Approach to sphincter of Oddi dysfunction

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Potential Sphincter of Oddi disorders

- Recurrent acute pancreatitis
- Biliary
  - GB dyskinesia
  - Biliary SOD
- Pancreatic
**Sphincter of Oddi**

- Facilitates filling of the gallbladder for the concentration and storage of bile
- Relaxation in response to food intake
- Neurohormonal control of biliary motility involves sympathetic, parasympathetic, and enteric nerves

**Rome III criteria for SO disorder**

- Epigastric and/or RUQ pain that meet all of the following:
  - Duration > 30 minutes
  - Recurrence at differing intervals
  - Builds to a steady level
  - Interrupts daily activities
- NOT relieved by:
  - BMs
  - Postural change
  - Antacids
- Exclude other structural disease that would explain symptoms

http://www.romecriteria.org/criteria
Supportive criteria

- Associated nausea and vomiting
- Radiation to the back or right infrascapular region
- Pain causes nocturnal awakening
- Elevated serum liver chemistries

Biliary
- Transient elevation in serum liver chemistries with episodes
- Duct dilation > 9mm

Pancreatic
- Transient elevation in pancreas chemistries > 2x ULN
- Duct dilation
  - head >6mm, body >5mm

Modified Milwaukee classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Rome III symptoms</th>
<th>Duct Dilation</th>
<th>Abnl Laboratories</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>II</td>
<td>+++</td>
<td>+++ OR</td>
<td>+++</td>
</tr>
<tr>
<td>III</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Confirmation with sphincter of Oddi manometry, basal sphincter pressure > 40mmHg
Criticisms

- High prevalence of concomitant:
  - Small bowel dysmotility
  - Visceral hyperalgesia
- Limited prospective data confirming a response to endoscopic or surgical sphincter ablation


Tests of sphincter function

**Less invasive testing**

- Scintigraphy (biliary)
  - CCK
  - Fatty meal
- US, EUS, MRCP
  - Duct compliance/Δ diameter
  - Secretin

**Manometry**

- Aspiration catheter: low compliance, water perfused system
- Solid state catheter
- Highest risk indication for ERCP
  - Irrespective of manometry technique

** Poor correlation with SOM and no correlation with response to sphincterotomy**
Definitions of “dysfunction”

<table>
<thead>
<tr>
<th>Measure</th>
<th>Abnormal threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal sphincter pressure</td>
<td>&gt; 40mmHg</td>
</tr>
<tr>
<td>Intraductal pressure</td>
<td>N/A</td>
</tr>
<tr>
<td>Phasic contractions</td>
<td></td>
</tr>
<tr>
<td>• Peak amplitude</td>
<td>&gt; 350mmHg</td>
</tr>
<tr>
<td>• Duration (seconds)</td>
<td>N/A</td>
</tr>
<tr>
<td>• Frequency (contractions/min)</td>
<td>&gt; 7</td>
</tr>
</tbody>
</table>

Behar et al., GIE 2006

Evidence for ERCP with SOM in 2013

<table>
<thead>
<tr>
<th>SOD Type</th>
<th>RCT</th>
<th>N</th>
<th>Improvement, sham</th>
<th>Improvement, ES</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td></td>
<td>~ 80-90%, irrespective of SOM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Geenen, NEJM 1989</td>
<td>47</td>
<td>30% (all)</td>
<td>65% (SOD)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25% (SOD)</td>
<td>91% (SOD)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>I-III</td>
<td>Toouli, Gut 2000</td>
<td>63</td>
<td>38% (SOD)</td>
<td>84% (SOD)</td>
<td>0.041</td>
</tr>
<tr>
<td>III</td>
<td>Sherman, GIE 1994 (abstract)</td>
<td>29</td>
<td>30%</td>
<td>62%</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Historical algorithm

Structural disease
- Rx
- Type I
  - ES
- Type II
  - ERCP with SOM
- Type III
  - Pharmacological trial

No structural disease
- ERCP with SOM

Behar et al., GIE 2006

Medical therapy for SOD

Medical targets
- Reduce spasm
- Neuromodulators
  - TCA
  - SSRI

- Short acting calcium channel blockers
  - Nitrates
  - anticholinergics

From: Effect of Endoscopic Sphincterotomy for Suspected Sphincter of Oddi Dysfunction on Pain-Related Disability Following Cholecystectomy: The EPISOD Randomized Clinical Trial

**Figure Legend:**
RAPID Score Distribution by Assigned Treatment Group and Visit. The boxes indicate interquartile ranges; circle within box, mean; horizontal line within box, median; error bars, 1.5 times the interquartile range; and circles, outliers. RAPID indicates Recurrent Abdominal Pain Intensity and Disability.
**EPISOD outcome**

**Definition of success**
- RAPID < 6 @ months 9 and 12
  - < 6 days of lost productivity
- No need for repeat intervention
- No need for narcotics

**Outcome**

![Graph showing comparison between Sham and ES outcomes](chart)

**Historical Updated algorithm**

Labs, US, EGD, EUS, MRCP

- Structural disease
  - Rx
  - Type I
  - ES
  - ERCP with SOM
- No structural disease
  - Type II
  - Type III
    - Pharmacological trial
    - ERCP with SOM

![Updated algorithm diagram](chart)
IDIOPATHIC RECURRENT ACUTE PANCREATITIS

Pancreatic duct obstruction is a cause of acute pancreatitis

- How would SOD cause RAP?
  - Intermittent or sustained ↑intraductal pressure
- Duct obstruction/spasm causes AP in animals
- Gallstone pancreatitis exists
- ERCP
  - Causes pancreatitis
  - PD stenting decreases risk
  - Over-injection increases risk

Mechanism of GS pancreatitis?
- Bile acid reflux into PD
- PD obstruction

2. SOD is prevalent (n=1854)

![Bar graph showing prevalence of SOD and Not SOD among different studies](image)

Adapted from Tan D and Sherman S., “Unexplained Acute Pancreatitis,” in Baron, Kozarek and Carr-Locke, ERCP 2nd edition

**RAP and SOD: Cause, Effect, Neither?**

- Among individuals with CBD stones, those having concomitant RAP have significantly higher basal sphincter pressures
  - This insinuates that pancreatitis (not choledocholithiasis) is the link to SOD
- SOD is prevalent in chronic pancreatitis

<table>
<thead>
<tr>
<th>Biopsy Site</th>
<th># of bx/pts</th>
<th>Inflammation n (%)</th>
<th>Fibrosis n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampulla</td>
<td>255/272</td>
<td>74 (29)</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Transampullary septum</td>
<td>234/272</td>
<td>35 (15)</td>
<td>64 (27)</td>
</tr>
</tbody>
</table>

Okazaki K, Yamamoto Y, Ito K. Gastroenterology 1986
How often does acute pancreatitis become RAP and iRAP?

**Risk of recurrence**

- Alcohol
- Idiopathic
- Other
- Bilary

**Age association**

- Alcohol
- Bilary
- Idiopathic

36% of 7,456 cases → idiopathic

Yadav D, et al., Am J Gastro 2012

Considerations in RAP

- Idiopathic
- Metabolic (hypertriglyceridemia, hypercalcemia), Medications
- Genetics (CFTR, PRSS, SPINK1, CTRC)
- Autoimmune
- Obstructive (Divisum*, IPMN, tumors, anomalous pancreatobiliary union)
- Alcohol, Gallstones, Smoking

Cote GA. "ERCP in Acute and Recurrent Acute Pancreatitis," In Cotton and Leung, ERCP, 2nd edition, in press
Be careful who you’re calling idiopathic

- Ampullary lesions
- Divisum
- Small tumors

Second tier diagnostics will identify an underlying etiology or factor in 40-75%

Wilcox CM, Varadarajulu S, Eloubeidi M. GIE 2006
Kaw M, Brodmerkel GJ, Jr. GIE 2002

What is the goal of sphincterotomy in RAP?

- Eliminate future episodes of AP
- Reduce the frequency of AP episodes
- Reduce/eliminate abdominal pain related to RAP
Pancreatic sphincter therapy for iRAP?

- 34 patients with normal pre-procedure evaluation and then normal ERCP with SOM
  - Randomization
    - Serial PD stenting q3 months for 9 months (19)
    - Sham (15)
- PD stenting
  - 5 or 7Fr barbed stent
- All patients underwent repeat ERP every 3 months for a total of 9 months of stenting
- Mean follow-up, including treatment
  - Stent group = 33 months (range 13 - 77 months)
  - Control group = 35 months (range 10 - 78 months)


Results: less AP, unchanged pain

RAP
- Stent 2/19 (11%) vs. sham 8/15 (53%, p<0.02)

Pancreatic-type abdominal pain
- Stent 6/19 (32%) vs. sham 6/15 (40%, p<0.61)

Chronic pancreatitis
- Stent 5/19 (26%) vs. sham 4/15 (27%)

Clinical trial of sphincter of Oddi manometry in iRAP

ERCP with pancreatic SOM

Elevated (≥40 mmHg) basal pancreatic sphincter pressure

- Biliary ES
- Dual ES

Normal basal biliary and pancreatic sphincter pressure

- Sham
- Biliary ES

1:1 randomization


Pre-ERCP work-up of those randomized:
CCY (65%) MRI/MRCP (35%) EUS (18%) Genetic Testing (42%)

Screen failure (n=50)
- Pancreas divisum (n=17)
- Chronic pancreatitis (n=12)
- Other (CBD stone, IPMN) (n=21)

RAP (n=139)

Pancreatic SOD (n=69)
- BES (n=33)
- DES (n=36)
- Normal SOM (n=20)
- Sham (n=9)
- BES (n=11)

Normal SOM (n=20)

Sham (n=9)

BES (n=11)

Preliminary data
Chronic pancreatitis developed in 17% during f/u (median 78 mos)
ERCP for RAP in 2014

- Work-up should be preceded by thorough diagnostics
  - History, S-MRCP, EUS, genetics (?)
- CCY when gallstones likely
  - Elevation in liver chemistries w/AP, gallstones
- Empiric biliary sphincterotomy unproven
- Pancreatic sphincterotomy unproven

Concluding remarks

- ERCP for suspected SOD only acceptable at referral centers
  - Medicolegal considerations
- Human studies on mechanisms of abdominal pain and minimally invasive interventions needed
- ERCP for abdominal pain only and IRAP should not be performed in routine practice