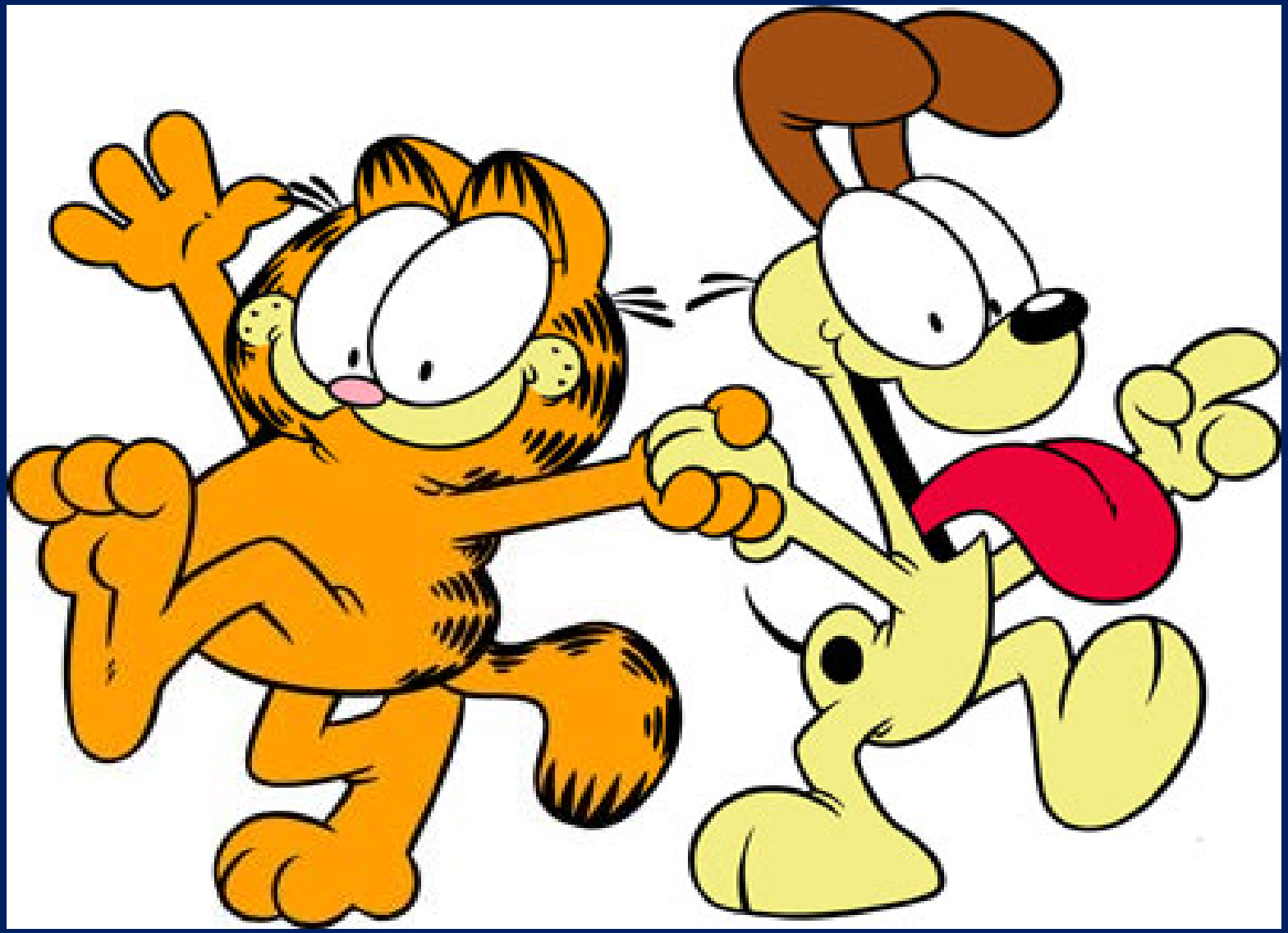
IU GI Motility Conference
August 5, 2015

Sphincter of Oddi Dysfunction: Where do we stand in 2015?

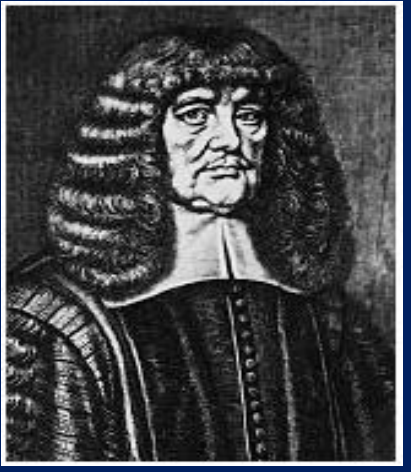
Evan L. Fogel, M.D.
Professor of Medicine
ERCP Fellowship Director
Division of Gastroenterology/Hepatology
Indiana University Hospital
Indianapolis, Indiana

OUTLINE

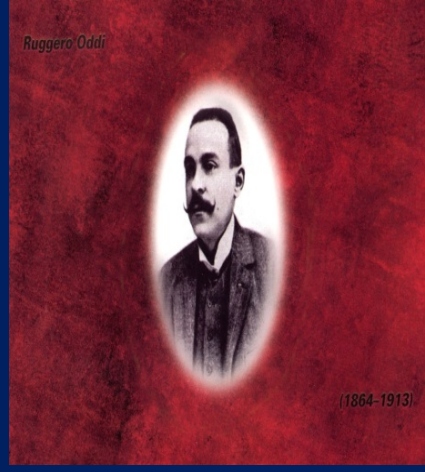
- sphincter of Oddi dysfunction: definition
- case presentation
- manometry
- outcomes

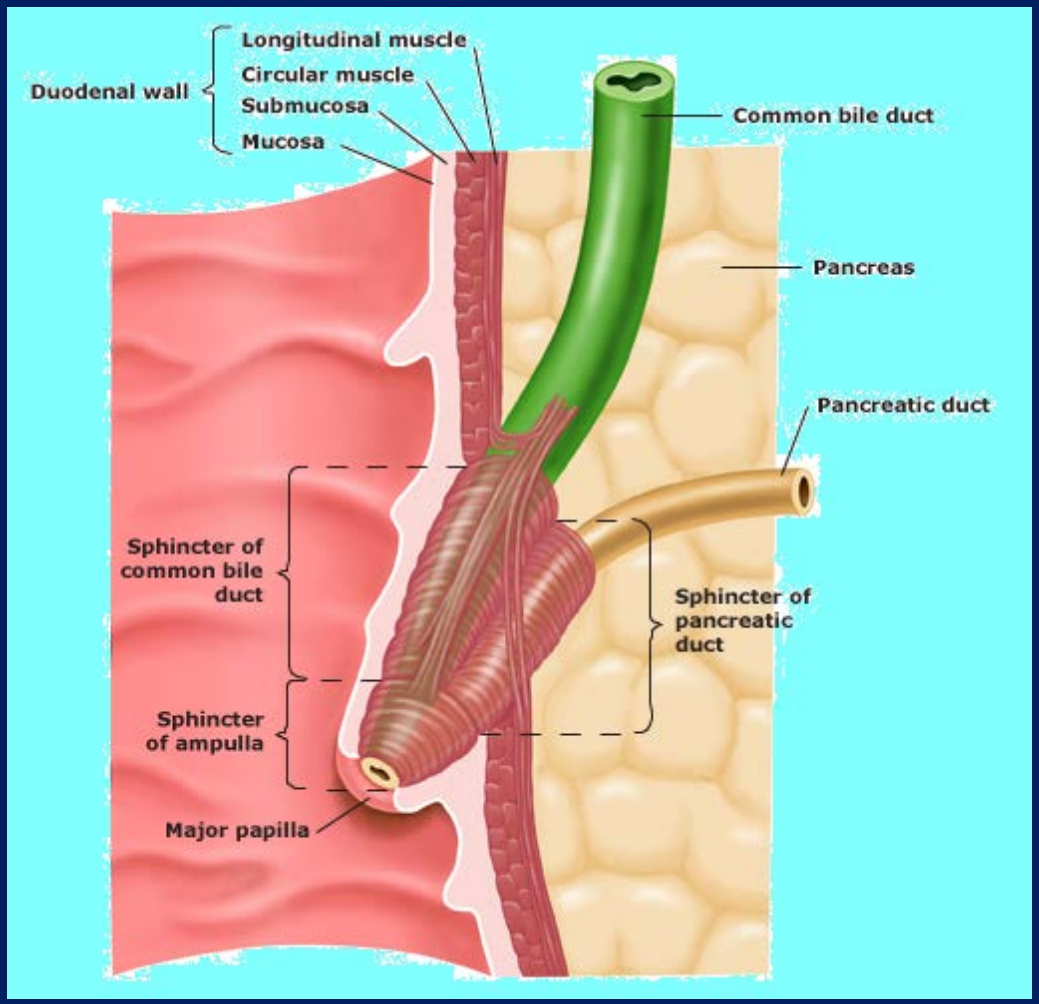


Garfield Odie

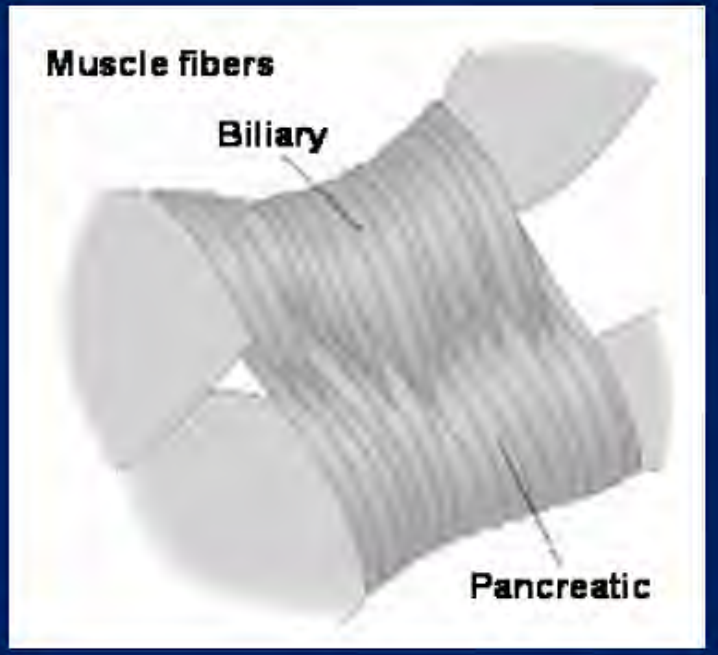


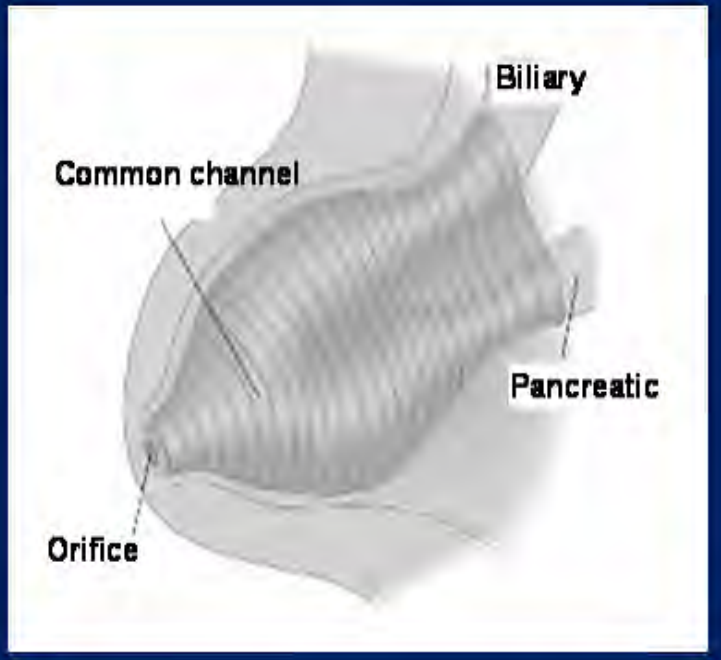
Sphincter of Oddi

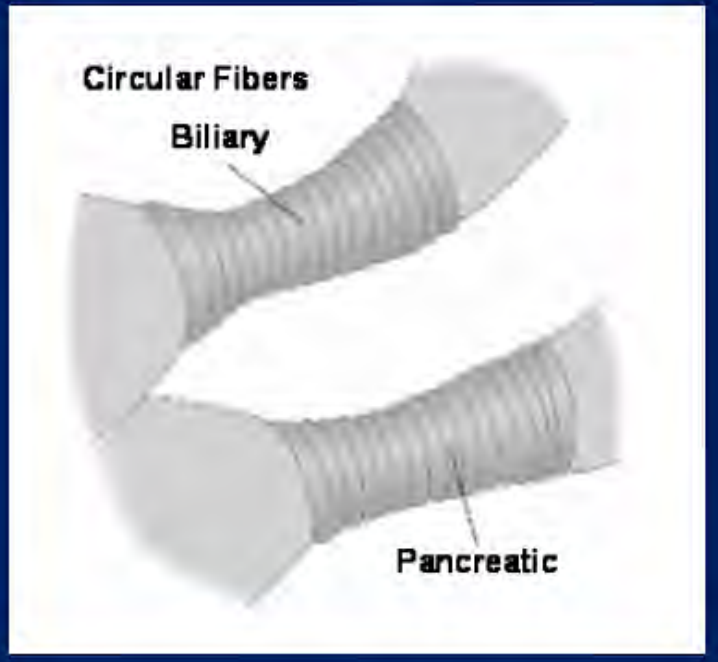


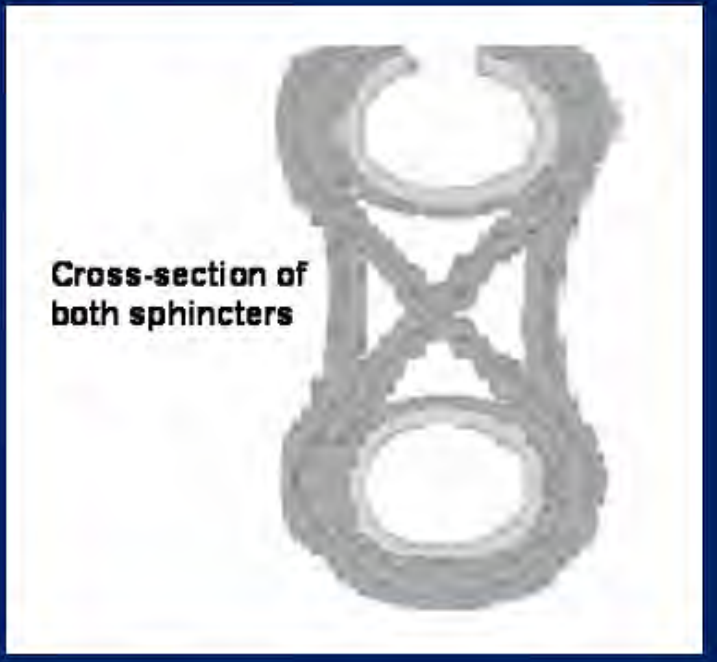


- regulates flow of bile/pancreas enzymes into duodenum
- maintains sterile intraductal milieu

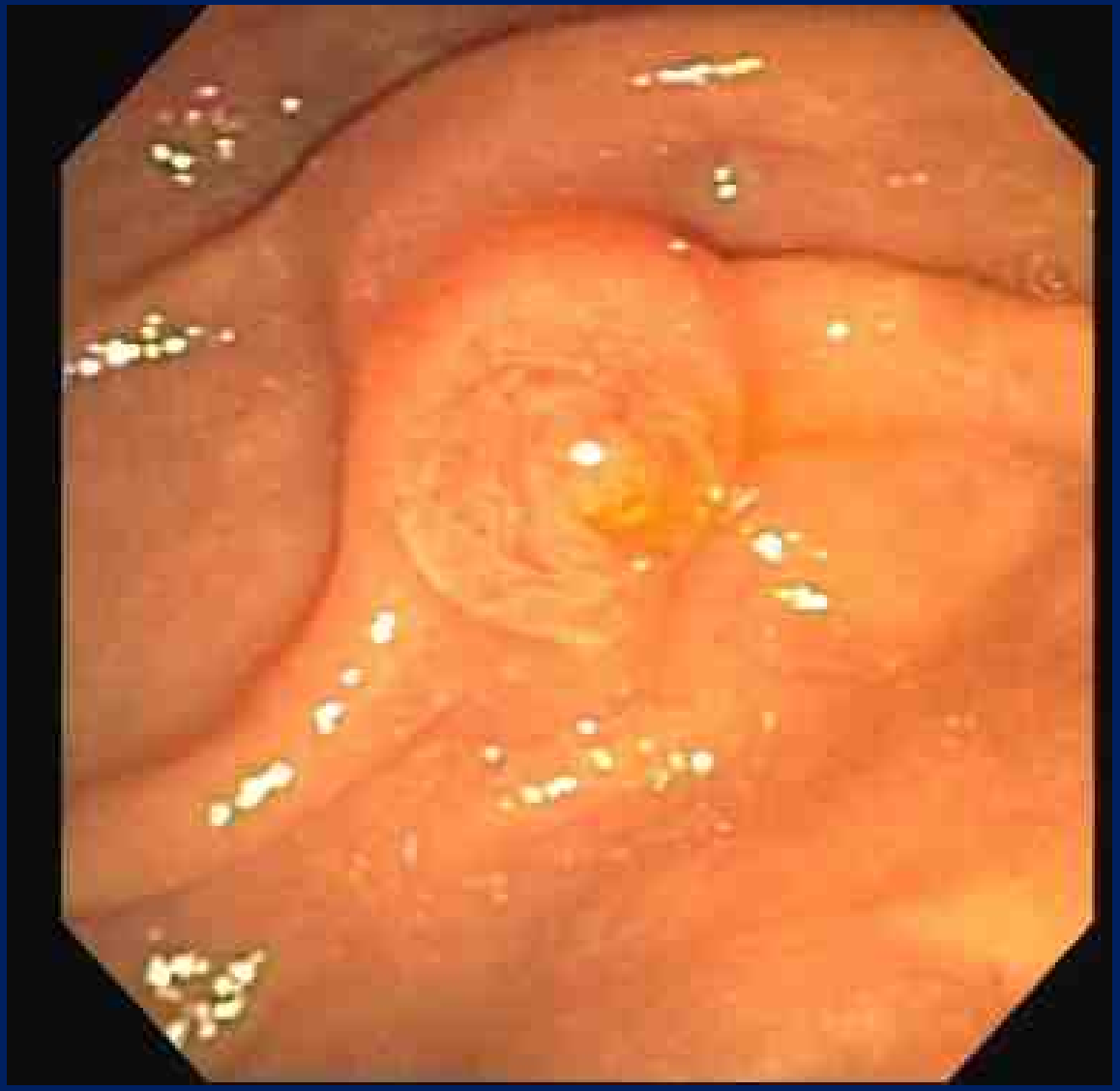

Muscle fibers
Biliary
Pancreatic


Biliary
Common channel
Pancreatic
Orifice


Circular Fibers
Biliary
Pancreatic


Cross-section of
both sphincters

Major Papilla



Sphincter of Oddi Dysfunction (SOD)

- an abnormality of SO *contractility*
- it is a benign, noncalculous, relative obstruction to flow of bile or pancreatic juice through the pancreatobiliary junction
- most common in young women
- may be manifested clinically by “pancreaticobiliary” pain, pancreatitis, abnormal LFTs, or abnormal pancreatic enzymes

Case: 30-year-old woman with RUQ pain

- six-month history
- constant discomfort, rated 2/10, with intermittent attacks of debilitating pain, identical to pain prior to cholecystectomy last year (“wasn’t functioning”)
- pain lasts 30-90 minutes, radiates to upper back, associated with nausea/vomiting

- Past medical history: cholecystectomy, otherwise negative

- Physical exam: upper abdominal tenderness, otherwise unremarkable

- ER visit: AST 82 (normal < 45), ALT 90 (<40), alkaline phosphatase 150 (<125), bilirubin 0.6 (<1.0), amylase 100 (< 89), lipase 60 (< 51)
    - all return to normal when pain-free

- CT scan unremarkable
    - normal pancreas and biliary tree

- referred to a local gastroenterologist

- EGD normal

what is your next step in the diagnostic evaluation of this patient?

- post-cholecystectomy pain resembling the patient's pre-operative biliary colic occurs in at least 10-20% of patients
- Here, the pain is similar to gallbladder-type pain, with mildly elevated LFTs, amylase/lipase
  - suggestive of pancreaticobiliary origin

Chronic abdominal pain of pancreaticobiliary origin

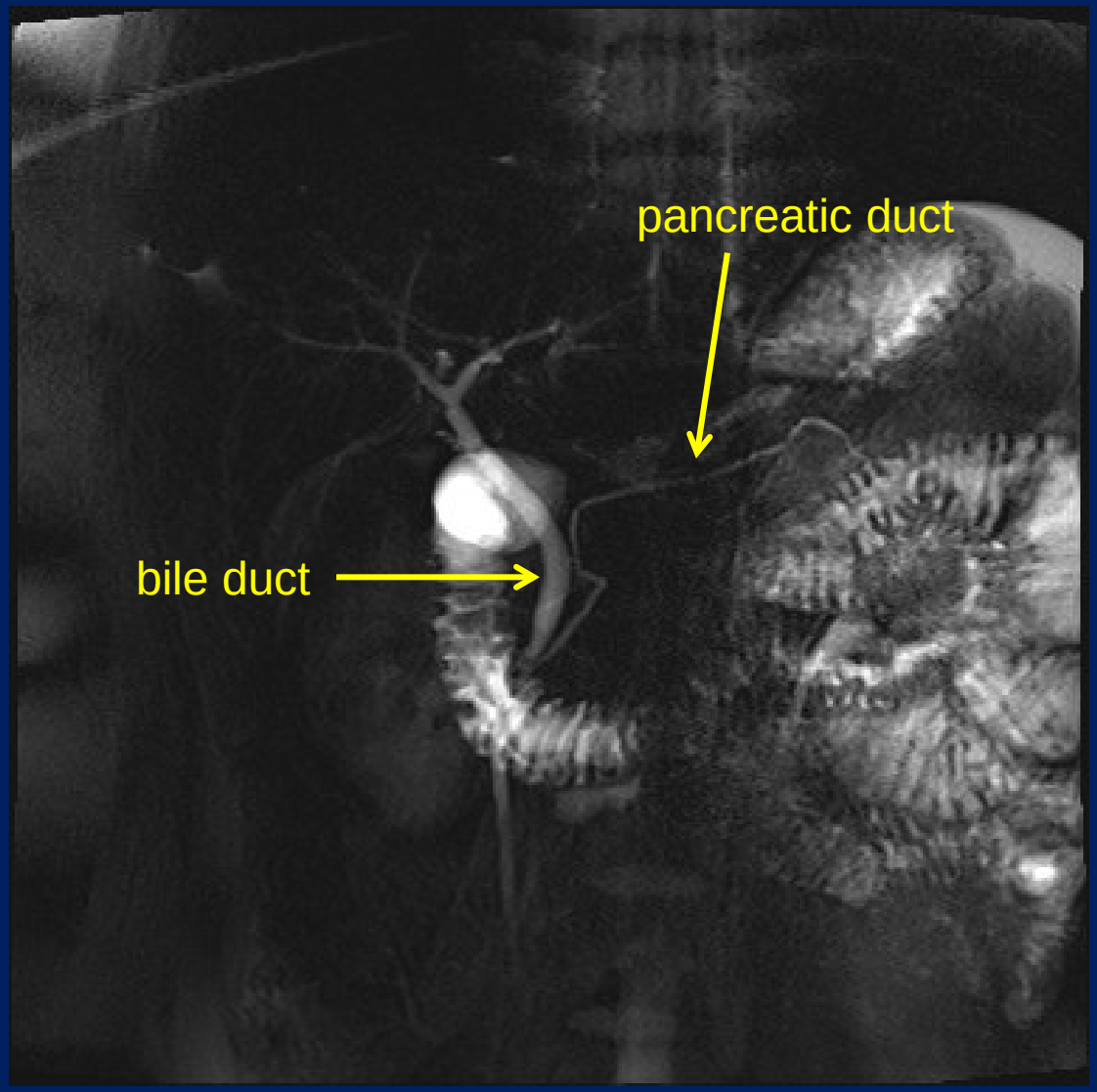
- Consider:
  - structural causes of biliary and pancreatic ductal obstruction (stones, tumors, strictures)
  - chronic pancreatitis (scarring/fibrosis)
  - sphincter of Oddi dysfunction (SOD)

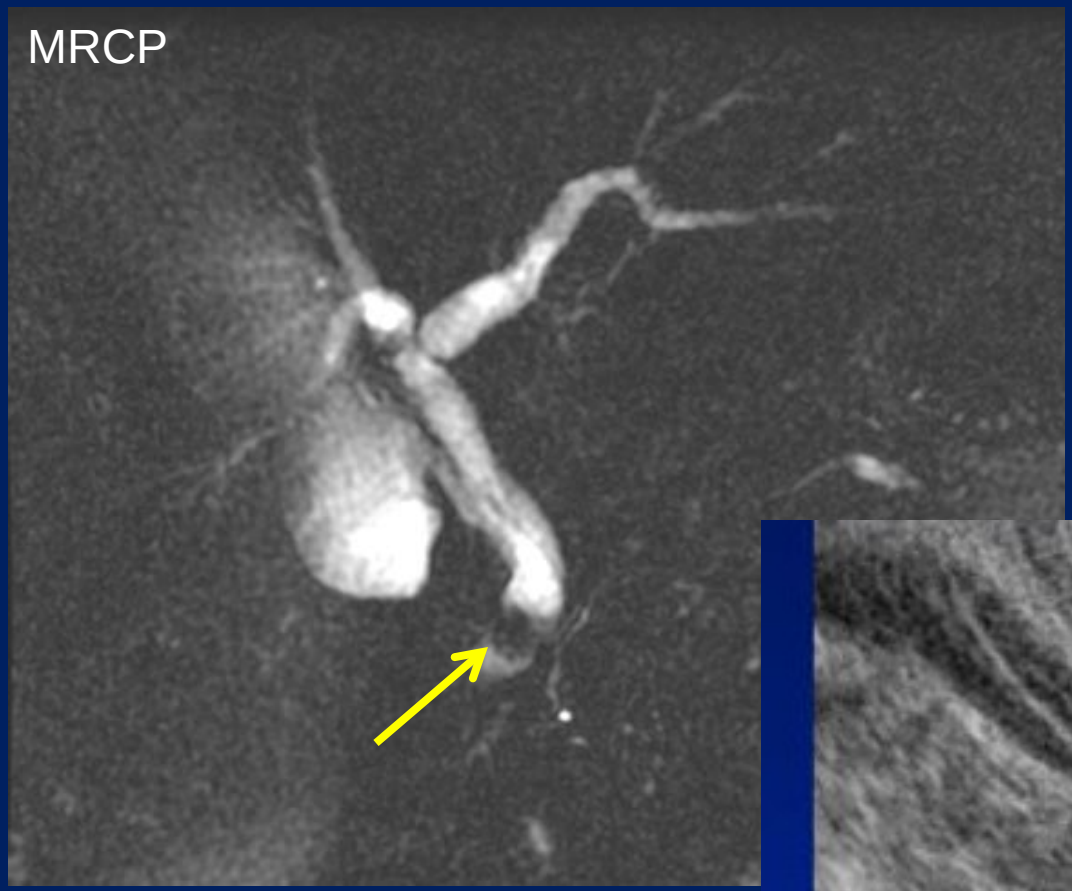
Initial evaluation

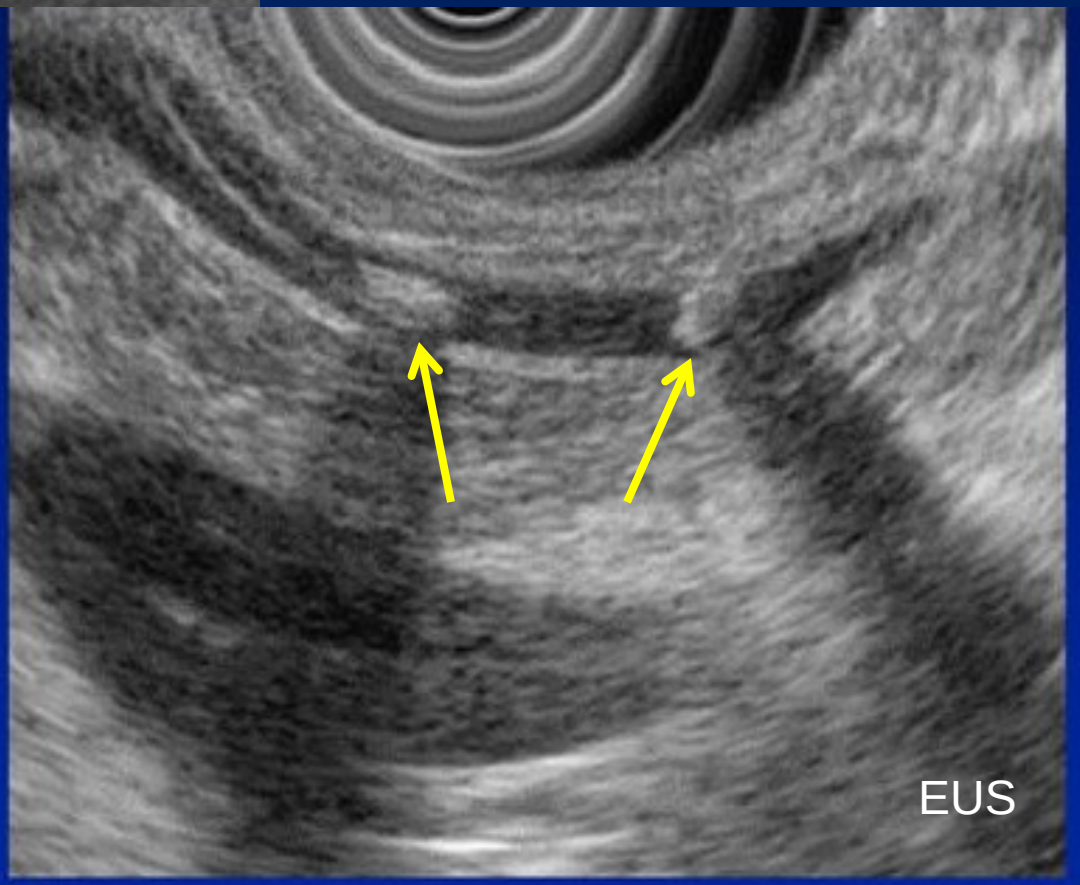
- History, physical examination
- Labs: LFTs, amylase and/or lipase (during an attack of pain)
- Imaging: ultrasound and/or CT scan

- Consider MRI/MRCP or endoscopic ultrasound (EUS) if available
- may detect pathology (stones, sludge, chronic pancreatitis, tumors) not visualized by other modalities

MRCP







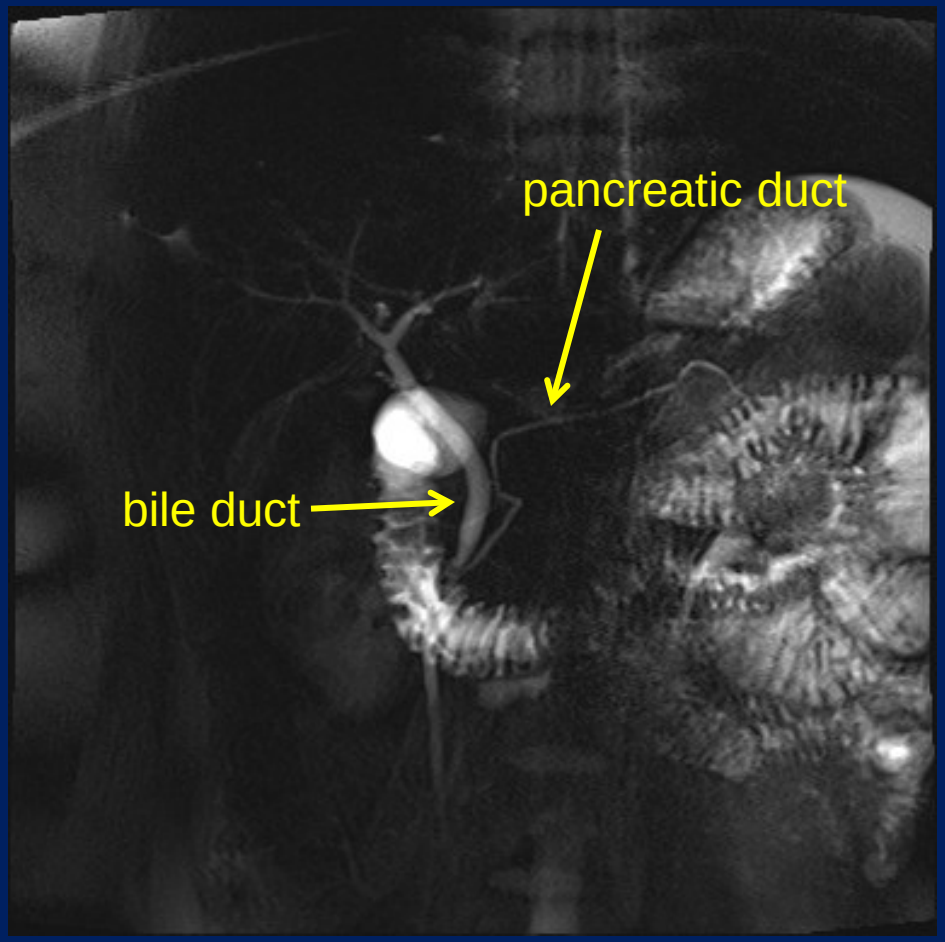
Proceed with ERCP!

Chronic Pancreaticobiliary Pain

What do I do
when the MRCP
and EUS are normal?

Chronic pancreaticobiliary pain: normal MRCP

- The residual group of patients may have SOD as a cause of their abdominal pain syndrome



SOD Evaluation:

Non-Invasive

vs

Invasive

Non-invasive Evaluation

- cholescintigraphy (nuclear med scan)
- secretin-MRCP, secretin-EUS

- Not sensitive
  - miss too many cases of SOD

- Not specific
  - suggest SOD when it isn’t there!

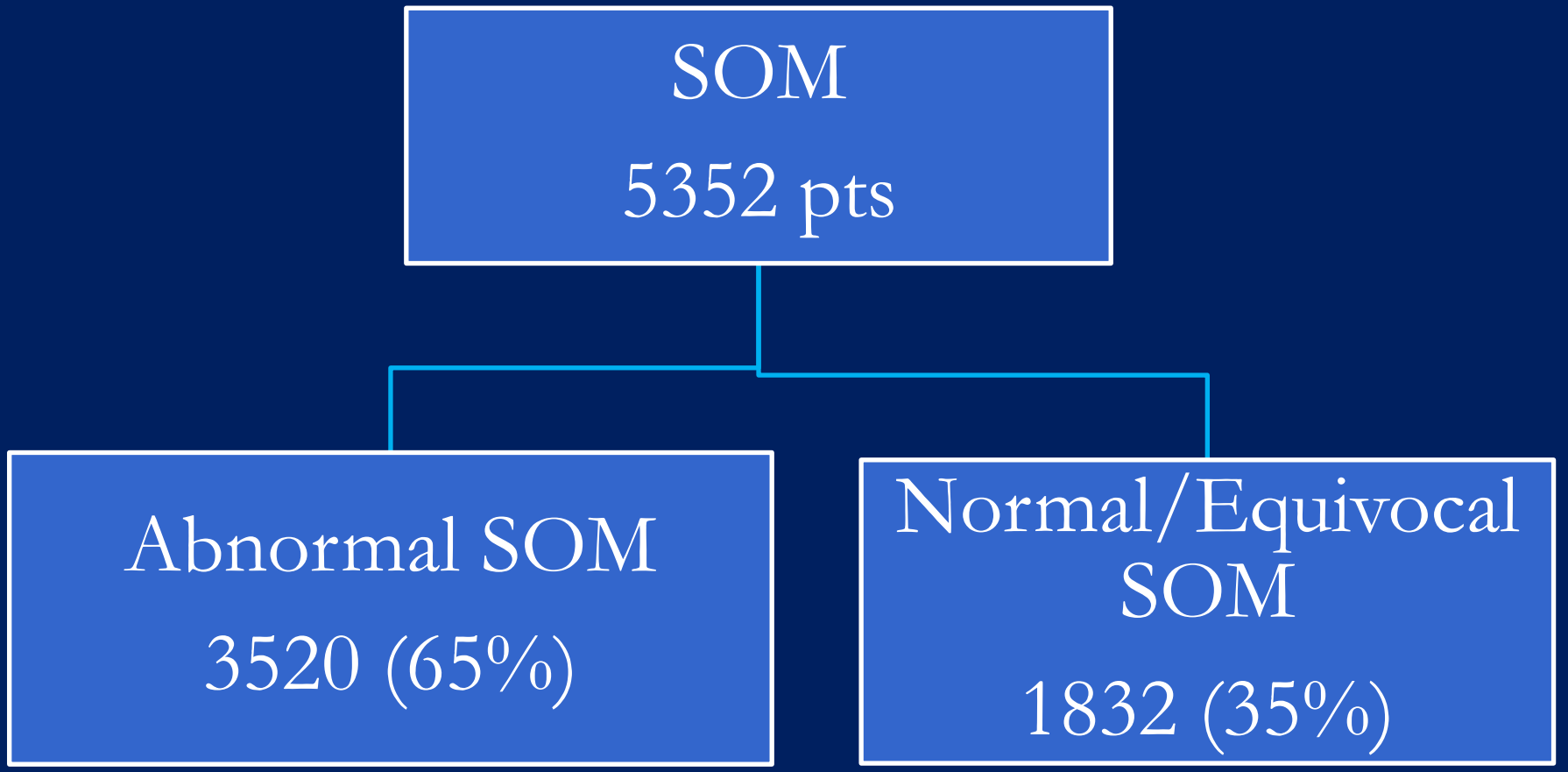
Diagnostic Evaluation

- Invasive tests
  - ERCP - provides structural evaluation of the pancreatic duct and bile duct
  - Sphincter of Oddi manometry – directly assesses pressure profile of the sphincter of Oddi

Indications for SOM 2013

- Unexplained, ***disabling*** pancreaticobiliary pain ± LFT and/or pancreatic enzyme abnormalities
- Idiopathic pancreatitis

IU Sphincter of Oddi Manometry (SOM): 1994-2007



SOD: Classification

Type	Biliary/Pancreatic		
	pain	abnormal labs	duct dilation
I	+	+	+
II	+	+	-
		-	+
III	+	-	-

Objective evidence →

Some objective evidence →

No objective evidence →

OK, we're going to proceed with ERCP / SOM!

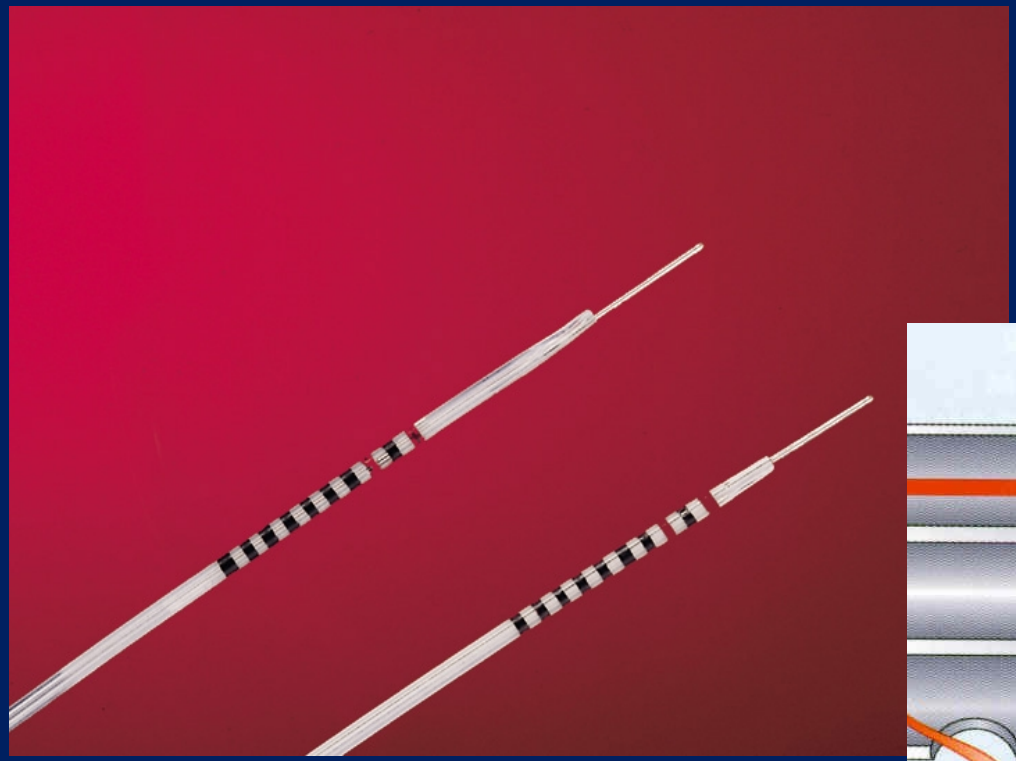
How do we do it?

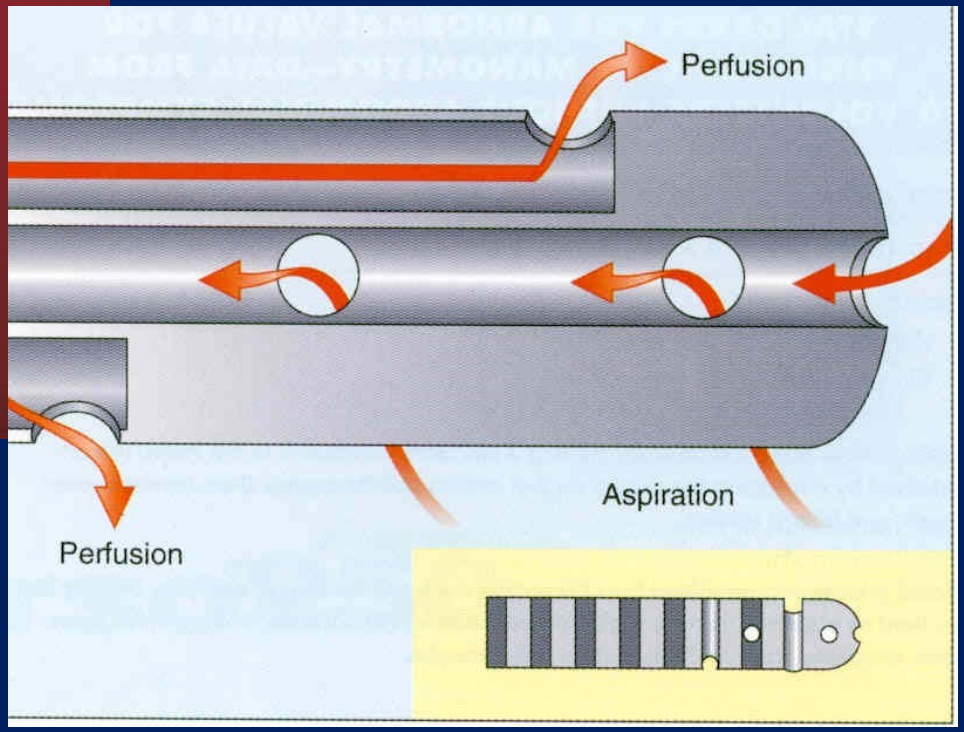
SOM Procedure Overview

- requires special equipment
- requires a cooperative, motionless patient
- a physician-driven procedure (failed cannulation → failed SOM)
- requires a knowledgeable, skilled endoscopist and an experienced manometrist to perform a successful study
- requires constant communication and teamwork
- computer and software program for SOM to view waveform

EQUIPMENT

- Water-perfused probe (“Lehman catheter“)





SOM Procedure

- the manometry catheter is advanced through the scope to the duodenum -- the duodenal baseline pressure is set to zero
- the pancreatic/bile duct is cannulated
- the catheter is withdrawn one band at a time
  - when a high-pressure zone is found, the pressure is recorded for 30 seconds
  - basal pressure must be elevated in both recording leads for a diagnosis of SOD

Manometry Tracing

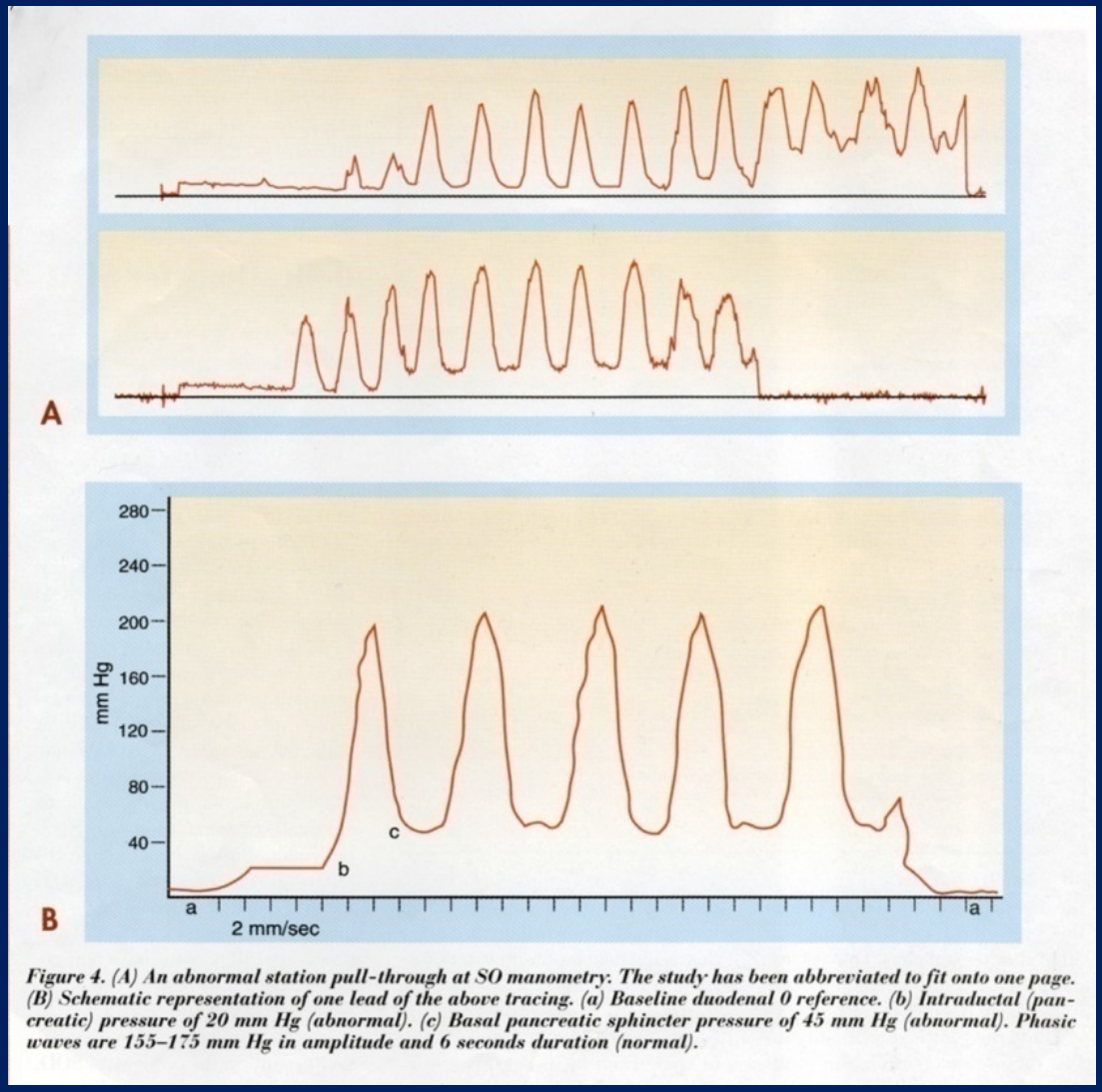


Figure 4. (A) An abnormal station pull-through at SO manometry. The study has been abbreviated to fit onto one page. (B) Schematic representation of one lead of the above tracing. (a) Baseline duodenal 0 reference. (b) Intraductal (pancreatic) pressure of 20 mm Hg (abnormal). (c) Basal pancreatic sphincter pressure of 45 mm Hg (abnormal). Phasic waves are 155–175 mm Hg in amplitude and 6 seconds duration (normal).

Aim of Therapy for SOD: Reduce Resistance to Flow of Bile or Pancreatic Juice

- Medical
- Surgical
- Endoscopic

Aim of Therapy for SOD: Reduce Resistance to Flow of Bile or Pancreatic Juice

- Medical

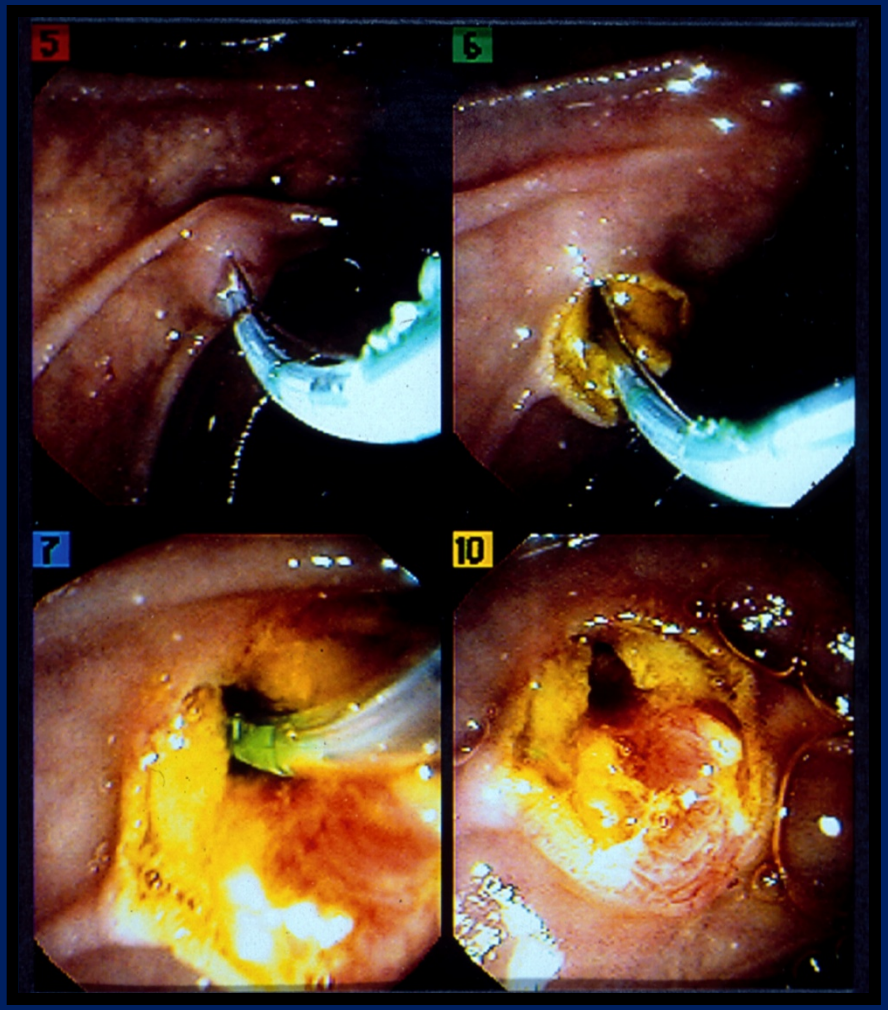
  - antispasmodics (smooth muscle relaxants, calcium channel blockers)

  - PPIs, tricyclic anti-depressants

Aim of Therapy for SOD: Reduce Resistance to Flow of Bile or Pancreatic Juice

- Medical
- Surgical
- Endoscopic
  - Sphincterotomy (cutting the muscle)
  - Botulinum toxin injection
  - Dilation
  - Stent

What is the long-term outcome after biliary sphincterotomy (BES) in SOD?



Long-term Outcome after BES: Type I SOD

Author/year	n	n Improved (%)	Mean follow-up (months)
Rosenblatt/2001	11	9 (82)	57.6
Cicala/2002	6	6 (100)	12
Thatcher/1987	15	15 (100)	28
Boender/1992	24	18 (77)	12.5
Sherman/1991	11	9 (82)	24
TOTAL	**67**	**57 (85)**	25.2

Long-term Outcome after BES: Type II SOD

Author/year	n	n Improved (%)	Mean follow-up (months)
Rosenblatt, 2001	30	22 (73)	57.6
Pereira, 2006	16	14 (88)	35.1
Cicala, 2002	8	7 (88)	13
*Toouli, 2000	13	11 (85)	24
Thatcher, 1987	15	7 (47)	20
*Geenen, 1989	18	17 (94)	48
*Sherman, 1994	6	5 (83)	39.6
Botoman, 1994	35	21 (60)	36
Wehrmann, 1996	22	13 (59)	30
Linder, 2003	5	2 (40)	18.1
Bozkurt, 1996	22	14 (64)	32.5
TOTAL	**190**	**133 (70)**	36.8

*Randomized controlled trial

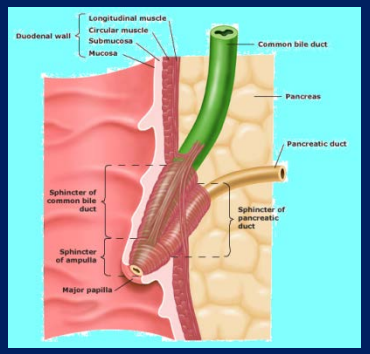
Long-term Outcome after BES: Type III SOD

Author/year	n	n Improved (%)	Mean follow-up (months)
Rosenblatt, 2001	32	9 (28)	57.6
Pereira, 2006	11	2 (18)	30.2
Wehrmann, 1998	22	11 (50)	15
*Sherman, 1994	13	8 (62)	40
Botoman, 1994	38	21 (55)	36
Wehrmann, 1996	29	2 (8)	30
Linder, 2003	15	6 (40)	18
Bozkurt, 1996	9	3 (33)	36.4
TOTAL	**169**	**62 (37)**	34.7

*RCT

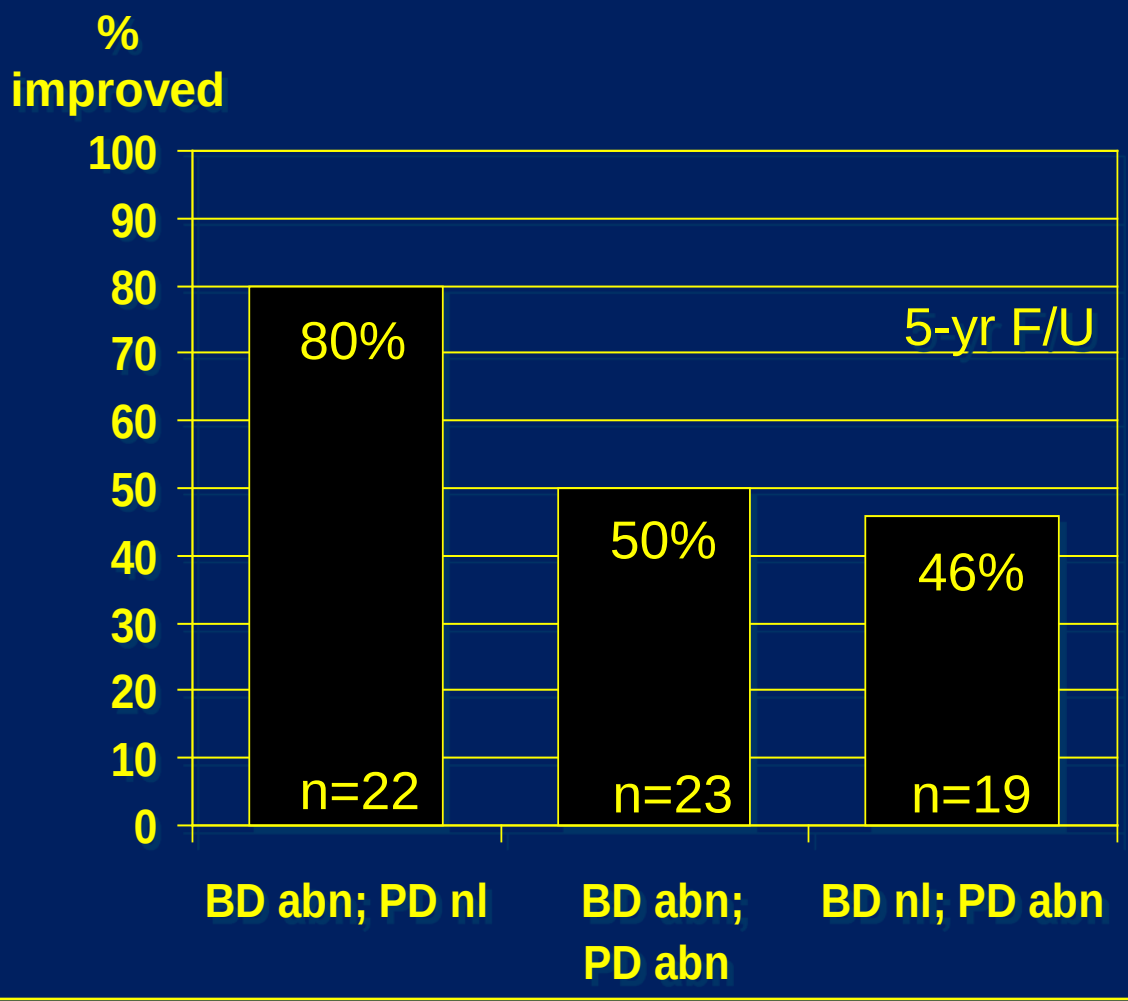
Causes for Persistent Symptoms after Biliary Sphincterotomy in SOD

- Residual or recurrent biliary SOD
- *Pancreatic SOD*
- Chronic pancreatitis



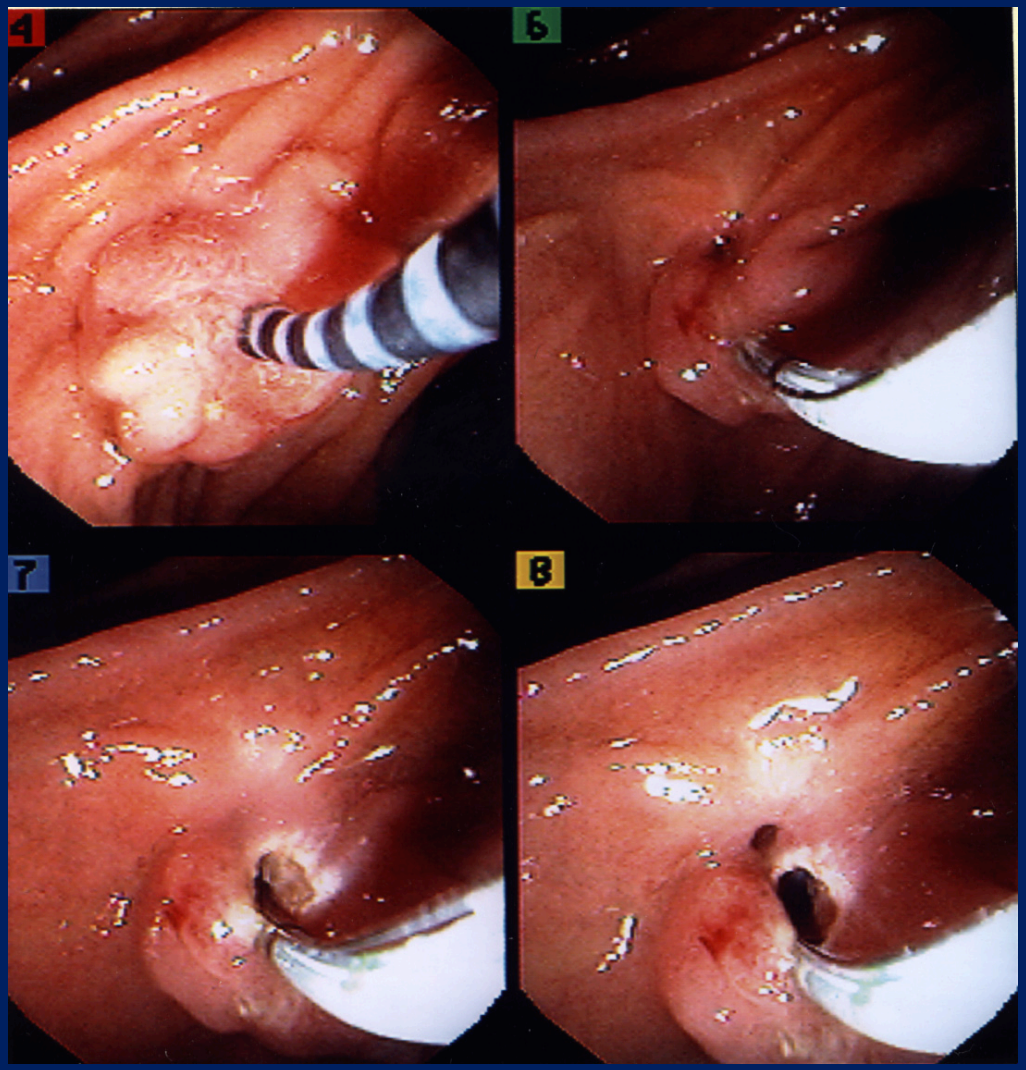
- Other untreated pancreaticobiliary disease
- Non-pancreaticobiliary diseases especially gut motility disorders

Long-term Outcome after Biliary Sphincterotomy alone depends on Pancreatic SO Pressure



Eversman et al., *GIE* 1999;49:AB78

Does the addition of a pancreatic sphincterotomy to biliary sphincterotomy in SOD patients improve outcome?



Symptomatic Improvement in Pancreatic SOD Patients after Pancreatic Sphincterotomy

Author/year	n	n Improved (%)	Mean follow-up (months)
Pereira, 2006	13	7 (54)	30.2
Okolo, 2000	15	11 (73)	16
Elton,1998	43	31 (72)	36.4
Soffer, 1994	25	16 (64)	13.7
Guelrud, 1995	27	22 (81)	14.7
TOTAL	**123**	**87 (71)**	23.9

Role for ERCP and SOM?
2013

SOD Type	ERCP	SOM
I	Yes	Not necessary
II	Yes	Highly recommended
III	Yes	Mandatory

SOD

- Approximately 60-80% achieve benefit from sphincterotomy
- Mostly small, retrospective studies
- Little prospective data in Type III patients
- High complications rates (10-20% PEP)

NIH State of the Science Conference: ERCP

- diagnosis and management of Type III SOD patients are most difficult

- invasive procedures should be delayed or avoided if possible …… the risk of complications exceeds potential benefit in many cases

- ERCP with SOM and sphincterotomy should ideally be performed at specific referral centers and in randomized controlled trials…….

Cohen GIE 2002

Evaluating **P**redictors & **I**nterventions in **S**phincter of **O**ddi **D**ysfunction: The **EPISOD** Trial

“EPISOD”

Medical University of South Carolina
Indiana University
Virginia Mason
University of Minnesota
Dallas
Yale University
St. Louis

Study Design

- a multi-center, randomized, sham-controlled study

- designed to assess the value of sphincterotomy as treatment in SOD III

- likelihood of finding SOD (by SOM) in these patients approaches 66% -- need 2:1 randomization in favor of treatment

- assuming a 30% placebo (sham) response rate, and 60% treatment response rate, 214 subjects required

RAPID Score

(**R**ecurrent **A**bdominal **P**ain **I**ntensity and **D**isability)

- modeled after migraine research
- captures, in past 3 months, days lost due to abdominal pain in 3 domains:
  - work
  - household activities
  - social/leisure activities

Durkalski, et al, WJG 2010

RAPID score

- Grade 1: 0-5 days missed (little or no disability)
- Grade 2: 6-10 days (mild disability)
- Grade 3: 11-20 days (moderate disability)
- Grade 4: >21 days (severe disability)

- Minimum score for eligibility: 11 days missed

Primary outcome

- **sphincterotomy will result in a higher success rate than the sham intervention**
- Success (definition):
  - Grade 1 disability as measured using the RAPID scale at months 9 and 12 post-randomization
  - no referral for possible re-intervention during the follow up period
  - no prescription analgesic use during months 10, 11 and 12 unless prescribed for pain other than abdominal pain (and then no more than 14 days)

Secondary Outcomes

- Is there an association between manometry result and treatment outcome?
- does addition of a pancreatic sphincterotomy improve outcome in patients with pancreatic sphincter hypertension (PSH)?

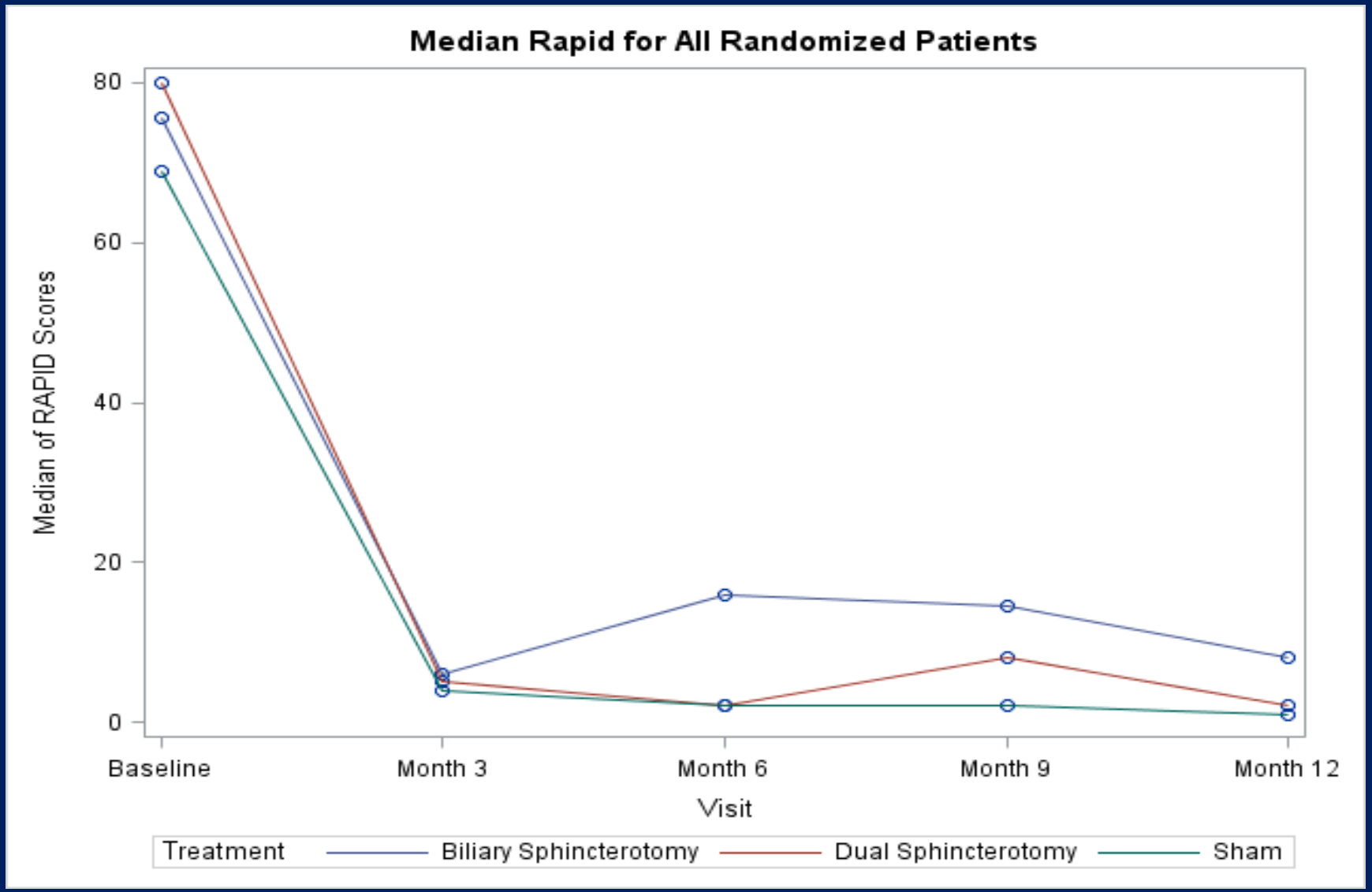
Primary outcome

Treatment	Number	Success
Sphincterotomy	141	31 (22.0%)
Sham	73	26 (35.6%)

p-value 0.03

Secondary outcome

Treatment	Number	Success
Biliary Sphincterotomy	94	18 (19.1%)
Pancreatic and Biliary (Dual) Sphincterotomy	47	13 (27.7%)
Sham	73	26 (35.6%)

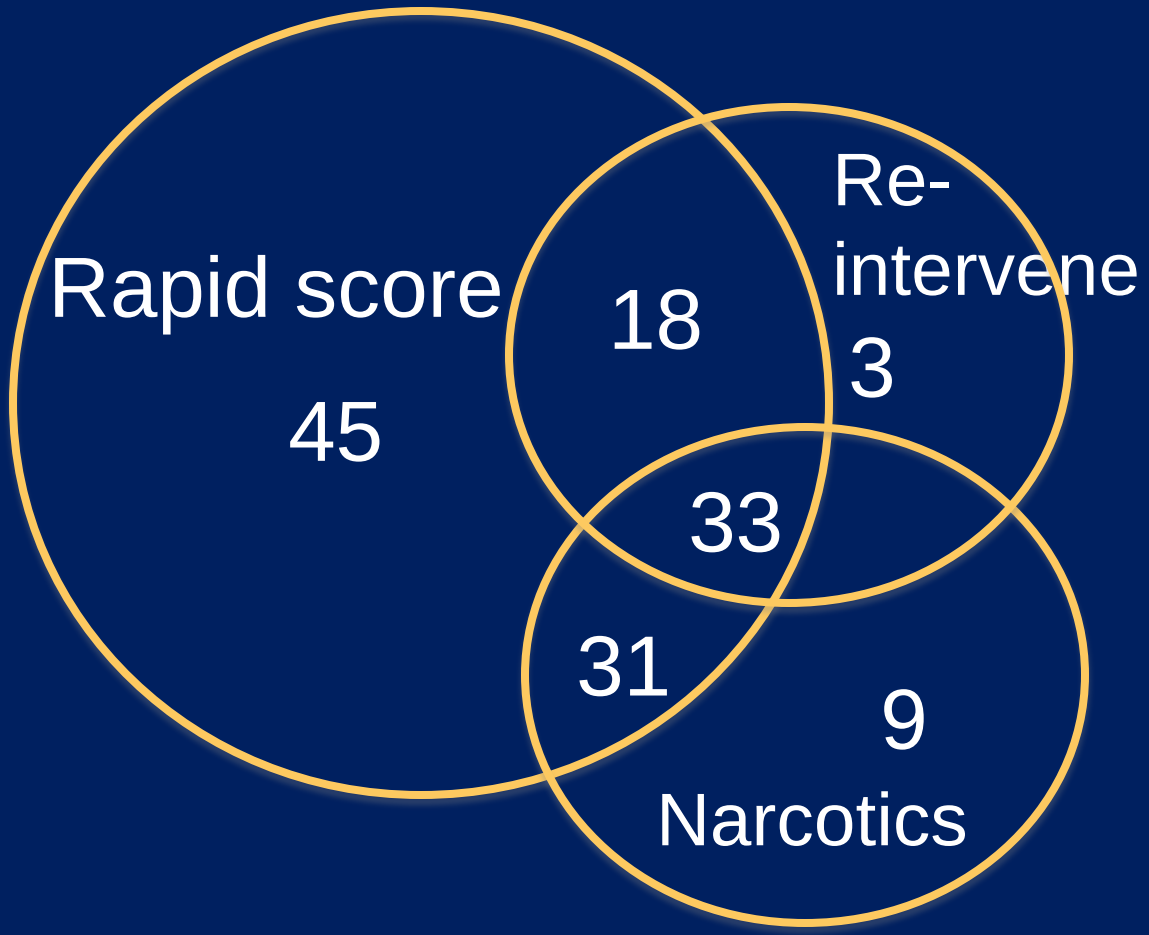


Median change in RAPID (days): Biliary=33 Dual=53 Sham=38

Success criteria too strict? Reducing the pain burden by half

Treatment	Number	Success
Biliary sphincterotomy	94	30 (32%)
Dual sphincterotomy	47	21 (45%)
Sham	73	32 (44%)

Reasons for failure



Manometry data

- Panc and Bil both abnormal 35%
- P abnormal, B normal 21%
- P abnormal, B not measured 9%

65% Panc abnormal

- B abnormal, P normal 11%
- Both normal 24%

Does manometry predict success?

Manometry		Number	Success		
Pancreas	Biliary		Biliary sph	Dual sph	Sham
+	any	[illegible]	[illegible]	**11/44 (25%)**	12/43 (28%)
any	+	98	**7/39(18%)**	7/29(24%)	7/30(23%)
-	- or ?	52	5/30 (17%)	1/1	**12/21 (57%)**

NO!

Potential criticisms

- Wrong subjects?
- Wrong definition of success?
  - too strict
  - wrong pain assessment tool (RAPID)
- Inadequate sphincterotomies?

Too strict?

Rates higher, but patterns the same with

- 50% reduction in RAPID
- 25% reduction in RAPID
- excluding the narcotics reason
- using re-intervention only

Wrong pain tool?

- RAPID measured pain-related disability
- Same results using SF 36 pain scores

SF 36 pain assessment

Treatment	Disability	Baseline	11-12 Months
Biliary	Pain; Moderate, severe, very severe	88%	44%
	Work interference; extreme, quite a bit	51%	16%
Dual	Pain; Moderate, severe, very severe	89%	36%
	Work interference; extreme, quite a bit	38%	6%
Sham	Pain; Moderate, severe, very severe	91%	32%
	Work interference; extreme, quite a bit	31%	10%

Conclusions

- sphincterotomy is not better than a sham procedure in Type III SOD, and manometry is NOT helpful in predicting treatment response
- these results should eliminate the use of ERCP in these patients, and thereby prevent many attacks of pancreatitis

Conclusions

- Further studies of the source of pain are needed in SOD III, with careful evaluation of other treatment options
  - behavioral and neuromodulator therapies
- Should we discard the term “SOD type III”, to divert attention away from the sphincter?

JAMA 2014;311:2101-9

Questions

- Are the results all due to placebo?
- Was our sham arm (ERCP/manometry/stent) actually therapeutic?
  - Would a no-touch blinded endoscopy have the same effect?
- Why did sphincterotomy patients do less well?
- How will GI docs and SOD patients respond?
  - Half the patients did get half better
  - Will patients keep coming?
  - *Would the patients do it again? Re-do Type IIIs?*

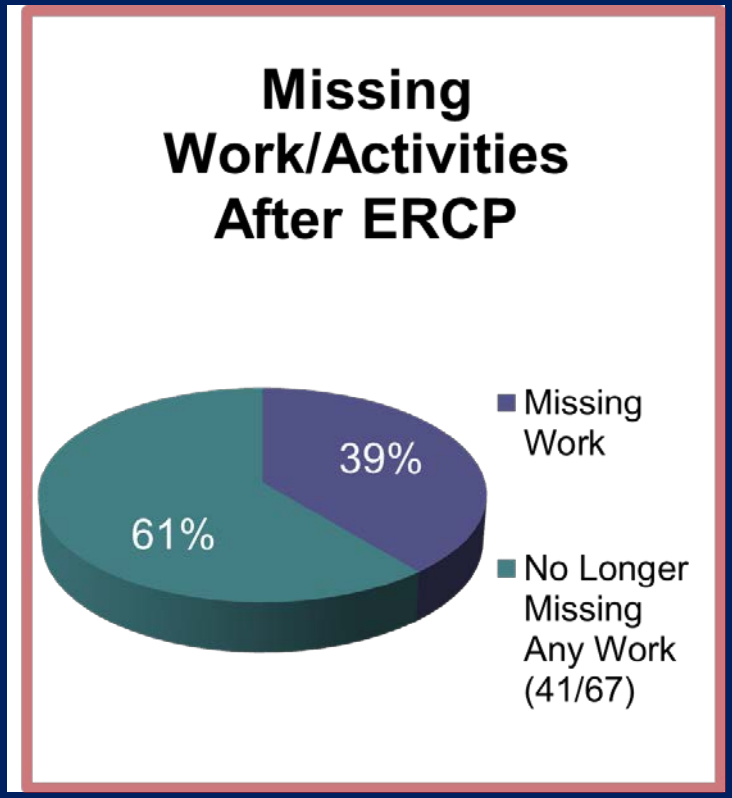
IU Experience

- IU contributed 32/214 patients to EPISOD
- 315 Type III SOD patients underwent ERCP at IU during the EPISOD era
  - what happened to these non-randomized patients?
- Charts reviewed, patients contacted by telephone
- 104 patients excluded (eg. normal SOM, …)
- 96 patients could not be reached, leaving 115 available for analysis (100 at time of DDW)

IU Experience: Results

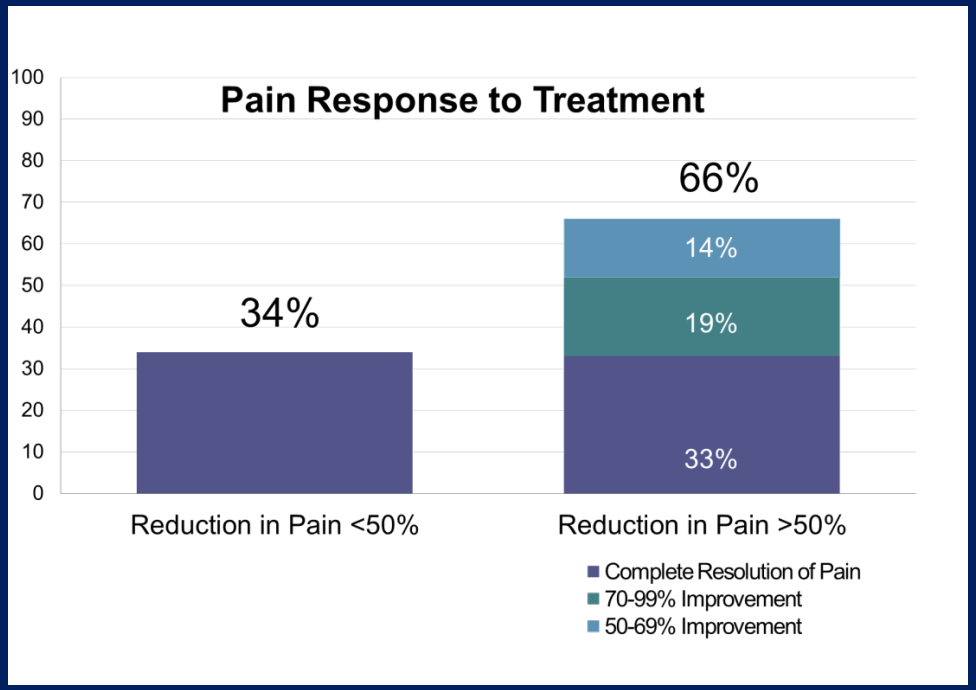
	n=100
Gender	
Male	10
Female	90
Age	
18-35	32
36-55	54
>55	14
Median Pain Duration (months) (Range: 1-144)	12
Patients with Daily Pain	60
Abnormal Manometry	
Pancreas	74
Biliary	45
Both	20
Pressures measured at both sphincters	46

Baseline characteristics

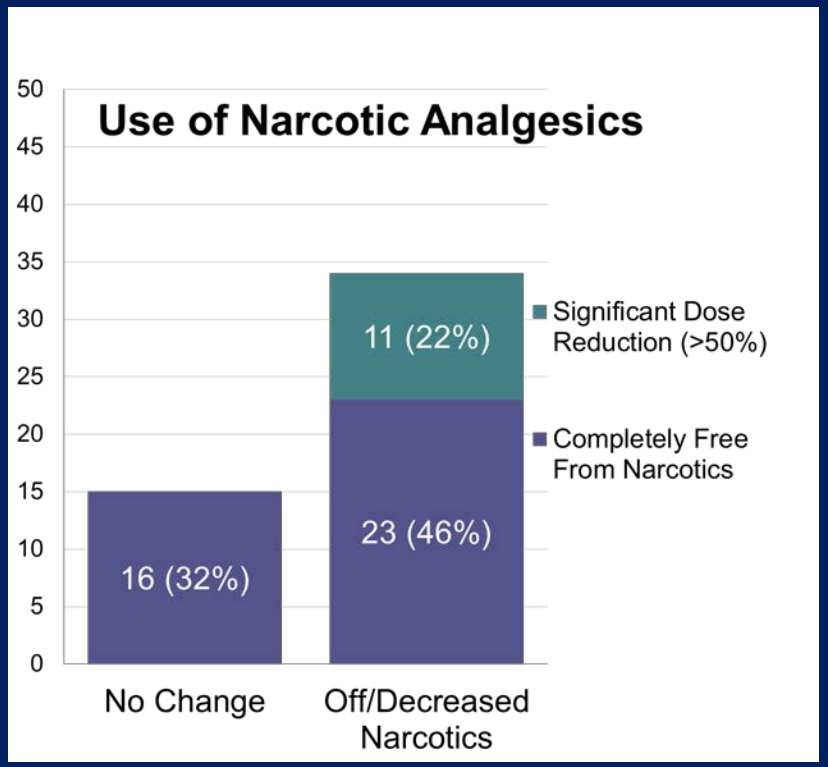


Of the 100 patients, 67 reported missing work or significant activities before ERCP

IU Experience: Results



66/100 patients (66%) had ≥ 50% improvement in pain, and 33% had complete resolution of pain



50/100 patients (50%) used narcotics for abdominal pain pre-ERCP

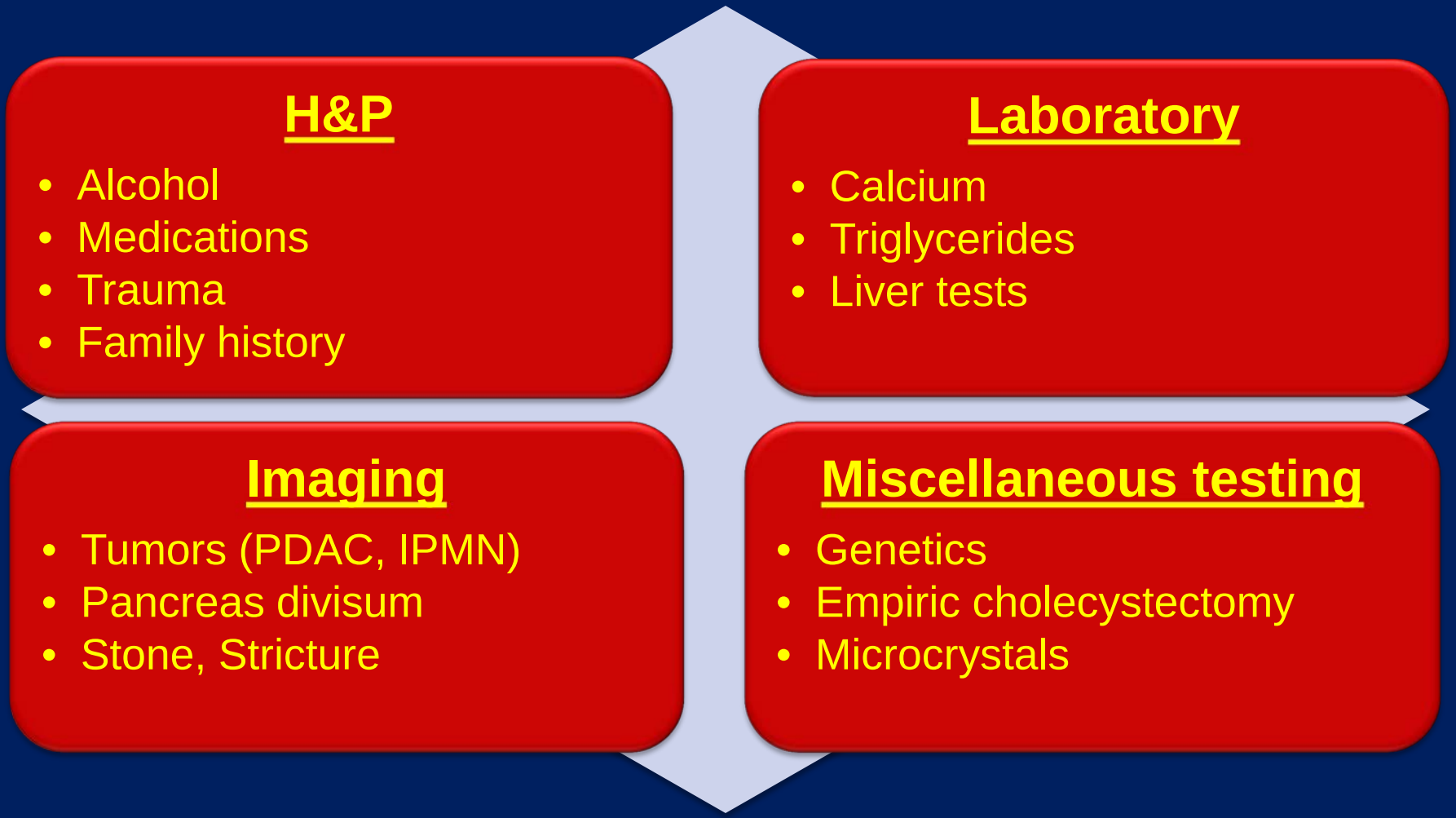
IU Experience

- Different from EPISOD?
- Not really
  - Retrospective
  - No control (sham) group
  - Similar to historical data

Indications for SOM: 2013

- Unexplained, ***disabling*** pancreaticobiliary pain ± LFT and/or pancreatic enzyme abnormalities
- Idiopathic pancreatitis

Defining idiopathic recurrent acute pancreatitis (IRAP)



ERCP for diagnosis and treatment

- The diagnostic yield of ERCP (ductography alone) ranges from 32-80%
- Elevated basal sphincter pressure has been reported in 30-65% of patients with idiopathic AP
  - Is this cause or effect?
- The therapeutic role of sphincterotomy is debated

IRAP and SOD: Therapy

Results of SOM predict outcome from sphincter ablation

→ limited data

→ no long-term F/U

→ small sample size

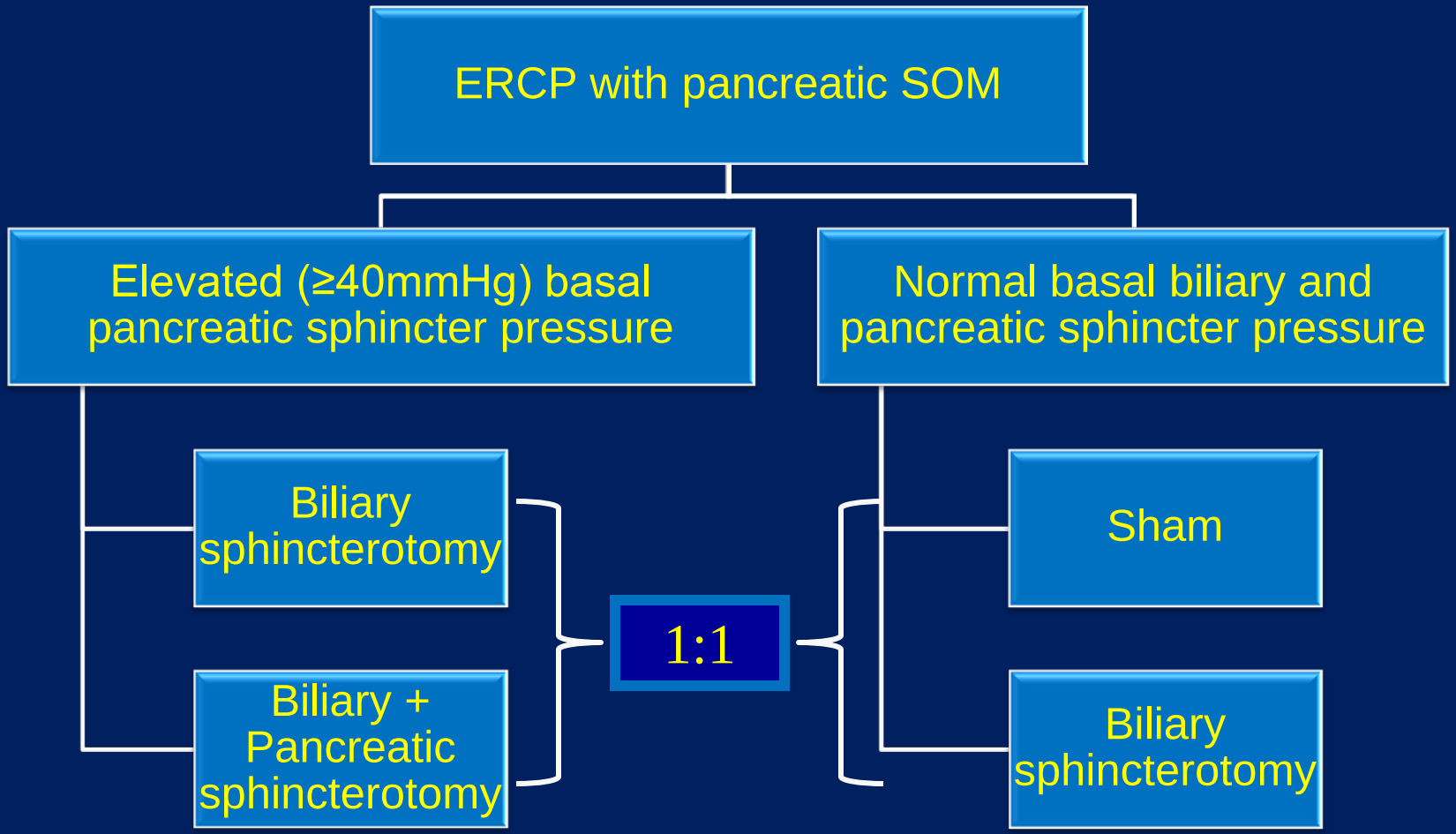
→ no randomized controlled trials

→ no outcome data of empiric sphincterotomy without SOM

IRAP and SOD: Prospective Randomized Trial

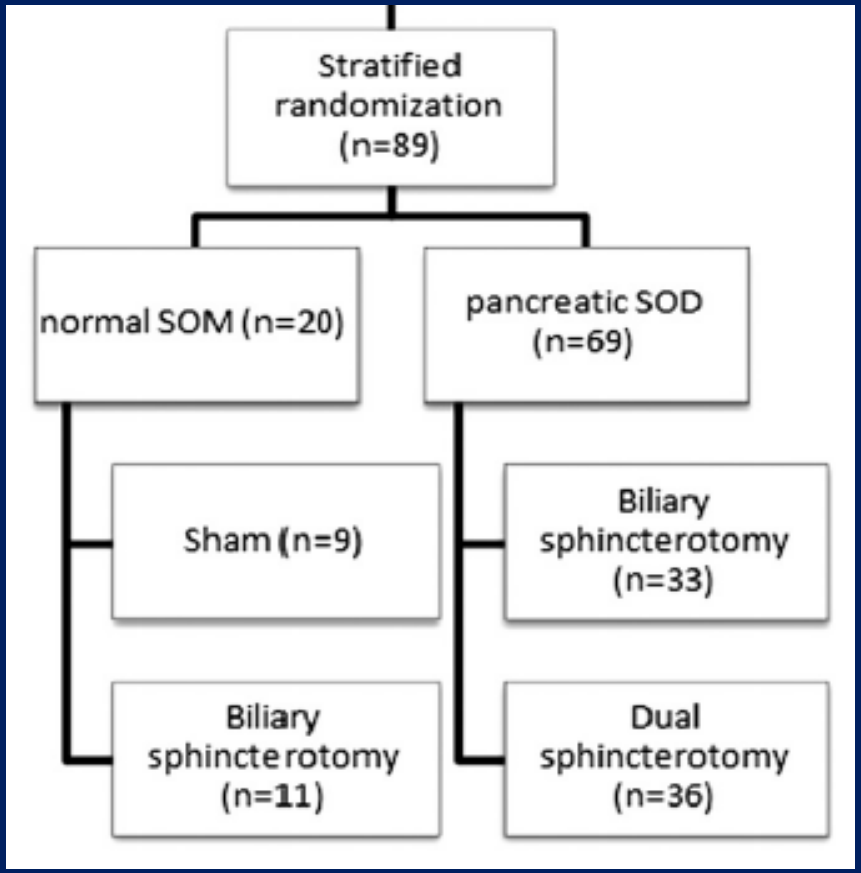
Coté et al. *Gastro* 2012;143:1502-9

Randomization



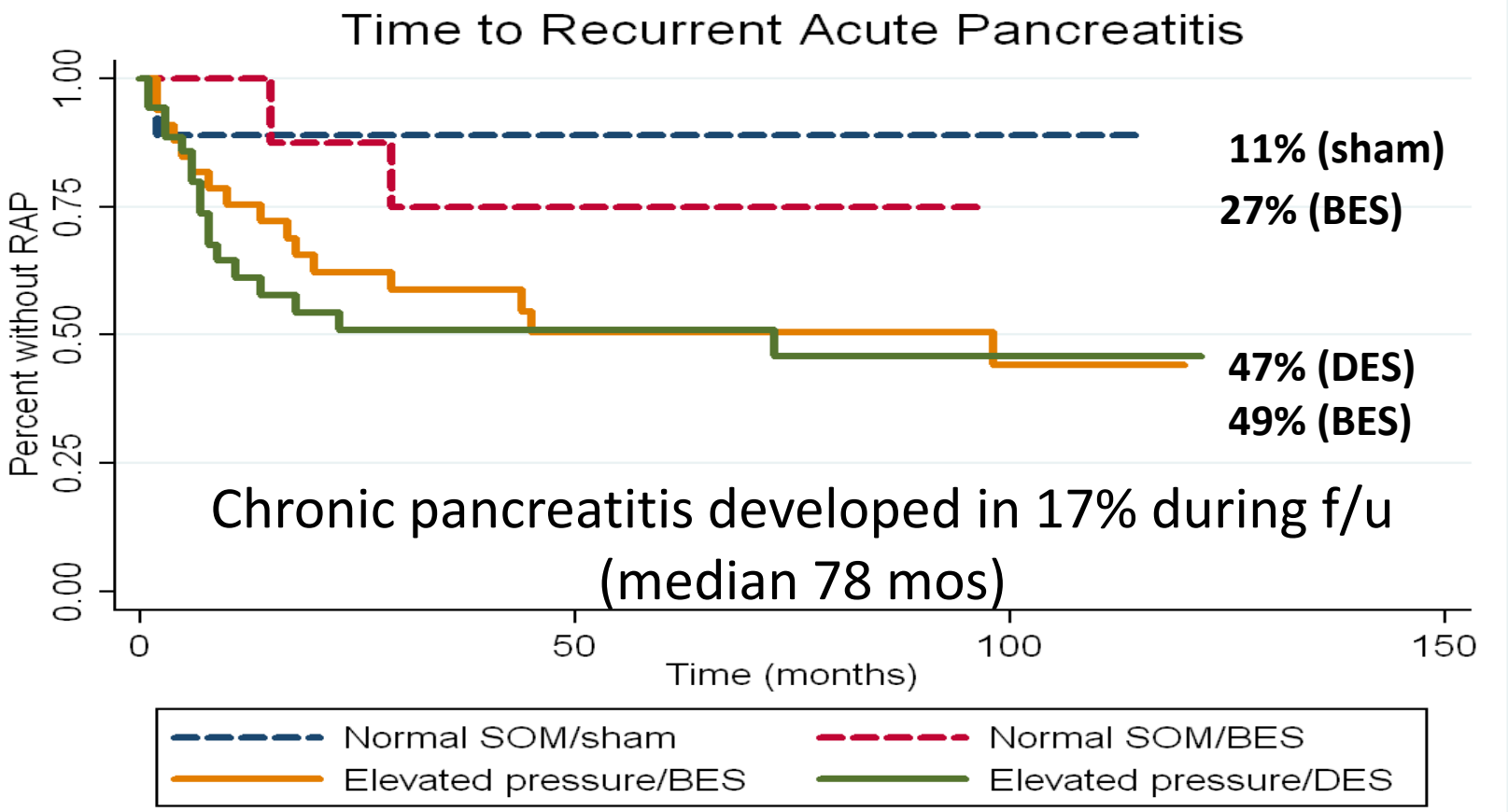
RCT

- N=89, median f/u 78 mos., all >12 months
- Endpoint: acute pancreatitis after sphincterotomy
- 77.5% positive manometry at the time of enrollment (n=89)



GASTROENTEROLOGY 2012;143:1502–1509

Randomized Trial



p = 0.59

p = 1.0

GASTROENTEROLOGY 2012;143:1502–1509

Post-Hoc Analysis

- Evaluate the impact of biliary and dual sphincterotomy on the episode density of iRAP with long term follow up (additional two years)
  - subsequent frequency (#/yr) of attacks
  - relative change in frequency (#/yr) of attacks

Easler et al., DDW 2015

Results: Pancreatitis

- Baseline Pancreatitis Rate (n=81)
  - Prior Episodes: median 2 (range 2-6)
  - Incidence rate 2.1 episodes/yr (range 0.09-12/yr)
- Following Sphincterotomy (*n= 74*)
  - 50% repeat episode of pancreatitis, median 1 episode
  - Incidence rate 0.22/yr (range 0-2/yr)
  - Incidence rate ratio 0.2 (rate was 20% of baseline)

Results: Sphincterotomy and iRAP

- Incidence rate of iRAP decreased following sphincterotomy
- No incremental benefit for pancreatic ES added to biliary ES in pancreatic SOD-iRAP
  - Equivalent rates of AP
  - Heavy repeat procedure burden in both groups

Conclusions: Pancreatic SOM and iRAP

- Role of SOM in guiding *therapy* is questionable:
  - >75% patients = positive SOM !
  - The incidence rate declined in all groups
  - No difference in “relative” rate after ES
- Prognostic value when SOM if positive?
  - Higher baseline rate (AP/yr) of iRAP
  - Higher rate (AP/yr) of pancreatitis after therapy
    - Predicts an aggressive phenotype

Conclusion:
ERCP and SOM

What's the final word in 2015?

Role for ERCP and SOM? 2013

SOD Type	ERCP	SOM
I	Yes	Not necessary
II	Yes	Highly recommended
III	Yes	Mandatory

Role for ERCP and SOM?

2015

SOD Type	ERCP	SOM
I	Yes	Not necessary
II	Yes	Highly recommended
III	No	No

SOM in IARP

- SOD is commonly identified in patients with IARP when detailed endoscopic evaluation is done
- the best therapy awaits further study
  - at present, the role of sphincter therapy remains unclear

2015

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

IU ERCP

Thank-you!