hr during and 8hr after (n=23)
- 0/39 pts in aggressive vs. 4/23 pts in std got PEP (p<0.02)
- No pts developed fluid overload

Buxbaum et al Clin Gastro Hep 2013
Prevention of PEP in high-risk pts

- Appropriate pt selection
- Risk-Benefit ratio
- Atraumatic technique

- Combination of PD stenting
  AND rectal IM for high risk pts
- Aggressive IVF resuscitation

UPMC practice

- Not in type III SOD
- Especially in RAP and type I-II SOD
- Cannulate the papilla with the care you would want getting a Foley placed
- 5 Fr 3 cm single pigtail stent;
- 100 mg IM PR immediately after ERCP
- At least 2 L of LR i.v.