Post-ERCP Pancreatitis

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of Hepatology
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ERCP is risky

Safety based on number of fatal events. Courtesy of Dr. Firas Al-Kawas.
Definition of PEP

- Cotton Criteria (GIE, 1991)
- 3-10% in reviews
- 9.7% in meta-analysis, .7% mortality
  - 14.7% in high-risk

**TABLE 2. Classification of post-ERCP pancreatitis**

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Clinical pancreatitis AND b) Amylase at least three times normal at more than 24 hours after the procedure AND c) Requiring admission or prolongation of planned admission to 2-3 days</td>
<td>Pancreatitis requiring hospitalization of 4-10 days</td>
<td>a) Hospitalization for more than 10 days OR b) Development of hemorrhagic pancreatitis, phlegmon, pseudocyst, or infection OR c) Need for percutaneous drainage or surgery</td>
</tr>
</tbody>
</table>

ASGE. GIE, 2016
Post-ERCP pancreatitis: why do we really care?

• Common: 2-15%
• Expensive: $200 million/year
• Leads to substantial patient suffering
• Causes significant endoscopist stress*
• Most common reason for malpractice lawsuits**

*Keswani et al. AJG 2011
**Cotton PB. GIE 2006
Prevention of Post-ERCP Pancreatitis

**Risk Stratification**
- Stratify risk on the basis of validated patient and procedure-related predictors
- Use risk stratification information to determine whether to:
  1. Proceed with ERCP
  2. Refer to a tertiary center
  3. Place a prophylactic pancreatic stent
  4. Administer rectal NSAIDs
  5. Administer aggressive IVF hydration
  6. Observe in the hospital after ERCP

**Patient Selection**
- ERCP should be a near-exclusively therapeutic procedure
- Use MRCP and EUS to select patients for ERCP who have a high likelihood of therapeutic intervention, in whom of the risk-benefit ratio is most favorable

**Procedural Technique**
- Employ wire-guided cannulation technique
- Implement alternate cannulation techniques early in the case of challenging biliary access
- Avoid contrast-facilitated cannulation, aggressive/repeated pancreatic injection, dilation of an intact biliary sphincter, and sphincter of Oddi manometry without aspiration

**Prophylactic Pancreatic Stenting:**
- Ensure appropriate training and expertise in stent placement
- Place 3, 4, or 5-french temporary stents in high-risk cases
- Ensure that internal tip is not placed at the pancreatic duct genu or in a side branch
- Consider the risk-benefit balance of prolonged stent placement attempt in challenging cases
- Consider selective wire access to the pancreatic duct prior to therapeutic intervention

**Pharmacoprevention:**
- Administer 100mg rectal indomethacin or diclofenac before, during, or after ERCP in high-risk cases
- Consider rectal NSAIDs in average-risk cases
- Administer NSAIDs in addition to prophylactic stent placement in high-risk cases
- Aggressive IV Lactated Ringer’s solution
Prevention of PEP

1) Appropriate patient selection
2) Risk stratification
3) Atraumatic/efficient procedural technique
4) Pharmacoprevention
5) Prophylactic pancreatic stent placement
Prevention of PEP

1) Appropriate patient selection

2) Risk stratification

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Prevention of PEP

1) Appropriate patient selection

2) Risk stratification

3) *Atraumatic/efficient procedural technique*

4) Pharmacoprevention

5) Prophylactic pancreatic stent placement
WHAT IS TECHNICAL SKILL IN ERCP?

DOES IT REALLY MATTER?
<table>
<thead>
<tr>
<th>Alignment and maintenance of positioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenoscope stability</td>
</tr>
<tr>
<td>Papillary alignment</td>
</tr>
<tr>
<td>Cannulation</td>
</tr>
<tr>
<td>Efficiency</td>
</tr>
<tr>
<td>Gentleness of manipulation</td>
</tr>
<tr>
<td>Positioning and trajectory of the catheter/wire</td>
</tr>
<tr>
<td>Sphincterotomy</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Trajectory</td>
</tr>
<tr>
<td>Avoidance of excess diathermy injury/charring</td>
</tr>
<tr>
<td>Adequacy of size for indication</td>
</tr>
<tr>
<td>Wire manipulation and positioning</td>
</tr>
<tr>
<td>Wire advancement, including roadmap</td>
</tr>
<tr>
<td>Stable and appropriate wire position</td>
</tr>
<tr>
<td>Cautious injection in the pancreas</td>
</tr>
<tr>
<td>Procedural judgement</td>
</tr>
<tr>
<td>Appropriate use of advanced cannulation techniques (double wire technique, PD stent placement, and precut sphincterotomy)?</td>
</tr>
</tbody>
</table>

**GLOBAL ASSESSMENT**
Please provide your overall impression of the endoscopist’s skill level independent of the above rating scale.
Prevention of PEP

1) Appropriate patient selection

2) Risk stratification

3) Atraumatic/efficient procedural technique

4) Pharmacoprevention

5) Prophylactic pancreatic stent placement
Pharmacoprevention

- > 35 unique agents studied
- ~ 120 clinical trials since 1977
- > 80 RCTs since 2000

- Most studies underpowered, inconsistent def
- Until recently, no medication in widespread use
The Graveyard

• Hormones
  – Glucagon
  – Calcitonin
  – Octreotide

• Sphincter relaxants
  – Nifedipine
  – Botox

• Antioxidants
  – Allopurinol
  – Beta-carotene
  – NAC

• Electrosurgical current

• Use of CO2

• Miscellaneous
  – Low osmolality contrast
  – Patient position

• Anti-inflammatory
  – Steroids
  – Interleukin-10
  – Heparin
  – Platelet-activating factor
  – Semapimod
  – 5 FU

• Protease inhibitors
  – Aprotonin
  – C1-INH
  – Gabexate
  – Ulinastatin
NSAIDs

- Mechanism unclear – PLA2, COX?
- Widely available, easy, safe, inexpensive
- Preclinical data suggesting efficacy
Meta-analysis of rectal NSAIDs

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>Weight (%)</th>
</tr>
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<tbody>
<tr>
<td>Murray</td>
<td>0.41 (0.18 to 0.95)</td>
<td>30.9</td>
</tr>
<tr>
<td>Sotoudehmanesh</td>
<td>0.47 (0.19 to 1.12)</td>
<td>27.3</td>
</tr>
<tr>
<td>Montaño Loza</td>
<td>0.40 (0.13 to 1.22)</td>
<td>18.2</td>
</tr>
<tr>
<td>Khoshbaten</td>
<td>0.15 (0.04 to 0.65)</td>
<td>23.6</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.36 (0.22 to 0.60)</td>
<td></td>
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(diclofenac)  (indomethacin)
NSAIDs for preventing PEP

• “Rectal administration of diclofenac or indomethacin is recommended” (Recommendation grade A)

• Rectal NSAID use in clinical practice was very limited

• Aim: to conduct an adequately powered, methodologically rigorous randomized trial

Dumonceau JM et al.
Endoscopy 2010
Dumonceau JM et al. GIE 2010
Indomethacin effective and safe

NNT=13

Elmunzer et al. NEJM 2012
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NSAIDs Events</th>
<th>NSAIDs Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
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<tbody>
<tr>
<td>Elmunzer Indomethacin</td>
<td>27</td>
<td>295</td>
<td>52</td>
<td>307</td>
<td>31.8%</td>
<td>0.54 [0.35, 0.84]</td>
</tr>
<tr>
<td>Katsinelos Diclofenac</td>
<td>12</td>
<td>255</td>
<td>27</td>
<td>260</td>
<td>16.7%</td>
<td>0.45 [0.23, 0.87]</td>
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<td>Khoshbaten Diclofenac</td>
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<td>50</td>
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<tr>
<td>Montano Loza Indomethacin</td>
<td>13</td>
<td>75</td>
<td>28</td>
<td>75</td>
<td>17.4%</td>
<td>0.46 [0.26, 0.82]</td>
</tr>
<tr>
<td>Murray Diclofenac</td>
<td>7</td>
<td>110</td>
<td>17</td>
<td>110</td>
<td>10.6%</td>
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<tr>
<td>Otsuka Diclofenac</td>
<td>2</td>
<td>51</td>
<td>10</td>
<td>53</td>
<td>6.1%</td>
<td>0.21 [0.05, 0.90]</td>
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<tr>
<td>Sotoudehmanesh Indometh</td>
<td>7</td>
<td>221</td>
<td>15</td>
<td>221</td>
<td>9.3%</td>
<td>0.47 [0.19, 1.12]</td>
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<tr>
<td>Total (95% CI)</td>
<td>1057</td>
<td>1076</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.44 [0.34, 0.57]</td>
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Total events: 70
Heterogeneity: Chi² = 3.99, df = 6 (P = 0.68); I² = 0%

Test for overall effect: Z = 6.09 (P < 0.00001)
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**Subanalysis**

- **Type of NSAIDs**
  - Indomethacin: 4 [10,11,13,17] 1422 0.54 (0.38-0.75) 0% 0%
  - Diclofenac: 5 [9,12,14-16] 711 0.42 (0.21-0.84) 55% 55%

- **Route administration**
  - Rectal route: 7 [10-15,17] 1846 0.45 (0.34-0.61) 0% 0%
  - Non rectal route: 2 [9,16] 287 0.81 (0.47-1.41) 22% 22%

- **Time of administration**
  - Before ERCP: 4 [10,13,15,17] 924 0.46 (0.28-0.74) 0% 0%
  - After ERCP: 4 [11,12,14,16] 1002 0.45 (0.32-0.64) 0% 0%

- **Patients inclusion criteria**
  - ERCP, all comers or cholestasis: 6 [9,10,13,15-17] 1211 0.57 (0.37-0.88) 23% 23%
  - ERCP, high risk patients: 4 [9,11,12,14] 1101 0.53 (0.30-0.93) 58% 58%
  - ERCP, low risk patients: 1 [9] 28 1.15 (0.08-16.67)
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### Figure

- **Subanalysis**: Studies (ref.) | Patients | Risk Ratio (M-H-Fixed-95% CI) | I²
  - Type of NSAIDs
    - Indomethacin: 4 [10,11,13,17], 1422, 0.54 (0.38-0.75), 0%
    - Diclofenac: 5 [9,12,14-16], 711, 0.42 (0.21-0.84), 55%
  - Route administration
    - Rectal route: 7 [10-15,17], 1846, 0.45 (0.34-0.61), 0%

- **Overall**: I-squared = 0.0%, p = 0.443

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>50% reduction in PEP

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Sethi S et al. Pancreas 2014
Sun HL et al. Surgeon 2014
Evaluation of Pharmacologic Prevention of Pancreatitis After Endoscopic Retrograde Cholangiopancreatography: A Systematic Review

Nisa M. Kubiliun,* a Megan A. Adams, †, a Venkata S. Akshintala, §§ Marisa L. Conte, ‖ Gregory A. Cote, ‖, # Peter B. Cotton, # Jean-Marc Dumonceau,** Grace H. Elta, † Evan L. Fogel, †, Martin L. Freeman, ‡‡ Glen A. Lehman, †‖ Mariam Naveed,* Joseph Romagnuolo, # James M. Scheiman, † Stuart Sherman, † Vikesh K. Singh, §§ and B. Joseph Elmunzer, †, # on behalf of the United States Cooperative for Outcomes Research in Endoscopy (USCORE)

Clinical Gastroenterology and Hepatology 2015;13:1231–1239

Table 1. Agents Categorized by Research Class

<table>
<thead>
<tr>
<th>Research class</th>
<th>Agent</th>
<th>Evidence</th>
<th>Benefit</th>
<th>Safety profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rectally administered NSAIDs</td>
<td>Very strong</td>
<td>Moderate</td>
<td>Very favorable</td>
</tr>
<tr>
<td>2</td>
<td>Nitroglycerin</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Favorable when administered sublingually</td>
</tr>
<tr>
<td>2</td>
<td>Bolus-administered somatostatin</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Favorable</td>
</tr>
<tr>
<td>2</td>
<td>Nafamostat</td>
<td>Strong</td>
<td>Moderate-high</td>
<td>Favorable</td>
</tr>
<tr>
<td>3</td>
<td>Topical epinephrine</td>
<td>Weak</td>
<td>Moderate-high</td>
<td>Very favorable</td>
</tr>
<tr>
<td>3</td>
<td>Aggressive intravenous lactated Ringers</td>
<td>Weak</td>
<td>Moderate-high</td>
<td>Moderate; favorable in young, healthy adults</td>
</tr>
<tr>
<td>3</td>
<td>Gabexate</td>
<td>Moderate</td>
<td>Unclear</td>
<td>Favorable</td>
</tr>
<tr>
<td>3</td>
<td>Ulinastatin</td>
<td>Moderate</td>
<td>Moderate-high</td>
<td>Favorable</td>
</tr>
<tr>
<td>3</td>
<td>Secretin</td>
<td>Weak</td>
<td>Moderate</td>
<td>Favorable</td>
</tr>
<tr>
<td>3</td>
<td>Antibiotics</td>
<td>Weak</td>
<td>Moderate-high</td>
<td>Favorable</td>
</tr>
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</table>
Routine rectal administration of 100mg of diclofenac or indomethacin, immediately before or after ERCP, is recommended (Recommendation grade A).

Prophylactic pancreatic stent placement is recommended to prevent PEP in patients who are at high risk for development of PEP (Recommendation grade A).
Prophylactic pancreatic stent placement

- Preserves pancreatic duct drainage (orifice edema)
- 12 RCTs & >12 non-randomized studies – benefit
- RRR ~60%; ARR 10-15%
- NNT 8 (95% CI, 6-11)
- Profound reduction in severe/necrotizing pancreatitis

Choudhary et al. Gastrointest Endosc 2011
Mazaki et al. J Gastroenterol 2014
Pancreatic stents: disadvantages

• Dangerous if attempted but unsuccessful*
• Non-pancreatitis stent complications (4-5%)**
• Stent-related pancreatic duct changes
• Inconvenient & costly
  Abdominal X-ray
  EGD to remove retained stent (10%)

*Choksi et al. GIE 2014
**Mazaki et al. Endoscopy 2010
Pancreatic stents: questions

• Precise estimate of benefit?
  - blinding
  - generalizability

• Optimal stent design

• Patients most likely to benefit

• Acceptable amount of time spent on insertion
Post-ERCP pancreatitis prevention

• Indomethacin effective *in addition* to pancreatic stent placement in high-risk cases*

• Given disadvantages of stent placement, can rectal indomethacin *replace* pancreatic stents in clinical practice?

*Elmunzer et al. NEJM 2012*
Can indomethacin reduce the need for pancreatic stent placement?

*Placement of pancreatic stent left to discretion of endoscopist

Elmunzer et al. Am J Gastro 2013
Indomethacin alone prophylaxis could:

- Reduce post-ERCP pancreatitis
- Reduce non-pancreatitis stent complications
- Reduce healthcare costs by $80-150 million/year*
- Allow more efficient delivery of endoscopic services

*Elmunzer et al. Am J Gastro 2013
SVI Trial

• Multi-center randomized double-blind non-inferiority study of rectal indomethacin alone vs. combination indomethacin & stent
• 2180 high-risk subjects (~1100 thus far)
• 15 US academic medical centers
• Bio-samples/bank for translational research

* First blinded assessment of stent placement
**Maintenance of blind**

- Endoscopist(s), ERCP tech/nurse *NOT* involved in clinical care of subject for 48hrs after ERCP

- Endoscopy report will *NOT* state whether pancreatic stent was placed
Outcome adjudication

• Independent panel of 3 ERCP experts
  *2 of 3 must agree

• Using consensus definition as a diagnostic framework, adjudication based on medical records and AE narrative of each subject hospitalized w/in 48hrs of ERCP

• Medical records redacted (information regarding stent status, radiographic findings)
Summary

• Patient selection is paramount

• Techniques to minimize risk
  – Minimize cannulation duration
    • Early pre-cut
  – Minimize PD manipulation
  – Indomethacin
  – Place PD stent in high-risk patients
    • Unclear if both PDs and IN better than either in high-risk
  – Hydration reasonable