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ADVANCES IN
GASTROENTEROLOGY & HEPATOLOGY

FEBRUARY 7-9, 2020

Hyatt Regency Coconut Point Resort & Spa
Bonita Springs, Florida

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ENDORSED BY

aga American Gastroenterological Association

Activity Information

MEDICAL SCHOOL
UNIVERSITY OF MICHIGAN

Advances in Gastroenterology and Hepatology

February 7 - 9, 2020

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DEPARTMENT OF INTERNAL MEDICINE CME COURSE CALENDAR

Thank you for attending the **Advances in Gastroenterology and Hepatology** course. We hope you enjoy it.

The U-M Department of Internal Medicine offers continuing medical education (CME) activities to provide lifelong learning experiences for physicians and other healthcare professionals that highlight innovative procedures and technologies, examine current methods of treatment, and update you on cutting-edge advances in the understanding and treatment of disease. The scope of our educational efforts provides the highest quality learning activities that lead to excellence in patient care.

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2020 CONFERENCES

Health Delivery and Technology in Today's Diabetes Care
Saturday, April 4, 2020
The Inn at St. John's, Plymouth, Michigan

Updates in Nephrology for the Primary Care Provider
Saturday, May 9, 2020
The Inn at St. John's, Plymouth, Michigan

8th Annual Internal Medicine Spring Review
Friday - Saturday, May 15-16, 2020
The Inn at St. John's, Plymouth, Michigan

Update on Arrhythmias and Syncope
Saturday, June 6, 2020
The Inn at St. John's, Plymouth, Michigan

38th Annual Internal Medicine Update
Friday - Sunday, July 31-August 2, 2020
Grand Hotel, Mackinac Island, Michigan

33rd Annual Cardiology Update
Friday - Sunday, August 21-23, 2020
Grand Hotel, Mackinac Island, Michigan

Home Mechanical Ventilation: A Multidisciplinary Approach
Friday, September 25, 2020
The Inn at St. John's, Plymouth, Michigan

Gastroenterology Update: A Case-Based Approach to Common GI Problems
Friday - Saturday, October 16-17, 2020
The Inn at St. John's, Plymouth, Michigan

33rd Annual Update in Pulmonary and Critical Care Medicine
Friday - Saturday, November 13-14, 2020
The Inn at St. John's, Plymouth, Michigan

23rd Annual Liver Disease Wrap-Up
Saturday, December 12, 2020
The Inn at St. John's, Plymouth, Michigan

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PROGRAM SCHEDULE

Friday, February 7, 2020

7:30 am Registration/Continental Breakfast

8:00 Welcome and Announcements

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8:10 **SIBO: Current Guidelines**
Richard Saad, MD, MS, FACG

8:45 **Refractory Constipation**
William Chey, MD

9:20 **Chronic Intestinal Pseudo-Obstruction**
William Hasler, MD

9:55 Questions and Answers

10:10 Break

Session 2: Endoscopy

10:40 **EMR: Tips and Tricks**
Richard Kwon, MD, MS

11:15 **Periprocedural Management of Antiplatelet/Anticoagulation Therapy**
Michelle Anderson, MD

11:50 **Endoscopic Management of Portal HTN**
Jessica Mellinger, MD, MSc

12:25 pm Questions and Answers

12:40 *Session Adjourns*

Saturday, February 8, 2020

7:30 am Continental Breakfast

8:00 Announcements

Session 3: Pancreas/Biliary/Therapeutic Endoscopy

8:10 **Pancreatic Cysts**
Richard Kwon, MD, MS

8:45 **Management of Chronic Pancreatitis**
Michelle Anderson, MD

9:20 **Small Bowel Bleeding**
Michael Rice, MD

9:55 Questions and Answers

10:10 Break

Session 4: Liver

10:40 **Updates in Chronic HBV**
Robert Fontana, MD

11:15 **Alcoholic Liver Disease**
Jessica Mellinger, MD, MSc

11:50 **Drug Induced Liver Injury**
Robert Fontana, MD

12:25 pm Questions and Answers

12:40 *Session Adjourns*

Sunday, February 9, 2020

7:30 am Continental Breakfast

8:00 Announcements

Session 5: IBD

8:10 **Current Landscape for Management of Crohn's**
Peter Higgins, MD, PhD, MSc

8:45 **Severe IBD: Prevention and Management Strategies**
Ryan Stidham, MD, MSc

9:20 **Pregnancy in IBD**
Peter Higgins, MD, PhD, MSc

9:55 Questions and Answers

10:10 Break

Session 6: General GI

10:40 **Gastroparesis**
William Hasler, MD

11:15 **Treatment of H. Pylori**
William Chey, MD

11:50 **Telemedicine in GI**
Ryan Stidham, MD, MSc

12:25 pm Questions and Answers

12:40 *Conference Adjourns*

PROGRAM PLANNING COMMITTEE / PROGRAM FACULTY

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Small Intestinal Bacterial Overgrowth (SIBO): Current Guidelines

Richard J. Saad, MD, MS, FACG
Associate Professor of Medicine
Division of Gastroenterology & Hepatology

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Disclosures

- Consultant for Takeda

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Objectives

- Definition of SIBO
- SIBO testing
- Risk Factors for SIBO
- When to consider testing for SIBO
- Treatment of SIBO
  - Initial treatment
  - Prevention of recurrence
  - Retreatment

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SIBO Guideline Landscape

- American College of Gastroenterology Clinical Guideline (2020)
- Consensus document for hydrogen & methane breath testing (2017)

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S

ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth

Mark Pimentel, MD, FRCP(C), FACG[1], Richard J. Saad, MD, FACG[2], Millie D. Long, MD, MPH, FACG (GRADE Methodologist)[3] and Satish S. C. Rao, MD, PhD, FRCP, FACG[4]

Small intestinal bacterial overgrowth is defined as the presence of excessive numbers of bacteria in the small bowel, causing gastrointestinal symptoms. This guideline statement evaluates criteria for diagnosis, defines the optimal methods for diagnostic testing, and summarizes treatment options for small intestinal bacterial overgrowth. This guideline provides an evidence-based evaluation of the literature through the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. In instances where the available evidence was not appropriate for a formal GRADE recommendation, key concepts were developed using expert consensus.

Am J Gastroenterol 2020;00:1–14. https://doi.org/10.14309/ajg.0000000000000501; published online January 8, 2020

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The GRADE Process

- Grading of Recommendations, Assessment, Development and Evaluation Process
- Quality of supporting evidence
  - Strong : Benefits outweigh negatives
  - Conditional: Balance of benefits:negatives unclear
- Quality of Evidence
  - High: further evidence unlikely to change outcome
  - Moderate: further evidence may change outcome
  - Low: further evidence likely to major impact on outcome
  - Very low: True outcome is likely to very different

Guyatt G et al, J Clin Epidemiol 2011:64:383-94

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ACG SIBO Clinical Guideline

- GRADED recommendations
  - Diagnosis of SIBO
  - Other conditions associated with SIBO
  - Treatment of SIBO
- Key concepts
  - Statements not amenable to GRADE process
    - Structure of statement
    - Lack of available evidence

Pimentel M et al, *Am J Gastroenterol* 2020

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Hydrogen and Methane-Based Breath Testing in Gastrointestinal Disorders: The North American Consensus

Ali Rezaie, MD, MSc, FRCP(C)[1], Michelle Buresi, MD[2], Anthony Lembo, MD[3], Henry Lin, MD[4], Richard McCallum, MD[5], Satish Rao, MD[6], Max Schmulson, MD[7], Miguel Valdovinos, MD[8], Salam Zakko, MD[9], Mark Pimentel, MD, FRCP(C)[1] and on behalf of The North American Consensus group on hydrogen and methane-based breath testing

CONCLUSIONS: **BT is a useful, inexpensive, simple and safe diagnostic test in the evaluation of common gastroenterology problems. These consensus statements should help to standardize the indications, preparation, performance and interpretation of BT in clinical practice and research.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

Am J Gastroenterol 2017; 112:775–784; doi:10.1038/ajg.2017.46; published online 21 March 2017

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North American Consensus: The Process

Topics identified by literature search

↓

Consensus group selection process:

- Physician-scientists with active & recent research in breath testing
- Those from high volume breath testing centers
- Representation from US, Canada and Mexico

↓

17 members identified and sent pre-meeting survey questionnaire

↓

10 members attend ½ day meeting in 2015 in which statement created

↓

Members vote anonymously on their level of agreement with statement (agree, disagree or uncertain)

↓

Strength of each recommendation assigned by the consensus group

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North American Consensus Document

- 28 statements developed on breath testing
  - Indications, preparation, performance & interpretation of results, and knowledge gaps
- Consensus reached on 26 statements
  - "we recommend" for strong recommendations
  - "we suggest" for weak recommendations
- Strength of statements
  - Resource and cost benefit
  - patients' values
  - Risk/benefit balance
  - Overall quality of evidence

Rezaie A, et al. Am J Gastroenterol. 2017 May;112(5):775-784

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What is SIBO?

- **Clinical syndrome**
  - Increased number of bacterial microorganisms in the small intestine
  - GI symptoms resulting from microbial overgrowth
    - Malabsorption of nutrients
    - Altered intestinal permeability
    - Inflammation
    - Immune activation

Pimentel M et al, *Am J Gastroenterol* 2020

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How SIBO Is Defined

- Excessive bacteria in the proximal small intestine based upon culture of luminal aspirate
- Measurable changes in exhaled gases due to bacterial metabolism of ingested carbohydrates or bile salts

Pimentel M et al, *Am J Gastroenterol* 2020

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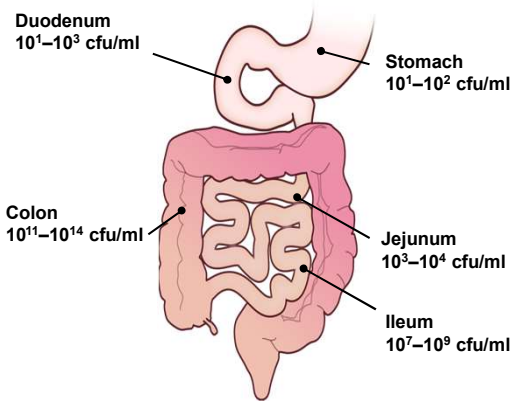
Normal Intestinal Microflora



Simrén M et al.Gut. 2013 Jan;62(1):159-76.

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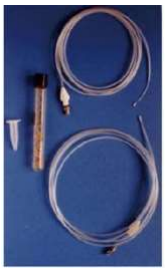
Small Bowel Aspiration & Culture

- Traditionally regarded as the gold standard
- Aspiration of luminal fluid from distal duodenum or jejunum during endoscopy
- Culture under aerobic & anaerobic conditions
  - Reported as colony forming units/milliter (CFU/ml)



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Limitations of Aspiration & Culture

- Lack of validation against controls
  - 3 of 50 studies (1996-2007)[1]
  - Methodological heterogeneity
    - Manner of fluid collection, location and quantity of the aspirate, technique in sample handing and culture
- Lack of standardization for a positive culture
  - > 10^4 CFU/ml to >10^7 CFU/ml[2-4]
  - Historically ≥10^5 CFU/ml regarded as positive
  - ≥10^3 CFU/ml suggested in ACG guideline & consensus document[5-6]

[1]Khoshini R, et al. *Dig Dis Sci.* 2008;53(6):1443-54, [2]Quigley EM, et al. *Infect Dis Clin North Am*. 2010;24(4):943-59, [3]Bures J et al. *World J Gastroenterol*. 2010;16(24):2978-90, [4]Schiller LR. *Curr Gastroenterol Rep*. 2007;9(5):373-7, [5]Rezaie A et al. *Am J Gastroenterol.* 2017; 112: 775-784, [6]Pimentel et al. *Am J Gastroenterol*, Published online Jan 8, 2020

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Small bowel Aspiration & Culture

Pros

- Can be performed at time of endoscopy
- Direct assessment for SIBO
- Allows identification of potential organism +/- antibiotic sensitivity

Cons

- Cost
- Invasive (EGD)
- Time/Labor commitment
- Risk of sampling error
- Accuracy of culturing
- Potential for missing distal small bowel bacterial overgrowth

Saad RJ, Chey WD. *Clin Gastroenterol Hepatol.* 2014 Dec;12(12):1964-72

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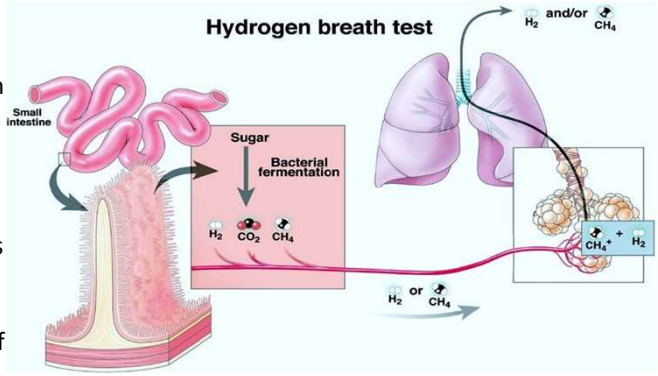
Breath Testing (BT) for SIBO

- Measure exhaled gases from the bacterial fermentation of orally ingested sugar
  - Hydrogen
  - Methane
- Gas measured in parts per millions(ppm)
- Indirect assessment of small bowel bacterial load



Saad & Chey, Gastroenterol 2007;133:1763

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Sugar Substrates for SIBO BT

- Glucose
- Lactulose
- Fructose*
- Lactose
- Sorbitol
- Sucrose

Can be positive in SIBO & carbohydrate malabsorption

*25 grams of fructose in 101 diabetics suspected of having SIBO demonstrated similar accuracy to glucose vs duodenal aspirate

*Bhagatwala et al, Gastroenterology 2018; 154:53-4

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BT for SIBO: Systematic Review & Meta-Analysis

- 14 studies (n = 624)
  - Breath testing compared to jejunal aspirate culture

	Glucose BT		Lactulose BT	
	Sensitivity	Specificity	Sensitivity	Specificity
Overall	54.5%	83.2%	42%	70.6%
Rise in H_2 by > 20 ppm	47.3%	80.9%		
Rise in H_2 other than or < 20 ppm	61.7%	86%		
Prior abdominal surgery	81.7%	78.8%		

Conclusions:

1. GBT seems to perform better than the LBT
2. A change in H2 excretion other than or < 20 ppm shows better results than > 20 ppm

Losurdo, G et al. J Neurogastroenterol Motil. 2020 Jan; 26(1): 16–28

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Maximizing Breath Test Accuracy

- Test preparation
  - Avoid antibiotics for 4 weeks*
  - Avoid prokinetics or laxatives for at least 1 week *
  - Avoid fermentable foods (complex carbs) for one day *
  - Overnight (8-12 hour) fast*
  - No smoking on day of test*
- Test performance
  - 75 grams glucose or 10 grams of lactulose*#
  - cigarette smoking during testing*
  - Limit physical activity during testing*

*North American Consensus statements
#Key concept in ACG SIBO Guideline

Rezaie A, et al. Am J Gastroenterol. 2017 May;112(5):775-784
Pimentel M, et al. Am J Gastroenterol. 2020

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Interpreting BT Results

- Suggested positive for SIBO (North American Consensus)
  - A rise in hydrogen of ≥ 20 ppm within 90 min of glucose or lactulose ingestion

  OR:
  - A rise in methane levels ≥10 ppm within 90 minutes of glucose of lactulose ingestion

Rezaie A, et al. Am J Gastroenterol. 2017 May;112(5):775-784

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How Is Bacterial Overgrowth Prevented?

- Gastric acid
- Migrating motor complex
- Intestinal mucosa integrity
- Gut immune system
- Enzymatic activities of intestinal, pancreatic & biliary secretions
- Effects of commensal bacterial within the small bowel
- Physical barrier created by the ileocecal valve

Quigley EM, Abu-Shanab A. *Infect Dis Clin North Am.* 2010;24:943-5

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Conditions Promoting Bacterial Overgrowth

- Anatomic abnormalities of the small bowel
- Surgical alteration of the GI tract
- Gastrointestinal Dysmotility
- Altered mucosal integrity
- Altered bacterial flora
- Immune system impairment
  - Systemic or gut-specific
- Altered enzyme production

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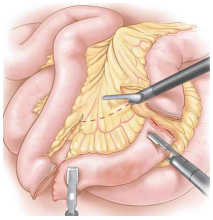
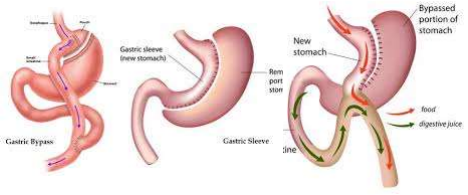
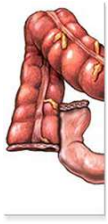
GI Surgery & Risk for SIBO



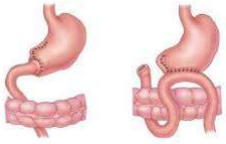
Small bowel Resection



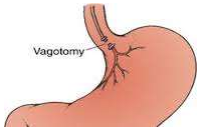
Bariatric surgery



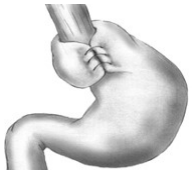
Ileocecal Resection



Gastric Resection



Vagotomy



Fundoplication

Paik CN et al. *Neurogastroenterol Motil.* 2011;23, Petrone P et al. *Arch Surg.* 2011;146
Sollier et al. *Obes Surg.* 2020 Jan 4

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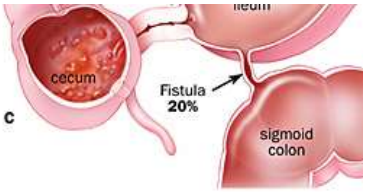
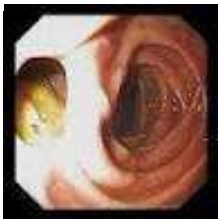
Small Bowel Anatomy & SIBO Risk



fistula



Diverticulosis

stenosis

Choung RS et al. *Aliment Pharmacol Ther*. 2011;33:1059-67

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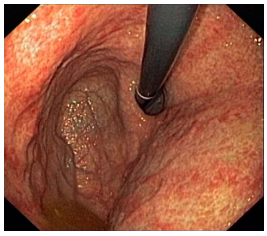
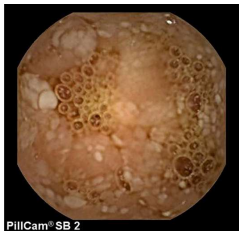
GI Diseases & SIBO Risk

- Achlorhydria
  - Atrophic gastritis
- Celiac disease
- Crohns disease
- Radiation enteritis
- Chronic pancreatitis
- Cirrhosis
- Altered GI Motility
  - IBS, CIPO, STC





Rubio-Tapia A et al. *J Clin Gastroenterol*. 2009;43(2):157-63
Bonnel AR et al. *Clin Gastroenterol Hepatol*. 2011;9(9):727-38

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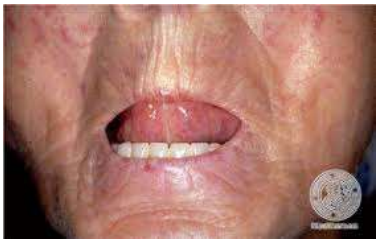
Systemic Disease & SIBO Risk

- Diabetes mellitus
- Scleroderma
- Amyloidosis
- Hypothyroidism
- Immune deficiency syndrome
- Chronic renal disease
- Cystic fibrosis
- Parkinson's
- Muscular Dystrophy
- Spinal Cord Injury



Ojetti V. et al. *Eur Rev Med Pharmacol Sci.* 2009;13(6):419-23
Marie I. et al. *Rheumatology.* 2009;48(10):1314-9
Matsumoto et al. *Dig Dis Sci.* 1991;36(12):1756-60
Ebert EC. *J Clin Gastroenterol.* 2010;44(6):402-6
Pignata C. et al. *Gut.* 1990;31(8):879-82
Strid H. et al. *Digestion.* 2003;67(3):129-37

Symptoms associated with SIBO

- Published evidence suggests as the most common symptoms in SIBO:
  - Bloating (most common)
  - Abdominal pain
  - Abdominal gas
  - Abdominal distention
  - Diarrhea
  - Flatulence

Pimentel M et al, *Am J Gastroenterol* 2020

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Do symptoms predict SIBO by Breath Testing?

5045 patients tested at Michigan Medicine for SIBO by Glucose Breath Test (1989-2014)

	Positive GBT N = 1680	Negative GBT N = 3365	P value
Heartburn	59.6%	62.8%	NS
Regurgitation	55.2%	56.9%	NS
Chest pain	39.1%	42.6%	NS
Nausea	64.8%	66.8%	NS
Vomiting	39.2%	33.3%	0.001
Abdominal pain	81.8%	83.7%	NS
Bloating	89.0%	89.1%	NS
Gas	87.2%	86.4%	NS
Diarrhea	81.9%	80.1%	NS
Constipation	59.3%	59.9%	NS

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SIBO & IBS

Irritable bowel syndrome
- Abdominal pain/discomfort & altered bowel habits

VS.

SIBO
- Abdominal Pain
- Cramping
- Diarrhea
- Bloating
- Gas
- Nausea

Systematic review and Meta-analysis
- 50 studies
- 8398 IBS, 1432 controls
- Pooled prevalence of SIBO in IBS 38% (95% CI 34-42%)
- Nearly 5 times more prevalent in IBS than controls
- Risk factors included female gender, older age and IBS with diarrhea

Chen B et al. J Gastroenterol. 2018 May 14

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SIBO & IBS: Meta-Analysis of Case-Control Studies

25 studies (3,192 IBS & 3,320 controls)

SIBO prevalence greater in IBS compared with:

- controls OR = 3.7, 95% CI 2.3-6.0)
- healthy controls OR = 4.9 (95% CI 2.8-8.6)

SIBO prevalence greater in IBS-D vs IBS-C, OR = 1.86 (95% CI 1.83-2.8)

	SIBO Prevalence	
	IBS	Controls
Breath testing	35.5% (95% CI 33.6-37.4)	29.7% (95% CI 27.6-31.8)
Culture-based (10^5)	13.9% (95% CI 11.5-16.4)	5.0% (95% CI 3.9-6.2)
Culture-based (10^3)	33.5% (95% CI 30.1-36.9)	8.2% (95% CI 6.8-9.6)

Shah H et al. Am J Gastroenterol. 2010. Jan 6

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ACG SIBO Guideline: When to test

1. We suggest the use of breath testing (glucose hydrogen or lactulose hydrogen) for the diagnosis of SIBO in patients with IBS (conditional recommendation, very low level of evidence).

2. We suggest using glucose hydrogen or lactulose hydrogen breath testing for the diagnosis of SIBO in symptomatic patients with suspected motility disorders (conditional recommendation, very low level of evidence).
3. We suggest testing for SIBO using glucose hydrogen or lactulose hydrogen breath testing in symptomatic patients (abdominal pain, gas, bloating, and/or diarrhea) with previous luminal abdominal surgery (conditional recommendation, very low level of evidence).

Pimentel M, et al. Am J Gastroenterol 2020

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PPIs & SIBO: Is there an Association?

Evidence For

- Most studies show increased risk in PPI users
- OR of 1.7 (95% CI 1.2 to 2.43 in meta-analysis of 19 studies (n = 7055)[1]
  - OR 1.31 (95% CI 1.01, 1.69) in high quality studies

Evidence Against

- PPIs not a risk factor in 2 meta-analyses assessing SIBO in IBS
  - 50 studies (n = 9830)[2]
  - 25 studies (n = 6512)[3]
- SIBO not seen by culture or DNA sequencing (n=148)[4]
- Effects of dose, duration, type of PPI unknown

[1]Su T et al. J Gastroenterol. 2018 Jan;53(1):27-36
[2]Chen B et al. J Gastroenterol. 2018 May 14
[3]Shah H et al. Am J Gastroenterol. 2010. Jan 6
[4]Weitsman et al. Gastroenterology. 2019; 156:S-206

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ACG SIBO Guideline: PPIs and SIBO

Recommendations

4. We suggest against the use of breath testing for the diagnosis of SIBO in asymptomatic patients on proton-pump inhibitors (PPIs) (conditional recommendation, very low level of evidence).

Pimentel M, et al. Am J Gastroenterol 2020

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Measuring Methane

- Methane associated with constipation
  - Meta-analysis of 9 studies (n = 1277)[1]
    - OR 3.51 (95% CI: 2.00-6.16)
    - Methane associated with delayed transit
    - Higher methane = worse constipation[2]
- Methane greater in IBS-C vs IBS-D
  - Meta-analysis of 25 studies (n = 6512)[3]
    - (OR = 2.3, 95% CI 1.2-4.2)
- Methane is produced by archaea
  - New proposed term
    - Intestinal methanogenic overgrowth[4]

[1]Kunkel D et al, Dig Dis Sci. 2011 Jun;56(6):1612-8
[2]Chatterjee S et al, Am J Gastroenterol. 2007; 102:837-41
[3]Shah H et al. Am J Gastroenterol. 2010. Jan 6
[4]Pimentel M et al, Am J Gastroenterol. 2020

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ACG SIBO Guideline: Methane

Recommendations

5. We suggest testing for methane using glucose or lactulose breath tests to diagnose the overgrowth of methane-producing organisms (IMO) in symptomatic patients with constipation (conditional recommendation, very low level of evidence).

Pimentel M, et al. Am J Gastroenterol 2020

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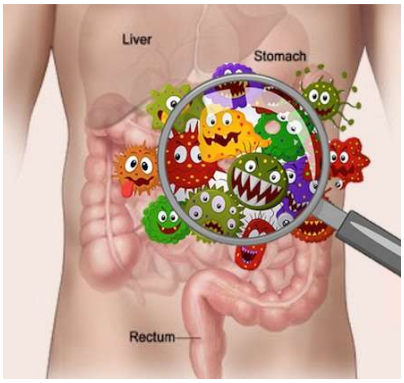
Treatment of SIBO

- Address underlying condition
- Antibiotics
- Dietary?
- Probiotics?
- FMT?



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Correct Underlying Cause of SIBO

- Surgical repair of anatomic causes
  - Strictures, fistulas, small bowel diverticula
- Treat cause of altered mucosa
  - IBD, celiac disease
- Treat dysmotility
  - Promotility therapy for gastroparesis, slow small bowel/colon transit
  - Eliminate drugs slowing motility
  - Treat constipation promoting fecal stasis

ACG Guideline: Treatment of the underlying cause represents the primary mode of SIBO prevention (to avoid the need for repeated courses of antibiotics)

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Dietary Interventions for SIBO

- Remove sugar substitutes
  - Sorbitol, aspartame, saccharine
- Reduce or eliminate poorly absorbed carbohydrates
  - FODMAPs
    - Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyos

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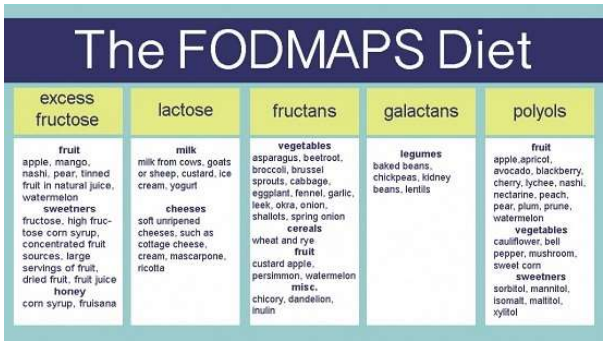
FODMAPs for SIBO:The Evidence

- There are no studies on SIBO
- Use in SIBO extracted from IBS studies
  - Reduced bloating, pain, gas & diarrhea



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Meta-analysis of Antibiotics for SIBO

Treatment	Number of Studies	Total Number of Subjects	% with Normalization of Breath Test
Rifaximin 1600 or 1650 mg/day	2	89	46.1
Rifaximin 1200 mg/day	6	176	60.8
Rifaximin 600 or 800 mg/day	1	60	21.7
Rifaximin monotherapy (all doses combined)	8	325	49.5
Rifaximin plus PHGG	1	40	85.0
Metronidazole	2	86	51.2
Neomycin	1	41	19.5
Ciprofloxacin	1	14	100.0
Chlortetracycline	1	11	27.3
All antibiotics	10	517	51.1
Placebo	4	92	9.8

Shah SC et al. Aliment Pharmacol Ther. 2013 Oct;38(8):925-34

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Rifaximin for SIBO

- Met-analysis of 32 clinical trials (through 3/15)
  - 24 cohort, 7 RCT and 1 randomized cross over trial
  - Total of 1331 patients
  - 17 used GBT, 13 used LBT, 2 used both
  - Dose of 600mg/d to 1600 mg/d
  - Treatment duration of 5 - 28 days
- Overall eradication rate of 70.8% (ITT), 72.9% (PP)
- AEs – 4.6%

Gatta L; Scarpignato C. Alimentary Pharmacology & Therapeutics. 45(5):604-616, 2017

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ACG SIBO Guideline: Treatment

Recommendations

6. We suggest the use of antibiotics in symptomatic patients with SIBO to eradicate overgrowth and resolve symptoms (conditional recommendation, low level of evidence).

Pimentel M, et al. Am J Gastroenterol 2020

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Antibiotics for SIBO

Table 5. Suggested antibiotics for treatment of small intestinal bacterial overgrowth

Antibiotic	Recommended dose	Efficacy
Nonabsorbable antibiotic		
Rifaximin	550 mg t.i.d.	61%–78%
Systemic antibiotic		
Amoxicillin-clavulanic acid	875 mg b.i.d.	~50%
Ciprofloxacin	500 mg b.i.d.	43%–100%
Doxycycline	100 mg q.d. to b.i.d.	[a]
Metronidazole	250 mg t.i.d.	43%–87%
Neomycin	500 mg b.i.d.	33%–55%
Norfloxacin	400 mg q.d.	30%–100%
Tetracycline	250 mg q.i.d.	~87.5%
Trimethoprim-sulfamethoxazole	160 mg/800 mg b.i.d.	~95%

[a]In the study, no testing performed to reassess small intestinal bacterial overgrowth, although all participants had other objective measures of improvement.

*There are no controlled trials regarding treatment duration and some experts recommend up to 14 days of therapy

**There is weak evidence suggesting the use of neomycin may improve response in methane positive cases

Pimentel M, et al. Am J Gastroenterol 2020

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SIBO Relapse

- Relapse is common
  - 13% at 3 mos & 44% at 9mos[1]
- Treatment strategies for relapse
  - Retreat for symptom reoccurrence
  - Scheduled retreatment*
    - One monthly
    - Every 2 weeks

    *Rotate antibiotics

No controlled trials exist to provide guidance on retreatment!

[1]Lauritano EC, et al. Am J Gastroenterol. 2008 Aug;103(8):2031-5

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Probiotics in SIBO

- Meta-Analysis & Systematic Review
  - 14 manuscripts and 8 abstracts
  - No study used the same probiotic (> 20 different organisms)
  - Widely variable treatment
    - Once to four times a day dosing
    - 5 days to 6 months for therapy
- Pooled decontamination rate superior 63%
  - RR 1.61 (95% CI: 1.19-2.17)
- Prevent of SIBO in at risk individuals not superior
  - RR 0.54 (95% CI: 0.19-1.52)

ACG Guideline: Lack of consistent data to support recommending specific probiotics in the treatment of SIBO

Zhong C, et al. J Clin Gastroenterol. 2017 Apr;51(4):300-311

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Fecal Microbiota Transplant in SIBO

- Prospective study of 20 adults with recurrent C. Difficile infection undergoing FMT[1]
  - All donors tested for SIBO by lactulose breath test
  - More post-FMT GI symptoms from donors with SIBO
    - 50% vs 14.2%, p=0.09
- Risk of multidrug resistant organism infection
- Case of severe constipation following FMT from a donor with methane positive breath test[2]

ACG Guideline: There is currently no basis for the use of fecal microbiota transplant in the treatment of SIBO

[1]Allegretti JR et al, Dig Dis Sci. 2018 Jan;63:193-197
[2]Chang BW & Rezaie A, Am J Gastroenterol. 2017; 112:186-7

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Summary

- Think about SIBO
  - Symptoms in those with predisposing conditions
    - IBS in particular
- Make an objective diagnosis
  - SB aspirate with culture OR Breath Test
  - Include methane in breath testing for constipation
- Treatment is multifaceted
  - Address underlying condition, antibiotics & diet
- Benefit of probiotics not established

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Management of CIC and IBS-C

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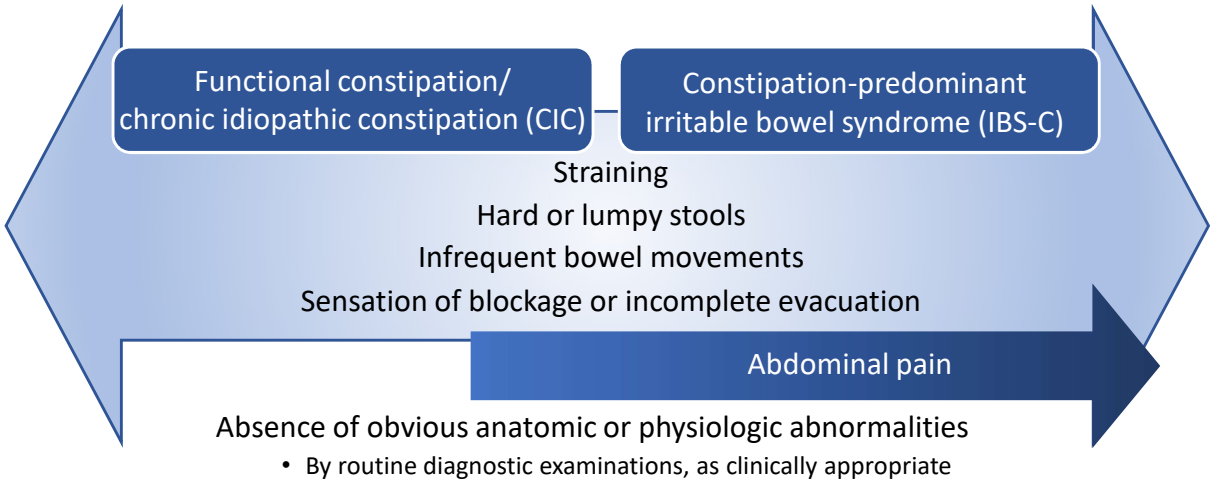
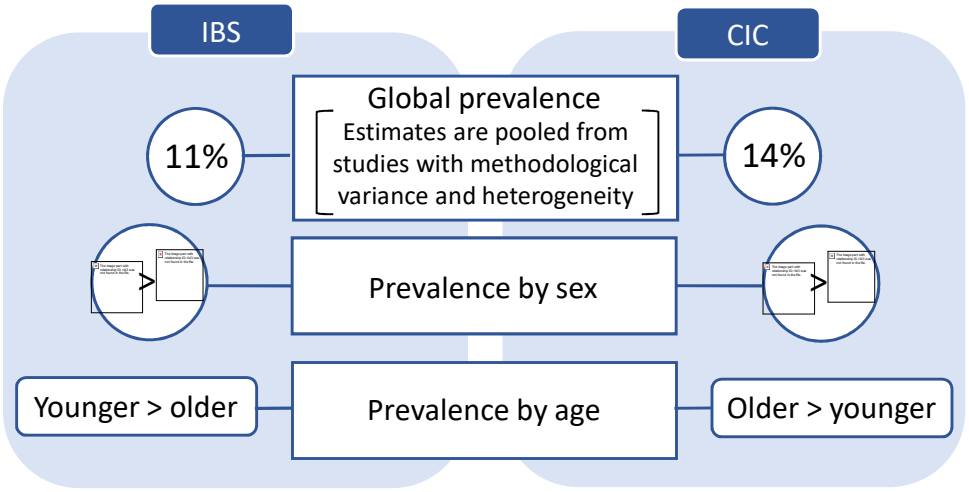
William D. Chey, MD, AGAF
Professor of Medicine
University of Michigan

Chronic Constipation Spectrum



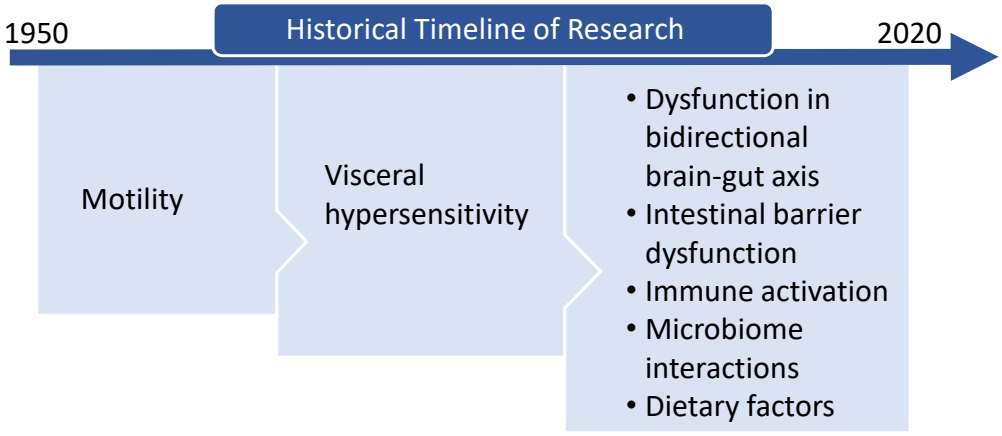
Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407.

Epidemiology of IBS and CIC



Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407; Lovell RM, Ford AC. *Clin Gastroenterol Hepatol*. 2012;10:712-721.e4; Sberber AD et al. *Gut*. 2017;66:1075-1082; Suares NC, Ford AC. *Am J Gastroenterol*. 2011;106:1582-1591.

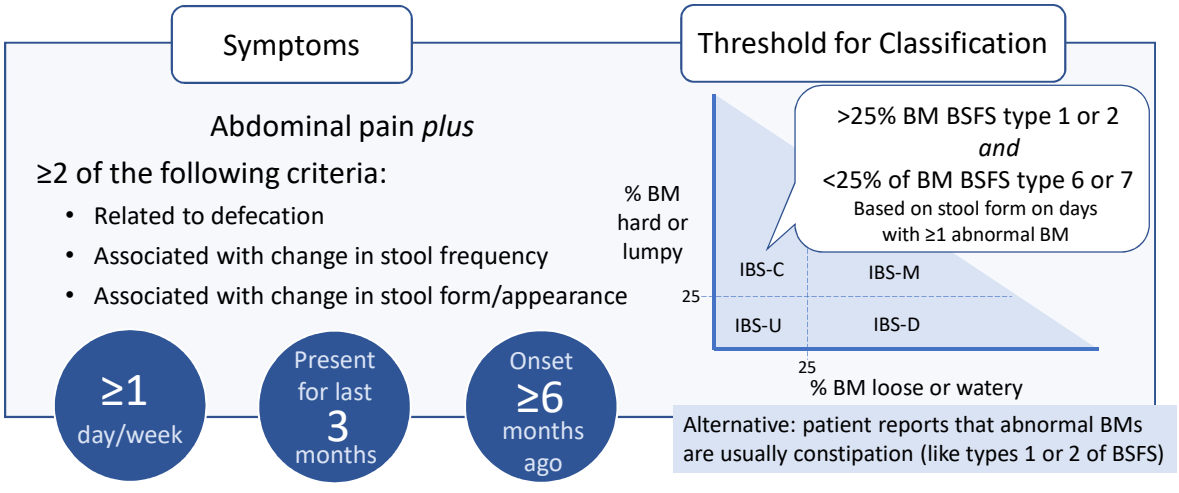
Evolving Understanding of the Pathophysiology of IBS-C and CIC



Drossman DA. *Gastroenterology*. 2016;150:1262-1279; Wiley JW, Chang L. *Gastroenterology*. 2018;155:1-4.

Diagnosis of IBS-C and CIC

IBS-C Diagnostic Criteria (Rome IV)



Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407.

CIC Diagnostic Criteria (Rome IV)

≥2 of the following, during ≥25% of defecations:

- Straining
- Hard or lumpy stools
- Sensation of incomplete evacuation
- Sensation of anorectal obstruction/blockage
- Manual maneuvers to facilitate defecation
- <3 spontaneous bowel movements per week

Loose stools are rarely present without use of laxatives

Insufficient criteria for IBS

≥1 day/week

Present for last 3 months

Onset ≥6 months ago

Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407.

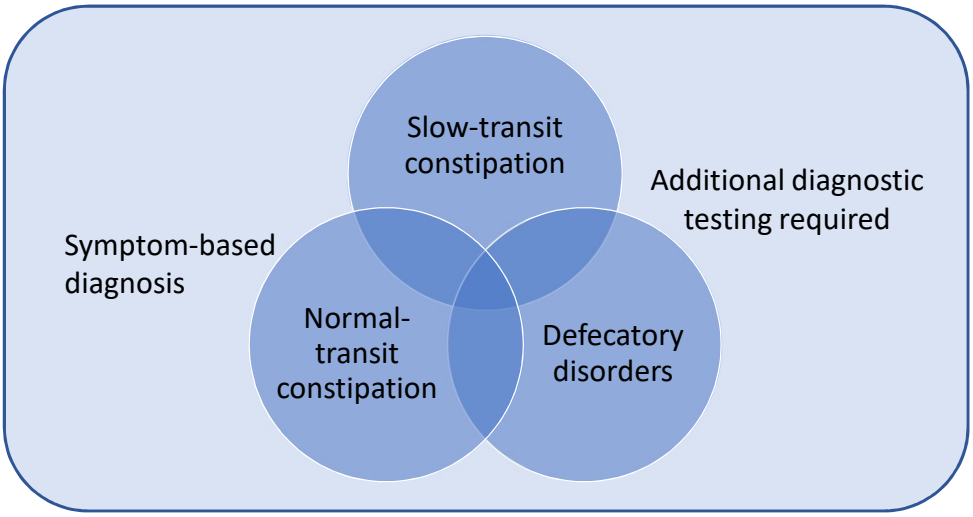
Red-Flag Symptoms and Warning Signs

- Recent changes in bowel habits
- Nocturnal passage of stools
- Unintentional weight loss (>10% in 3 months)
- Overt GI bleeding (in the absence of bleeding hemorrhoids or anal fissures)
- Age over 50 without prior colon cancer screening
- Family history of inflammatory bowel disease or colorectal cancer (or familial polyposis syndromes)
- Palpable abdominal mass or lymphadenopathy
- Anemia

Colonoscopy and/or further testing as indicated

Black CJ, Ford AC. *Med J Aust*. 2018;209:86-91; Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407; Lacy BE, Patel NK. *J Clin Med*. 2017;6. pii: E99.

Subtypes of Chronic Constipation



Bharucha AE et al. *Gastroenterology.* 2013;144:211-217; Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407.

Causes of Secondary Constipation

Neurological conditions
- Parkinson disease
- Multiple sclerosis

Metabolic disorders
- Diabetes
- Hypothyroidism
- Hypercalcemia

Medications
- Opiates
- Tricyclic antidepressants
- Calcium-channel blockers

Mechanical obstruction
- Previous pelvic (eg, gynecologic) surgery

Black CJ, Ford AC. *Med J Aust*. 2018;209:86-91; Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407; Tse Y et al. *Can J Gastroenterol Hepatol*. 2017;2017:8612189.

Building a Strong Clinician-Patient Relationship

- Identify predominant and/or most troubling symptoms
- Work together to improve symptoms and make treatment decisions
- Listen actively
- Display empathy
  - Acknowledge the impact of the condition
- Reassure the patient about their condition
- Set realistic expectations for therapy

Di Palma JA, Herrera JL. *J Clin Gastroenterol.* 2012;46:748-751; Lacy BE, Patel NK. *J Clin Med.* 2017;6. pii: E99.

Evaluating Bowel Habits — Key Considerations

Stool form

Stool frequency

Associated symptoms

Bristol Stool Form Scale (BSFS)

Type	Description
1	Separate hard lumps; like nuts; hard to pass
2	Sausage-shaped but lumpy
3	Like a sausage but with cracks on the surface
4	Like a sausage or snake, smooth and soft
5	Soft blobs with clear-cut edges
6	Fluffy pieces with ragged edges; mushy
7	Watery; no solid pieces; entirely liquid

Constipation

Diarrhea

Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407.

Laboratory and Other Tests in Patients With Chronic Constipation Symptoms

- Laboratory tests that may be indicated based on clinical history and/or exam findings
  - CBC to check for iron deficiency anemia
  - CRP to lower suspicion for inflammatory bowel disease
  - Thyroid-stimulating hormone
  - Serum calcium
  - Celiac testing, ideally in setting of adequate gluten consumption
- Colonoscopy (per national screening recommendations in patients without warning signs)
- Specific tests to evaluate constipation pathophysiology

Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407; Lacy BE, Patel NK. *J Clin Med.* 2017;6. pii: E99.

Functional Defecation Disorders: Dyssynergic Defecation

- Impaired coordination of pelvic floor and abdominal wall muscles
- Most common disorder of rectal evacuation
- Acquired and learned behavioral problem, often resulting from dysfunctional toilet habits
- Associated with sexual abuse
- Can coexist with a structural cause
- Confirmation of diagnosis often requires objective measures
  - Balloon expulsion testing
  - Anorectal manometry
  - Defecography

It is important to identify dyssynergic defecation because it has a distinct pathophysiology and is more likely to respond to biofeedback therapy

Black CJ, Ford AC. *Med J Aust*. 2018;209:86-91; Rao SS et al. *Gastroenterology.* 2016;pii: S0016-5085(16)00175-X.

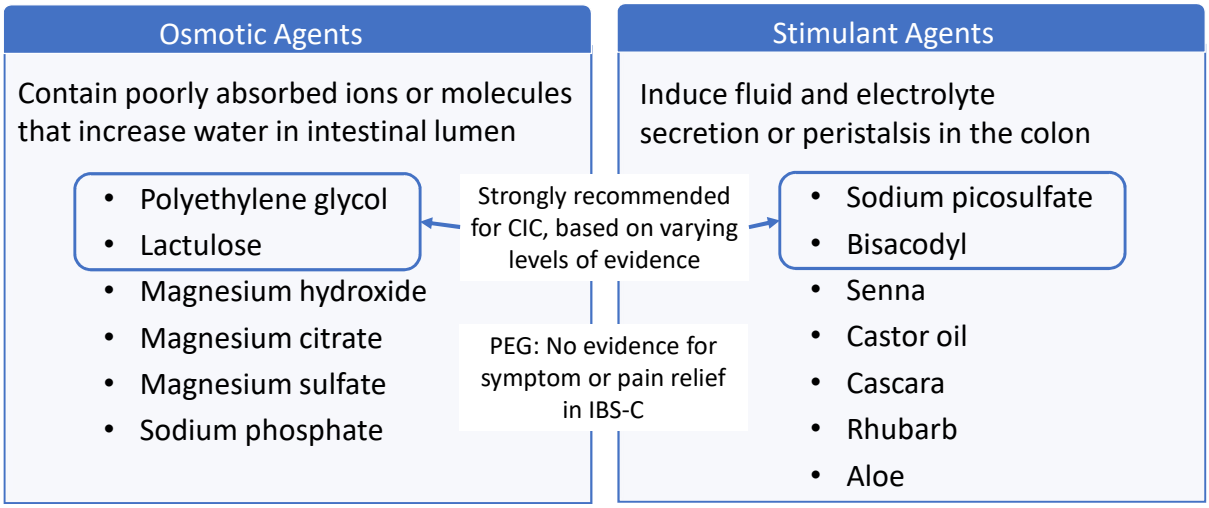
Treatment of IBS-C and CIC

Dietary and Lifestyle Approaches to Managing Symptoms of Chronic Constipation

- Dietary modifications and supplementation
  - Increased fiber (25–30 g/day)
    - Soluble preferred over insoluble
    - Increase dose gradually to minimize side effects
  - FODMAP restriction
    - May have benefits for pain and bloating in IBS-C but remains to be proven
  - Prebiotics, probiotics and synbiotics
    - Limited data suggest beneficial effects, especially on abdominal pain and bloating
- Hydration
- Exercise

Black CJ, Ford AC. *Med J Aust*. 2018;209:86-91; Ford AC et al. *Am J Gastroenterol*. 2014;109:1547-1561; Halmos EP et al. *Gastroenterology*. 2014;146:67-75. Lacy BE et al. *Gastroenterology*. 2016;150:1393-1407; Tse Y et al. *Can J Gastroenterol Hepatol*. 2017;2017:8612189.

Osmotic and Stimulant Laxatives



Ford AC et al. *Am J Gastroenterol.* 2014;109(Suppl 1):S2-26.

Prosecretory Agents

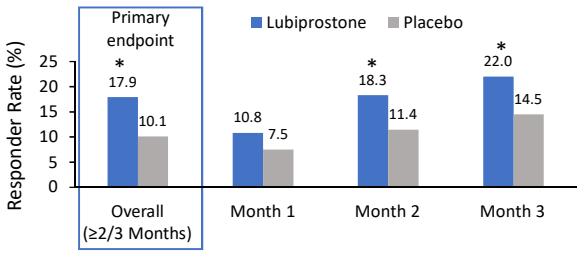
Drug	Description/Mechanism	FDA Indication(s)	Dosing and Administration
Chloride channel activator			
Lubiprostone	Prostaglandin E1 analogue; activates chloride channel type 2 (CIC-2) on apical surface of intestinal epithelium	IBS-C in women ≥18 years	8 mcg orally twice daily with food and water
		CIC in adults OIC in adults	24 mcg orally twice daily with food and water
Guanylate cyclase-C (GCC) agonists			
Linaclotide	14-amino acid peptide; binds to membrane-bound GCC receptor on luminal epithelial cells in a pH-independent manner; may be active throughout the small intestine and colon	IBS-C in adults	290 mcg orally once daily, ≥30 minutes before breakfast
		CIC in adults	145 mcg or 72 mcg orally once daily, depending on individual presentation or tolerability
Plecanatide	16-amino acid peptide; binds to GCC receptor in a pH-dependent manner with increased activity in the acidic portion of the proximal small intestine	IBS-C in adults	3 mg orally once daily with or without food
		CIC in adults	3 mg orally once daily with or without food

OIC=opioid-induced constipation. Ford AC et al. *Am J Gastroenterol.* 2014;109(Suppl 1):S2-26; Thomas RH, Luthin DR. *Pharmacotherapy*. 2015;35:613-630; FDA. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 2, 2019; Shah ED et al. *Am J Gastroenterol.* 2018;113:329-338.

Lubiprostone in IBS-C

Combined analysis of 2 placebo-controlled phase 3 trials
- A total of 1171 patients with IBS-C (Rome II criteria) randomized 2:1

Responder Analysis at Week 12 (n=1154)



Monthly responder:
Rated IBS symptoms as moderately or significantly relieved for all 4 weeks of the month or significantly relieved for ≥2 weeks of the month, with no ratings of moderately or severely worse

Abdominal Symptoms:
Change (Improvement) in Rating from Baseline

Symptom Measure	Month 1	Month 2	Month 3
Abdominal discomfort/pain		*	*
Abdominal bloating		*	

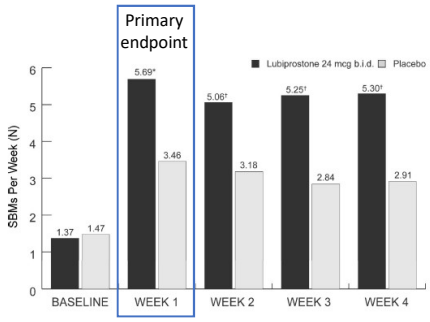
Initial improvements were maintained during a 36-week open-label extension study (n=476)

*P<0.05; Drossman DA et al. *Aliment Pharmacol Ther.* 2009;29:329-341; Chey WD et al. *Aliment Pharmacol Ther*. 2012;35:587-599.

Lubiprostone in CIC

Placebo-controlled, phase 3 trial of adults with chronic constipation randomized 1:1

Bowel Movement Response (N=242)



Additional findings (lubiprostone vs placebo):
- More patients with SBM within 24 hours (57% vs 37%) and within 48 hours (80% vs 61%) of first dose
- Fewer patients needing rescue medications
- Higher percentage of full responders (SBM frequency of ≥3 per week)
- Patient-reported improvements in stool consistency, straining, and constipation severity, abdominal bloating, and abdominal discomfort during all or most weeks of study

Similar results were seen in a separate 4-week, placebo-controlled phase 3 trial

*P=0.0001 vs placebo; †$P \leq 0.002$ vs placebo.
Johanson JF et al. *Am J Gastroenterol.* 2008;103:170-177; Barish CF et al. *Dig Dis Sci.* 2010;55:1090-1097.

Safety and Tolerability of Lubiprostone

Most Common Treatment-Related Adverse Events (AEs)

	IBS-C		CIC	
AE (%)	Lubiprostone 8 mcg bid (n=1011)	Placebo (n=435)	Lubiprostone 24 mcg bid (n=1113)	Placebo (n=316)
Nausea	8	4	29	3
Diarrhea	7	4	12	<1
Abdominal pain	5	5	8	3
Abdominal distention	3	2	6	2

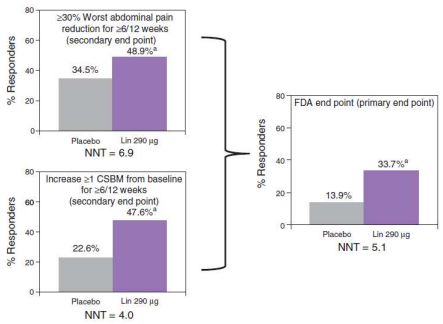
Other AEs occurring more frequently with 24 mcg bid lubiprostone than with placebo in patients with CIC include flatulence (6%), vomiting (3%), loose stools (3%), dyspepsia (2%)

FDA. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed July 23, 2019.

Linaclotide in IBS-C

Placebo-controlled phase 3 trial of adults meeting modified Rome II criteria for IBS-C

Overall Responders at Week 12 (N=804)



Additional findings (linaclotide vs placebo):

- Higher rate of combined response that required ≥9 of 12 weeks of all the following:
  - ≥30% improvement in worst abdominal pain
  - Increase of ≥1 CSBM/week from baseline
  - ≥3 CSBMs/week
- Greater improvements from baseline in other symptoms
  - Straining, stool consistency, abdominal bloating, fullness, and cramping

Treatment effects were sustained over a randomized treatment period of up to 26 weeks

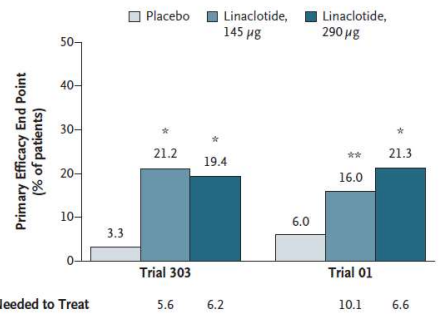
Similar results were seen in a separate 12-week, placebo-controlled phase 3 trial

Chey WD et al. *Am J Gastroenterol.* 2012;107:1702-1712; Rao S et al. *Am J Gastroenterol.* 2012;107:1714-1724.

Linaclotide in CIC

Two randomized, placebo-controlled phase 3 trials of adults with chronic constipation

Overall Responders at Week 12 (N=1272)



Overall responder: ≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline for ≥9 of 12 weeks

Additional findings (linaclotide vs placebo):

- Greater improvements from baseline in stool consistency, straining severity, abdominal discomfort and bloating, and constipation severity

Separate study of linaclotide 72 mcg daily:

- 12-week CSBM overall response
  - 13.4% linaclotide vs 4.7% placebo; *P*<0.0001
- Sustained response (12-week CSBM overall responders who met weekly CSBM responder criteria for ≥3 of the final 4 weeks of treatment)
  - 12.4% linaclotide vs 4.7% placebo; *P*<0.0001

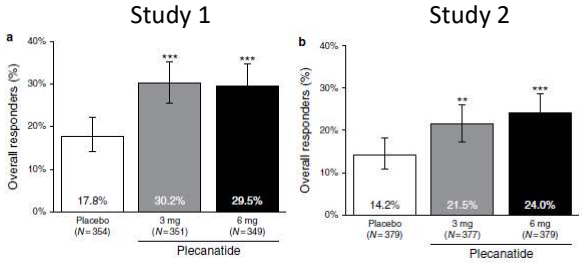
*P≤0.001, vs placebo; **P≤0.01, vs placebo.

Lembo AJ et al. *N Engl J Med.* 2011;365:527-536; Schoenfeld P et al. *Am J Gastroenterol.* 2018;113:105-114.

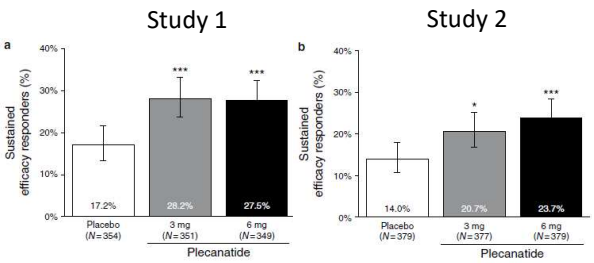
Plecanatide in IBS-C

Two identical randomized, phase 3 trials of adults meeting Rome III criteria for IBS-C

Overall Responders at Week 12



Sustained Efficacy Responders



Overall responder:

≥30% improvement in worst abdominal pain plus an increase of ≥1 CSBM/week from baseline for ≥6 of 12 weeks

Sustained responder:

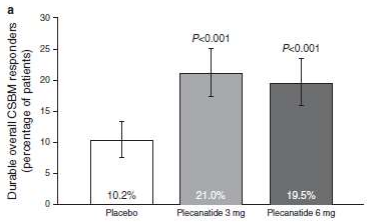
Overall responder plus a weekly responder for ≥2 of the last 4 weeks of the 12-week treatment period

Brenner DM et al. *Am J Gastroenterol.* 2018;113:735-745.

Plecanatide in CIC

Placebo-controlled, phase 3 trial of 1394 adults meeting Rome III criteria for CIC

Durable Overall Responders at Week 12



Durable overall responder: Overall responder (≥3 CSBMs/week and an increase of ≥1 CSBM/week from baseline for ≥9 of 12 weeks) who met weekly responder criteria for ≥3 of the last 4 weeks

Additional findings (plecantide vs placebo):

- Greater improvements from baseline in stool consistency, straining severity, abdominal discomfort and bloating, and constipation severity
- In general, treatment effects were similar with both doses of plecanatide vs placebo

Similar results were seen in a separate 12-week, placebo-controlled phase 3 trial in patients meeting modified Rome III criteria for CIC

Miner PB et al. *Am J Gastroenterol.* 2017;112:613-621; DeMicco M et al. *Therap Adv Gastroenterol.* 2017;10:837-851.

Safety and Tolerability of GCC Agonists in IBS-C and CIC

Most Frequently Reported Treatment-Emergent AE

Diarrhea

Reported in up to ≈20% of patients

- Mostly mild or moderate in severity
- Led to discontinuation rates of approximately 1%–6%
- Long-term studies suggest that:
  - Frequency decreases over time
- Linaclotide should be taken on an empty stomach
- Plecanatide can be taken with or without a meal

- Studies of plecanatide used a more stringent definition of diarrhea, likely explaining the lower rates of diarrhea than those that were reported with linaclotide

Chey WD et al. *Am J Gastroenterol.* 2012;107:1702-1712; Rao S et al. *Am J Gastroenterol.* 2012;107:1714-1724; Lembo AJ et al. *N Engl J Med.* 2011;365:527-536; Schoenfeld P et al. *Am J Gastroenterol.* 2018;113:105-114; Nee JW et al. *Expert Rev Gastroenterol Hepatol.* 2019;13:397-406; Brenner DM et al. *Am J Gastroenterol.* 2018;113:735-745; Miner PB et al. *Am J Gastroenterol.* 2017;112:613-621; DeMicco M et al. *Therap Adv Gastroenterol.* 2017;10:837-851; Shah ED et al. *Am J Gastroenterol.* 2018;113:329-338.

Similar Efficacy and Tolerability of GCC Agonists

Systematic review and meta-analysis
- 8 linaclotide trials (5 CIC; 3 IBS-C) and 7 plecanatide trials (4 CIC; 3 IBS-C)
- Indirect comparisons from meta-regression

	CIC		IBS-C	
Dosing	**Linaclotide 72 mcg/day vs Plecanatide 3 mg/day**	**Linaclotide 145 mcg/day vs Plecanatide 3 mg/day**	**Linaclotide 290 mcg/day vs Plecanatide 3 mg/day**	**Linaclotide 290 mcg/day vs Plecanatide 6 mg/day**
Efficacy	OR=0.77 (*P*=0.77)	OR=0.78 (*P*=0.66)	OR=1.28 (*P*=0.45)	OR=1.38 (*P*=0.34)
Diarrhea as an adverse event	OR=0.95 (*P*=0.97)	OR=0.93 (*P*=0.90)	OR=5.20 (*P*=0.13)	OR=4.72 (*P*=0.19)
Study withdrawal owing to diarrhea	OR=3.51 (*P*=0.51)	OR=1.58 (*P*=0.57)	OR=0.29 (*P*=0.55)	OR=0.27 (*P*=0.57)

Shah ED et al. *Am J Gastroenterol.* 2018;113:329-338.

Prokinetic Agents

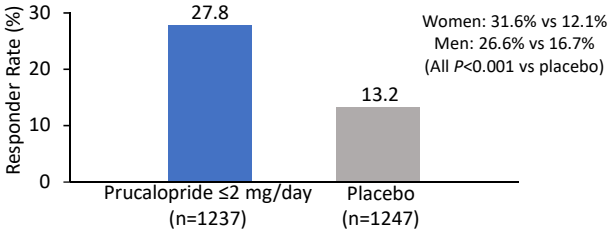
Drug	Description/Mechanism	FDA Indication(s)	Dosing and Administration
Selective serotonin-4 (5-HT_4) receptor agonist			
Prucalopride	Dihydrobenzofurancarboxamide compound with high affinity for 5-HT_4 receptors; stimulates GI motility, especially colonic	CIC in adults	2 mg orally once daily, with or without food (1 mg daily in patients with severe renal impairment)
Nonselective 5-HT_4 receptor agonist			
Tegaserod	Indole carbazimidamide derivative of 5-HT; in addition to 5-HT_4, also has affinity for 5-HT_1 and 5-HT_2 receptors and some monoamine transporters; facilitates GI motility and intestinal secretion and reduces visceral sensitivity	IBS-C in women <65 years	6 mg orally twice daily, ≥30 minutes before meal

5-HT=5-hydroxytryptamine. Camilleri M et al. *Dig Dis Sci.* 2016;61:2357-2372; De Maeyer JH et al. *Neurogastroenterol Motil.* 2008;20:99-112; Layer P et al. *Ther Clin Risk Manag.* 2007;3:107-118; FDA. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 2, 2019.

Prucalopride in CIC

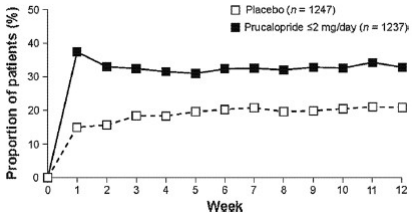
Integrated analysis of 6 randomized, placebo-controlled phase 3 and 4 clinical trials
- A total of 2484 adult patients with ≤2 SBMs per week for ≥6 months

Overall Response: Patients with Mean Frequency ≥3 SCBMs/Week Over 12 Weeks



Women: 31.6% vs 12.1%
Men: 26.6% vs 16.7%
(All *P*<0.001 vs placebo)

Proportion of Patients with ≥3 SCBMs Each Week



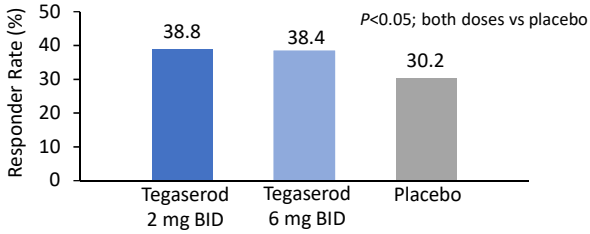
Additional beneficial effects (prucalopride vs placebo):
- Median time to SCBM after first dose
- Proportion of patients with increase of ≥1 SCBM/week
- Use of rescue medications
- Change from baseline stool, abdominal, and rectal symptoms (PAC-SYM scores)

SCBM=spontaneous complete bowel movement; PAC-SYM=Patient Assessment of Constipation Symptoms questionnaire.
Camilleri M et al. *Dig Dis Sci.* 2016;61:2357-2372.

Tegaserod in IBS-C

Randomized, placebo-controlled phase 3 clinical trial
- A total of 881 adults (83% female) with IBS-C (Rome I criteria)

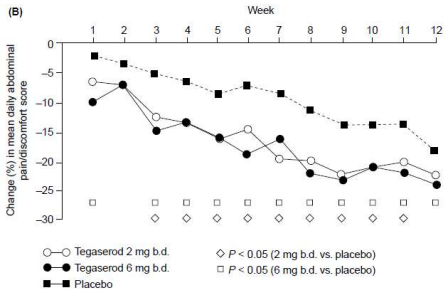
Subject's Global Assessment (SGA) of Relief



P<0.05; both doses vs placebo

Responder: Symptoms were "completely relieved" or "considerably relieved" at least 50% of the time or "somewhat relieved" 100% of the time during the final 4 weeks the study

Abdominal Pain and Discomfort



Additional placebo-controlled trials have shown similar beneficial effects on symptoms

Müller-Lissner SA et al. *Aliment Pharmacol Ther.* 2001;15:1655-1666; Layer P et al. *Ther Clin Risk Manag.* 2007;3:107-118.

Safety and Tolerability of 5-HT_4 Receptor Agonists

Prucalopride in CIC

Most common TEAEs across studies (≥5%)

- Headache
- Abdominal pain
- Nausea
- Diarrhea

- Mostly mild or moderate in severity
- Led to discontinuation in 5.2%
- 2.0% experienced any adverse cardiovascular events (vs 1.8% for placebo)

Tegaserod in IBS-C

Most common TEAEs (frequencies vary across studies)

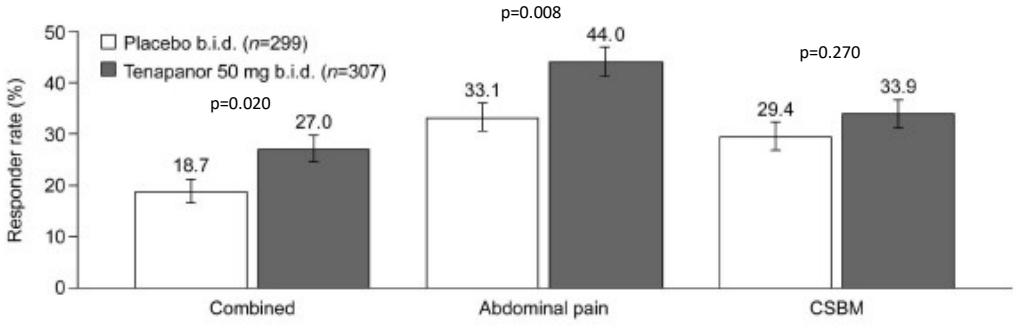
- Headache
- Diarrhea
- Abdominal pain

- Mostly mild in severity and transient
- <8% of patients discontinued due to AEs
- Safety considerations
  - Major adverse cardiovascular events and ischemic colitis have been reported
  - Contraindicated in patients with history of MI, stroke, TIA, angina, or ischemic colitis

TEAE=treatment-emergent adverse event; MI=myocardial infarction; TIA=transient ischemic attack.
Camilleri M et al. *Dig Dis Sci.* 2016;61:2357-2372; Layer P et al. *Ther Clin Risk Manag.* 2007;3:107-118; FDA. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 5, 2019.

Phase III Study: Tenapanor for IBS-C

- Minimally absorbed NaHE3 inhibitor
- 629 IBS-C pts randomized to tenapanor 50 mg or placebo BID x 12 weeks
- Most common AE: Diarrhea (14.6 vs 1.7%), Discontinuation (6.5 vs 0.7%)

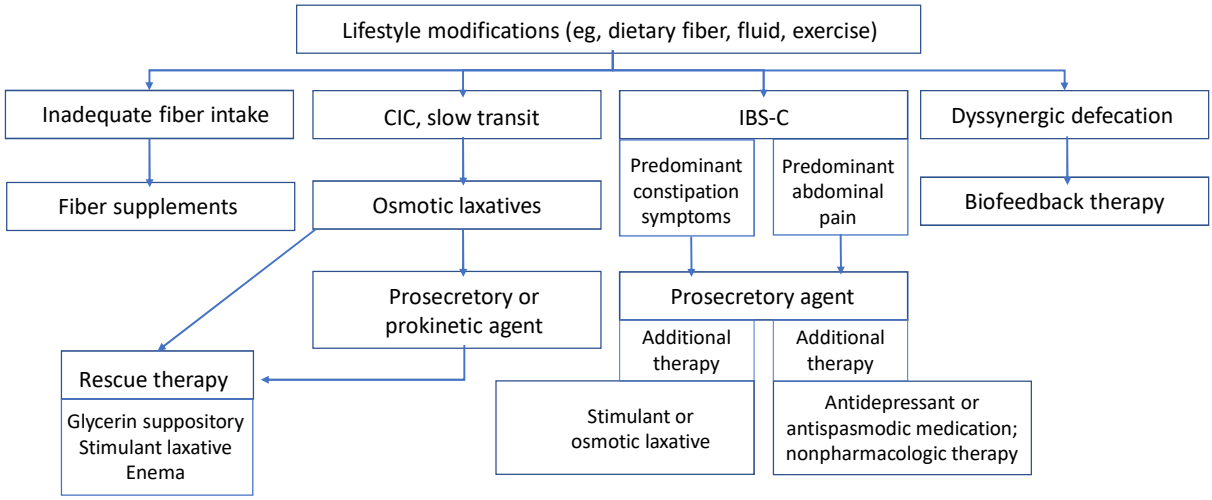


Chey et al. Am J Gastroenterol 2020;115:281-93

Other Potential Therapies for IBS-C and/or CIC

Wang X, Yin J. *Evid Based Complement Alternat Med*. 2015;2015:396396; Payne SC et al. *Nat Rev Gastroenterol Hepatol*. 2019;16:89-105; Rao SS et al. *Gastroenterology*. 2016;pii: S0016-5085(16)00175-X.

Proposed Algorithm for Treatment of Chronic Constipation



Tse Y et al. *Can J Gastroenterol Hepatol*. 2017;2017:8612189.

Summary and Conclusions

Diagnosis

- IBS-C and CIC are functional bowel disorders that exist on a spectrum
  - Distinguished from each other mainly by the presence and severity of abdominal pain
- Diagnosis of IBS-C and CIC is primarily based on a careful and thorough history
- DRE is an essential component of the physical exam
- Warning signs or symptoms of other conditions require further investigation

Treatment

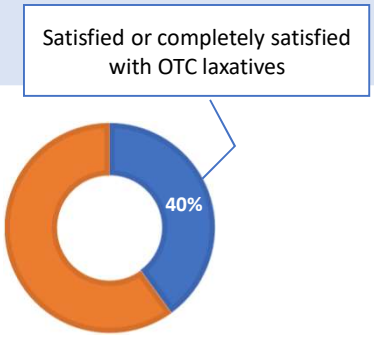
- Effective treatment options for normal and slow-transit constipation include lifestyle modifications, laxatives, prosecretory, and prokinetic agents
- Biofeedback is an effective therapy for dyssynergic defecation
- Treatment plans should be individualized, through open communication and active partnership with patients

Patient Satisfaction With Laxative Treatments

BURDEN-CIC

- US-based online survey
- 1223 adult patients with CIC

- In total, 40% of all CIC patients reported using some form of over-the-counter (OTC) laxative
- Patients used an average of 3 OTC products prior to consulting a healthcare professional



European study:

- 28% of patients were very dissatisfied with their laxative treatment
- No relationship between type of laxative and degree of satisfaction

Harris LA et al. *Adv Ther.* 2017;34:2661-2673; Müller-Lissner S et al. *Aliment Pharmacol Ther.* 2013;37:137-145.

Select Emerging Therapies in Later Phases of Clinical Development for IBS-C and/or CIC

Compound/Agent	Description/Mechanism of Action	Status
SYN-010	• Modified release formulation of lovastatin, an HMG-CoA reductase inhibitor • Interferes with cell membranes of intestinal anerobic methanogens, leading to reduction in methane production	Phase 2 randomized, placebo-controlled trials in IBS-C: NCT02495623 completed NCT03763175 recruiting
Tenapanor	• Small-molecule inhibitor of the gastrointestinal sodium/hydrogen exchanger isoform 3 • Reduces absorption of sodium and phosphate, enhancing intestinal fluid volume and transit	Phase 3 trials in IBS-C completed NCT02621892 NCT02686138 Long-term phase 3 trial: NCT02727751

Muskal SM et al. *F1000Research.* 2016;5:606; Shin A et al. *Aliment Pharmacol Ther.* 2014;39:239-253; Chey WD et al. *Am J Gastroenterol.* 2017;112:763-774. Clinicaltrials.gov. Accessed August 6, 2019.

Chronic Intestinal Pseudo-Obstruction

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Disclosures

- No potential conflicts of interest

Chronic Small Intestinal Motility Disorders

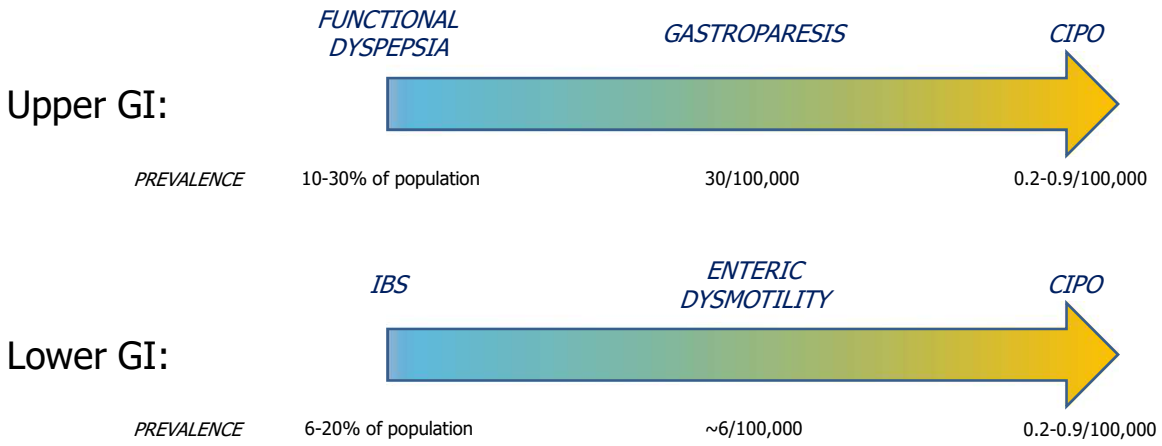
- Chronic intestinal pseudo-obstruction (CIPO)—altered small bowel contractile function leads to symptoms of intestinal obstruction with radiographic evidence of intestinal dilation
- Enteric dysmotility (ED)—milder variant with similar symptoms but no small bowel dilation

Overlapping Presentations of Gastroparesis vs. IBS vs. CIPO

	Gastroparesis	IBS	CIPO
Symptoms	▪ Nausea/vomiting ▪ Pain/discomfort ▪ Bloating ▪ Fullness ▪ Early satiety	▪ Bowel disturbance ▪ Pain/discomfort ▪ Bloating ▪ Nausea/vomiting ▪ Fullness/early satiety	▪ Pain/discomfort (80-96%) ▪ Bloating and distention (77%) ▪ Nausea and vomiting (75%) ▪ Constipation (46%) ▪ Diarrhea (?SIBO)(20-40%) ▪ Impaired digestion, malnutrition, weight loss (54%)
Other manifestations	▪ POTS/dysautonomia ▪ Hypermobility/Ehlers-Danlos	▪ POTS/dysautonomia ▪ Hypermobility/Ehlers-Danlos	▪ POTS/dysautonomia ▪ Hypermobility/Ehlers-Danlos ▪ Pneumatosis intestinalis ▪ Genitourinary involvement

Lindberg et al., Scand J Gastroenterol 2009

The Spectra of GI Motility Disorders



Clinical Features of CIPO

- More common in women
- 89% have continuous symptoms
- Average delay in diagnosis 4.7-8 years
- Average of 3 surgeries prior to diagnosis
- Two thirds develop nutritional deficiencies
- Most cases are idiopathic (some post-infectious)
- May have Herpes viral DNA in myenteric plexus; ?role of polyomaviruses-John Cunningham [JC] virus

Mann et al., Gut 1997
Stanghellini et al., Clin Gastroenterol Hepatol 2005
Amiot et al., Am J Gastroenterol 2009
Lindberg et al., Scand J Gastroenterol 2009
De Giorgio et al., Transplant Proc 2010
Sinagra et al., Clin J Gastroenterol 2019

Classification of CIPO

- Neuropathy—damaged myenteric plexus nerves, loss of coordinated propulsion, normal contractile amplitudes
- Myopathy—damaged smooth muscle layers, reduced contractile amplitudes, worse prognosis than neuropathy
- *Mesenchymopathy—damage to interstitial cells of Cajal (connect nerves to smooth muscle, pacemaker cells), loss of coordinated propulsion, only detectable on full thickness intestinal biopsy*
- Mixed
- Within each category—degenerative vs. inflammatory

Main Secondary Causes of CIPO

Connective Tissue Diseases	Neuromuscular Disorders	Miscellaneous Conditions	Endocrine Disorders (mimic CIPO)
Scleroderma Autoimmune ganglionitis Dermatomyositis Mixed connective tissue disease SLE	Parkinson's disease Chagas disease Dysautonomia Myotonic dystrophy Muscular dystrophy	Paraneoplastic disease Amyloidosis Mitochondrial disorders Crohn's disease Storage disease (Fabry)	Diabetes Hypothyroidism Hyperparathyroidism Adrenal insufficiency

Focus on Two Etiologies

- Scleroderma:
  - 18/40 with CIPO had scleroderma in one series—11 myopathic, 5 neuropathic
  - Nearly universal reports of Raynaud's
  - Some cases present without other systemic manifestations
- Autoimmune ganglionitis:
  - A 15 antibody panel (against ion channels, receptors, autoimmune markers)—developed to screen for paraneoplastic CIPO (can precede tumor detection by 2 years)
  - Of 24 patients with autoimmune GI dysmotility in one series (achalasia in 8, gastroparesis in 12, CIPO in 7), 11 had cancer (lung, breast, GI), pos antibodies included neuronal voltage gated Ca^{2+} channel, ACh receptor, neuronal voltage gated K^{+} channel, ANNA-1
  - Histopathologic studies show lymphocytic or eosinophilic infiltration of myenteric nerves
  - May be amenable to immunomodulatory therapy

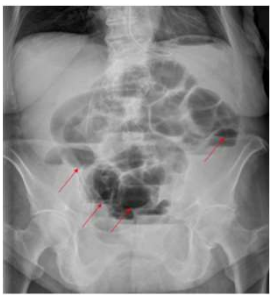
Sjolund et al., Eur J Gast Hep 2005
Lindberg et al., Gut 2009
Dhamija et al., Clin Gastroenterol Hepatol 2008
Vernino et al., NEJM 2000
Tornblom et al., Scand J Gastroenterol 2007
Akazawa et al., Virchows Arch 2019

When to Consider a Diagnosis of CIPO

- Existing diagnosis of different "motility" disorder (e.g. gastroparesis, functional dyspepsia, IBS) not responsive to standard therapies and:
  - Multiple evaluations/admissions for suspected SB obstruction
  - Prior surgeries for presumed SB obstruction without benefit
  - Pronounced abdominal distention and radiographic evidence of SB dilation without transition point
  - Refractory SIBO
  - Difficulties maintaining adequate nutrition
  - Does not tolerate jejunal feedings
  - Known/suspected systemic diseases associated with SIBO

Approach to Work-Up of Suspected CIPO

- Standard testing:
  - EGD—exclude outlet obstruction
  - Plain films and/or CT/MRI (enterography)—assess for SB dilation
  - Gastric scintigraphy—assess for associated gastroparesis—amenable to treatment
  - Testing for bacterial overgrowth (SIBO)—amenable to treatment
  - Nutritional status (prealbumin, Fe, vit A, D, E, K, B_{12}, folate)—need for nutritional support
- Diagnosis of CIPO:
  - Dilated SB without transition point on radiography +/- air-fluid levels
  - Roles of SB transit testing, intestinal manometry, full thickness biopsy to direct treatment
  - Additional specialized tests for amyloid, mitochondrial disease, autonomic function
- Diagnosis of enteric dysmotility (ED):
  - Normal SB caliber on radiography
  - SB transit testing and/or intestinal manometry to confirm intestinal dysmotility



Tests of Small Intestinal Transit

Test	Pros	Cons
Barium small bowel radiography	Widely available Well tolerated Assesses proximal and distal intestine	Variable methods Non-standardized interpretation Radiation exposure
Small intestinal scintigraphy	Well tolerated Assesses proximal and distal intestine	Not widely available Poorly standardized Radiation exposure
Wireless motility capsule	Reasonably available Well tolerated Standardized methods and interpretation	Potential for capsule retention Not validated for CIPO

Barium Radiography to Measure Small Bowel Transit

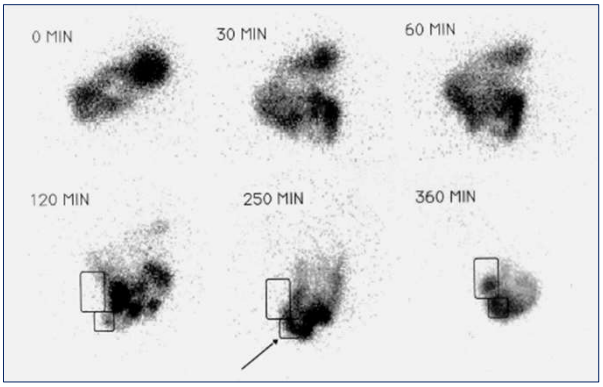
Reference	Methods	Transit Findings
Lonnerblad, Acta Radiol Scand 1951	111 students, 200 mL barium	Orocecal transit 178±93 min
Kim, Am J Roentgen 1968	315 patients, 473 mL barium	SB transit mean 90 min
Thompson et al., Gastrointest Radiol 1982	48 volunteers, 450-650 mL barium	Jejunocecal transit mean 45 min

- Inconsistencies:
  - Barium volumes/consistency
  - Patient positioning
  - Transit measurements

Szarka and Camilleri, Sem Nuc Med 2012

Small Intestinal Scintigraphy

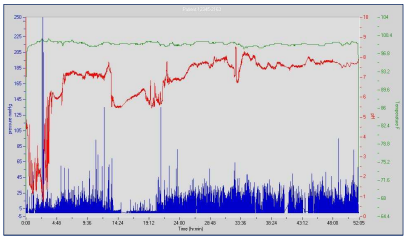
- Method:
  - ^{111}In-labeled water
  - ^{99m}Tc-sulfur colloid labeled eggs
  - ^{99m}Tc-HIDA
  - ^{99m}Tc-labeled Amberlite resin
- Interpretation:
  - 10% label passed into colon
- Findings:
  - Mean SB transit time=221±49 min
- Variability:
  - Normal range 131-322 min
- Limited availability:
  - ~Half dozen centers in US perform



Argenyi EE et al., Am J Gastroenterol 1995
Miller MA et al., Dig Dis Sci 1997
Stivland T et al., Gastroenterology 1991
Degen et al., Eur J Nuc Med 2002

Wireless Motility Capsules to Measure Small Bowel Transit

- Wireless motility capsule provides information on:
  - pH (±0.5 units)—pH changes reflect transition zones
  - Pressure (±5 mmHg <100 mmHg, ±10% >100 mmHg)
  - Temperature (±1°C)—food intake in stomach and anal expulsion



Measure	Normal
Gastric emptying	<5 hours
SB transit	<6-8 hours
Colon transit	<59 hours

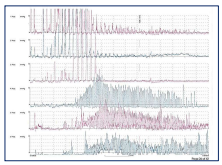
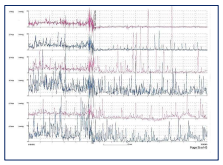
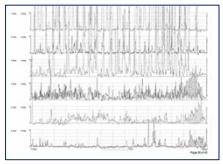
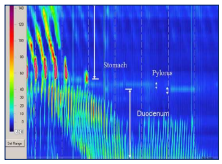
Wireless Motility Capsules to Measure Small Bowel Transit

- No studies have specifically focused on small bowel transit (SBT) defects in patients with suspected SB dysmotility
- Usually avoid with pronounced SB dilation on radiography (concern for capsule retention)
- SBT delays in prospective investigations:
  - SBT delayed in 16% of 210 NIH Gastroparesis Registry patients—70% with gastric emptying delays
  - SBT delayed in 23% of 167 patients with suspected gastroparesis—35% with gastric emptying delays

Hasler et al., Neurogastroenterol Motil 2017
Lee et al., Clin Gastroenterol Hepatol 2019

Antroduodenal Manometry to Test Small Bowel Motility

- Indications:
  - Evaluate unexplained nausea and vomiting
  - Define small bowel neuropathy or myopathy (?may avoid full thickness biopsy)
- Measures:
  - Migrating motor complex (fasting)—phase III every 90-120 min, serves as housekeeper
  - Fed motor pattern—irregular contractions that grind food lasting 2-4 hr
  - Response to prokinetics—macrolides, octreotide (UM), neostigmine (Mayo)
  - High resolution methods in use to better assess propagation
- Utility:
  - Drawbacks—technically demanding, some recordings show both neuropathy and myopathy
  - Treatment decisions altered in 19-28%
  - Normal study may be most useful finding

FASTING  *FED*  *ERYTHROMYCIN*  *HIGH RES* 

Camilleri et al., Gastroenterology 1998
Rao et al., Neurogastroenterol Motil 2011
Parthasarathy et al., Neurogastroenterol Motil 2015

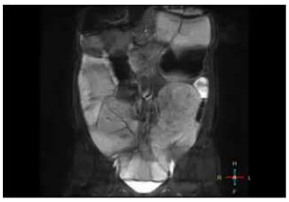
Abnormal Findings on Antroduodenal Manometry

	Visceral Neuropathy	Visceral Myopathy
Manometric findings	▪ Normal amplitude contractions ▪ Loss of migrating motor complex ▪ Failed fed conversion	▪ Low amplitude contractions (<20 mmHg) ▪ Migrating motor complex may or not be preserved ▪ Fed conversion may occur
Differential diagnosis	▪ Idiopathic ▪ Early scleroderma ▪ Early amyloidosis ▪ Paraneoplastic neuropathy ▪ Autoimmune neuropathy ▪ Chagas' disease ▪ Familial neuropathies	▪ Advanced scleroderma ▪ Dermatomyositis ▪ Advanced amyloidosis ▪ Muscular dystrophies ▪ Familial visceral myopathies

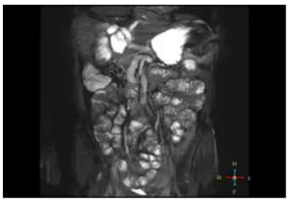
Cine-MRI in CIPO

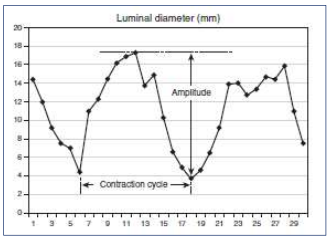
- Methods: 33 patients with SB dysmotility studied—23 (70%) with CIPO, 10 (30%) with enteric dysmotility
- Potential drawbacks: Limited recording time, expense, overlapping bowel loops

CIPO



ENTERIC DYSMOTILITY





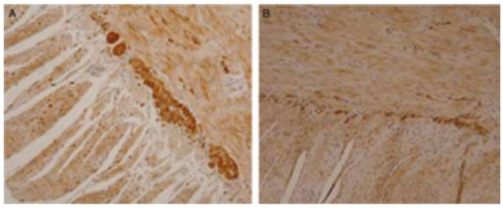
Parameter	CIPO	Enteric Dysmotility	P Value
Contraction ratio (%)	18±10	61±8	<0.001
BMI (kg/m^2)	17±3	18±4	0.33
Albumin (g/dL)	3.8±0.7	4.4±0.5	0.04
TPN	52.4	11.1	0.03
Tube feedings	61.9	33.3	0.15

Fuyuki et al., J Gastroenterol 2017

Full Thickness Small Bowel Biopsy in Small Intestinal Dysmotility

- Not routinely recommended due to postop risks and limited alterations in management
- Consider for elusive diagnosis (e.g. cannot tolerate testing) or to exclude inflammatory ganglionitis (to consider immunomodulatory therapy)
- Three series of 21-115 patients:
  - Histology in CIPO: myopathy 22-43%, neuropathy 10-48%, mesenchymopathy 6%, mixed neuromyopathy 10-30%
  - Histology in enteric dysmotility: myopathy 5%, neuropathy 83%, mixed 12%
  - Inflammatory component in ~one third

CONTROL *CIPO*

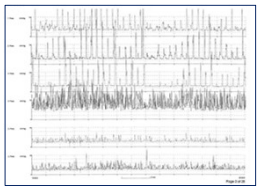


Billiauws et al., Clin Nutr 2014
Amiot et al., Am J Surg Pathol 2008
Lindberg et al., Gut 2009

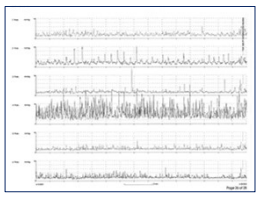
Case 1: Diet/Medication Management

- VE is a 56 year old woman with refractory nausea, vomiting, bloating/distention, abdominal pain, and 20 lb weight loss
- Symptoms began 2 years ago after food poisoning; no longer maintains oral nutrition with liquid supplements and failed a Dobhoff feeding trial
- EGD negative, CT normal, GE scan 28% 4 hour retention, SB follow through 4 hour SB transit time
- No response to domperidone, erythromycin, antiemetics, tricyclics
- Performed antroduodenal manometry—showed visceral neuropathy; autoimmune work-up negative
- Given diagnosis of idiopathic enteric dysmotility

FASTING



POSTPRANDIAL



Diet Recommendations for Intestinal Dysmotility

- No studies of diet therapy in ED/CIPO
- Common sense recommendations to improve efficiency of digestion:
  - Liquid predominant (to facilitate distribution of nutrients in poorly functioning intestine)
  - Additional liquid nutrient supplements with vitamin replacement (A, D, E, K, B_{12}, folate)
  - Low fat, low fiber, low residue (to minimize impact on impaired propagation)
  - Low FODMAP (to limit gas production)
- Intestinal insufficiency defined as reduced gut function impairing nutrient assimilation but with capability to maintain health via enteral route—indication for tube feeding
  - Tube feeds can be gastric or intestinal but usually with continuous low rate infusion

Thapar et al., J Ped Gastro Nutr 2018
Pironi et al., Clin Nutr 2015

Antibiotic Use for SIBO in Intestinal Dysmotility

- Limited data on SIBO in CIPO, but SIBO control is mainstay of CIPO therapy
- SIBO likely esp. if dilated SB or markedly delayed gastric or SB transit
- Multiple antibiotics with efficacy:
  - Prefer non-absorbable if covered (rifaximin, neomycin) vs. systemic (quinolones, tetracyclines, amoxicillin, metronidazole, trimethoprim-sulfamethoxazole)
- Different strategies:
  - Antibiotics as needed for symptom control
  - Scheduled antibiotics at regular intervals (e.g. first 10-14 days of each month) or cycling of different antibiotics (10-14 day intervals)
- Pilot study of fecal transplant (daily x 6 d thru NJ tube) in 9 patients reduced symptoms, improved tube feeding tolerance, and eliminated SIBO

Thapar et al., J Ped Gastro Nutr 2018
Pironi et al., Clin Nutr 2016
Gu et al., J Neurogastroenterol Motil 2017

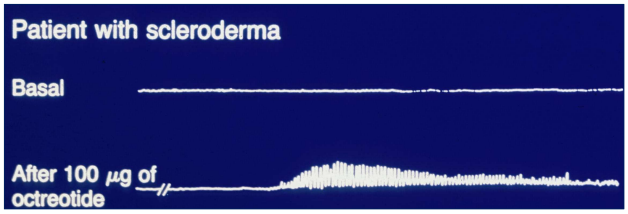
Prokinetics for Small Intestinal Dysmotility

- Prokinetics with SB stimulation:
  - Erythromycin/azithromycin—6/15 CIPO pts responded to erythromycin
  - Pyridostigmine—improved symptoms in 3/4 CIPO pts in one series
  - Octreotide
  - Prucalopride/tegaserod
  - ?Opioid antagonists—naloxegol, methylnaltrexone
- Prokinetics with activity restricted to stomach (for associated gastroparesis):
  - Metoclopramide/domperidone (no data in CIPO)

Emmanuel et al., Aliment Pharmacol Ther 2004
O'Dea et al., Colorectal Dis 2010

Octreotide for SIBO with CIPO

- Effects of 3 wks octreotide studied in 6 controls and 5 scleroderma pts with SIBO
- Octreotide decreased fasting hydrogen from 25±5 to 4±2 ppm and hydrogen after glucose from 46±24 to 8±7 ppm

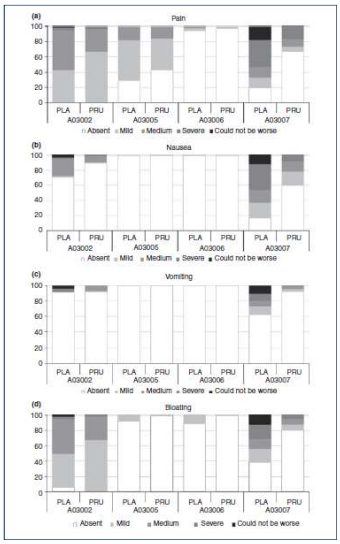


- Other reports:
  - Series of 3 CIPO pts improved symptoms on octreotide; dose-escalation required
  - 5/14 CIPO pts responded to octreotide plus erythromycin
  - In 16 CIPO pts, octreotide bid improved tolerance of tube feeds

Soudah et al., NEJM 1991
Perlemuter et al., Arth Rheum 1999
Verne et al., Dig Dis Sci 1995
Ambartsumyan et al., Ped Drugs 2016

Prucalopride for CIPO

- Background:
  - Prucalopride (5-HT_4 agonist) approved for chronic constipation
  - Accelerates SB transit in capsule endoscopy
- Methods: 4 patients (1 neuropathy, 3 myopathy) treated over 6 mo courses of placebo crossing over with prucalopride 2-4 mg daily
- Results: Prucalopride improved pain in 3/4, N/V in 2/4, bloating in 4/4



Emmanuel et al., Aliment Pharmacol Ther 2012
Alsahafi et al., Chin J Gastro Hep 2017

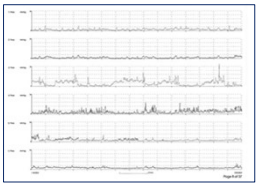
Case 1: Follow-Up

- Initially referred to dietician to initiate low fat, low fiber, low residue, low FODMAP diet
- Glucose breath test positive for SIBO—maintained on antibiotics the first 10 days of each month
- Maintained on pyridostigmine liquid 30-60 mg before meals; recently added prucalopride 2 mg daily
- GJ tube placed 3 years ago for intermittent tube feeds
- Serial labs show prealbumin levels ~20 mg/dL (normal 16-40 mg/dL) with normal vitamin levels

Case 2: Non-Medication Therapy

- AC is a 48 year old man with severe nausea and vomiting, bloating, constipation, and 50 lb weight loss
- 15 year history of progressive scleroderma with severe pulmonary and skin involvement
- 3 years of progressive GI symptoms with multiple admissions for dehydration; unable to tolerate solid food; failed Dobhoff feeding trial
- EGD retained fluid, CT dilated SB loops, GE scan 43% 4 hour retention, glucose breath test positive
- No response to metoclopramide, erythromycin, antiemetics, rifaximin
- Performed antroduodenal manometry—showed visceral myopathy
- Given diagnosis of CIPO secondary to scleroderma

FASTING



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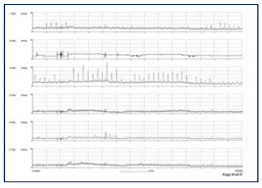

Other Therapies of CIPO

- Immunotherapy (several cases IV immunoglobulin, 1 case rituximab, 1 case steroid/6-MP, 1 case cyclophosphamide produced GI benefits)
- Resection (localized)
- Surgical venting enterostomy/ileostomy (postop mortality 8%, reoperation 17%, morbidity 58%)
- PEG-J decompression (improved BMI, albumin in 7 CIPO patients)
- Gastric stimulator surgery (helpful in 4 cases)
- TPN
- Small bowel transplant

Sabbaugh et al., Neurogastroenterol Motil 2013
Chun et al., Dig Dis Sci 2012
Andersson et al., Neurogastroenterol Motil 2006
Maier et al., Medicine 2015
Koga et al., Brain Nerve 2013
Coret J Neurooncol 2009
Koike, Sobue, Hand Clin Neurol 2013
Di Nardo et al., Neurogastroenterol Motil 2017
Ohkubo et al., Neurogastroenterol Motil 2017

TPN for Chronic Intestinal Dysmotility

- Indication: Intestinal failure (reduction in gut function below minimum necessary to absorb macronutrients and/or water and electrolytes)
- 49% of CIPO and 14% of ED patients require TPN at some time; 25-50% can come off TPN at some point
- Complications: sepsis (3/patient over 8 yr), gallstone pancreatitis, cirrhosis
- Survival 94%, 82%, 75%, and 68% at 1, 5, 10, and 15 yr for CIPO
- Death more often due to liver failure than line infection
- Increased mortality: age >40 or <2 years, myopathic CIPO, scleroderma, no po intake

Pironi et al., Clin Nutr 2014
Pironi et al., Clin Nutr 2012
Amiot et al., Am J Gastroenterol 2009
Lindberg et al., Scand j Gastro 2009
Vasant et al., Clin Nutr 2018
Lehmann et al., Nutr Clin Pract 2019

Small Bowel Transplant for CIPO

- CIPO is reason for 11% of all SB transplants in adults
- Older series:
  - In 9 CIPO patients, graft survival 60% at 5 years and 45% at 10 years; patient survival 70% at 5 years and 56% at 10 years
- Newer series:
  - 55 patients with CIPO underwent SB transplant—42% children, 58% adults
  - Graft survival: 87% at 1 year, 56% at 5 years
  - Patient survival: 89% at 1 year, 69% at 5 years
  - 23/33 long term survivors able to discontinue TPN

Bond, Reyes, Semin Pediatr Surg 2004
Lauro et al., Transplant Proc 2013
Sogawa et al., Ann Surg 2019

Case 2: Follow-Up

- Labs show hypoproteinemia (prealbumin ~11-14 mg/dL)
- PICC line placed and TPN begun
- Brief trials of pyridostigmine 60 mg tid and octreotide 50-100 mcg qhs ineffective
- Placed on rotating antibiotics amoxicillin x 2 weeks alternating with metronidazole x 2 weeks
- Failed brief trial of elemental tube feedings
- Maintained on long-term TPN—gained 35 lbs over 1 year
- Passed away 3 years later from progressive pulmonary fibrosis

Take Home Points

- Consider CIPO/ED for refractory functional symptoms mimicking SBO especially with malnutrition/weight loss
- Testing involves assessment of SB dilation, nutritional evaluation, determination of associated SIBO and gastroparesis
- Specialized tests (SB transit, manometry, full thickness biopsy) when diagnosis uncertain or considering specialized therapies
- Diet measures include low fat, low fiber, low residue, low gas foods
- Medications include prokinetics with SB activity and aggressive SIBO therapy
- Immunomodulators unproved but a consideration
- Despite best efforts, many cases (esp. myopathic) will require TPN or consideration of SB transplant

EMR: tips and tricks

Richard Kwon, MD, MS

February 7, 2020

Disclosures

None

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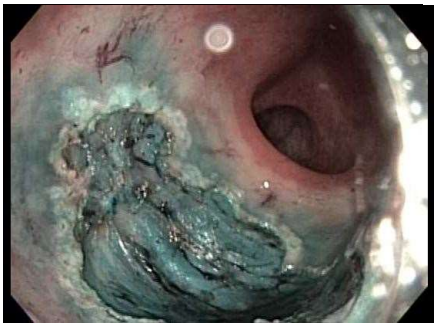
What is the goal of EMR?

- Complete removal of adenomatous tissue
  - Minimal number of resections
  - Fewest instruments
  - Without complication
  - Without recurrence
- Prevent cancer
- Avoid surgery



Factors to consider

- Appearance
- Size
  - Length
  - Circumference
- Location and lineup
- Sedation
- Experience/comfort

Appearance: surface morphology

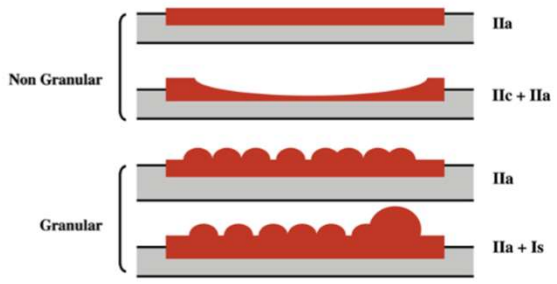


Figure 3. LST lesions. Models of granular and nongranular LST of neoplastic lesions, with the corresponding classification according to the categories of the Paris classification.

Kudo GIE 2008

Appearance: surface morphology

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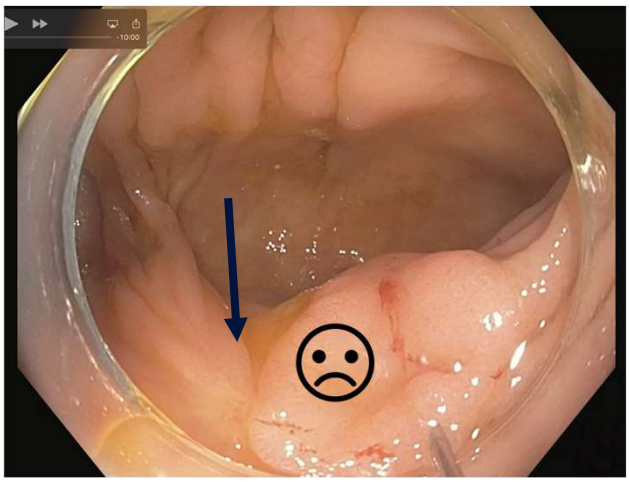
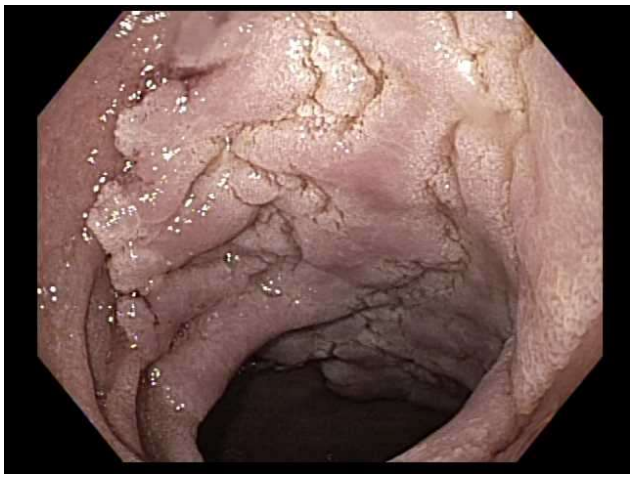
Appearance: prior treatment?



Size matters



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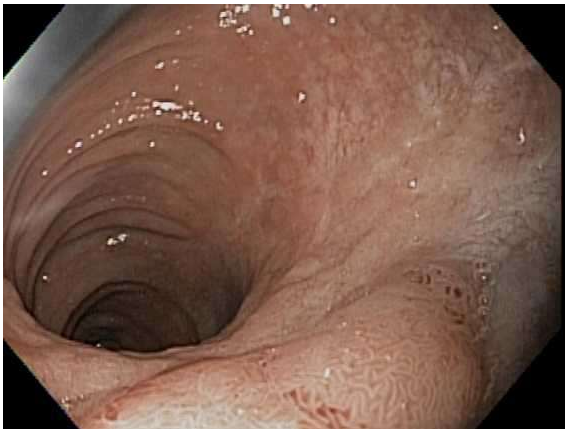
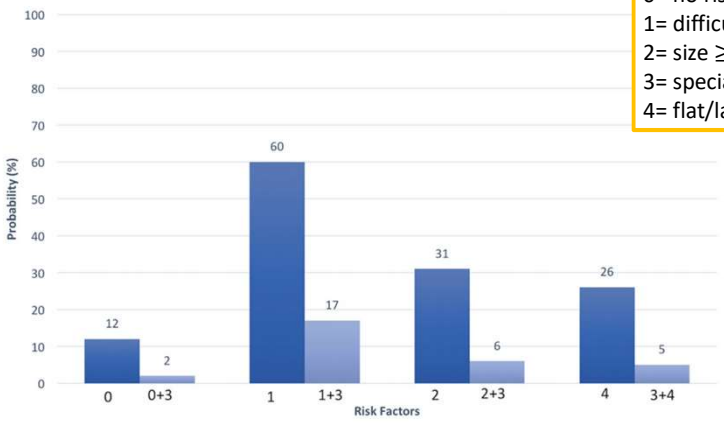


Lineup

- Preferable to have at 5-7 o'clock
- Folds
- Sweeps/curves
- Be cognizant of where instruments come out

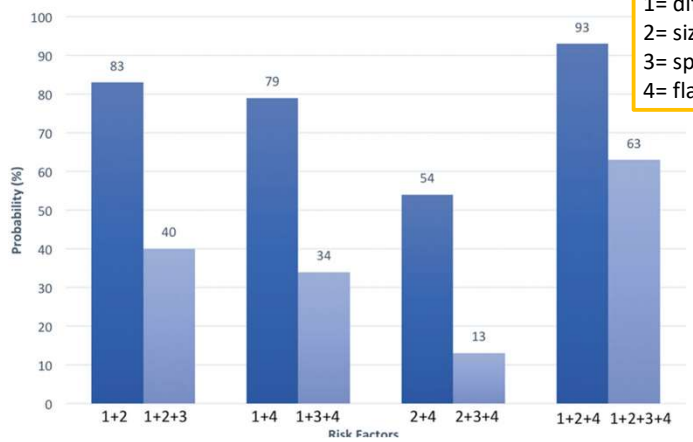
Factors for incomplete resection



0= no risk factors
1= difficulty lifting
2= size ≥4cm
3= specialist endoscopist
4= flat/lateral spread

Tavakkoli A, Kwon RS. Dig Dis Sci 2017

Factors for incomplete resection



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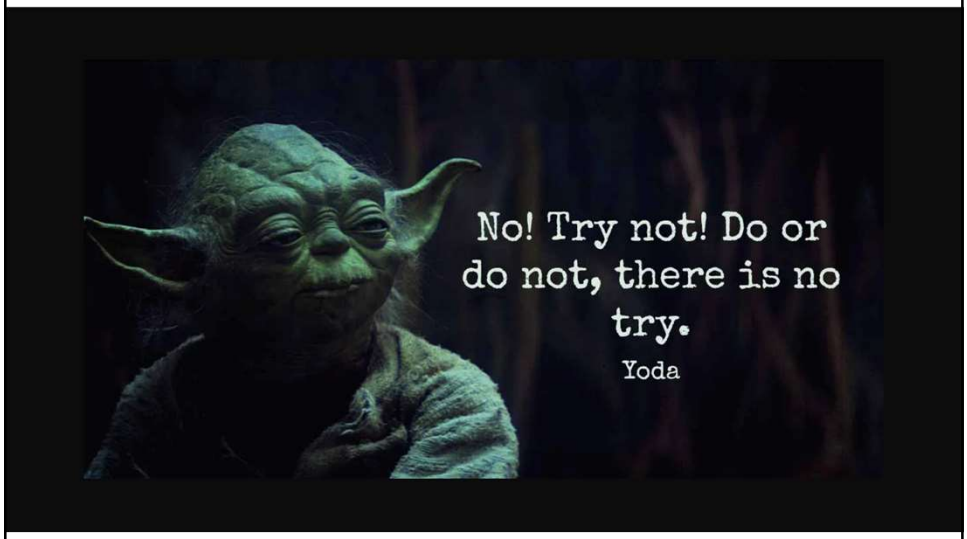

Technique

- Submucosal injection
- Tools
- Technique
- Other considerations

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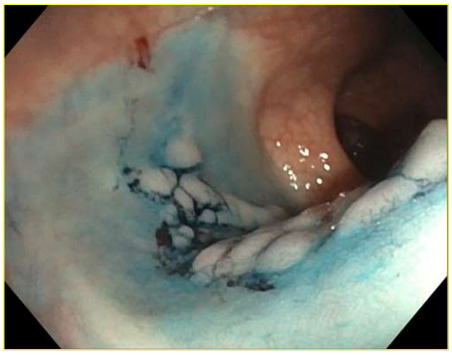
Submucosal injection

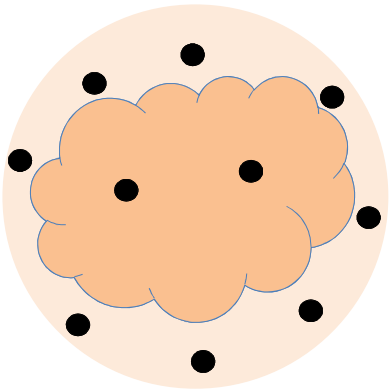
- Lifts the polyp away from the muscle and serosal layers, creating safety cushion
- Facilitates recognition of polyp borders
- Define the deep margin after polypectomy

Submucosal injection

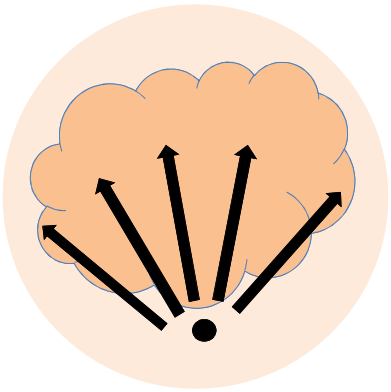
Base	Contrast Agent	Vasoconstrictor
Normal saline Hetastarch Artificial tears (HPMC) Hyaluronic Acid Glycerol Succinylated Gelatin	Methylene Blue Indigo Carmine	Epinephrine (1:60,000)



Submucosal injection



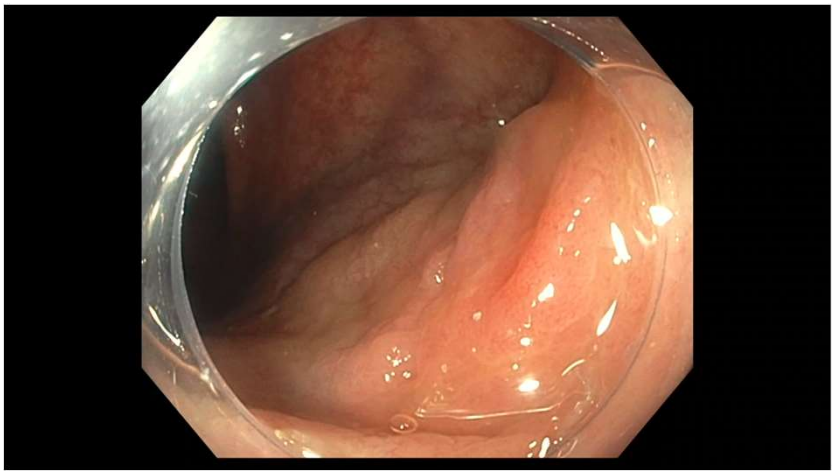
Multiple injection sites



Dynamic submucosal injection

Soetikno GI Clin N Am 2010

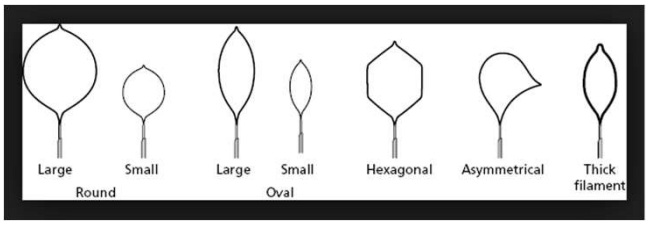
Submucosal injection



Video courtesy of Dr. Ryan Law

Tools: snares

- Shapes (oval, crescent, hexagonal, duckbill)
- Sizes (one size, multi-size)
- Specialty characteristics (barbed, needle tip, rotatable)
- Combination with injector needle
- Hot v cold



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Hot polypectomy

- Use of electrosurgical generator
  - Cutting (High current density): Cells rapidly "burst," resulting in cutting effect
    - Increased immediate bleeding risk
  - Coagulation (Lower current density): Cells desiccate, resulting in coagulation effect
    - Increased thermal injury
  - Blended: Alternating cutting and coagulation (best of both modes)

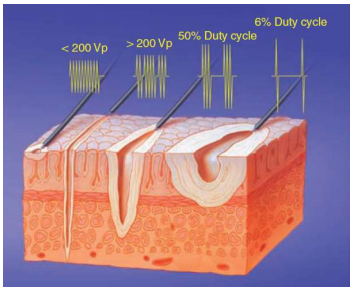
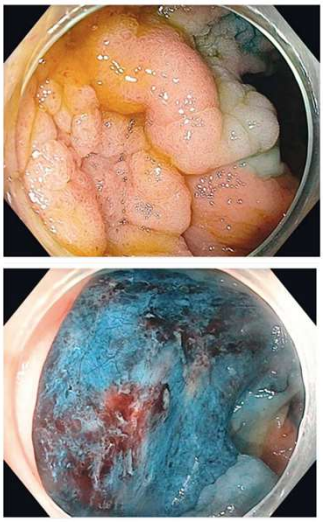


Image Courtesy of Dr. Wong Kee Song

Cold polypectomy

- Reduction in delayed bleeding and perforation
- Limited data available
- 0% adverse events in 73 patients, 94 polyps, ~50% were >2cm)
- Residual/recurrent adenoma in ~10%

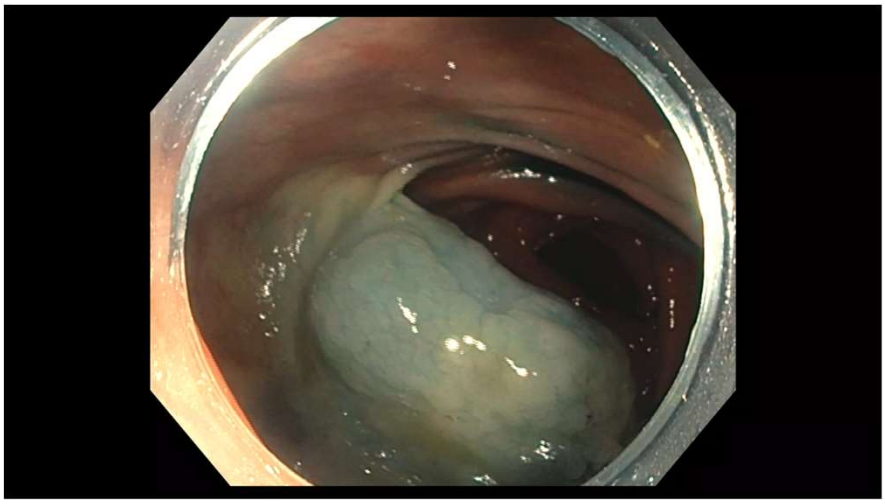


Piraka EIO 2017

Technique

- Edges
- Overlap
- Snare position

Technique: piecemeal resection

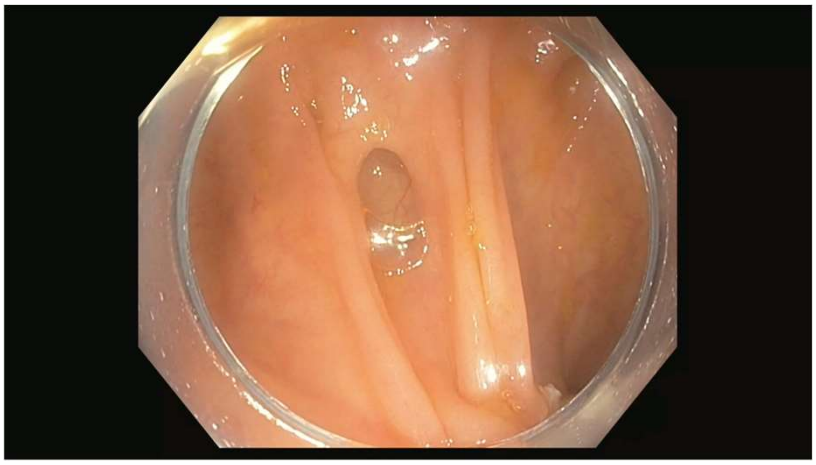


Video courtesy of Dr. Ryan Law

Challenges: remaining lesion

- Central islands, edges
  - Can be removed with snare or forceps (hot vs. cold)
  - Treat lesion edges (APC vs. soft coagulation [snare tip vs hot forceps])

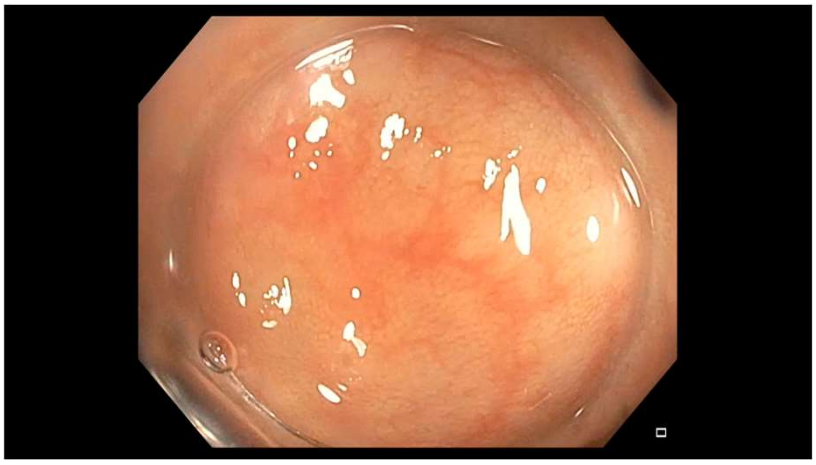
Technique: avulsion



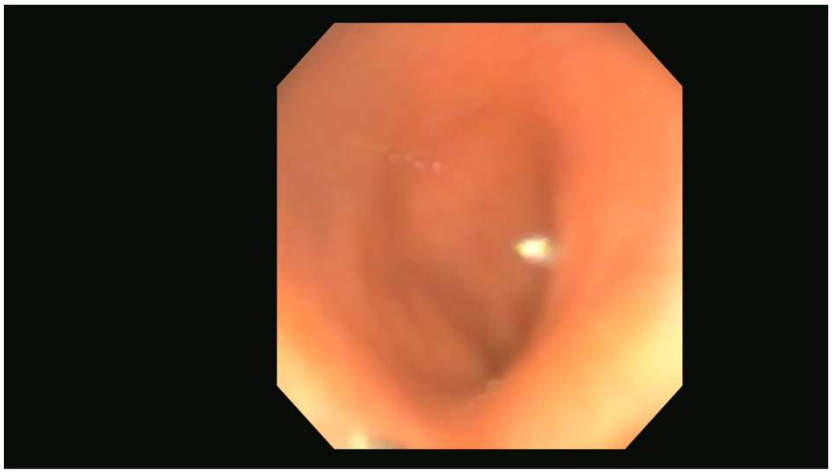
Other considerations

- Cap
- Underwater
- Change scope:
  - Gastroscope
  - Double channel colonoscope
- Retroflexion

Technique: underwater + avulsion



Technique: underwater + avulsion

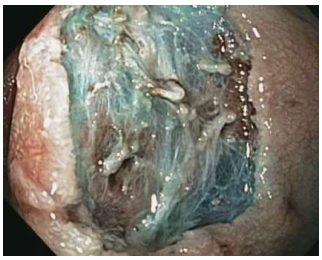


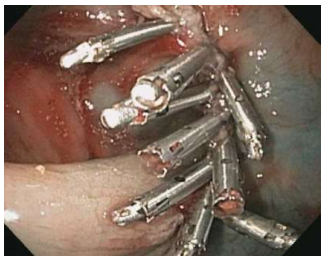
Complications

- Bleeding
  - Soft coagulation (snare tip v hot forceps v coag grasper)
  - No role for preventative treatment
- Perforation
  - Small: hemoclips or over-the-scope clip
  - Large: surgical consultation

Post-polypectomy: defect closure

- Hemoclips or endoscopic suturing
- No solid data to suggest reduction in delayed bleeding or perforation
- Recently completed RCT in US to address question





Tattoos

- Do:
  - Opposite wall
  - Distal and/or proximal
  - Small volume
- Do not:
  - Inject the lesion
  - Inject next to the lesion
  - Large volume

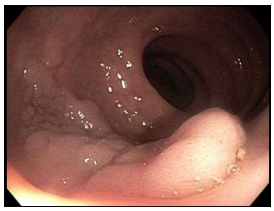
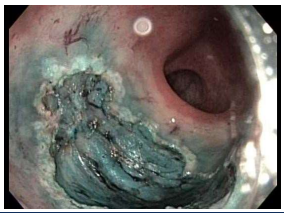
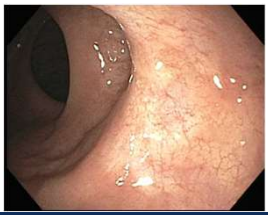
Post-polypectomy: management

- Resume diet
- Restart antithrombotics in 1-2 days
- No antibiotics

Post-polypectomy: surveillance

- Repeat colonoscopy in 3-6 months to assess for recurrence/residual adenoma
- 25% risk of residual adenoma at follow-up
- Residual adenoma is generally treatable
- If no obvious adenoma, always biopsy the scar

Buchner GIE 2012

Summary

- Endoscopic mucosal resection provides therapeutic benefit for patients– preventing cancer and avoiding surgery
- Maximize the chance of success with careful patient selection and endoscopic technique

Thank You

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Periprocedural Management of Anti-Platelets & Anti-Coagulant Therapy

Michelle A. Anderson MD, MSc, FASGE

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Disclosures

Consultant

Boehringer-Ingelheim, Boston Scientific, Olympus of the Americas

DSMB

GSK

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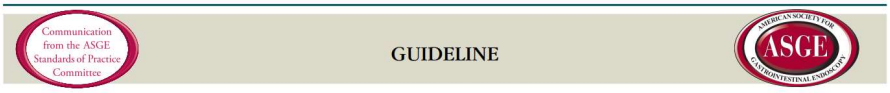
Management of Drugs in Endoscopy

- Elective:
  - To continue or not to continue
  - Bridge or No Bridge
  - When to restart
- Special Populations:
  - ACS/Cardiac Stents
  - LVAD

Updated Guideline Published January 2016



Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE

The management of antithrombotic agents for patients undergoing GI endoscopy

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

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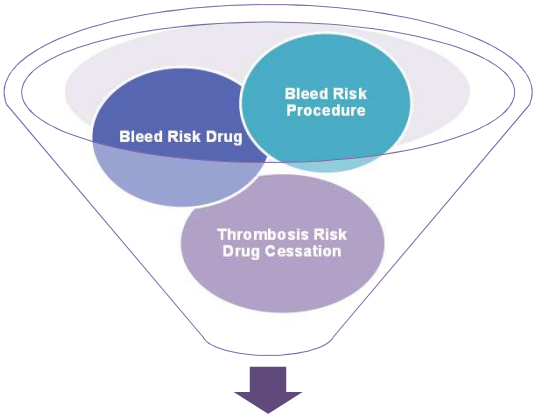
Decisions to Hold Antithrombotics Should Balance Risk and Benefit



Case

- **55 year old male with DM, HTN, Afib presents requesting screening colonoscopy. He is currently taking aspirin plus warfarin How do you manage?**

A. Proceed but hold the warfarin and aspirin for 5 days before the scope
B. Proceed but hold only the warfarin for 5 days before the scope
C. Consult with his cardiologist
D. Order a DCBE instead
E. Forego screening

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What the Guideline says about ASA and antiplatelets

TABLE 2. Antithrombotic drugs: duration of action and approach to reversal when indicated

Drug class	Specific agent(s)	Duration of action	Approach to reversal based on procedural urgency	
			Elective	Urgent
APAs	Aspirin	7-10 days	NA	Hold, can give platelets
	NSAIDs	Varies	NA	Hold

Even in the case of bleeding, decision to hold aspirin should be made after consideration of risks and benefits and in cooperation with other services

Acosta, R et al. GIE 2016

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Procedure Risk for Bleeding

TABLE 3. Procedure risk for bleeding (overall)

Higher-risk procedures	Low-risk procedures
Polypectomy	Diagnostic (EGD, colonoscopy, flexible sigmoidoscopy) including mucosal biopsy
Biliary or pancreatic sphincterotomy	ERCP with stent (biliary or pancreatic) placement or papillary balloon dilation without sphincterotomy
Treatment of varices	
PEG placement*	Push enteroscopy and diagnostic balloon-assisted enteroscopy
Therapeutic balloon-assisted enteroscopy	Capsule endoscopy
EUS with FNA†	Enteral stent deployment (Controversial)
Endoscopic hemostasis	EUS without FNA
Tumor ablation	Argon plasma coagulation
Cystgastrostomy	Barrett's ablation
Ampullary resection	
EMR	
Endoscopic submucosal dissection	
Pneumatic or bougie dilation	
PEJ	

PEJ, Percutaneous endoscopic jejunostomy.
*PEG on aspirin or clopidogrel therapy is low risk. Does not apply to DAPT.
†EUS-FNA of solid masses on ASA/NSAIDs is low risk.

Polypectomy bleeding (0.3% to 10%) risk factors: Size, location, morphology, resection technique, use of cautery

Acosta, R et al. GIE 2016

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Aspirin

- For **MOST** procedures including screening colonoscopy, we should continue ASA without interruption

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Large polyp EMR & Bleeding

- Prospective study of colonic EMR
- Antithrombotic mgmt standardized
- "Significant" bleeding = hospitalized
- 17 pts "on" antithrombotics (avg ASA hold = 5.4 days)

AP/AC group	Adj OR	95% CI
None	1	
ASA	6.3	1.8-22.5
Other AP/AC	3.1	0.7-12.8

Other significant variables, OR (95% CI):

- Location: Right 4.4 (1.3-14.1)
- Age, per decade: 1.7 (1.0-2.9)

Endoscopy. 2011 Jun;43(6):506-11.

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Case

- 68 yo male Jehovah witness, h/o CAD, s/p 2V CABG ‘95 presents with unstable angina
- Has cardiac cath → DES x 2, 2b3a GPI, heparin, asa, plavix
- 13 months later presents for EMR for a large rectal polyp seen on screening colonoscopy done prior to cardiac events

Now what?

A. Stop clopidogrel and proceed with colonoscopy
B. Stop ASA and proceed with colonoscopy
C. Stop both and proceed with colonoscopy
D. Stop neither and use hot snare
E. Send him to the surgeons

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Non-Aspirin antithrombotics

Is there an increased risk of bleeding with polypectomy on these meds?

Meta-analysis: PPB on Clopidogrel

Study or Subgroup	Clopidogrel Events	Clopidogrel Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Feagins and Iqbal 2013	16	219	14	297	49.8%	1.55 [0.77, 3.11]
Grossman 2010	3	70	26	2380	25.3%	3.92 [1.22, 12.66]
Singh 2010	3	142	26	1243	24.9%	1.01 [0.31, 3.29]
Total (95% CI)		431		3920	100.0%	1.76 [0.90, 3.46]
Total events	22		66			

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 2.86$, df = 2 ($P = 0.24$); $I^2 = 30\%$
Test for overall effect: $Z = 1.64$ ($P = 0.10$)

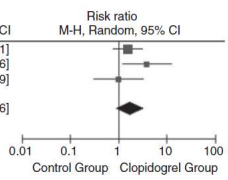

Figure 2 | Continued clopidogrel and immediate post-polypectomy bleed. Events = immediate post-polypectomy bleed.

Study or Subgroup	Clopidogrel Events	Clopidogrel Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Feagins 2011	1	118	6	1849	10.3%	2.61 [0.32, 21.52]
Feagins and Iqbal 2013	5	210	0	286	5.5%	14.96 [0.83, 269.11]
Grossman 2010	3	70	15	2380	31.0%	6.80 [2.01, 22.95]
Rodino 2011	1	25	4	400	9.9%	4.00 [0.46, 34.47]
Singh 2010	5	142	12	1243	43.3%	3.65 [1.30, 10.20]
Total (95% CI)		565		6158	100.0%	4.66 [2.37, 9.17]
Total events	15		37			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.58$, df = 4 ($P = 0.81$); $I^2 = 0\%$
Test for overall effect: $Z = 4.45$ ($P < 0.00001$)

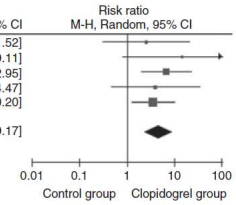

Figure 3 | Continued clopidogrel and delayed post-polypectomy bleed. Events = delayed post-polypectomy bleed.

Gandhi S, et al APT 2013

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Meta-analysis: PPB on Clopidogrel

Table 1 | Summary of pooled analysis

	Clopidogrel group	Control group	Relative risk ratio	Lower 95% CI	Upper 95% CI	*P* value	I^2%
Immediate PPB (%)	22/431 (5.10)	66/3920 (1.68)	1.76	0.90	3.46	0.10	30
Delayed PPB (%)	15/565 (2.65)	37/6158 (0.60)	4.66	2.37	9.17	<0.00001	0
Total PPB (%)	37/574 (6.45)	103/6169 (1.67)	2.54	1.68	3.84	<0.00001	2

There is little doubt that polypectomy on thienopyridines is associated with an increased risk of bleeding

Gandhi S, et al APT 2013

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Polypectomy on Warfarin

TABLE 3. Comparison of bleeding in patients with cold snare polypectomy (Cold group) and conventional polypectomy (Conventional group)

	Cold group	Conventional group	*P*	OR (95% CI)
Immediate bleeding	5.7% (2/35)	23% (8/35)	.042	4.9 (.96-25.0)
Hematochezia*	5.7% (2/35)	8.6% (3/35)	.500	1.5 (.24-9.9)
Delayed bleeding*	0% (0/35)	14% (5/35)	.027	
Total	11% (4/35)	46% (16/35)	.0015	6.5 (1.9-22.5)

OR, Odds ratio; *CI*, confidence interval.
*Hematochezia (mild uninvestigated bleeding) and delayed bleeding within 2 weeks after each polypectomy were recorded. Difference between Cold group and Conventional group was compared using the Fisher exact test.

Horiuchi A GIE 2014

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Heparin bridge + Hot snare versus Continuous AC + Cold snare for small (< 1 cm) polyps

Annals of Internal Medicine®

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ORIGINAL RESEARCH | 16 JULY 2019

Continuous Anticoagulation and Cold Snare Polypectomy Versus Heparin Bridging and Hot Snare Polypectomy in Patients on Anticoagulants With Subcentimeter Polyps: A Randomized Controlled Trial

*Yoji Takeuchi, MD; Katsuhiro Mabe, MD, PhD; Yuichi Shimodate, MD; Shinji Yoshii, MD, PhD; Shinya Yamada, MD; Mineo Iwatate, MD, PhD; Takuji Kawamura, MD, PhD; Kinichi Hotta, MD; Koji Nagaike, MD; Nobuaki Ikezawa, MD; Tomoaki Yamasaki, MD; Yoriaki Komeda, MD, PhD; Satoshi Asai, MD; Yasuhiro Abe, MD; Takuji Akamatsu, MD, PhD; Yuko Sakakibara, MD; Hisatomo Ikehara, MD, PhD; Yuzuru Kinjo, MD; Takashi Ohta, MD; Yoko Kitamura, MD; Takashi Shono, MD, PhD; Takuya Inoue, MD, PhD; Yoshio Ohda, MD, PhD; Nozomu Kobayashi, MD; Tokuma Tanuma, MD, PhD; Ryu Sato, MD; Taku Sakamoto, MD, PhD; Naohiko Harada, MD, PhD; Akiko Chino, MD, PhD; Hideki Ishikawa, MD, PhD; Masanori Nojima, MD, PhD, MPH; Toshio Uraoka, MD, PhD; for the Madowazu Study Group **

Article, Author, and Disclosure Information*

Shimodate Y, et al #476, DDW 2019

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Bridge therapy

Where the answer is coming from

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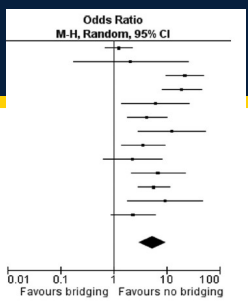
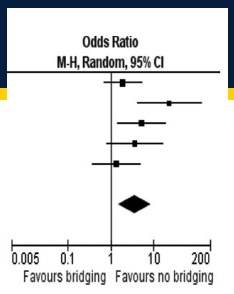
Bridge therapy – The Growing Truth

Siegal D Circulation 2012



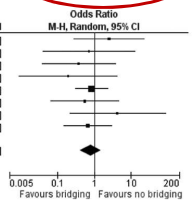
Overall Bleeding
OR 5.40 (3.00, 9.74)



Major Bleeding
OR 3.60 (1.52, 8.50)

Study or Subgroup	Bridging Events	Total	No bridging Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Daniels et al., 2009	4	342	1	213	8.8%	2.51 [0.28, 22.60]
Garcia et al., 2008	0	108	7	1185	5.2%	0.72 [0.04, 12.76]
Jaffer et al., 2010	1	229	3	263	8.2%	0.38 [0.04, 3.68]
Marquie et al., 2006	0	114	2	114	4.6%	0.20 [0.01, 4.14]
McBane et al., 2010	10	514	6	261	40.5%	0.84 [0.30, 2.35]
Tompkins et al., 2010	1	155	6	513	9.4%	0.55 [0.07, 4.59]
Varkarakis et al., 2005	0	25	3	762	4.7%	4.25 [0.21, 84.56]
Wysokinski et al., 2008	3	204	4	182	18.6%	0.66 [0.15, 3.01]
Total (95% CI)		**1691**		**3493**	**100.0%**	**0.80 [0.42, 1.54]**
Total events	19		32			

Heterogeneity: Tau² = 0.00; Chi² = 3.68, df = 7 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)



TE Events
OR 0.80 (0.42, 1.54)

Figure 2. Forest plot of thromboembolic events. M-H indicates Mantel-Haenszel; CI, confidence interval.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

James D. Douketis, M.D., Alex C. Spyropoulos, M.D., Scott Kaatz, D.O., Richard C. Becker, M.D., Joseph A. Caprini, M.D., Andrew S. Dunn, M.D., David A. Garcia, M.D., Alan Jacobson, M.D., Amir K. Jaffer, M.D., M.B.A., David F. Kong, M.D., Sam Schulman, M.D., Ph.D., Alexander G.G. Turpie, M.B., Vic Hasselblad, Ph.D., and Thomas L. Ortel, M.D., Ph.D., for the BRIDGE Investigators*

Inclusion/Exclusion Criteria

Inclusion criteria
All of the following 5 criteria must be satisfied for trial eligibility:

1) Adult male or female, age 18 years or older
2) Receiving warfarin therapy (for at least 3 months), administered to achieve a target international normalized ratio range of 2.0 to 3.0
3) Require temporary interruption of warfarin for pre-specified elective procedure or surgery
4) Have *at least one* of the following conditions:
   a. Chronic (permanent or paroxysmal) nonvalvular atrial fibrillation* or atrial flutter, confirmed by at least one prior electrocardiography recording or pacemaker/ACD interrogation
   b. Chronic (permanent or paroxysmal) valvular atrial fibrillation* or atrial flutter with evidence of mitral valvular heart disease, confirmed by same criteria as nonvalvular atrial fibrillation* or atrial flutter
5) Have *at least one* of the following major stroke risk factors:
   a. Age >75 years
   b. Hypertension
   c. Diabetes mellitus
   d. Congestive heart failure or left ventricular dysfunction
   e. Previous ischemic stroke, systemic embolism, or transient ischemic attack

Supplementary Appendix Table S1. Classification of Type of Surgery or Procedure*

Minor or low-bleeding-risk surgery/procedure
• gastrointestinal endoscopy (with or without biopsy)
• cardiac catheterization (with or without percutaneous coronary intervention)
• dental surgery or other dental procedure
• dermatologic surgery or other dermatologic procedure
• cataract removal or other ophthalmologic procedure
• any other surgery or procedure lasting <1 hour
Major or high-bleeding-risk surgery/procedure
• intra-abdominal surgery (e.g., bowel or visceral organ resection)
• intra-thoracic surgery (e.g., lung resection)
• major orthopedic surgery (e.g., hip or knee replacement)
• peripheral arterial revascularization (e.g., abdominal aortic aneurysm repair, vascular bypass)
• urologic surgery (e.g., prostatectomy, bladder tumor resection)
• permanent pacemaker or internal defibrillator insertion
• major procedure (e.g., colonic polyp resection, biopsy of kidney or prostate)
• any other surgery or procedure lasting ≥1 hour

*Patients who satisfied the trial eligibility criteria were classified according to this suggested classification, although the final designation as minor/low bleeding risk or major/high bleeding risk was left to the discretion of the site investigator.

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Study Outcomes.

Table 3. Study Outcomes.

Outcome	No Bridging (N=918)	Bridging (N=895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

* P value for noninferiority.
† P value for superiority.

Douketis JD et al. N Engl J Med 2015;373:823-833.

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Risk Factors for PPB in patients on Antithrombotics

- 59 cases & 174 matched controls at UCSF & VA
- PPB in 14.9% on bridge Rx
- No difference based on specific drug

- Multivariate Analysis

Factor	OR
Restart < 1 week	4.50
Polyp > 2 cm	5.94
Right side heat	2.61
Multiple large	2.92
Bridge Rx	12.27

Lin, D, et al. GIE April 2018.

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Risk of PPB Bleeding Due to Antithrombotic Agents

	OR	95% CI	*p* value
Age	0.95	0.93–0.97	<0.001*
Number of lesions per examination	1.27	1.17–1.39	<0.001*
Antithrombotics			
1 (ref.)			
Heparin bridge	33.1	10.1–108.6	<0.001*
Single			
Anticoagulant	3.89	0.90–16.7	0.068
Antiplatelet	1.09	0.38–3.16	0.867
Multi			
Anticoagulant + antiplatelet	7.73	1.75–34.2	0.007*
Antiplatelet	3.42	1.00–11.7	0.050

* $p < 0.05$.
PPB, post-polypectomy bleeding.

Kishida, Y et al. Digestion March 2018

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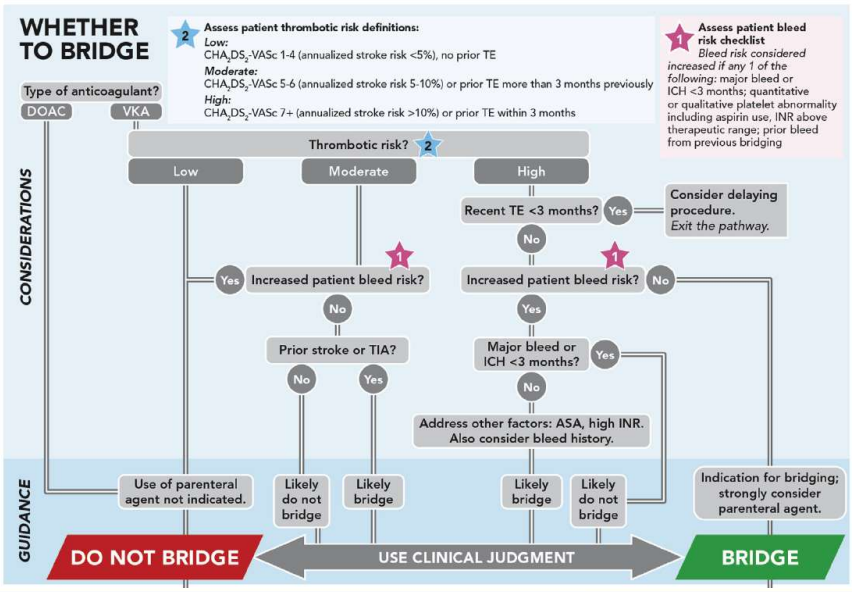
FIGURE 4 Algorithm: Whether to Bridge, and How to Bridge for DOACs and VKAs



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When should I re-start these medications?

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Time is everything

Blacker, *Neurology* 2003

	CVA	No CVA
	11	253
Days off drug	9.0 ± 4	6.9 ± 4

Garcia, *Arch Int Med* 2008

Off Drug	Proportion w/ stroke		95% CI
≤ 5 days	4/984	0.4%	0.2-1.0
≥ 7 days	3/135	2.2%	0.8-6.3

In a study of patient preferences, patients would rather undergo > 4 major bleeding events than suffer a single disabling stroke – a fate they see as "worse than death"
- LaHaye S, et al Thromb Haemost 2014

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Case

- **75 year old female with Afib and prior hx TIA undergoes polypectomy of a 1.5 cm sessile adenoma of the R colon after holding warfarin for 5 days. When should you resume drug?**
  - A. Restart in 5 days
  - B. Restart in 7 days
  - C. Restart within 24 hours
  - D. Restart in 48 hours
  - E. Restart in 10 days

Recommendations for Management of Anticoagulants in Periendoscopic Period

Drug	Half-Life*	Hold Period*	Resume After
Dabigatran	14 hours	1-3 Days	- Immediately following Low Risk Procedures - 48-72 Hours following High Risk Procedures #
Rivaroxaban	8-12 hours	1-2 Days	
Apixaban	8-15 hours	1-2 Days	
Edoxaban	8-17 hours	> 1 day	
Fondaparinux	18 hours	2-4 Days	
Desirudin	2 hours	2 Hours	

* In patients with normal CrCl
# See next slide

Adapted from Baron, TH, et al CGH Feb 2014

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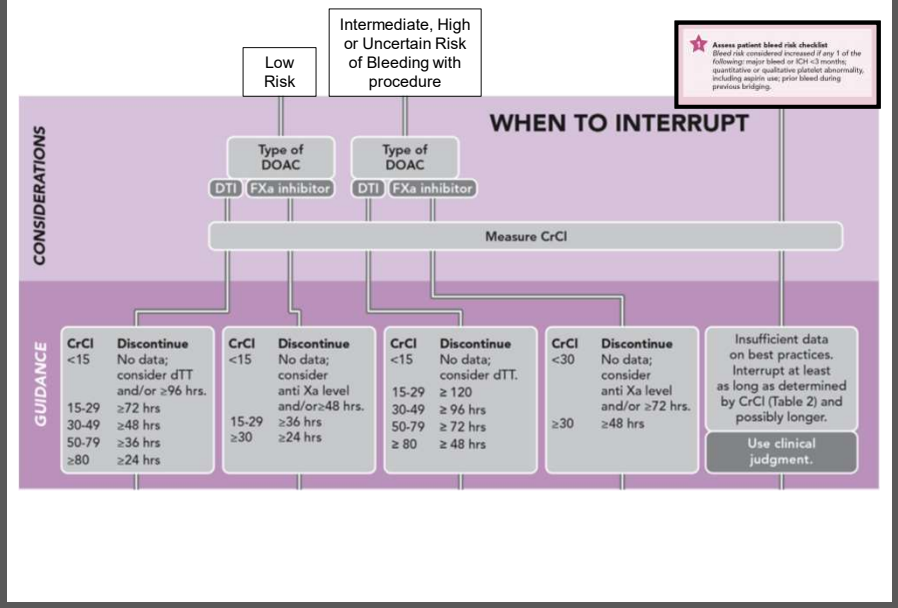

Doherty, et al Periprocedural Anticoagulation Pathway
JACC 2017

TABLE 2 Recommended Durations for Withholding DOACs Based on Procedural Bleed Risk and Estimated CrCl When There Are No Increased Patient Bleed Risk Factors

	Dabigatran					Apixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	≥80	50-79	30-49	15-29	<15	≥30	15-29	<15
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)	6-15	Apixaban: 17 Edoxaban: 17 Rivaroxaban: 9	Apixaban: 17 (off dialysis) Edoxaban: 10-17 (off dialysis) Rivaroxaban: 13 (off dialysis)
Procedural bleed risk								
Low	≥24 h	≥36 h	≥48 h	≥72 h	No data. Consider measuring dTT and/or withholding ≥96 h.	≥24 h	≥36 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥48 h
Uncertain, intermediate, or high	≥48 h	≥72 h	≥96 h	≥120 h	No data. Consider measuring dTT.	≥48 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥72 h.	

NOTE: The duration for withholding is based upon the estimated DOAC half-life withholding times of 2 to 3 half-lives for low procedural bleeding risk and 4 to 5 drug half-lives for uncertain, intermediate, or high procedural bleeding risk (46,60-67).

CrCl = creatinine clearance; DOAC = direct-acting oral anticoagulant; dTT = dilute thrombin time.

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Principles of DOAC Anticoagulant Re-initiation

- All Direct Oral Anticoagulants (and SubQ Drugs) have rapid onset of action (1-3 hours)
- All now have reversal agents although simply holding med usually resolves bleeding
- Delay re-initiation of these drugs (but not warfarin) for 48-72 hours (high risk procedures).
- For patients with high risk for delayed bleed and low risk for TE event, consider waiting 7 days to re-start
- Warn about late (7-14 days) bleed risk

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Special Circumstances

Case

❖ **65 year old female presents requesting surveillance colonoscopy but had a MI 4 months ago resulting in 2 drug-eluting stents. She is currently taking aspirin plus clopidogrel. What should you do?**

A. Proceed as usual but hold the clopidogrel for 5 days before the scope

B. Proceed as usual but hold the ASA 5 days ahead

C. Consult with her cardiologist

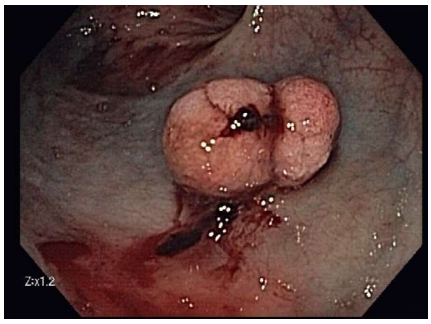
D. Stop both ASA and clopidogrel 5 days ahead

E. Reschedule the test, this is just too risky

Elective Endoscopy in Patients with Coronary Stents

- Delay until "minimum" course of Rx completed per current guidelines
  - Minimum 1 mo after bare metal stent
  - DES: ideally 12 mo if not at high risk for bleeding* Circulation 2017
  - Risk never zero; highest in 1st 30 days

Case Part #2 Clopidogrel held, Colonoscopy shows…



- You successfully resect the polyp w/o immediate bleeding. Should you:

A. Restart clopidogrel within 24-48 hours
B. Continue to hold the clopidogrel for 5 more days
C. Resume the clopidogrel but clip the defect site closed
D. Change the patient to a newer antiplatelet med like Prasugrel and start immediately

Elective Endoscopy in Patients with Coronary Stents

- Once “minimum” period has elapsed
  - Hold clopidogrel/ prasugrel for 7-10 days; continue asa.
  - If not taking aspirin, consider adding it to reduce risk.
  - Clopidogrel or prasugrel may be reinitiated as soon as deemed safe with consideration of the patient’s condition and therapy performed.
  - Consultation with the patient’s cardiologist or other relevant provider may help determine the optimal management of these patients.

Recommendations for Management of Antiplatelet Agents in Periendoscopic Period

Drug[$]	Half-Life*	Hold Period	Resume After Endoscopy
Clopidogrel	7-8 hours	5 days	Within 24-48 hours ALL
Ticagrelor	12 hours	5 days	Within 24-48 hours#
Prasugrel	8-15 hours	7 days	
Vorapaxar	5-13 days	?	?
Ticlodipine	8 hours	5 days	Same Day
Dipyridamole	7-10 hours	7 days	
Aggrenox	15 hours	7 days	

[$] New drug: Anagrelide → similar parameters to clopidogrel

*In patients with normal CrCl
See Next Slide

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Principles of Antiplatelet Re-initiation

- As prasugrel and ticagrelor have a rapid onset of action and are potent antiplatelet inhibitors, re-initiation immediately after high risk procedures should be done with caution[1]
- Clopidogrel or Prasugrel "loading" may rapidly restore antiplatelet therapy in patients who did not have high risk procedures

[1] Baron H Clin Gastro Hep 2014

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ERCP and sphincterotomy

TABLE 3. RISK FACTORS FOR HEMORRHAGE AFTER SPHINCTEROTOMY IN THE UNIVARIATE AND MULTIVARIATE ANALYSES.*

RISK FACTOR	PATIENTS WITH HEMORRHAGE (N=48)	ALL PATIENTS (N=2347)	UNIVARIATE P VALUE	ADJUSTED ODDS RATIO (95% CI)†
Significant in the multivariate analysis				
Coagulopathy before procedure — no. (%)‡	10 (21)	120 (5)	<0.001	3.32 (1.54–7.18)
Anticoagulation within 3 days after procedure — no. (%)§	4 (8)	37 (2)	<0.001	5.11 (1.57–16.68)
Cholangitis before procedure — no. (%)	17 (35)	339 (14)	<0.001	2.59 (1.38–4.86)
Mean case volume of endoscopist ≤1/wk — no. (%)	35 (73)	1189 (51)	0.002	2.17 (1.12–4.17)
Bleeding during procedure — no. (%)¶	23 (48)	678 (29)	0.004	1.74 (1.15–2.65)
Significant in the univariate analysis only				
Cirrhosis — no. (%)	5 (10)	73 (3)	0.003	
Stone as indication for procedure — no. (%)	41 (85)	1600 (68)	0.01	
Periampullary diverticulum — no. (%)	14 (29)	382 (16)	0.02	
Distal bile-duct diameter — mm	10.7±5.5	9.3±4.4	0.03	
Not significant				
Extension of previous sphincterotomy — no. (%)	3 (6)	101 (4)	0.50	
Ampullary tumor — no. (%)	1 (2)	36 (2)	0.75	
Length of incision — mm	10.0±3.0	9.9±3.7	0.82	
Aspirin or NSAID use within 3 days — no. (%)‖	6 (12)	292 (12)	0.99	

Freeman, ML NEJM 1996

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Post-Sphincterotomy Bleeding on APAs

Drug	Freq (%)	P value
No drug	16 (0.8)	
Any APA	19 (5.4)	<0.001
ASA	12 (4.7)	<0.05
Single APA*	3 (6.3)	< 0.05
Mult. APAs	4 (8.3)	<0.05

*Any APA other than ASA
- All comparisons versus "no drug"

Factor	OR	CI	P value
Country			
USA	1		
Korea	0.124	0.042-0.361	<0.001
Intervention			
Pull	7.83	1.41-43.45	0.019
Needle	0.41	0.09-1.83	0.244
Balloon	0.43	0.14-1.32	0.141

Oh, H et al Gut & Liver 2018

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EUS-FNA on antithrombotics

TABLE 1. Comparison of bleeding events among study groups

Event	Group A (patients taking aspirin or NSAIDs) (n = 26)	Group B (prophylactic LMWH) (n = 6)	Group C (control) (n = 190)	*p* Value
Overall bleeding events (%)	0	2 (33.3)	7 (3.7)	0.023
Immediate bleeding				
Extraluminal	0	1	5	NA
Intraluminal	0	0	1	NA
Late bleeding				
Hematemesis	0	1	1	NA

NA, Not applicable.

Kien-Fong, C, et al GIE 2006

"Is this GI? THANK GOD!!

I have a patient with a GI bleed and I need you to scope him NOW!!"

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Drug Management in the Bleeding Patient

Drug Class	Agent	Approach
Anticoagulant Therapy	All	Hold drug
	Warfarin	Administer 1) PCC and Vit K or 2) FFP
	DOACs	Consider reversal agents (andexanet or idarucizumab)
Antiplatelet Agents	All	Consider holding*
	Aspirin	Can give platelets

*Consider continuing in patients with the following:
- •Recent (< 1 year) DES
- •Bare Metal stent < 1 month prior
- •ACS within 90 days

Modified from Acosta, R et al. GIE 2016

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Previous use of Antithrombotics in patients with UGIB is NOT associated with worse outcomes

Table 3

Clinically Relevant Outcomes Per Antithrombotic

	No AT-intake (n = 315)	AT taken (n = 253)	*P* value	Aspirin (n = 187)	Thienopyrimidine (n = 61)	VKA (n = 57)	LMWH (n = 8)	Thrombin-inhibitors (n = 1)	Fac Xa-inh (n =
Rebleeding	49 (17)	34 (14)	NS	27 (16)	9 (15)	6 (11)	1 (14)	1 (100)	1 (1
Surgery/TAE	22 (7.0)	16 (6)	NS	10 (5.4)	2 (3.3)	5 (8.8)	2 (25)	0 (0)	0 (0
Mortality, bleeding related	19 (6.0)	3 (1)	.003	3 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0
Mortality, overall	37 (12)	11 (4)	.002	9 (4.8)	3 (4.9)	0 (0)	0 (0)	0 (0)	0 (0
Mean length of stay (95% CI)	7.9 (2–26)	6.9 (2–23)	.4	6.3 (2–16)	6.4 (1.5–16)	7.7 (2–25)	12.5 (2–31)	4 (4–4)	4.4
Mean units of blood transfused (95% CI)	3.1 (0–9)	3.0 (0–9)	NS	3.1 (0–9)	2.8 (0–8)	3.3 (0–8)	3.5 (0–16)	9 (9–9)	1.9

Dunne, P et al CGH 2018

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Case

- **56 yo male with CHF, s/p Continous flow LVAD 90 days ago presents with near-syncope, hemoglobin of 7 and heme + stool. Which of the following is true?**
  - A. Blood loss is likely lower GI and colonoscopy should be performed asap.
  - B. Anemia is due to hemolysis and no endoscopy is needed
  - C. Blood loss is likely upper GI and EGD should be performed asap
  - D. Blood loss is gastrointestinal but endoscopy is of questionable benefit

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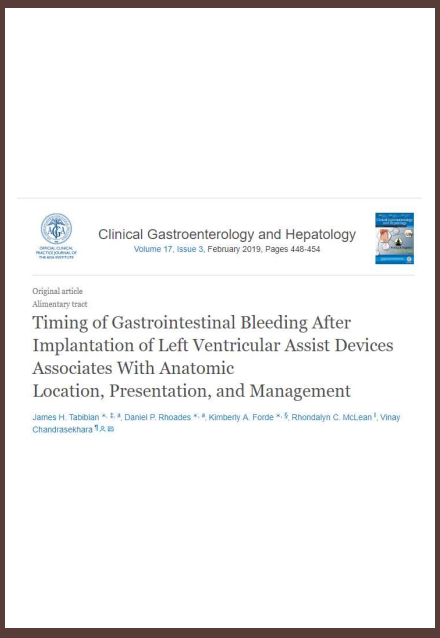

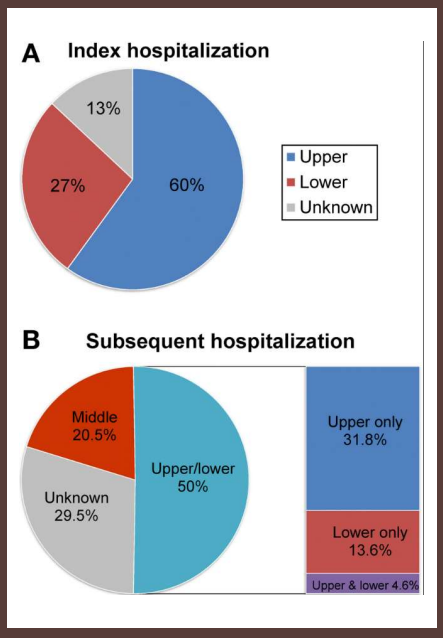

LVAD Bleeding: Pathophysiology

3 Synergistic Mechanisms:

- Coagulopathy (anticoag + ASA)
- Acquired von Willebrand disease
- Continuous non-pulsatile blood flow

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LVAD-related Bleeding

- ~20-30% incidence; All have vWF deficiency
- Continuous flow LVADs (85%)
- Anywhere in the GI tract
  - Most series report upper > lower source
- Endoscopy identifies site in 2/3 cases
- Risk factors

  age, low bmi, prior hx GI bleed, smoking

Clinical Gastroenterology and Hepatology 2015;13:107–114 Gastrointest Endosc 2012;75:973-9 Ann Cardiothoracic Surg 2014; 3(5):475-47
Dig Dis Sci (2011) 56:3241–3246 J Am Coll Cardio 2014; 63(9): 880-888 J Heart Lung Transplant 2014;33:60-64

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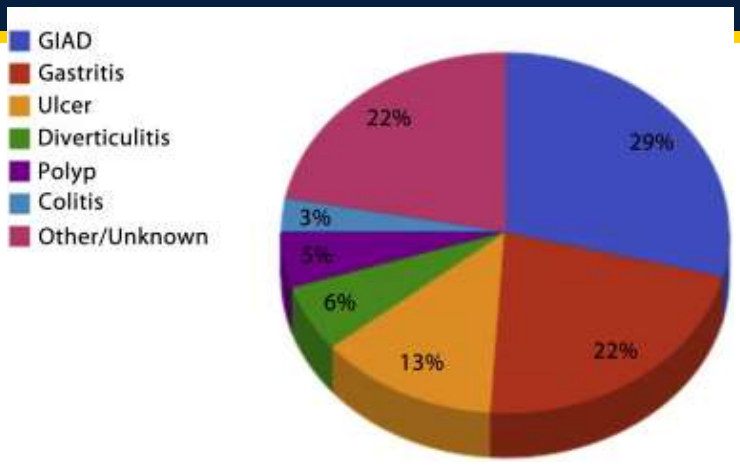
Causes of LVAD–related GI bleeding



Gastrointestinal Endoscopy, Volume 80, Issue 3, 2014, 435–446.e1

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Meta-Analysis Rx GIB in LVAD Patients

- 17 case-control and cohort studies
- 1839 patients (92% continuous flow LVAD)
- Incidence 23%; Time to bleed = 88 days
- Most common Rx: sclerosants for ADLs
- Endoscopy →
  - Earlier resolution of GIB
  - Fewer blood transfusions
  - Fewer diagnostic tests

Gastrointestinal Endoscopy, Volume 80, Issue 3, 2014, 435–446.e1

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LVAD GIB: Prevention Strategies

- Prevention strategies to prevent re-bleed:
  - low pump speed
  - INR at low end of spectrum (1.5-2)
  - Frequent monitoring of heme parameters
  - Consider PPI for patients on DAP Rx
- Patients with GIB on LVAD have a 7-fold increased risk of subsequent TE event

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Take Home Points

- Aspirin can and should be continued for 99.9% of our endoscopies, even therapeutic
- Antithrombotics increase bleeding risk. Further data is needed on benefits of continuing these meds in the peri-endoscopic period
- These meds should be re-started as soon as safely possible after endoscopy
- Bridge therapy is current SOC for High (?Mod) risk patients with Afib but guidelines are changing

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Stay Calm and Carry On
Rangiroa, French Polynesia

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Endoscopic Management of Portal Hypertension

Jessica Mellinger MD MSc
Advances in Gastroenterology & Hepatology
February 7-9, 2020

Please consider the environment before printing this PowerPoint

Disclosures

- No disclosures

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Patient K

- 72 man with hepatitis C cirrhosis, compensated
  - Recently diagnosed after routine HCV screening showed + HCV and cirrhosis
  - On Epclusa for treatment of HCV (week 1)
  - Presented as an outpatient for routine EGD screening for esophageal varices
  - Had never had screening for varices before
  - No history of bleeding, hematemesis, melena
  - Had a colonoscopy with conscious sedation 4 years ago without incident

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Patient K –Further History

- **PMH**- HCV Cirrhosis, HTN, HL, DM, h/o MI 3 years ago s/p DES (now on aspirin monotherapy), Peripheral arterial disease, COPD
- **PSH**: remote cholecystectomy, prostatectomy for prostate cancer 10 years ago (recurrence free)
- **Social Hx**: **active tobacco use**, remote EtOH use (20 years ago), remote h/o IV drug use
- **Family Hx**: none significant
- **No allergies**
- **Meds:** insulin, aspirin 81 mg daily, HCTZ, Lisinopril, simvastatin, Spiriva, Epclusa

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Patient K- Physical Exam

- Vital signs: Normal temp, HR 74, BP 143/82, BMI 42
- HEENT: No icterus, MMM and pink.
- Skin: no jaundice or rash. + spider angiomas on upper chest
- Pulm: CTAB with mildly prolonged end expiratory phase
- CV: RRR, no murmur
- Abd: central adiposity, soft, NT/ND, no organomoegaly noted. BS active
- Ext: WWP, no clubbing, no edema.

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Patient K- Labs

- **CBC:** 7.3>13.4<**110** Normal differential
- **BMP:** Normal
- **LFTs: AST 78, ALT 63**, alk pho and total bilirubin normal. Albumin normal
- **INR:** 1.1 PTT normal
- **AFP** 3

Routine HCC screening ultrasound:

Cirrhotic liver with mild splenomegaly, no ascites, patent portal vein.

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Should Screening EGD for Varices be Performed?

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Should Screening EGD be Performed?

- **Yes!**
- *AASLD Guidance*: “Patients with a liver stiffness score (as measured by transient elastography) of less than 20 kPa *and* platelet counts >150,000 mm^3 have very low (<5%) probability of having high-risk varices and EGD can be circumvented. Patients not meeting this criteria should undergo screening EGD for gastroesophageal varices at the time the diagnosis of cirrhosis is made.”

Garcia-Tsao G, et al *AASLD Portal Hypertension Bleeding Practice Guideline. 2016*

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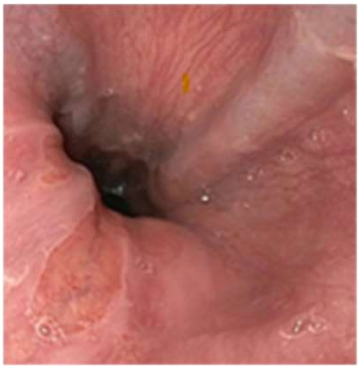
EGD Findings



- Medium sized Grade 2 esophageal varices (3 columns)
- Mild portal hypertensive gastropathy
- No gastric varices
- Possible 1 cm segment salmon-colored mucosa (not biopsied given concern for varices)

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What should you do with these varices?

1. Band them to eradication
2. Nothing
3. Nothing endoscopically but add a non-selective beta-blocker on discharge from the procedure unit
4. Inject cyanoacrylate
5. Set up an appointment with IR to place a prophylactic Transjugular Intrahepatic Portosystemic Shunt (TIPS)

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What should you do with these varices?

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5. Set up an appointment with IR to place a prophylactic Transjugular Intrahepatic Portosystemic Shunt (TIPS)

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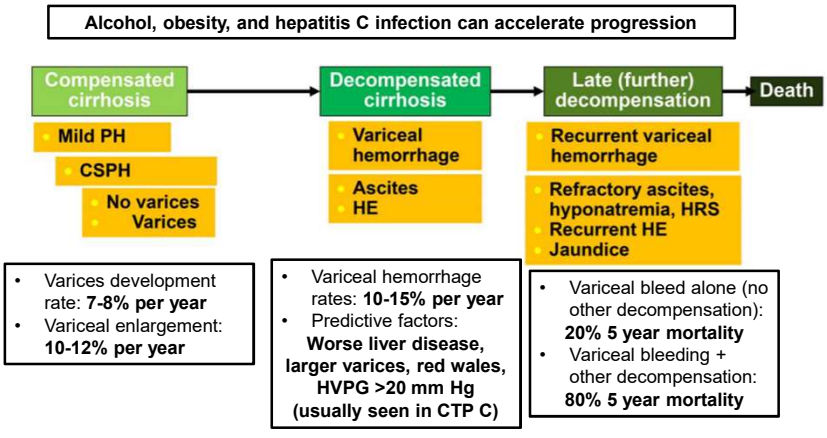
Natural History of Cirrhosis and Portal Hypertension



Garcia-Tsao G, et al *AASLD Portal Hypertension Bleeding Practice Guideline, 2016*

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Primary Prophylaxis: More than Just Banding

TABLE 3. Management of Patients With Moderate/Large Varices That Have Not Bled

Therapy	Recommended Dose	Therapy Goals	Maintenance/Follow-up
Propranolol	• 20-40 mg orally *twice* a day • Adjust every 2-3 days until treatment goal is achieved • Maximal daily dose: ○ 320 mg/day in patients without ascites ○ 160 mg/day in patients with ascites	• Resting heart rate of 55-60 beats per minute • Systolic blood pressure should not decrease <90 mm Hg	• At every outpatient visit make sure that heart rate is on target • Continue indefinitely • No need for follow-up EGD
Nadolol	• 20-40 mg orally *once* a day • Adjust every 2-3 days until treatment goal is achieved • Maximal daily dose: ○ 160 mg/day in patients without ascites ○ 80 mg/day in patients with ascites	• Resting heart rate of 55-60 beats per minute • Systolic blood pressure should not decrease <90 mm Hg	• At every outpatient visit make sure that heart rate is on target • Continue indefinitely • No need for follow-up EGD
Carvedilol	• Start with 6.25 mg *once* a day • After 3 days increase to 6.5 mg twice-daily • Maximal dose: 12.5 mg/day (except in patients with persistent arterial hypertension)	• Systolic arterial blood pressure should not decrease <90 mm Hg	• Continue indefinitely • No need for follow-up EGD
EVL	• Every 2-8 weeks until the eradication of varices	• Variceal eradication (no further ligation possible)	• First EGD performed 3-6 months after eradication and every 6-12 months thereafter

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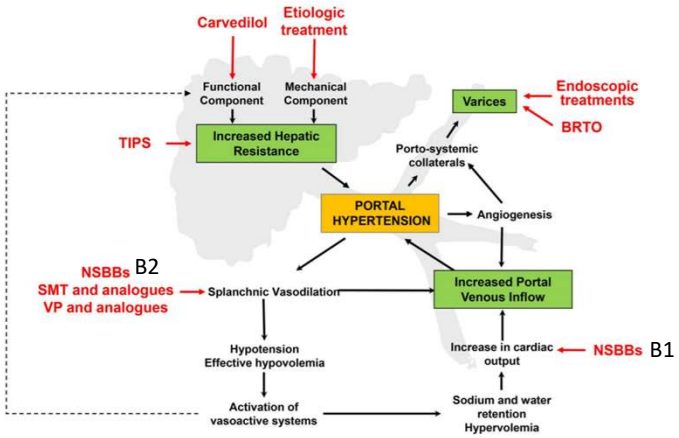
Treatment Options for Varices



Garcia-Tsao G, et al *AASLD Portal Hypertension Bleeding Practice Guideline, 2016*

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Treatment Decision…

- Started carvedilol 6.25 mg once daily
- Patient tolerated well so titrated up to 6.25 mg BID
- Continued to tolerate this well
- Completed his HCV treatment course
- Achieved SVR

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Lost to follow-up and represented 2 years later….

- Presented to an outside hospital with hematemesis
- Reported that he had felt lightheaded and nauseated then vomited large amount of maroon blood and clot at home
- Drove himself to local ED
- VS: Temp normal, HR 126, BP 115/76
- Hgb 7.6, Plts 76, LFTs normal, INR 1.2
- Local ED has no GI doctor so stabilizes with IVFs and 1 u pRBCs and transfers to our ED

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Tertiary Care Center Course

- On arrival in ED, VS 102, BP 123/65
- No further hematemesis
- Hgb after 1 U pRBCs, 7.7 (previously 7.6)
- Started on PPI gtt, octreotide gtt
- Given 1 g IV ceftriaxone
- NG lavage performed, **positive for maroon blood**
- Intubated for airway protection
- 5 hours after arrival, EGD is performed

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Tertiary Care Center Course: Optimal Care?

- On arrival in ED, VS 102, BP 123/65
- No further hematemesis
- Hgb after 1 U pRBCs, 7.7 (previou
- Started on PPI gtt, octreotide gtt
- Given 1 g IV ceftriaxone
- NG lavage performed, **positive for maroon blood**
- Intubated for airway protection
- 5 hours after arrival, EGD is performed

Did he need the RBCs?
- Restrictive transfusion threshold (hgb <7.0) produced better outcomes, esp in decompensated cirrhotics[1]

[1]Villaneuva et al *NEJM* 2013.

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Tertiary Care Center Course

- On arrival in ED, VS 102, BP 123/65
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- Given 1 g IV ceftriaxone
- NG lavage performed, **positive fo blood**
- Intubated for airway protection
- 5 hours after arrival, EGD is performed

Does he need octreotide gtt?
- 50 ucg bolus + 50 ucg/hr for 3-5 days
- Addition of splanchnic vasoconstrictors improves 7 day mortality in variceal bleeding and control of acute bleeding[1]

[1]Wells et al *Aliment & Pharm Ther* 2012.

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Tertiary Care Center Course

- On arrival in ED, VS 102, BP 123/65
- No further hematemesis
- Hgb after 1 U pRBCs, 7.
- Started on PPI gtt, octrec
- Given 1 g IV ceftriaxone
- NG lavage performed, **positive for maroon blood**
- Intubated for airway protection
- 5 hours after arrival, EGD is performed

Does he need antibiotics?
- Yes! Antibiotics in cirrhotics with any GI bleed improves mortality[1]

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Tertiary Care Center Course

- On arrival in ED, VS 102, BP 123/65
- No further hematemesis
- Hgb after 1 U pRBCs, 7.7 (previously 7.6)
- Started on PPI gtt, octreotid
- Given 2 g IV ceftriaxone
- NG lavage performed, **posit**
  blood
- Intubated for airway protecti
- 5 hours after arrival, EGD is

Is an NG tube safe?
- Yes. It is safe to place an NG tube in the presence of varices.

How soon should someone get an EGD if variceal bleed is considered?
- Within 12 hours

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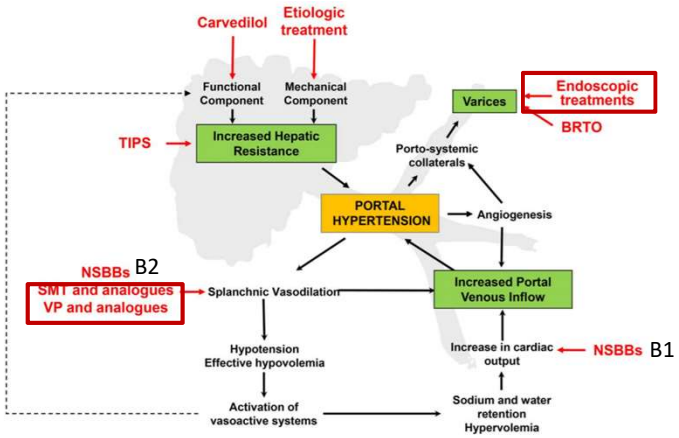
Treatment Options for Varices with Bleeding



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EGD Findings

- Several columns of large varices
- Red spot consistent with recent bleeding noted
- Large gastric varix without stigmata of bleeding noted
- Esophageal varices banded successfully
- Recovered will, completed antibiotics and octreotide
- Discharged to get repeat banding in 2-4 weeks
- Discharged on continued carvedilol

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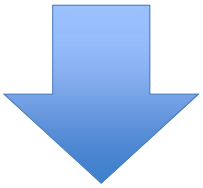
If banding had failed…endoscopic rescue options?

- Sclerotherapy?
- Cyanoacrylate injection?
- Balloon Tamponade
- Esophageal stent



TIPS

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If banding had failed…endoscopic rescue options?

- ~~Sclero~~
- ~~Cyano~~ injection?
- Balloon Tamponade
- Esophageal stent

TIPS

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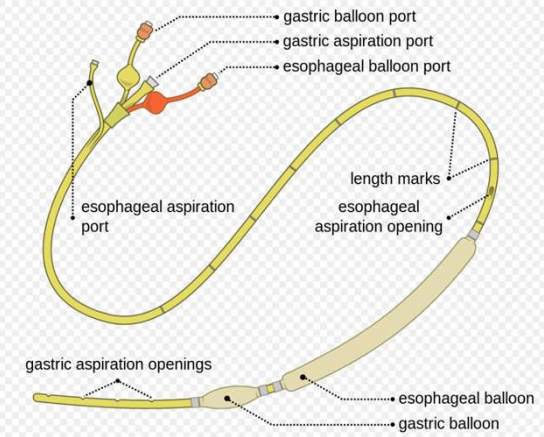
If banding had failed…Balloon tamponade?



- Acts as physical tamponade on bleeding esophageal or gastric varices
- **Bridge to definitive therapy**
- Requires intubated and sedated patient
- Should **not be left up longer than 24 hours** due to increased risk of esophageal rupture
- **High rate of adverse events (20-60%):** aspiration pna, esophageal rupture, esophageal ulcer, tonge/nose/lip necrosis, chest pain, arrhythmia

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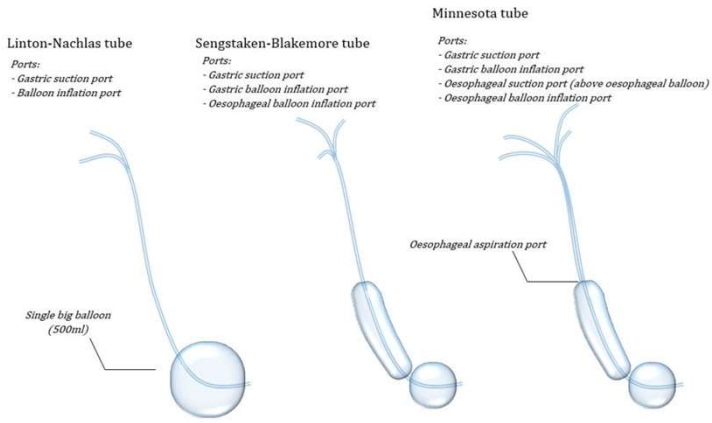
Types of balloon tamponade devices



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Balloon tamponade (BT) associated with worse outcomes: chicken or the egg?

- National cohort: 5.5% of acute variceal hemorrhage required balloon tamponade
  - **Higher mortality (1.17, 95% CI 1.01-1.37)**
- Paired single-center study (10.1% required BT)
  - Associated with **alcohol abuse** (50.4% vs 21.4%, p=0.04) and **HCC** (35.7% vs 8.8%, p=0.01), higher **MELD** (26.3% vs 15.5%, p=0.002) and **active bleeding** (64% vs 27%, p=0.01)
  - Failure to provide 4 key quality metrics (endo within 12 hours, band-ligation, pre-endo abx, and octreotide) **increased use of BT** (OR 16.7, p<0.0001)

Tapper EB et al *Liver Int* 2017

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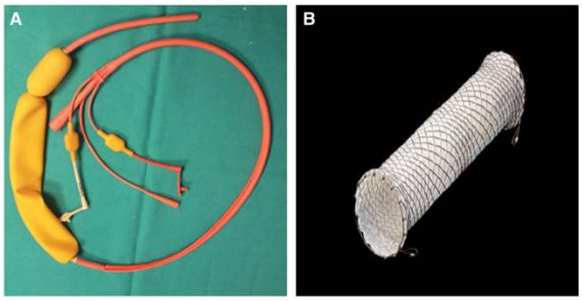
Balloon tamponade vs esophageal stenting: a better option?

Multi-center (Spain) RCT of BT vs SEMS
Cirrhosis with acute variceal bleeding not controlled by pharm/endoscopic tx or who had massive, hemodynamically unstable variceal bleed
Exclusions: age <18, esophageal pathology (rupture, tumor, stenosis/stricture, large hiatal hernia), known HCC beyond Milan, terminal disease

Sengstaten-Blakemore tube



SX-ELLA Danis stent

Escorsell et al *Hepatology* 2016

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SEMS vs BT: Trends for benefit, but small numbers

TABLE 2. Main Results of the Study (ITT Analysis)

Variable	Esophageal Stent (n = 13)	Balloon Tamponade (n = 15)	*P* Value
Inclusion criteria, n (%)			0.93
Failure of combined therapy	8 (62)	9 (60)	
Massive bleeding	5 (38)	6 (40)	
Interval admission-inclusion, days*	1.5 (0-7)	1 (0-25)	0.60
Success of therapy, n (%)	8 (66)	3 (20)	0.025
Absence of bleeding, 15 days, n (%)	11 (85)	7 (47)	0.037
Absence of SAEs, n (%)	11 (84)	8 (53)	0.077
Survival at 15 days, n (%)	9 (69)	8 (47)	0.39
Absence of bleeding, 6 weeks, n (%)	7 (54)	7 (47)	0.25
Absence of device-related SAE, n (%)	12 (92)	9 (60)	0.049
Causes of death (15 days; n)			0.044
Hypovolemic shock	1	6†	
MOF after sepsis	3	1	
Survival at 6 weeks, n (%)	7 (54)	6 (40)	0.46
Use of additional resources (during the hospital stay), n (%)	4 (31)	11 (73)	0.059

- **No difference in primary outcome (mortality at 6w)**
- Greater number of adverse events in BT (14 vs 6)
- SEMS could stay in longer, allowing for planning procedures
- Many SEMS patients avoided TIPS placement but no longer term data on how they fared without TIPS

Escorsell et al *Hepatology* 2016

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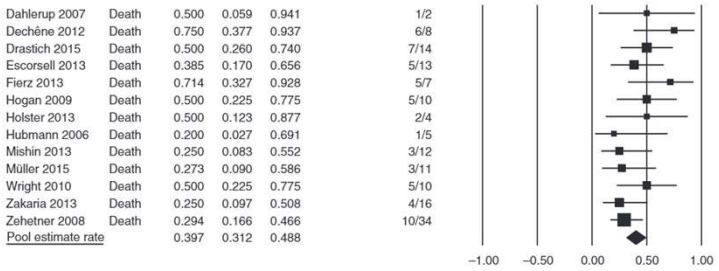
Meta-analysis: Comparable to balloon tamponade

- 13 studies (case series and 1 RCT): All used the SX-ELLA stent, except one study
- Event rate for mortality ~40% for SEMS, 18% for failure to control bleeding



Dahlerup 2007	Death	0.500	0.059	0.941	1/2
Dechêne 2012	Death	0.750	0.377	0.937	6/8
Drastich 2015	Death	0.500	0.260	0.740	7/14
Escorsell 2013	Death	0.385	0.170	0.656	5/13
Fierz 2013	Death	0.714	0.327	0.928	5/7
Hogan 2009	Death	0.500	0.225	0.775	5/10
Holster 2013	Death	0.500	0.123	0.877	2/4
Hubmann 2006	Death	0.200	0.027	0.691	1/5
Mishin 2013	Death	0.250	0.083	0.552	3/12
Müller 2015	Death	0.273	0.090	0.586	3/11
Wright 2010	Death	0.500	0.225	0.775	5/10
Zakaria 2013	Death	0.250	0.097	0.508	4/16
Zehetner 2008	Death	0.294	0.166	0.466	10/34
Pool estimate rate		0.397	0.312	0.488	

Marot et al *APT* 2015

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6 months later….

- Patient has continued getting serial EGDs with banding to eradication each time
- Last was 3 months ago
- Presents to the ED again with massive hematemesis
- VS: 101, BP 126/72, stable and protecting his airway
- Receives octreotide gtt, PPI gtt, IV ceftriaxone
- Ultrasound Doppler is a poor study, can't really see the portal vein well
- Intubated for EGD

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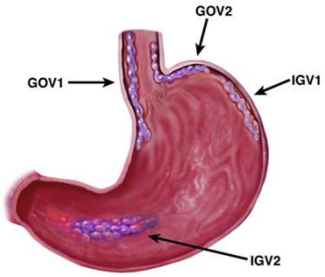
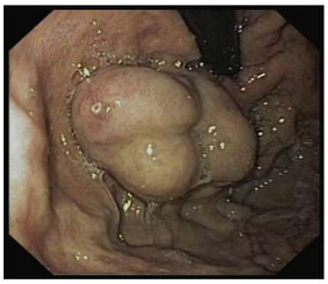
EGD results…

- Small, low-risk, grade 1 varix
- Lots of scar in lower esophagus from banding
- Large gastric varix with evidence for recent bleeding→ IGV1





Garcia-Pagan JC et al *CGH* 2014

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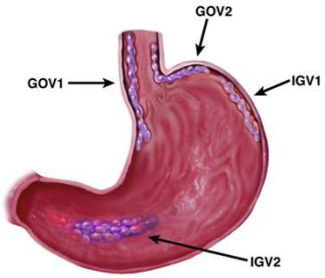
Gastric varices: less common, but dramatic bleeds



Type	Definition	Relative frequency	Overall bleeding risk without treatment
GOV 1	OV extending below cardia into lesser curvature	70%	28%
GOV 2	OV extending below cardia into fundus	21%	55%
IGV 1	Isolated varices in the fundus	7%	78%
IGV 2	Isolated varices else in the stomach	2%	9%

GOV, gastro-oesophageal varices; IGV, isolated gastric varices; OV, oesophageal varices.

- Risk factors similar to those for esophageal varices
  - Larger varix size
  - Red spots
  - More severe liver disease (CTP C>B>A)

Garcia-Pagan JC et al *CGH* 2014;
EASL Complications of Cirrhosis Guidelines 2017

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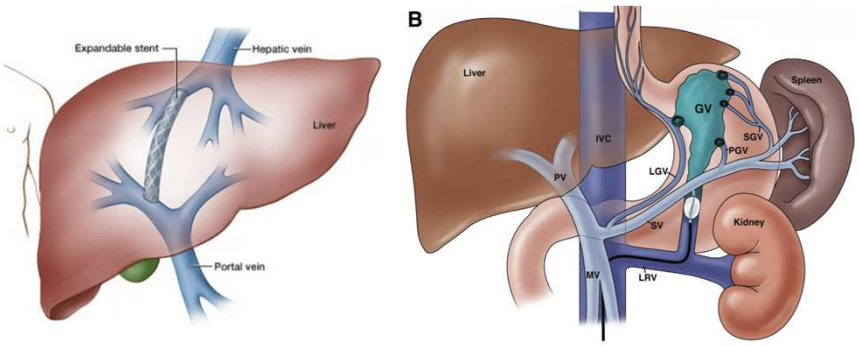
Frequently resort to non-endoscopic management

- TIPS +/- Balloon-occluded retrograde transvenous obliteration (BRTO)



Garcia-Pagan JC et al *CGH* 2014

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TIPS vs BRTO: depends on the patient

- Meta-analysis of 5 studies (only 1 RCT, remainder observational)
- 436 patients (Korea, US): 308 BRTO, 127 TIPS
- Comparable MELD, CTP scores between groups

References	Country	Age	Design	Sample Total	Size BRTO	Size TIPS	Follow-up (Mean)	Cirrhosis Etiology (Top 3)	Varices Classification	Outcomes
Choi et al[7]	Korea	Mean 57 Range: 42-80	Randomized controlled trial Single-center	15*	8	7	14.4 mo	HBV: 52.4% HCV: 28.6% Alcohol: 19%	GOV 1 and 2	Technical success rate, rebleeding, ascites, hepatic encephalopathy, survival Child-Pugh
Sabri et al[8]	USA	Median, range TIPS: 55, 31-79 BRTO: 52, 23-83	Retrospective cohort Single-center	50	23	27	BRTO 18.2 mo vs. TIPS 19.5 mo	Alcohol: 24% Alcohol/HCV: 22% HCV: 16% Cryptogenic: 16%	IGV 1 and 2	Technical success rate, procedure-related complications, hepatic encephalopathy, rebleeding
Lee et al[9]	Korea	Mean: 58.1	Retrospective Cohort Multicenter	142†	95†	47†	28.2 mo	Alcohol: 44.4% HBV: 42.3% 4.9%	GOV 1 and 2, IGV 1 and 2	Overall survival, rebleeding rate, liver function tests, Child-Pugh, survival
Kim et al[10]	USA	Mean, range TIPS: 58, 34-81 BRTO 59, 26-86	Retrospective cohort Single-center	52	25	27	BRTO 727 d vs TIPS 917 d	Alcohol 38.5% HBV/HCV: 36.5% NASH: 11.5% Cryptogenic: 11.5%	IGV 1 and 2	Technical Success, procedural complication, liver function test, MELD score, hepatic encephalopathy, ascites, rebleeding, survival
Gimm et al[11]	Korea	Mean TIPS 54.4 BRTO 59.4	Retrospective cohort Single-center	176†	157†	19†	Up to 10 y	HBV: 49.4% Alcohol: 23.9% HCV: 14.8%	GOV 2, IGV 1 and 2	Overall survival, bleeding control rate, rebleeding, reduction in gastric varix, hepatic encephalopathy, ascites, liver function, MELD, Child-Pugh, liver function test

Yu et al *J Clin Gastro* 2019

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TIPS vs BRTO

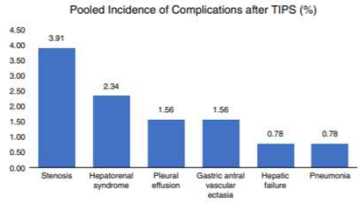
- Comparable technical success rates, lower gastric varix rebleed rate with BRTO, similar immediate bleed control rates (97% vs 95%)
- Mix of gastric varix types may play a role in outcomes
- Higher risk of ascites with BRTO (due to rise in portal pressure)

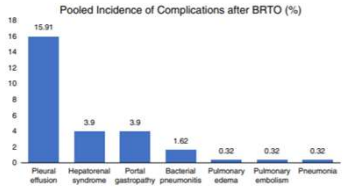
TABLE 3. Pooled Technical Success Rate of BRTO Versus TIPS

References	Successful BRTO	Total BRTO	Successful TIPS	Total TIPS
Sabri et al[8]	21	23	27	27
Kim et al[10]	22	25	27	27
Lee et al[9]	106	123	49	60
Gimm et al[11]	159	166	19	22
Total	308	337	122	136
Success rate	308/337	91.4%	122/136	89.7%

TABLE 5. Rebleeding Rate From GV Source, Pooled Study

References	GV Rebleed From BRTO	Total BRTO	GV Rebleed From TIPS	Total TIPS
Sabri et al[8]	0	23	3	27
Kim et al[10]	2	25	2	27
Lee et al[9]	7	95	6	47
Choi et al[7]	0	8	1	6
Total	9	151	12	107
Rebleed rate	9/151	6.0%	12/107	11.1%





Yu et al *J Clin Gastro* 2019

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But what if you don't have TIPS or BRTO?

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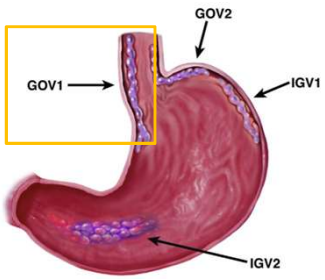
What can we do *endoscopically* for bleeding gastric varices?



- GOV1: banding (if technically feasibly) vs glue injection possible
  - **Caution with banding directly on the gastric varix however as difficult to get whole gastric varix** and resulting ulcer can lead to catastrophic, difficult to control bleeding
  - Frequently, banding esophageal varices will result in disappearance of GOV1

Garcia-Tsao G, et al *AASLD Portal Hypertension Bleeding Practice Guideline, 2016*

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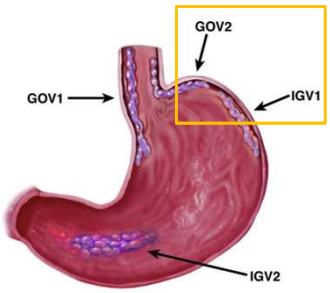
What can we do *endoscopically* for bleeding gastric varices?



- GOV2/IGV1:
  - Cyanoacrylate (tissue adhesive or “glue”) injection
  - Meta-analysis of 3 RCTs→ glue equally effective as EVL and has lower rebleeding rate *but most studies included mostly GOV1*
  - **Not available in the US**
  - **TIPS +/- BRTO preferred**

Garcia-Tsao G, et al *AASLD Portal Hypertension Bleeding Practice Guideline, 2016*

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Patient stabilized, IR intervention planned

- MRI liver obtained
  - Showed a large PVT (80% occlusive in main PV, 60% in right PV, extension into SMV)
  - Cirrhotic liver
  - No HCC or mass
  - Large gastrosplenorenal shunt feeding large gastric varix
- Patient was VERY concerned about risk of hepatic encephalopathy with TIPS

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EUS Guided Coil Embolization of Fundal Varices

- More recent technique involving EUS-guided insertion of coils +/- tissue adhesive into fundal varices (GOV2/IGV1)
- Tissue adhesive injection alone associated with more serious, sometimes fatal adverse events (glue embolization)
- Addition of coils acts as a “scaffold” to keep glue in the varix, decreasing risk of embolization and amount of glue needed
- Initially smaller case series showed feasibility and promising safety profile and efficacy

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Largest series: Retrospective 152 cases

- 2009-2015, UCSF case series
- Only fundal varices (GOV2**, IGV1**)
- 152 treated: 112 secondary prophlaxis, 40 (26%) primary prophylaxis
  - 53% of all patients were on NSBB
- Technical success: 151 patients
  - Avg 1.4 coils used, 2 mL glue
- 125 patients had follow-up

Characteristic	Value
Varix type (IGV-1/GOV-2)	143/9
Mean varix size, largest diameter in mm (range)	21 (10-60)
Mean coil number (range)	1.4 (1-4)
Mean glue volume, mL	2 (.5-6)
Technical success	151 (99%)
Adverse events (n = 125)	9 (7%)
Pain	4
Embolization*	1
Bleeding from coil/glue extrusion	4
Patients with EUS follow-up	100
EUS confirmed obliteration of GFV	93 (93%)
Patients with EGD/clinical follow-up	25
Patients with no follow-up	26
Post-treatment bleeding (n = 125)**	20 (16%)
Early	12
Late	8
Post-treatment bleeding etiology	
Gastric varices	10
Esophageal varices	4
Portal hypertensive gastropathy	5
Arteriovenous malformation	1
Mean follow-up, days (n = 125) (range)	436 (30-2043)

Bhat et al *GIE* 2016

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EUS guided coil embolization

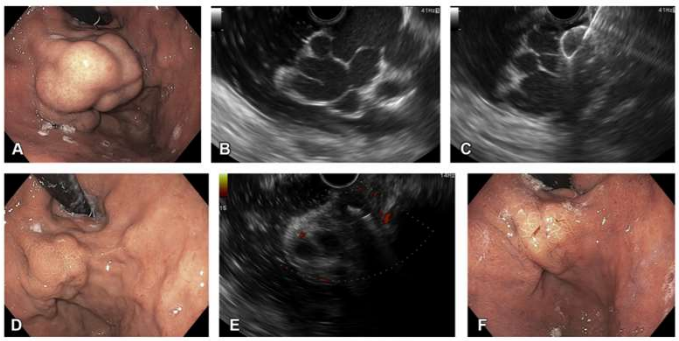

Figure 1. A, Large, type 1 isolated gastric variceal conglomerate in a patient with a history of bleeding. **B,** EUS showing same 4-cm varices conglomerate. **C,** Transesophageal deployment of coil through a 19-gauge needle. **D,** 1-month follow-up endoscopy showing markedly smaller variceal complex with cracked earth pattern suggesting obliteration. **E,** EUS showing variceal conglomerate at 1-month follow-up. Absent flow on color Doppler. **F,** 9-month follow-up showing eradicated varices.

Bhat et al GIE 2016

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Patient K

- Expertise with EUS guided coil embolization was unavailable
- Ultimately underwent staged BATO followed by TIPS with embolization/sclerosis of splenorenal shunt
- Doing well
- Minimal encephalopathy

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Conclusions

- Know when to start screening for varices
- Know when to band and when not to band
- EV→ band ligation + NSBB, TIPS for refractory bleed or re-bleed
- Gastric varices → TIPS, BRTO, can consider glue or EUS-guided coil embolization, if expertise is available

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Pancreatic Cystic Neoplasms: Where are we in 2020?

Richard Kwon, MD, MS
Clinical Associate Professor
Division of Gastroenterology and Hepatology
February 8, 2020

Acknowledgement

Sponsored by AGA-Covidien Research and Development Pilot Award in Technology

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Outline

- Clinical relevance
- Differential diagnosis
- Approach
- Diagnosis
- Management
- Future directions

Epidemiology

- Estimated prevalence ranges from 3-45%
- Incidence increases with age

- Source of patient/clinician anxiety: is it cancer?
- Inevitable rise in health care utilization
- Challenge: establish the most cost effective workup and management

Scheiman JM, et al. AGA Tech Review.Gastroenterology 2015

The cancer scare

- Only identifiable precursor to pancreatic cancer
- 17% of asymptomatic pts had in-situ or invasive cancer, and 42% had a premalignant lesion

Fernandez-del Castillo C, et al. Arch Surg. 2003;138:427-3
Scheiman JM, et al. AGA Tech Review. Gastroenterology 2015

Overestimation?

- Southern California Kaiser
  - 2.9% of 1815 pts developed malignancy
  - Incidence 0.4% per year during surveillance
- Recent systematic review
  - Risk of malignancy 0.017% (max 0.25%)
  - Risk of malignancy over 20y : <1%

Wu BU, et al. AmJ Gastro 2014
Scheiman JM, et al. AGA Tech Review. Gastro 2015

So why do we care?

- Chance for early diagnosis of pancreatic cancer

So why do we care?

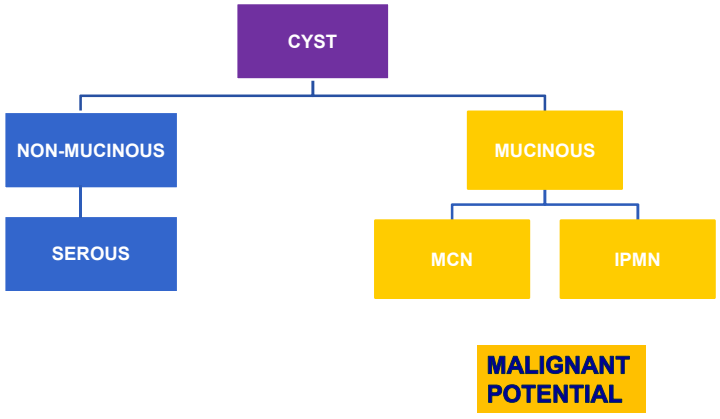
- Large number of resections for benign disease
- Mortality from pancreatic surgery 2.1% (1.5-2.7%)
- Morbidity from pancreatic surgery 30% (25-35%)

Scheiman JM, et al. AGA Tech Review. Gastro 2015

Outline

- Differential diagnosis
- Approach
- Diagnosis
- Management
- Future directions

Pancreatic cysts



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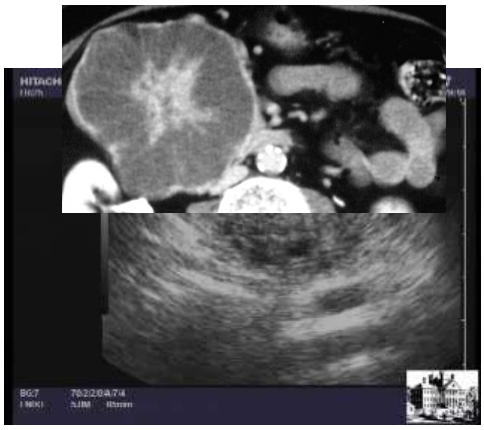
Serous cystadenoma

- Unilocular, microcystic
- Glycogen-rich, cuboidal epithelium
- F>M, age 70s
- Benign



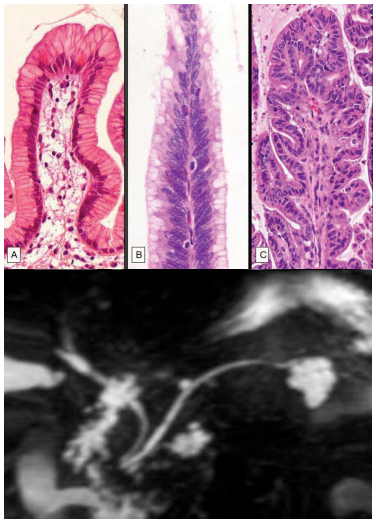
Cyst Zebras

- Solid pseudopapillary neoplasm
- Lymphangioma
- Cystic degeneration of malignancy

Jani N, et al. Endoscopy 2008; 40: 200-03

Intraductal papillary mucinous neoplasm (IPMN)

- Mucin secreting columnar papillary epithelium
- Main duct ± side-branch
- M~F, mean age 60s
- Head>body/tail



IPMN- risk of malignancy

- Tied to location
  - Side-branch
  - Main duct or mixed duct

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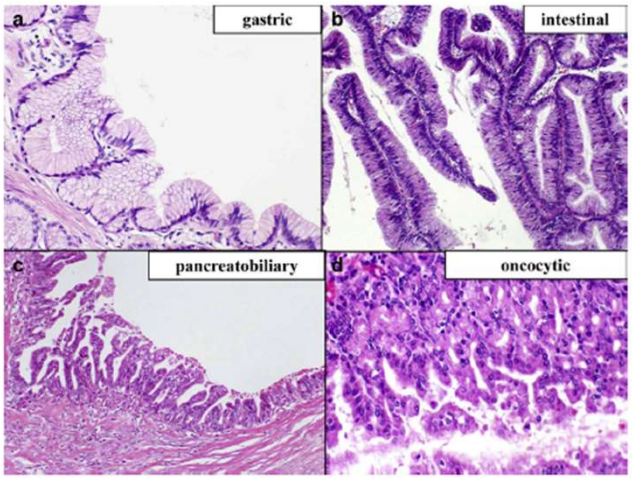
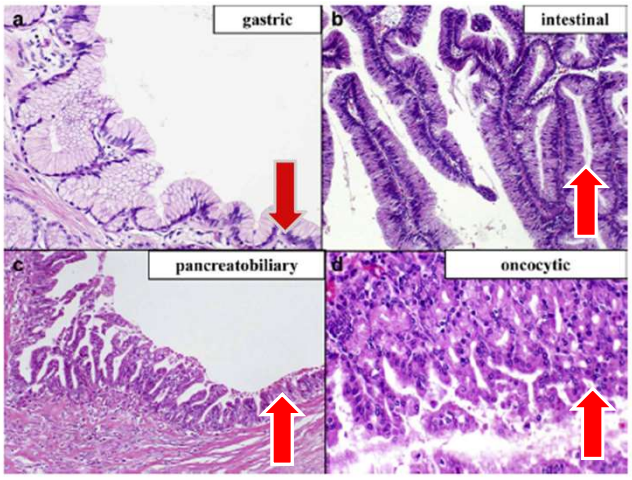
IPMN subtypes



Furukawa T, et al. Virchows Arch 2005
Furukawa T et al. Gut 2011
Mino-Kenudson, M et al. Gut 2011
Distler M, Ann Surg 2013

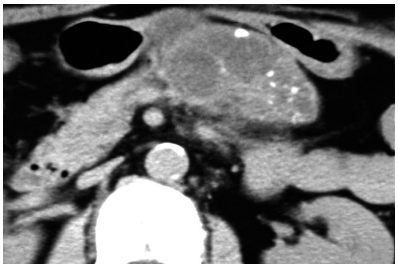
IPMN subtypes- malignant risks

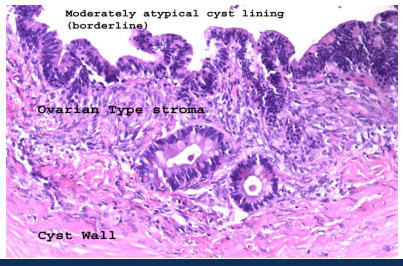


Furukawa T, et al. Virchows Arch 2005
Furukawa T et al. Gut 2011
Mino-Kenudson, M et al. Gut 2011
Distler M, Ann Surg 2013

Mucinous cystadenoma

- Characterized by ovarian stroma + mucinous epithelia. No duct involvement
- Unifocal, macrocystic
- F>M, mean age 48y
- Body/tail





Reddy RP, et al. Clin Gastroenterol Hepatol 2004

MCN- risk of malignancy

- Ranges from 0 to 34%
- Risk factors
  - Age: pts with malignancy older (55yo v 44yo)
  - Cyst: size ≥ 4cm, mural nodules, peripheral calcifications
- Challenge: no biomarker to identify MCN

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Outline

- Differential diagnosis
- Approach
- Diagnosis
- Management
- Future directions

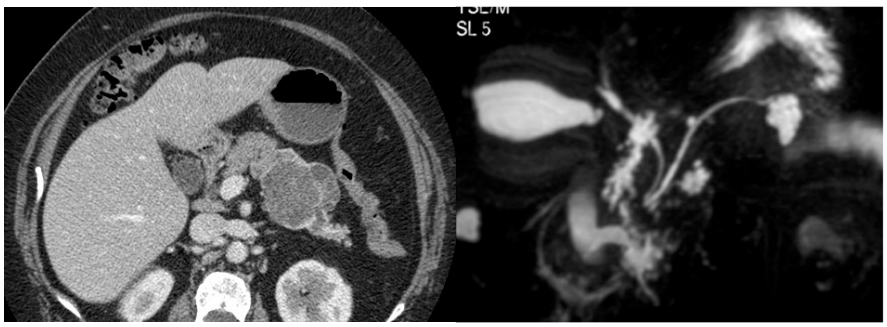
History

- Symptoms
  - Pain
  - Jaundice
  - Weight loss
- History of pancreatitis
- Family history of pancreatic cancer

Outline

- Clinical relevance
- Differential diagnosis
- Approach
- Diagnosis
- Management
- Future directions

Tools: imaging



"pancreas protocol" CT MRCP

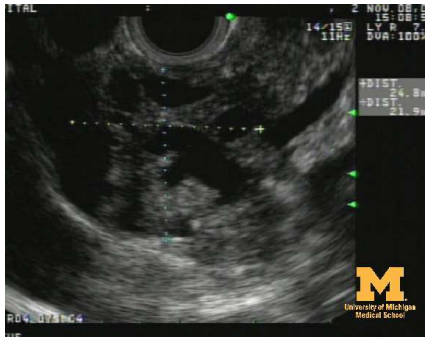
- Insensitive for differentiating types of cysts
- Accuracy only 40-60%

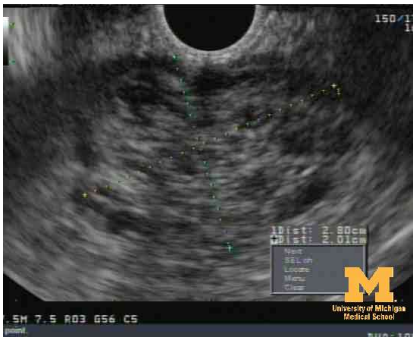
Do RKG et al. AJR 2014;203:973-9
De Jong K et al. Pancreas 2012;4:278-82

Imaging

- Main duct dilation
- Size
- Relation to main duct
- Nodules or mass
- Septations
- Calcifications

Tools: EUS





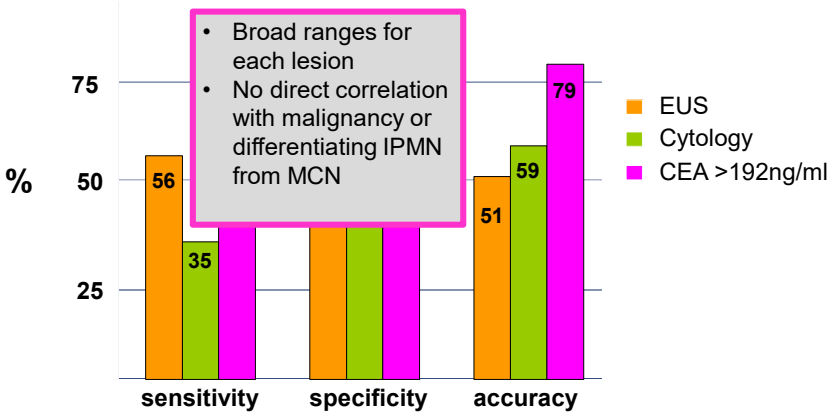
- Lackluster interobserver agreement
- Cannot reliably differentiate between benign and malignant cystic lesions

Fine needle aspiration (FNA)

- Cytology
- CEA
- DNA analysis

Cyst Fluid CEA

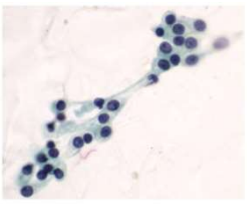
- Most accurate test to distinguish mucinous from non-mucinous lesions.

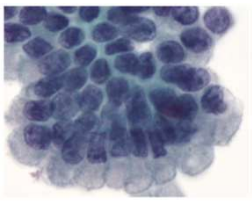


Brugge WR, et al. Gastroenterol 2004;126:1330-1336

Cytology

- Overall accuracy is 50%
- Useful to identify malignancy
- Low negative predictive value
- Limitations:
  - insufficient cellularity
  - cross-contamination





Cyst fluid DNA: GNAS

- Surrogate markers for mucinous lesions and/or malignancy
- *GNAS* mutation at codon 201
- Present in ~60% IPMN
  - 100% intestinal
  - 71% pancreaticobiliary
  - 51% gastric
  - 0% oncocytic
- NO correlation with location, malignancy or survival

Outline

- Differential diagnosis
- Approach
- Diagnosis
- Management
- Future directions

Who gets cancer?

- Size >3cm
- Solid mass/nodule
- Dilated main duct*
- Family history of pancreatic cancer

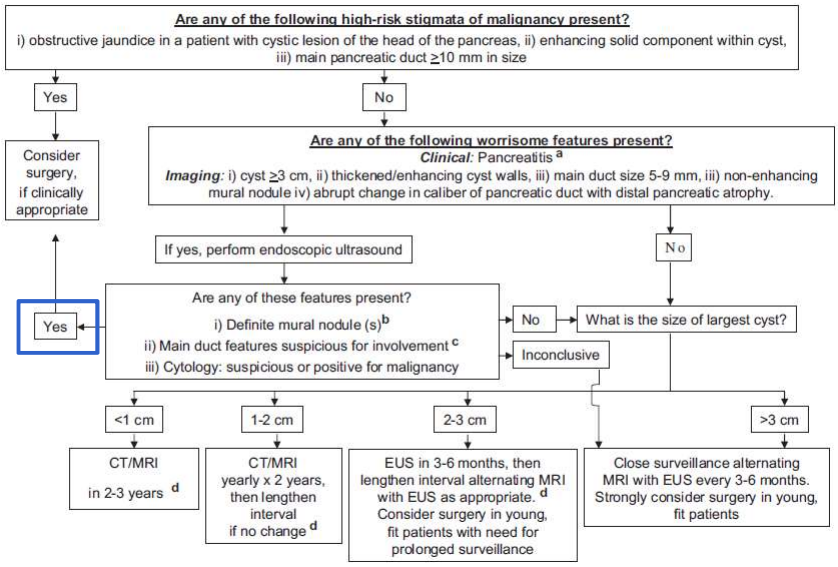
Scheiman JM, et al. AGA Tech Review. Gastro 2015
Nehra D et al. Pancreatology 2012

	Risk Increase	Lifetime Risk
Family History		
Any with PCa	2.4x	**4%**
3 or more relatives	6.8x	**12-20%**

Syndrome	Gene (s)	Lifetime Risk PDAC
Hereditary Breast Ovarian Cancer	*BRCA1* *BRCA2* *PALB2*	5-10%
Lynch Syndrome	*MLH1* *MSH2* *MSH6* *PMS2*	4-10%
Familial Melanoma (FAMMM)	*CDKN2A*	10-30%
Peutz Jeghers Syndrome	*STK11*	10-30%
Familial Adenomatous Polyposis	*APC*	1-5%
Li Fraumeni Syndrome	*TP53*	
Ataxia Telangiectasia	*ATM*	1-5%
Hereditary Pancreatitis	*PRSS1*	50%

IAP consensus guidelines

- Main duct or mixed duct IPMN:
  - Resect, regardless of symptoms
- Side-branch IPMN:
  - Resect if symptomatic
  - Monitor if <3cm, no main duct dilatation or mural nodule
- MCN
  - Resect, regardless of symptoms



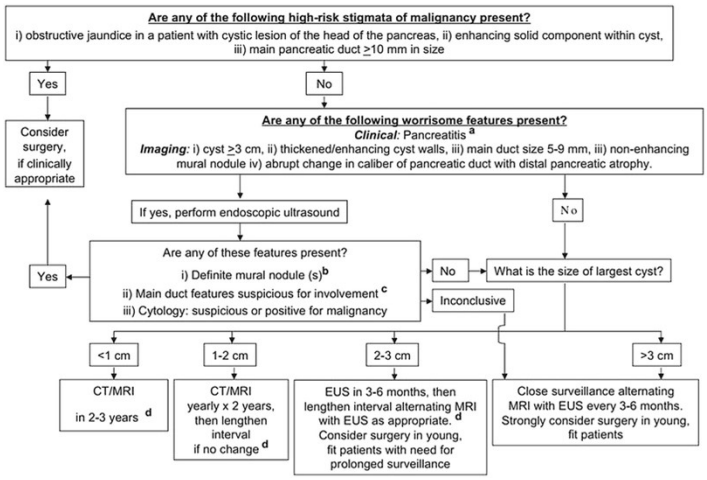
Tanaka M, et al. Pancreatology 2012

Guidelines performance

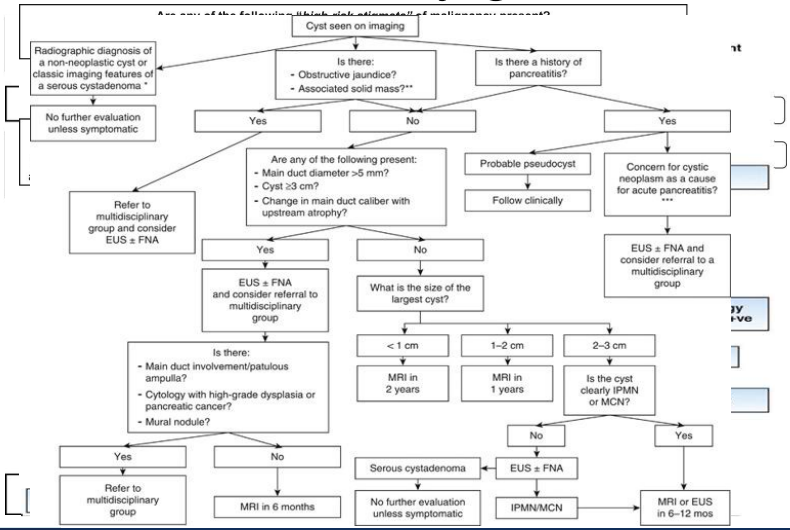
- 9 studies pooled for analysis
- Malignancy detection:
  - Negative predictive value: 90-100%
  - Positive predictive value: 11-52%
- New guidelines may improve sensitivity at expense of specificity
- Surgeries for benign disease

Go BK J Gastrointest Surg 2013
Jang JY Br J Surg 2014

Guidelines…



Guidelines, so many guidelines



AGA Guidelines

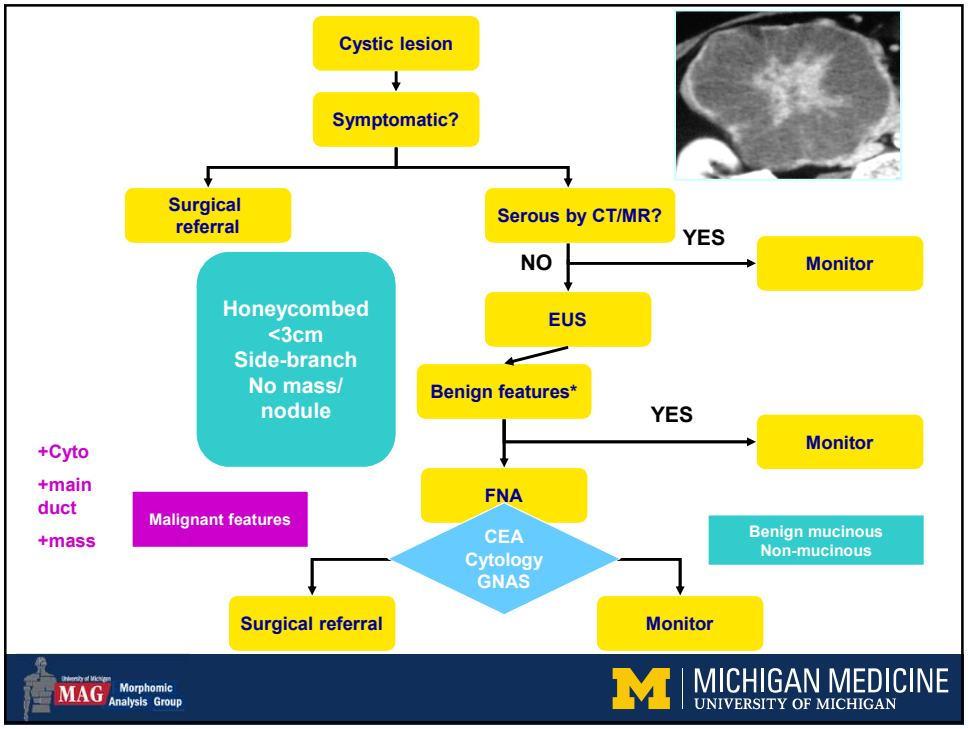
- Cysts < 3cm w/o worrisome features: serial MRI
- Cysts ≥ 3cm ± worrisome features: EUS/FNA
  - If 2+ high risk features, then operate
  - If no high risk features, then serial imaging
- Surveillance
  - Change in characteristics, then EUS
  - Stop after 5 years

AGA Guidelines

- Surgery should be at expert centers
- Post-op surveillance
  - If cancer or dysplasia, then serial imaging
  - If no dysplasia, then no imaging

How the guidelines differ

	2012 IAP	2015 AGA	2018 ACG
Target population	Suspected mucinous cysts	All incidental cysts	All incidental cysts
Recommended imaging	Panc protocol CT or MRI	MRI/MRCP	MRI/MRCP
Indication for surgery	1 risk factor	≥2 risk factors	2 risk factors
Surveillance recommendations in unresected cysts	CT/MR based on size	MRI in 1 year then q2yr	MRI based on size
When to stop surveillance	No recommendation for unresected cysts. Post-resection: SCA or benign MCN	After 5 years if stable, no development of high risk features. Post-resection: BD-IPMN < HGD.	Non-surgical candidates. Until age 75 for healthy candidates (individualized for >75). Post-resection: SCA, benign MCN.



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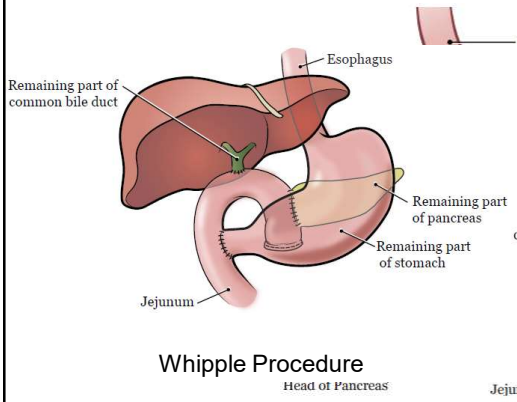
Follow-up Studies
(CT, MRI or EUS)

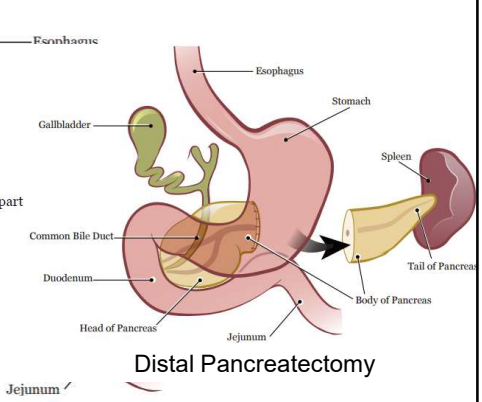
- No significant change in size or behavior after mean 24 months – 9 years
- Incidence of adenoCA in follow up of suspected IPMN: 2.8 - 3.7%
- Timing of interval follow-up unclear

Pausawasdi N, et al. Surgery 2010;147:13-20
Scheiman JM, et al. AGA Tech Review. Gastro 2015
Crippa S et al. Dig Liver Dis 2016;48:473-479

Surgical considerations



Whipple Procedure



Distal Pancreatectomy

Post-op surveillance

- SCA: not recommended
- MCN: not recommended
- IPMN: recommended
  - Recurrence: 0-17%
    - main duct IPMN: 50-90%

Outline

- Differential diagnosis
- Approach
- Diagnosis
- Management
- Future directions

Clinical challenges

- Differentiating between mucinous and non-mucinous cysts
- Differentiating between MCN and IPMN
- Identifying lesions with HGD or CA
- Clarify natural history: identifying lesions that will progress onto HGD or CA

Clinical challenges

- Who benefits most from going to EUS or OR?
- How can we avoid unnecessary procedures?

Future directions

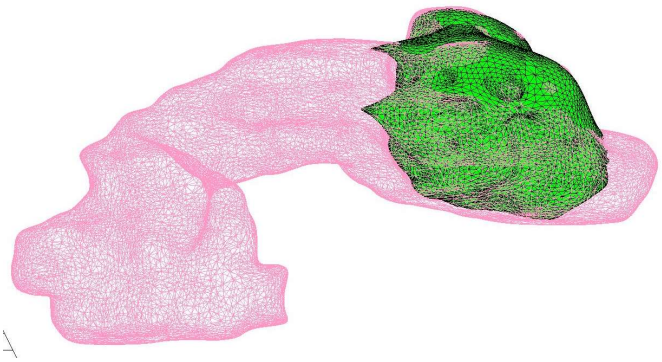
- Improve diagnostic accuracy
  - Imaging technology
  - Biomarkers

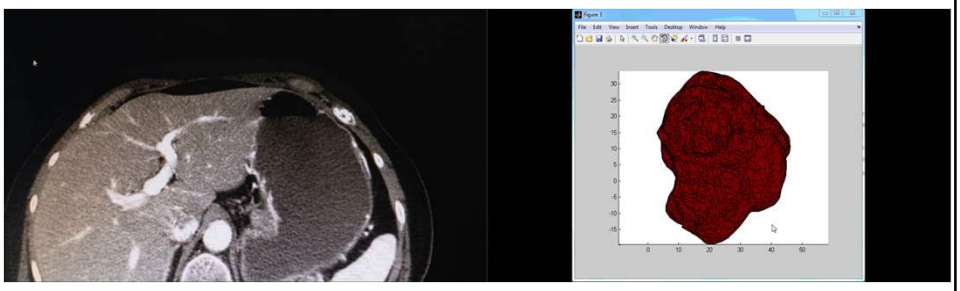
Improve diagnostic accuracy of imaging

- Minimize those who require surveillance
- Minimize those who need surgery

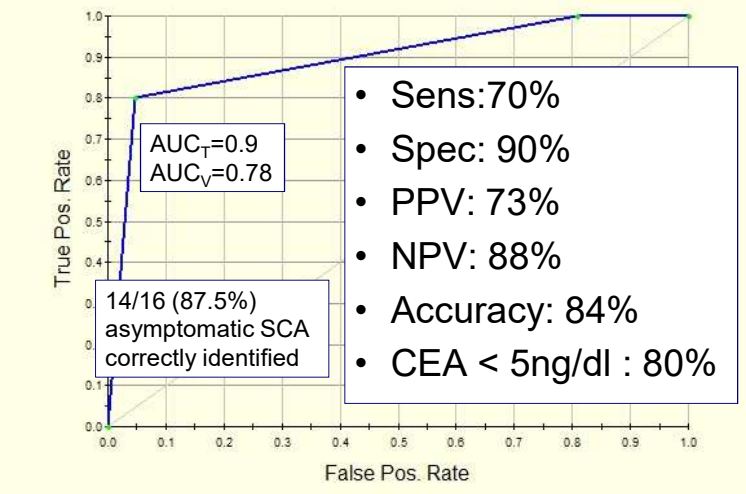
Das A, et al. Gastrointest Endosc 2009

3D model of a pancreas

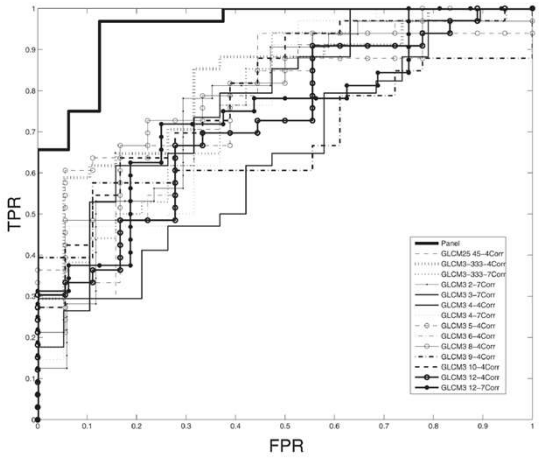




Performance of SCA prediction model (non-mucinous v mucinous)



Quantify risk of malignancy?

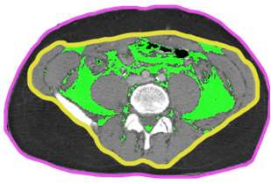


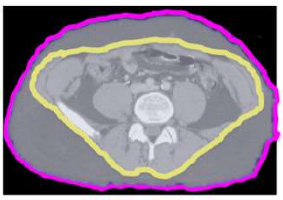
Hanania AN, et al. Oncotarget 2016

Risk assessment

- Risk of cancer
- Risks of surgery
- Can we improve upon (or personalize) patient counseling regarding surgical risks?

Risk assessment: body composition





Results	
VFTBA	OR 3.1, 95%CI 1.4,6.4

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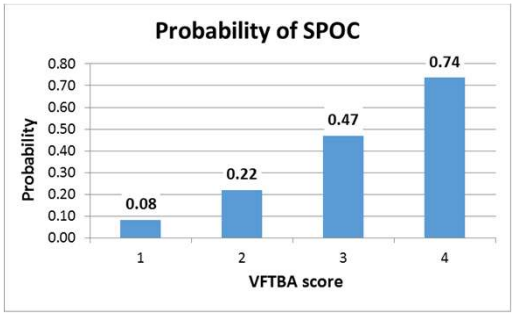
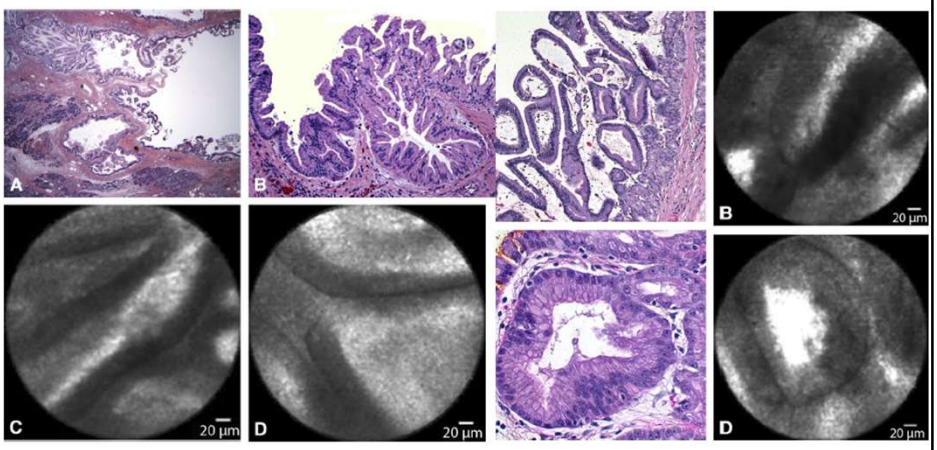
Multivariate Analysis



- Probability of SPOC is 8.2% for patients in lowest quartile (VFTBA score 1)
- Probability of SPOC is 74% for patients in the highest quartile (VFTBA score 4)

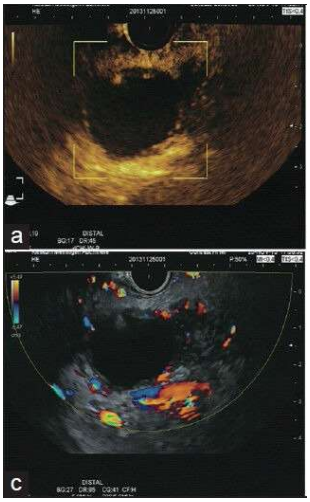
Confocal imaging in cysts



Konda VJA et al. GIE 2011
Nakai Y et al. GIE 2015

Other imaging of cysts

- Spectroscopy
- OCT
- Contrast EUS
- Scanning fiber endoscopy



Tumor biomarkers

- Cyst fluid
  - Relatively easy to obtain
  - Presumed concentration of biologically relevant material
- Multiple methods
  - Genomic (RNA, DNA)
  - Proteomic
  - Metabolomic

Cyst fluid biomarkers

Genetic biomarkers
DNA-based
K-ras
GNAS
VHL
RNA-based
miR-21
miR-155
Protein-based biomarkers
Prostaglandin E(2)
Interleukin-1ß
mAb Das-1
MUC1
MUC2
MUC4
MUC5AC
MUC5B
MUC6
MUC16
MUC18

Protein-based biomarkers
CA 19-9
Plectin-1
S100-A6, 8, 9, 11
CEACAM 1, 5, 6, 7
BGP-1
Tspan-8, 27, 28
CD55
E-cad
Glutathione S-transferase P
Olfactomedin-4
Prostate stem cell antigen
Pyruvate kinase isozymes M1/M2
Ras-related protein Rab-8A
Rho-related GTP-binding protein RhoC
Trefoil factor 1,2
VE-cadherin
Protein Z-dependent protease inhibitor
Von Willebrand antigen 2

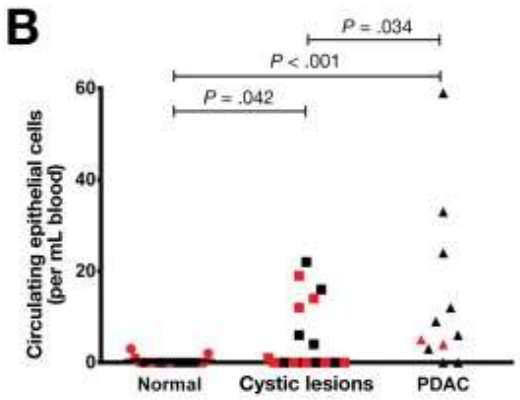
Metabolomic biomarkers
Glucose
Kynurenine

Combinations

Table 3. Identification of Pancreatic Cyst Type

	Composite molecular markers			
Type of cyst	Any of these present	Any of these absent	Sensitivity, % (95% CI)	Specificity, % (95% CI)
SCA	*VHL*[b] chr3 LOH[b,c]	*KRAS* *GNAS* *RNF43* chr5p aneu chr8p aneu	100 (74–100)	91 (84–95)
SPN	*CTNNB1*	*KRAS* *GNAS* *RNF43* chr18 LOH	100 (69–100)	100 (97–100)
MCN	None	*CTNNB1* *GNAS* chr3 LOH chr1q aneu chr22q aneu	100 (74–100)	75 (66–82)
IPMN	*GNAS* *RNF43*[d] chr9 LOH chr1q aneu chr8p aneu	None	76 (66–84)	97 (85–99.9)

Circulating tumor cells



Rhim A, et al. Gastroenterology 2014

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Xenograft models & cell lines

- MCN cell line
- Invasive IPMN cell line

Sorio C, et al. Virchow Arch 2005;446:239-245
Fritz S, et al. Pancreas 2010;39:308-14

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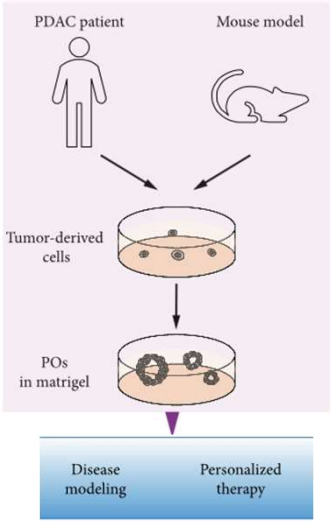
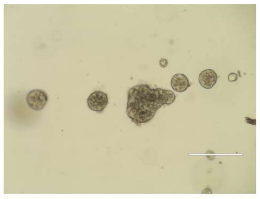
Organoids

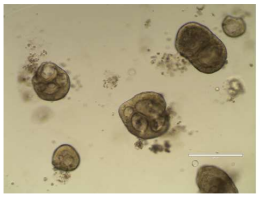


Organoids grown from cyst fluid

1254



1255



Specimen	Acquisition	Final Path
1254	Core of 2.4 x 1.3 cm cyst	Benign epithelium
1255	Fluid from 8.0 x 4.3 cm cyst	Granular debris, degenerated cells, and macrophages, no epithelium found

Summary

- Pancreatic cystic lesions are a clinical challenge.
- Decision to proceed with further invasive testing must be made in context of clinical setting and performed when the results will affect clinical management.
- Imaging and cyst fluid analysis are helpful in determining the etiology of cystic lesions.

Summary

- Improved diagnostic accuracy to distinguish mucinous v. nonmucinous and malignant v. benign cysts is needed.

Management of Chronic Pancreatitis

Michelle A. Anderson MD, MSc, FASGE

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Disclosures

Consultant

Boehringer-Ingelheim, Boston Scientific, Olympus of the Americas

DSMB

GSK

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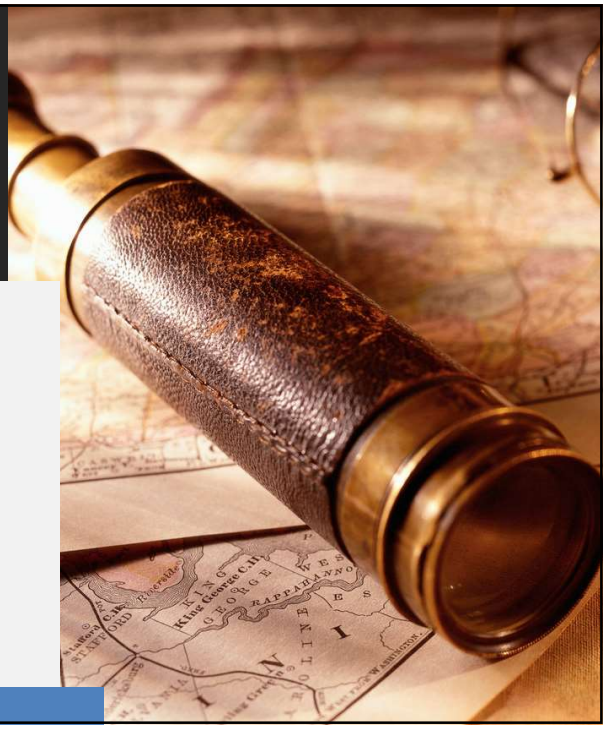
Focus

- Lifestyle
- Nutrition and Panc Enzyme Insufficiency
- Pain
- Endoscopic Rx



Case

54 year old male with recurrent acute on chronic pancreatitis

- Episodes: abrupt without obvious prec. q 6-8 weeks
- Prev heavy drinker
- Non-drinker since first episode; PPD tobacco
- All w/u negative inc. EUS, MRI, blood

What is your BEST next step?

A. Secretin-stim MRI
B. ERCP with sphincterotomy
C. Smoking cessation plan
D. Referral for total pancreactectomy with islet cell transplant

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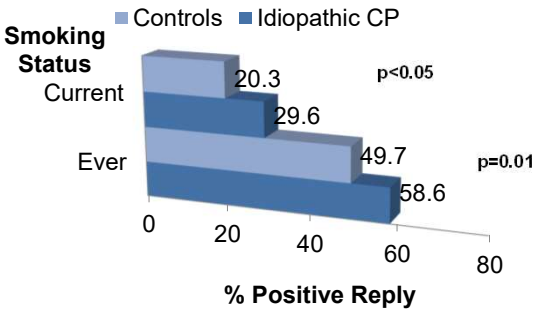
Understanding the Role of Tobacco Use in Chronic Pancreatitis

Contribution of Tobacco Use to CP Risk in US

- NAPS2 Cohort Study 2000-2006, CP=539 Controls 695
- 3 Groups: EtOH, Non-EtOH, Idiopathic
- After controlling for age, gender, BMI and EtOH, ever smoking, current smoking and dose of tobacco use were <u>independently</u> associated with idiopathic CP.
- Attributable Risk = 25%!



Cote' G, et al. Clin Gastroenterol Hepatol 2011

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To Quit or Not to Quit Smoking

Not to Quit

- 166 patients Italian & Swiss
- Idiopathic CP, longitudinal 5+ years
- Smoking → HR 2.09 (95% CI 1.07-4.10) panc calcifications, in shorter interval as well as diabetes (HR 3.94; 95% CI 1.14-13.6)

Maisonneuve, et al. Pancreas 2006

To Quit

- 360 patients Verona, Italy
- Mixed etiology, inc EtOH
- Compared to never-smokers, ex-smokers were no more likely to develop calcifications (OR 0.56, 95% CI 0.2-1.4) while those that did were [OR 1.95 for ½ ppd and 1.76 for ppd]

Talamini, et al. Pancreas 2007

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Smoking is Under-Recognized

- More than 2/3 of Patients in NAPS2 smoked, yet cited as risk < ½ time*
- More likely to recognize if*:
  - Alcohol etiology, current user, heavy user, longer duration of use
- Strength of association is independent of recognition and all co-variates*
- Growing evidence that inhaled marijuana is equally harmful#

**Yadav, et al. Pancreatology 2010;*
#Chen J Gastroenterol Hepatol 2016

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Case

68 yo male with calcific chronic pancreatitis presenting with weight loss of >50#, chronic abd pain, bloating and malodorous stools

- Describes worsening of pain with eating
- Consuming > 3000 kcal/day
- 2-3 loosely formed, large volume stools per day
- Ex-Etoh, Ex- Tobacco
- Recent comprehensive metabolic profile = NL

Which of the following is the next best step?

A. Endoscopic ultrasound
B. Qualitative fecal fat & fecal elastase
C. Quantitative 72-hour fecal fat
D. Fasting blood glucose and Hbg A_1C
E. Feeding tube placement

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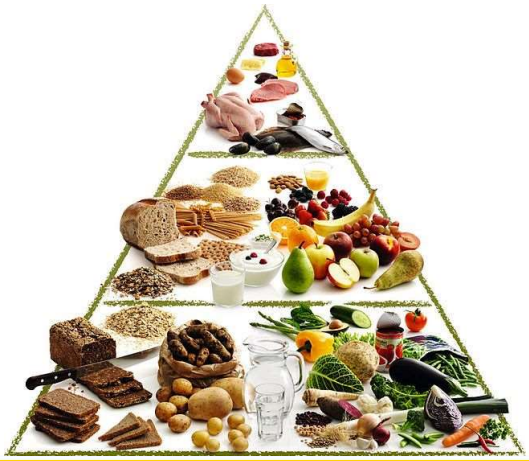
Nutrition and PEI in CP



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Malabsorption in CP

- Typically low fecal water: weight
- DO observe fat-soluble vit def (A,D,E,K)
  - Should be monitored annually
  - CAN cause bone disease[1]
- Usually takes 10-20 years to develop
- Occurs when secretion < 10% baseline
  - i.e. when > 90% exocrine function is lost

Dx
- Fecal Fat
- Fecal Elastase

Rx
- PERP
- Min= 500 Lipase IU/kg/meal

F/U
- Compliance
- Acid
- Cancer?

1 Tignor, Am J Gastroenterol 2010

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Case

- 56 yo female with CP w/ 3-6/10 epigastric pain
  - Daily, unremitting
  - Worse w/food
  - Using tramadol, APA, NSAIDs, PPI
  - CT → No PD or Bil dil
  - No Sx/Sx PEI, DM, weight loss
- What is the next best step?
  A. Add a neuromodulator
  B. Add MS Contin
  C. Add Norco prn
  D. Refer to Pain Clinic
  E. Refer for ERCP

Pain

INFLAMMATION

MECHANICAL

NEURO-REMODELING

MALABSORPTION

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Hospitalization for CP Pain

- More than 90% of patients with CP have had at least 1 hospitalization for pain *
- Almost 20% of patients with severe and/or unremitting pain have had ≥ 10 *
- Mean length of stay for "CP" DRG = 5.1 days #
- Average charge of $28,634 #
- Aggregate cost = $172, 012, 000 #

** Mullady, et al Gut 2011 # Peery, et al Gastroenterol 2012*

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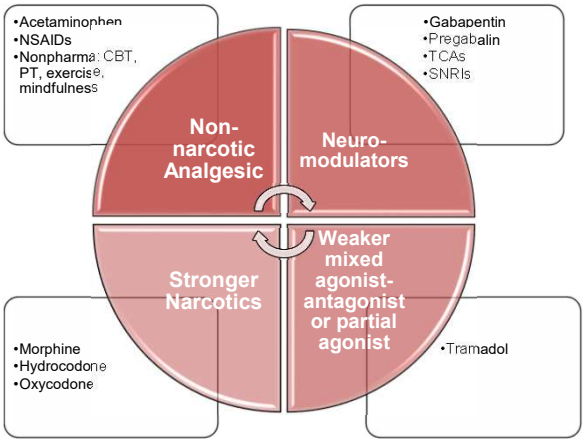
Medical Therapy in CP



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Narcotic Use in Painful CP

Drug	# Prescriptions	Prescription Cost
Hydrocodone/Acetaminophen	171,121	6,524,330
Oxycodone/Acetaminophen	76,199	3,970,182
Oxycodone	25,097	2,629,763
Promethazine	20,846	184,599
Codeine/Acetaminophen	8,808	89,625
Acetyl Salicylic Acid/Oxycodone	964	30,971
Meperidine	1,139	21,709

More than 300,000 Rxs* → $13, 451, 179

* In 2004

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What we learned from NAPS II

- Pain in CP is a continuum – even 5 categories did not "capture" all experiences = COMPLEX DISEASE
- Pain impacts **ALL** facets of patients' lives
- Temporal nature of pain (frequency) has significant impact on endpoints → Tools which assess only severity alone aren't sufficient

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Medical Rx for Pain

- PERP
- Acetaminophen/ NSAIDs
  - Not for advanced disease → Ulcer disease
- Weak Opioids – e.g. Tramadol or codeine
- Neuromodulating meds – TCAs, SSRIs, Gabapentin
- Stronger Opioids – Morphine, et al

Case Study

- 34 yo female with h/o symptomatic choledocholithiasis post-partum
- S/P cholecystectomy, ERCP with CBD stone extraction 1 yr ago
- Diabetes following pregnancy (normal BMI) on liraglutide
- Presents with episodic epigastric pain, normal comp, A/L

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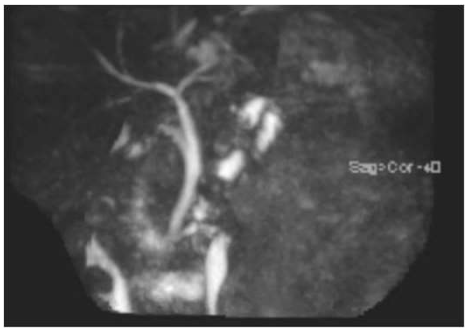
MRCP



What is your next BEST step?

A. Chronic narcotics
B. Referral for pancreatectomy
C. Initiate PERP
D. Oral prednisone
E. ERCP

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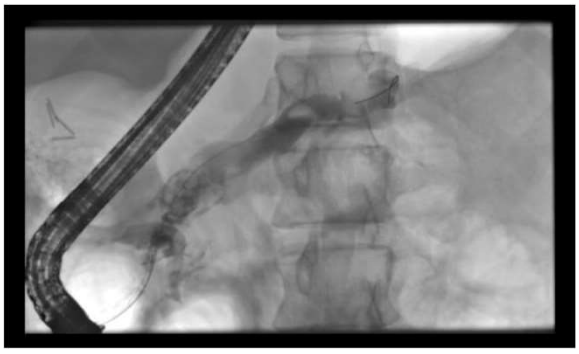
ERCP



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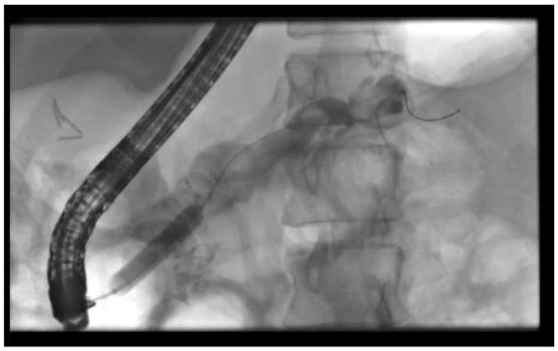
ERCP



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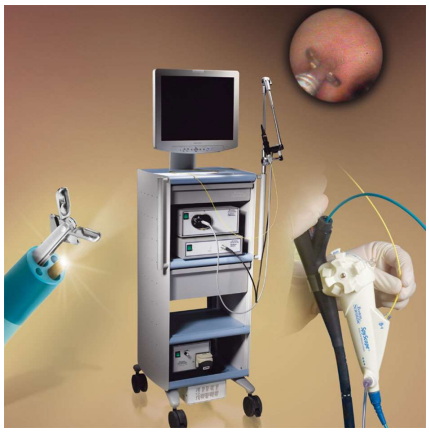
Spyglass with EHL



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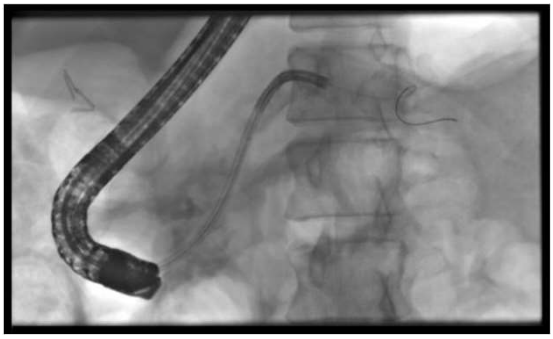
ERCP



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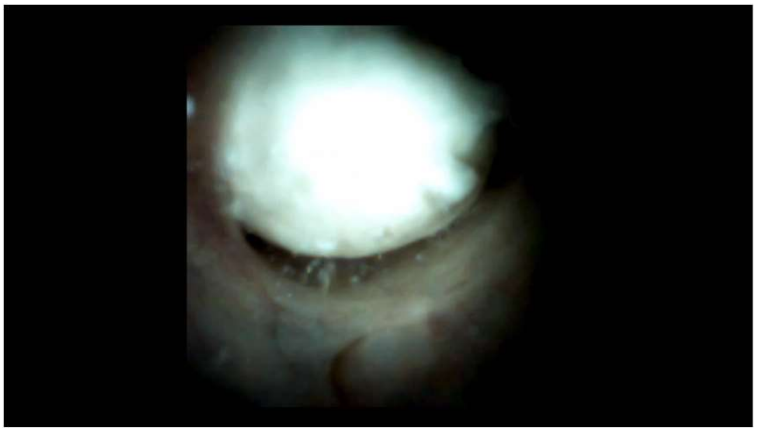
EHL PD stones



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Endoscopic Rx for CP

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Endotherapy vs. Surgery

- RCT surg vs endotherapy in 72 pts*
  - Initial pain relief similar
  - 5 yr f/u: Pain relief 86% after surgery vs 61% after endo RX
  - Problems: no ESWL in this study, efficacy non-blind
- RCT surg vs endotherapy in 39 pts**
  - 2 yr f/u: Pain relief 75% surgery vs 32% endotherapy
  - 5 yr f/u: Pain relief 80% surgery vs 30%***
  - Problems: small study with low technical success w endotherapy (53%)

*Dite Endoscopy 2003 **Cahen NEJM 2007 ***Cahen Gastro 2011

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Use of endoscopy and surgery in CP in the U.S.

Endoscopic Therapy	Tried n (%)	Effective n (%)
Biliary sphincterotomy	215 (41.7)	86 (40.0)
Biliary stent	71 (13.8)	29 (40.8)
Pancreatic duct stent	185 (35.9)	87 (47.0)

Surgical Therapy	Tried n (%)	Effective n (%)
Biliary sphincteroplasty	22 (4.3)	10 (45.5)
Cyst removal	38 (7.4)	30 (76.3)
Drainage procedure	51 (9.9)	36 (70.6)
Resection procedure	64 (12.4)	47 (73.4)

More patients treated with endoscopy than surgery (60.8% versus 30.5%)
Surgery perceived to be more effective overall (68.5% versus 42.8%)
and for pain (69.6% versus 38.8%)

Glass, et al Pancreas 2014

Endotherapy for Chronic Pancreatitis

- MPD obstruction can cause pain although treatment of obstruction only relieves pain in about 80% (multifactorial)
- MPD obstruction*:
  - Due to strictures in 47%
  - Due to stones in 18%
  - Due to combination stricture and stones in 32%

* Rosch Endoscopy 2002

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Pancreatic Stricture Endotherapy

- Case series pain relief: 65-84%*
- Endotherapy pts needing surgery: 4-26%
- Endoscopic therapy recommended as first line therapy given low morbidity compared to surgery**
- Small cases series of FCSEMs in pancreas:
  - Complications: migration 30%, new stricture 16%
- Trial of FCSEMs in U.S. recently completed - ? results

*Chandrasekhara ASGE Guideline 2015
**Dumonceau ESGE guideline 2012

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Therapy recommendations in CP

- Medical therapy should be first line (Evidence: 1b; GRADE: B)
  - Behavior modification, Pain meds, PERT, (?) antioxidants
- Endoscopic therapy can be beneficial in certain settings (Evidence 2b; GRADE: B)
  - PD dilation/stricture; PD stones, pseudocysts, leaks
- Surgery is indicated when medical and/or endoscopic Rx fails (Evidence 2b; GRADE: C)
  - Surgery preferred over endoRx if high stone burden esp. in body/tail or with strictures of CBD/PD

Anderson, et al Pancreatology 2016

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Pearls

- Encourage smoking cessation in all patients with chronic pancreatitis who smoke as this increases the risk for recurrent attacks and progression of disease
- Monitor for PEI and prescribe adequate PERP
- Treat pain using targeted endoRx when appropriate and medical therapy in others

THANK YOU!

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A 20/20 look at: Endoscopy in the management of Small Bowel Bleeding

Advances in Gastroenterology and Hepatology
Bonita Springs, FL
February 8, 2020

Michael D. Rice, MD, AGAF

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Disclosures

- Consultant - Medtronic

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CASE

- 65 yo male
- Hx of Atrial Fibrillation on apixiban
- 3 days of melena, hemoglobin 8.0
- EGD and colonoscopy – negative
  - except for melena
- Bleeding spontaneously stops

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What is next step?

A. Discharge patient to clinic to consider outpatient capsule endoscopy
B. Inpatient capsule endoscopy
C. Tagged RBC scan
D. Oral Fe therapy- work up is complete.

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Outline

- Definition of Obscure/Small bowel GIB
- History of endoscopic eval of small bowel
- Algorithm - Small Bowel Bleeding
- Cases
  - Evidence based approach

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History of Endoscopy: the Small Bowel

- Development of endoscopic equipment
- Endoscopists became increasingly relevant
  - Diagnosis and Management
  - Esophageal, gastric, duodenal, colonic, pancreatico-biliary disorders
- Majority of small bowel was out of reach

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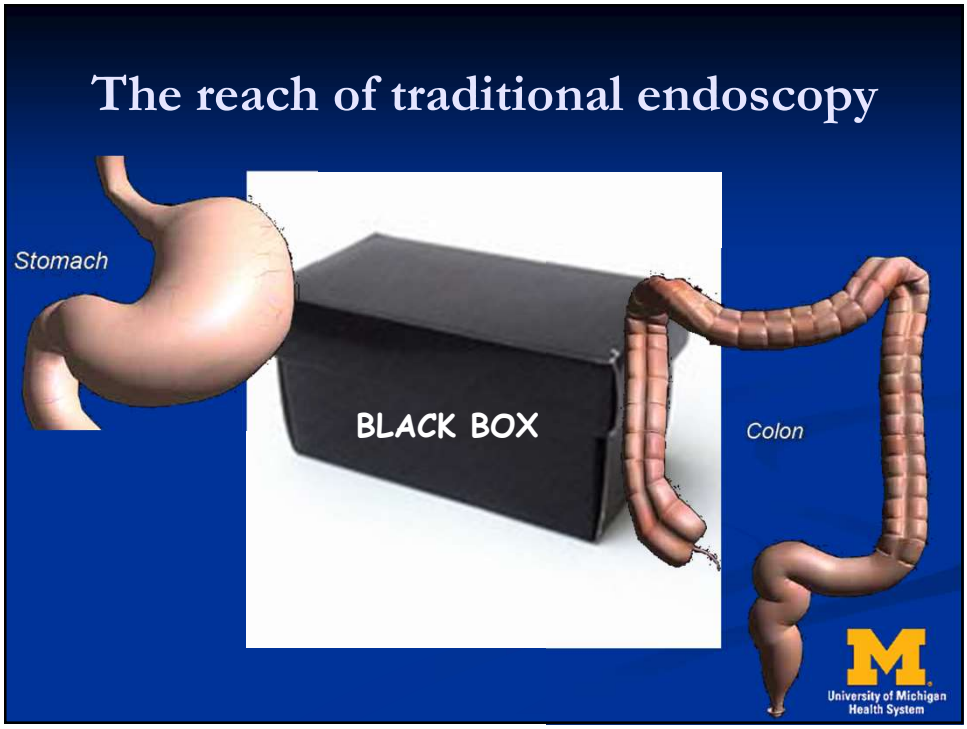

Challenge of Obscure GI Bleeding

- Paradigm frustrating for obscure GIB (5%)
  - Repeatedly admitted, explored, operated upon
  - Unfruitful evaluation
  - Forced to cope with morbidity as inherent to their condition

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Historical Definition: Obscure GI Bleeding (OGIB)

- GI Bleeding of unknown origin that persists or recurs
- "EGD + colonoscopy does NOT reveal source"
- "**Overt**" OGIB
  - hematochezia or melena
- "**Occult**" OGIB
  - FOBT+ or Fe-deficiency anemia

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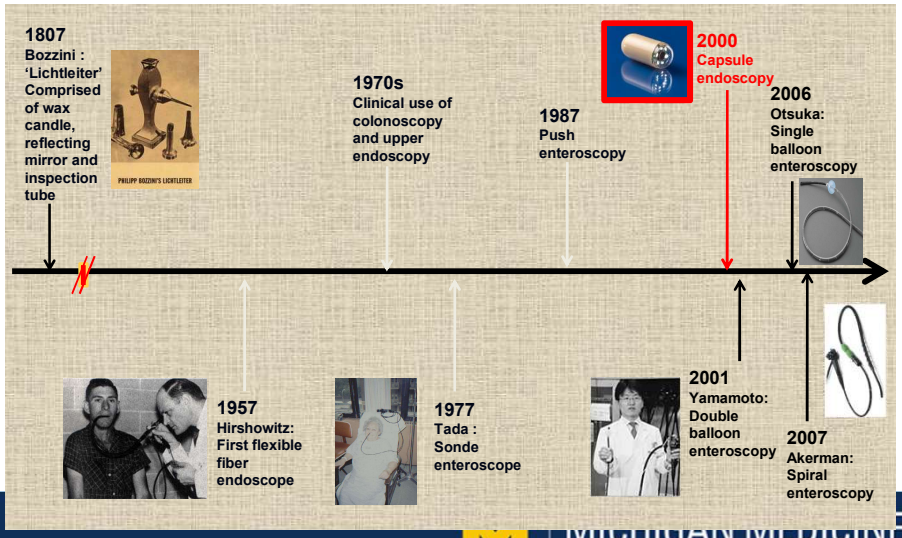
Endoscopy Timeline



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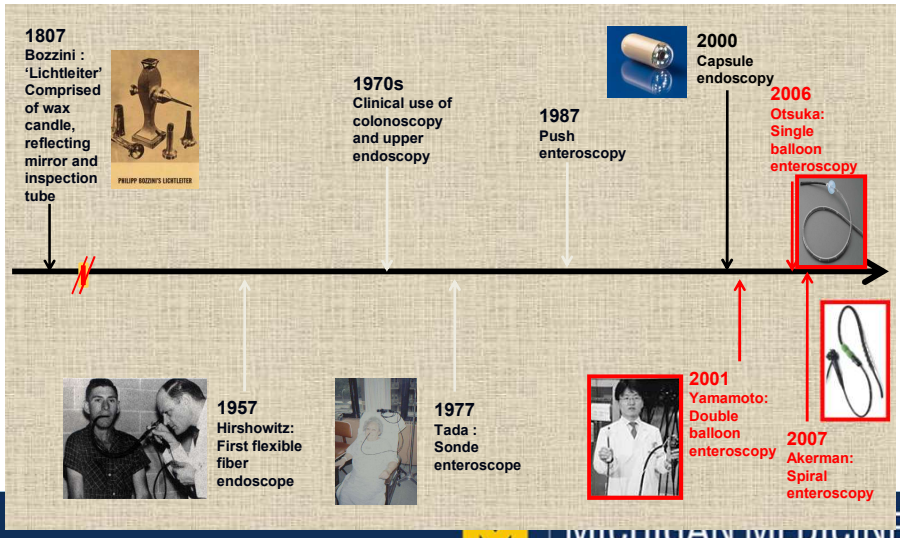
Endoscopy Timeline



"Small Bowel Bleeding"

- Advances in small bowel imaging
  - VCE, DAE, radiographic imaging modalities
  - Bleeding can be detected in majority of patients
- Reclassified to "**Small Bowel Bleeding**"
  - Bleeding distal to ampulla for Vater and proximal to the ICV in patients
  - normal EGD and Colonoscopy
  - Overt (melena/hematochezia)
  - Occult (Fe defic anemia +/- FOBT+)
- Small intestinal bleeding 5-10% of all GIB pts

Gerson LB, Fidler JL, Cave DR, et al. ACG clinical guideline: diagnosis and management of small bowel bleeding. Am J Gastroenterol 2015;110:1265-87..

Obscure GI Bleeding

- **Obscure GI bleeding** term
  - now reserved for patients source of bleeding not identified anywhere in GI tract
  - may represent a source of bleeding outside of the small bowel

Gerson LB, Fidler JL, Cave DR, et al. ACG clinical guideline: diagnosis and management of small bowel bleeding. Am J Gastroenterol 2015;110:1265-87.

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Endoscopy Timeline

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Historic Enteroscopy methods

- Length and tortuosity of SB limited exam to the most proximal and distal portions
- Passage of endoscope beyond L.O.T.
  - Push enteroscopy
  - Sonde enteroscopy
  - Intraoperative enteroscopy
- Differ in ability to reach distal SB, therapeutic interventions

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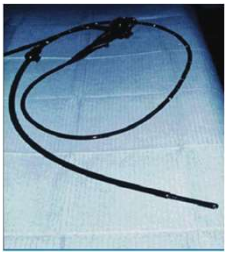
Push Enteroscopy (PE)

- Limited to proximal 150cm of SB
  - Modestly extended with overtube
  - 50-90cm into winding distensible jejunum
- Looping/Discomfort
- Ability to perform dx and tx maneuvers
- Increased diagnostic yield from 8-35%



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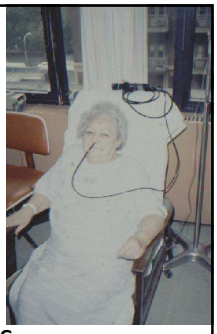
Sonde enteroscopy



- Tada - 1977
- Long flexible fiberoptic enteroscope
  - Without controls
  - Passively propelled by intestinal peristalsis
- Endoscopic exam is performed during withdrawal
- Time consuming (7 hours)
- Patient discomfort
- Does not permit biopsy or therapeutic maneuvers
- Rarely performed

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Interoperative Enteroscopy (IOE)

- Surgeon telescopes bowel over endoscope
- Per-oral, per-rectal, through enterostomy
- Entire length of small bowel >90%
- 60 to 88% diagnostic yield
- Remained gold standard
  - diagnosis and mgmt of small bowel conditions

Bombeck et al. Surg Clin North Am. 1975;55:135–142

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Risk of IOE

- Invasive
  - Significant morbidity
  - Cost
- In one study:
  - Morbidity (serosal tears – two requiring resection), avulsion of SMV, CHF, azotemia, prolonged ileus
- Reserved as last option for OGIB

Ress, AM, Benacci, JC, Sarr, MG. Efficacy of intraoperative enteroscopy in diagnosis and prevention of recurrent occult gastrointestinal bleeding. Am J Surg 1992; 163:94.

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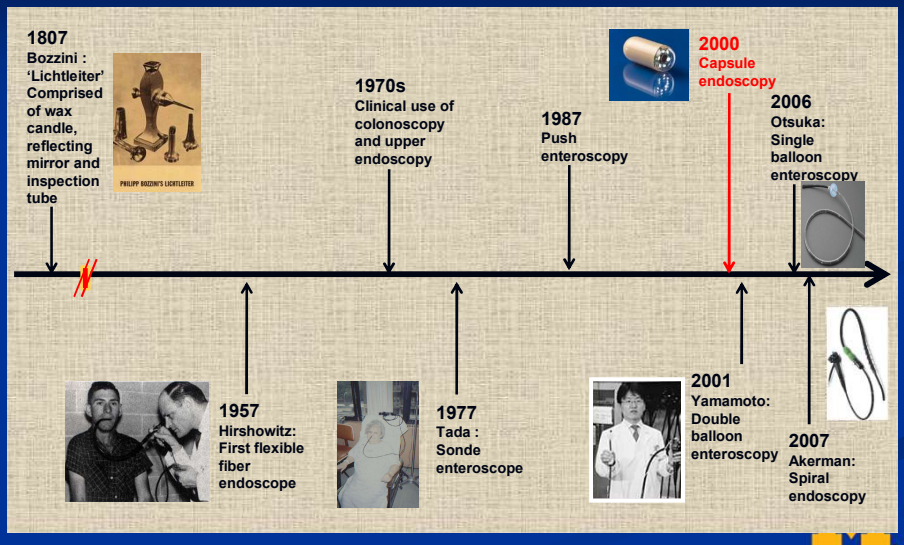
Endoscopy Timeline



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Video Capsule Endoscopy

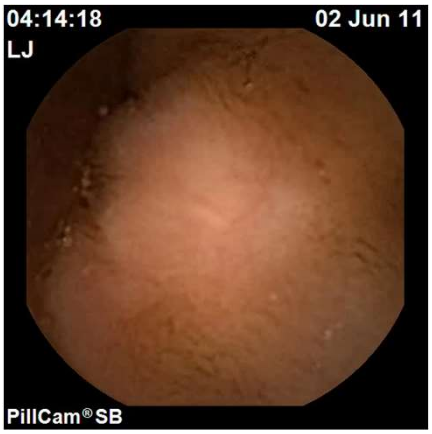
- Design specifications
  - Disposable 3.0 g biocompatible plastic capsule
  - 11.4 mm x 26.2mm
  - Propelled by peristalsis
  - 140° field of view (156°)
  - 8x magnification
  - 2-6 frames per second
  - Battery life ≥8 hours

Video Capsule Endsocopy Systems

Capsule	Pill Cam® SB3	EndoCapsule® 10	CapsoCam® SV1	MiroCam®	OMOM®
Manufacturer	Given Imaging	Olympus	Capsovision	IntroMedic	Jianshan
Length (mm)	26	26	31	24.5	28
Diameter (mm)	11	11	11	10.8	13
Weight	3.0 g	3.3 g	4 g	3.25 g	6 g
Frame rate	2-6	3.3	4	3	2
Battery Life (h)	8-12	12	15	12	8
Field of View	156°	160°	360°	170°	140°
FDA approved	Yes	Yes	Yes	Yes	No
Data transmission	Radiofreq	Radiofreq	VCE retrieval download	Radiofreq	Radiofreq

"Physiologic Endoscopy"

- Bowel is visualized in its normal state
  - No "scope trauma"
  - Air insufflation not a factor
- Exam can be performed on anticoagulation



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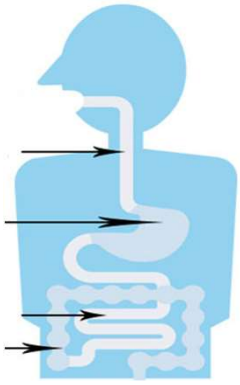
Average Transit Times

- Stomach: ~1 hour
- Small Intestine: 4 hours
- Colon: 2-3 days



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Indications for VCE

- Suspected SB bleeding
- Evaluation for extent
  - Crohn's or Celiac disease
- Suspected malabsorption
- Abnormal small intestinal imaging
- Surveillance of polyposis syndromes

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Contraindications

Absolute:

- Known or suspected small intestinal obstruction

Relative:

- Pacemakers/AICDs
- Pregnancy
- Motility disturbances: Gastroparesis/Achalasia
- Other swallowing disorders
- Small bowel diverticulosis
- Poor surgical candidates

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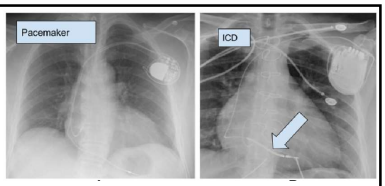
VCE and implantable cardiac devices



- Numerous studies
- VCE is feasible and safe in patients with implanted cardiac devices
  - pacemakers, cardioverter defibrillators, and left heart assist devices (LVAD)

- LVADs potential to interfere with image acquisition of the capsule video.
  - placed in the upper abdomen (peds)
  - potential for interference may be overcome
    - Position capsule leads as far away as possible from the LVAD to assure image acquisition.

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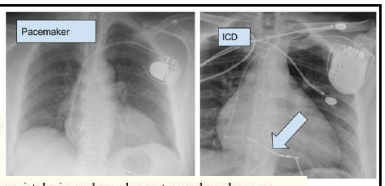

Studies investigating patients with cardiac pacemakers who underwent capsule endoscopy

Author	Year	Number of p cardiac pace (n)
Harris [3]	2013	76
Bandorski [12]	2012	300
Cushieri [4]	2012	14
Bandorski [5]	2011	49
Dirks [6]	2008	5
Bandorski [7]	2008	21
Bandorski [9]	2006	1
Payeras [10]	2005	20
Bandorski [11]	2005	45
Dubner [15]	2005	100
Guyomar [13]	2004	1
Leighton [14]	2004	5
Chung [27]	2012	3

Studies investigating patients with implantable cardioverter defibrillators endoscopy

Author	Year	Numbe cardiac
Harris [3]	2013	
Bandorski [12]	2012	
Cushieri [4]	2012	
Bandorski [5]	2011	
Dirks [6]	2008	
Bandorski [7]	2008	
Bandorski [9]	2006	
Payeras [10]	2005	
Bandorski [11]	2005	
Dubner [15]	2005	
Guyomar [13]	2004	
Leighton [14]	2004	
Chung [27]	2012	

Studies investigating patients with ventricular assist devices who underwent capsule endoscopy

Author	Year	Number of patients/ cardiac pacemakers (n)	Brand of cardiac pacemaker	Kind of study	Interference	Brand of capsule endoscopy
Harris [3]	2013	76	Medtronic, Guidant and others	*In vivo*	No	Given Imaging
Bandorski [12]	2012	300	No specification	*In vivo*	No	Given Imaging Olympus
Cushieri [4]	2012	14	Medtronic, St. Jude Medical, Ela	*In vivo*	No	Given Imaging
Bandorski [5]	2011	49	Medtronic, Vitatron, Ela, Guidant, St. Jude Medical, Biotronik, Boston Scientific	*In vivo*	No	Given Imaging+ Olympus
Dirks [6]	2008	5	No specification	*In vivo*	No	Given Imaging
Bandorski [7]	2008	21	Medtronic, Osypka, Siemens, Vitatron, Ela, Guidant, St. Jude Medical	*In vitro*	No	Given Imaging+ Olympus
Bandorski [9]	2006	1	Biotronik	*In vitro*	No	Given Imaging
Payeras [10]	2005	20	No specification	*In vitro* *In vivo*	No No	Given Imaging (Test Cap)
Bandorski [11]	2005	45	No specification	*In vivo*	No	Given Imaging
Dubner [15]	2005	100	St. Jude Medical, Medtronic, Guidant, Biotronik, Sorin	*In vivo*	Yes (n=4, noise mode)	Given Imaging (Test Cap)
Guyomar [13]	2004	1	ELA	*In vivo*	No	Given Imaging
Leighton [14]	2004	5	No specification	*In vivo*	No	Given Imaging
Chung [27]	2012	3	St. Jude Medical, Medtronic	*In vivo*	No	Intromedic

Bandorski, Annals Gastroenterol 2014

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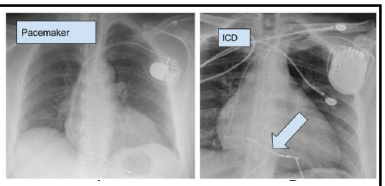
VCE and implantable cardiac devices



- Wireless telemetry can cause dysfunction of capsule endoscopy recording
- Future: certain bandwidth reservation should be instituted for each group of devices to minimize or eliminate overlap interference

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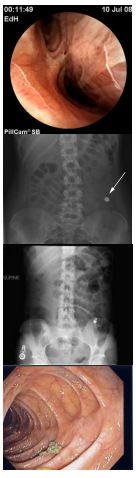
Informed Consent: Risks

- Aspiration: Rare
- Retention of capsule: 1-5%
- Bowel obstruction: .5 %
- Does not replace exam stomach or colon
- Incomplete study



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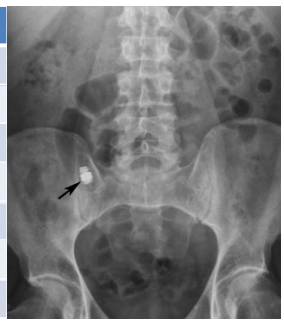
Capsule Retention Rates

Volunteers/Patients	Frequency
All	0.75%
Healthy Volunteers	0%
Suspected Crohn's	1.4%
Known Crohn's	5%
Obscure GIB	1.5% (up to 5%)
Neoplastic Lesions	2.1%
Suspected Bowel Obstruction	21%



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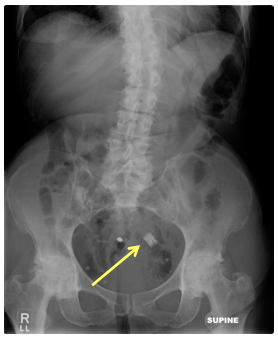
Patency Capsule

Intended to verify adequate patency

- Known/suspected strictures
- Crohn's
- Chronic NSAID use
- SB tumors
- Radiation enteritis
- Adhesive disease
- Anastomotic stenosis



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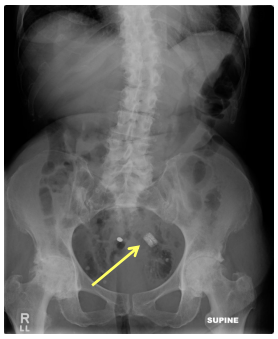
Patency Capsule

- Same dimensions as capsule
- Dissolvable and biodegradable
  - Lactose body
  - 10% barium
    - Xray or fluoroscopy visualization
- Radio Frequency ID tag (RFID)



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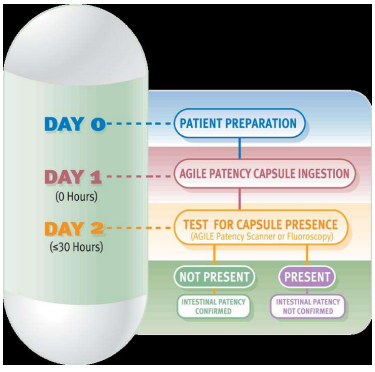
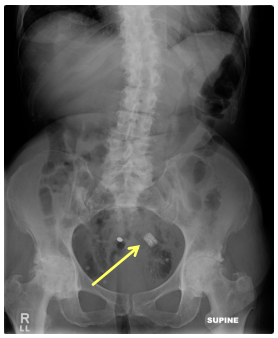
Patency Capsule





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VCE Limitations

- Ø therapeutic capabilities
- Ø control movement
- Ø obtain tissue
- ↑rate of incidental findings
- Difficulty in localizing
- Potential to miss single mass lesions
- False negative rate 11% (all SB findings)
  - 19% of single mass lesions including neoplasms
- Risk of retention

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Other Limitations of VCE

- Technical failure
- Poor visualization
  - Poor Prep excess debris
  - Incomplete Study
    - Capsule doesn't reach cecum during battery life
    - Incomplete rates: 20-30%

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VCE Preparation

- Impaired visualization
  - Air bubbles, food residue, bile, blood clots
- Adequate bowel cleansing is mandatory for successful VCE
- No ability to suction or rinse during VCE exam
- Lesions can be obscured, overlooked, missed

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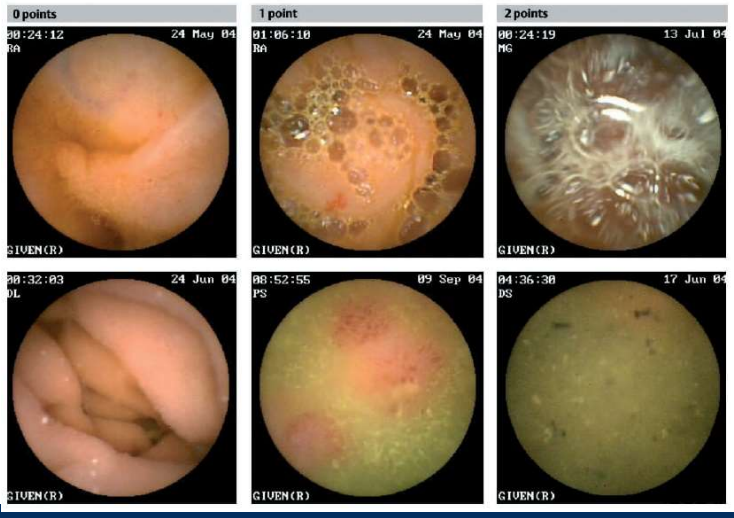
VCE Bowel Prep



ICCE consensus for bowel preparation and prokinetics

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Incomplete VCE Studies

- Difficult to interpret
- Lead to delays in diagnosis
- Repeat VCE, radiologic or endoscopic interventions to help delineate the diagnosis
- Increased Costs
- Inconvenience to patient

Risk Factors for Incomplete VCE

TABLE 3. Multivariate logistic regression analysis for factors associated with incomplete CE procedures*

Variable	OR	95% CI	*P*
Previous small-bowel surgery	5.64	2.09-15.27	.001
GTT > 45 min	3.03	1.57-5.83	.001
Hospitalization	2.87	1.19-6.93	.019
Bowel cleansing (moderate-poor)	2.78	1.39-5.54	.004

*Significance of model: $\chi^2 = 45.137$, $P < .001$.

Westerhof et al., GIE 2009.

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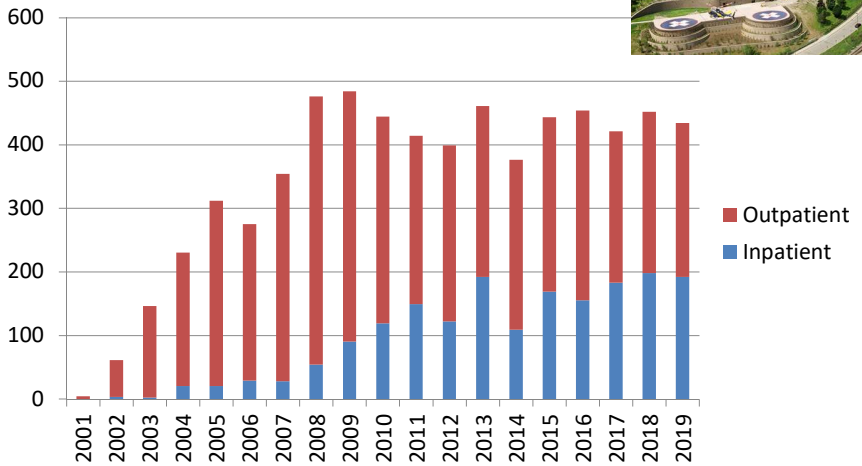
UM VCE Volume



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Challenges In Achieving Deep Enteroscopy

- Long
  - 400-600 cm
- Tortuous and mobile
  - Loop formation
    - Gastric
  - Small bowel / mesentery
  - Colonic (sigmoid, transverse)
- Thin wall
  - Increased risk of perforation
- Diminish transmission of force to tip of scope

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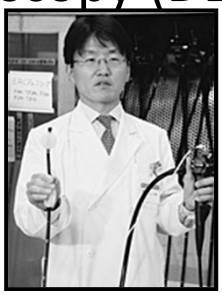
Double Balloon Enteroscopy (DBE)



- Conceived in 1999 by Yamamoto
- Two fulcrum points two balloons
  - Tip of enteroscope
  - End overtube
- Developed in 2001
  - collaboration with Fujinon
- Introduced in USA in 2004
- Potentially visualize and treat 400-600 cm of adult SB

Double Balloon Enteroscopy

Specifications

JOHNS HOPKINS MEDICINE

Scopes	EN-580T	EN-450P/20	EC580BT (soon)
Viewing direction	Forward	Forward	Forward
Distal end Diameter	9.4mm	8.5mm	9.4mm
Channel Diameter	3.2mm	Paused	3.2mm
Working Length	2,000mm	2,000mm	1,550mm

Overtubes	Therapeutic	Diagnostic	Short
Outer Diameter	13.2mm	12.2mm	13.2mm
Inner Diameter	10.8mm	10mm	10.8mm
Working Length	1,350mm	1,350mm	950mm
Material on the Balloon	Latex	Latex	Latex

DOUBLE BALLOON ENTEROSCOPY

- High resolution video endoscope
- Working length of 200cm
- Flexible overtube
- Latex balloons at the tip of the enteroscope and on the overtube

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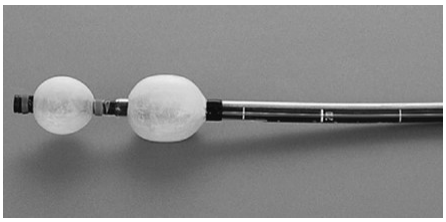
DOUBLE BALLOON ENTEROSCOPY

- Serial inflation and deflation of balloons
- Pressure-controlled pump
- Alternating pushing and pulling maneuvers
- Small bowel telescoped onto the overtube



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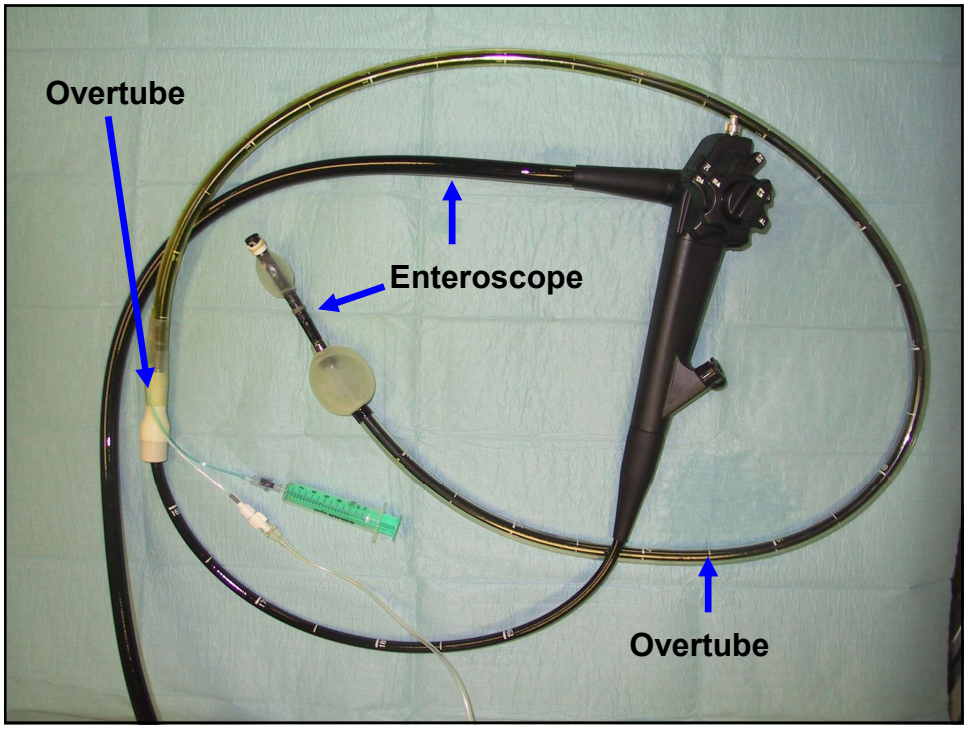

DOUBLE BALLOON ENTEROSCOPY

- Diagnostic and therapeutic advantages
  - Biopsies
  - Hemostasis
  - Polypectomy
  - Dilation
  - Tattoos
  - Foreign body removal

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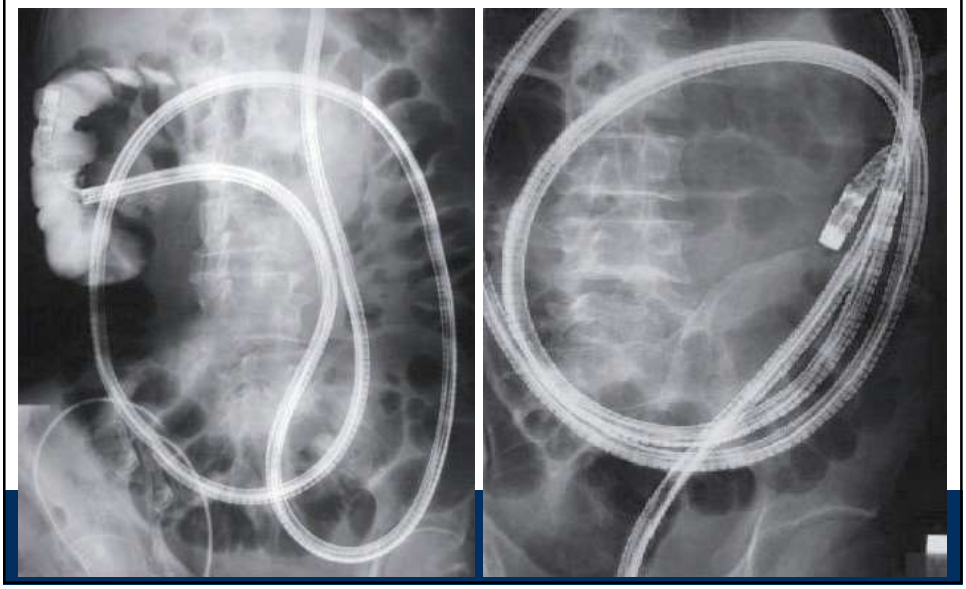
Potential Uses For DBE

- Small bowel bleeding
- Enteropathies
  - Crohn's, NSAIDS, UJI, XRT
- Small bowel strictures
- Post-surgical anatomy (Whipple, Bariatric)
- Celiac disease (refractory, SB malignancy)
- Abnormal imaging or capsule endoscopy
- Foreign body removal
  - Retained capsules, PD stents
- Management of polyposis syndromes (PJS)
- Difficult colonoscopy
- D-PEJ

DBE

- Main limitations
  - Invasive nature
  - Prolonged duration
  - Latex containing balloons
  - Requirement of additional personnel (MD, RN, MA)
- Complication rate
  - Diagnostic procedures 0.8%
  - Therapeutics up to 5% (electrocoagulation, polypectomy and dilation)
    - Ileus, pancreatitis, bleeding and perforation

Potential to transverse the entire small bowel



Safety of DBE

- DBE Register in Germany – 64 Centers
- N=3894 DBE (Oral 2685, anal 1209)
- 48 complications overall (1.2%) – all oral
  - Pancreatitis 0.34%
  - Perforation 8 cases
    - 6 post polypectomy (3.4% s/p polypectomy)
  - Major bleeding 6 cases (endoscopically treated)
    - 4 s/p polypectomy
    - 2 s/p biopsy

May et. al. Z Gastroenterol. 2008 Mar;46(3):266-70.

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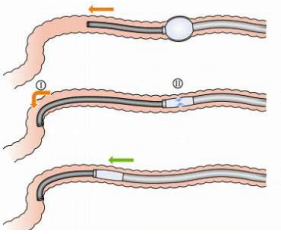
Other Device Assisted Enteroscopy

- Single Balloon Enteroscopy



- Spiral Enteroscopy

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Examination Time

Study			Patient no.	Mean exam time (min)	Type
Yamamoto	Japan	2004	123	123	DBE
Di Caro	Europe	2005	62	160	DBE
Heine	Netherland	2006	275	200	DBE
Mehdizadeh	US	2006	188	197	DBE
Gross and Stark	US	2008	137	197	DBE
Tsujikawa	Japan	2008	41 (78 procedures)	133	SBE
Ramchandani	India	2009	106 (131 procedures)	137	SBE
Akerman	US	2008	101	17	Spiral
Esmail	US	2009	57	28	Spiral
Morgan	US	2009	148	34	Spiral

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Depth of Insertion

Study			Patient no.	Mean depth Oral (cm)	Mean depth Anal (cm)	Type
Di Caro	Europe	2005	62	254	180	DBE
Heine	Netherland	2006	275	270	156	DBE
Mehdizadeh	US	2006	188	360	183	DBE
Gross and Stark	US	2008	137	220	124	DBE
Tsujikawa	Japan	2008	41 (78 procedures)	270		SBE
Ramchandani	India	2009	106 (131 procedures)	255	163	SBE
Akerman	US	2008	75	249		Spiral
Esmail	US	2009	57	246		Spiral
Morgan	US	2009	148	250		Spiral

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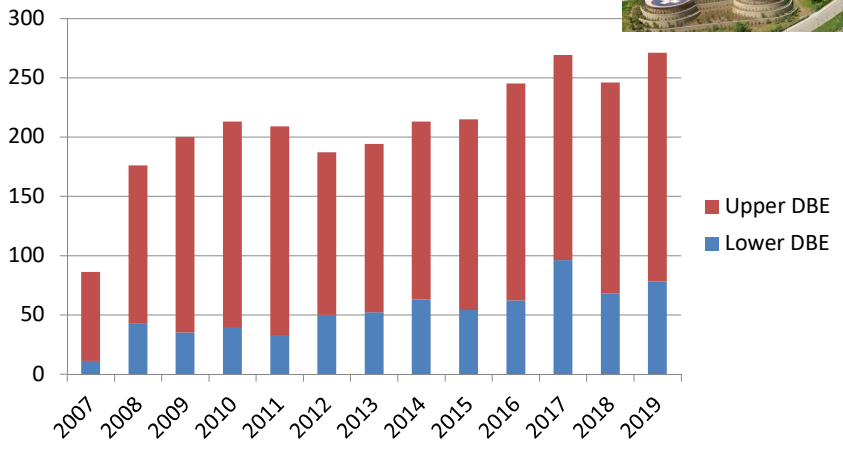
UM DBE Volume



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Back to our CASE

- 65 yo male
- Hx of Atrial Fibrillation on apixiban
- 3 days of melena, hemoglobin 8.0
- EGD and colonoscopy negative
- Bleeding spontaneously stops

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What is next step?

A. Discharge patient to clinic to consider outpatient capsule endoscopy
B. Inpatient capsule endoscopy
C. Tagged RBC scan
D. Oral Fe therapy- work up is complete.
E. Patient was transferred to MM

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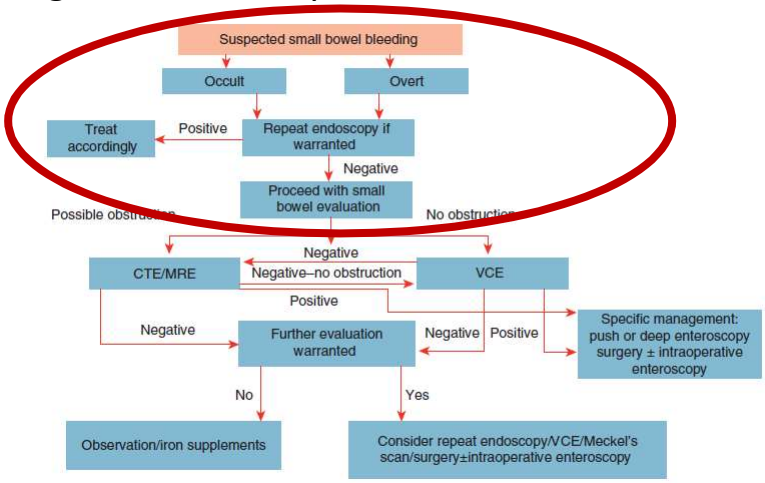
Algorithm for suspected small bowel bleeding



ACG Guidelines 2015 for Diagnosis and Management of Small Bowel Bleeding

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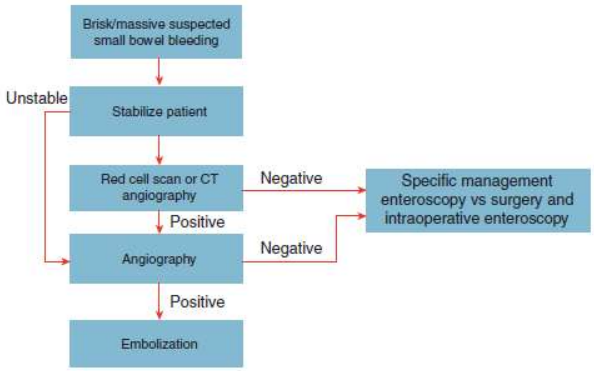
Algorithm for brisk or massive suspected small bowel bleeding



ACG Guidelines 2015 for Diagnosis and Management of Small Bowel Bleeding

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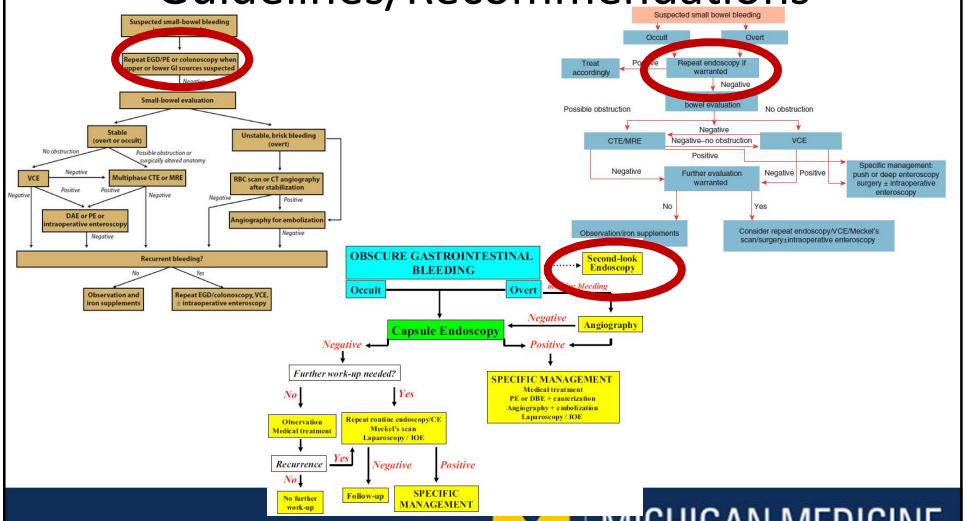
GI Society Guidelines/Recommendations



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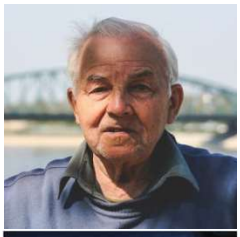
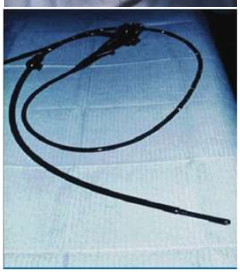
CASE

- EGD negative
- Colonoscopy with melena
- Patient was transferred to MM

- Push enteroscopy





Zaman A, Katon, RM. Push enteroscopy for obscure gastrointestinal bleeding yields a high incidence of proximal lesions within reach of a standard endoscope. Gastrointest Endosc 1998; 47:372.

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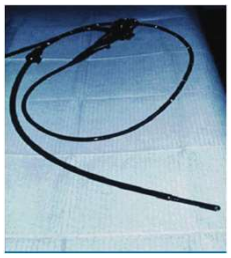
Push Enteroscopy

- N=95 with obscure GI bleeding underwent PE
- Suspected source detected in 39 (41%)
  - 16 underwent endoscopic treatment
- Many lesions (64%) detected
    - in reach of standard endoscope
- Indicating careful repeat standard upper endoscopy may be appropriate prior to PE



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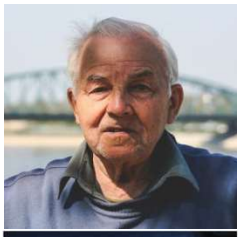
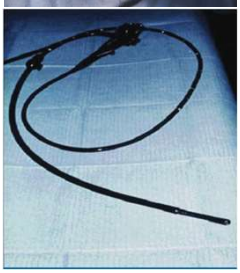
CASE





- EGD negative
- Colonoscopy with melena
- Patient was transferred to MM

- Push enteroscopy
  - Negative
- Endoscopic placement of video capsule

Zaman A, Katon, RM. Push enteroscopy for obscure gastrointestinal bleeding yields a high incidence of proximal lesions within reach of a standard endoscope. Gastrointest Endosc 1998; 47:372.

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RAPID COMMUNICATIONS

Outcome of Patients With Obscure Gastrointestinal Bleeding After Capsule Endoscopy: Report of 100 Consecutive Cases

MARCO PENNAZIO,* RENATO SANTUCCI,* EMANUELE RONDONOTTI,† CARLA ABBIATI,† GIZELA BECCARI,† FRANCESCO P. ROSSINI,* and ROBERTO DE FRANCHIS†
*Division of Gastroenterology, S. Giovanni Antica Sede Hospital, Turin; and †Gastroenterology and Gastrointestinal Endoscopy Service, Department of Internal Medicine, University of Milan, IRCCS Maggiore Policlinico Hospital, Milan, Italy

- 100 consecutive pts with OGIB
  - Active Overt-Obscure GI: 26 pts
  - Occult-obscure: 43 pts
- 620 negative diagnostic tests performed prior to VCE
- VCE overall Diagnostic Yield: 50%

Pennanzio et al., Gastro 2004

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VCE Timing and Type of Bleeding

Table 3. Diagnostic Yield of Capsule Endoscopy According to Type of Bleeding

	Type of finding (%)		
Type of bleeding	Positive	Suspicious	Negative
Overt-ongoing (n = 26)	24 (92.3)	0 (0.0)	2 (7.7)
Overt-previous, overall (n = 31)	4 (12.9)	5 (16.1)	22 (71.0)
10–14 days (n = 3)	2 (66.6)	0 (0.0)	1 (33.3)
3–4 weeks (n = 3)	1 (33.3)	2 (66.6)	0 (0.0)
2–3 months (n = 9)	0 (0.0)	2 (22.2)	7 (77.8)
4–6 months (n = 11)	1 (9.1)	0 (0.0)	10 (90.9)
7–12 months (n = 5)	0 (0.0)	1 (20.0)	4 (80.0)
Occult (n = 43)	19 (44.2)	10 (23.2)	14 (32.6)

Pennanzio et al., Gastro 2004

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AdvanCE Delivery Device

- Capsule is preloaded into endoscope
- Holder is attached to catheter
- Capsule snaps into holder
- Guidewire ejects capsule when in position

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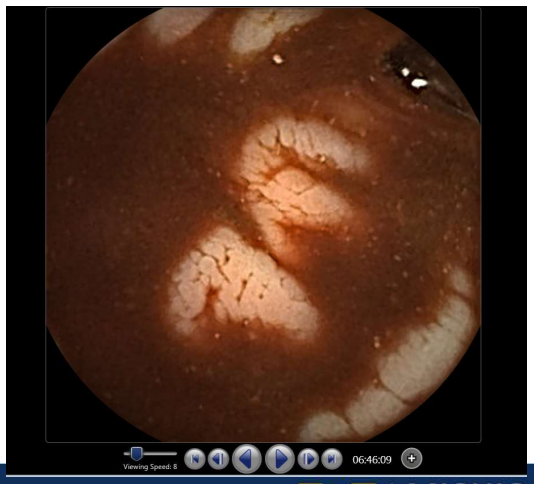
Capsule Findings



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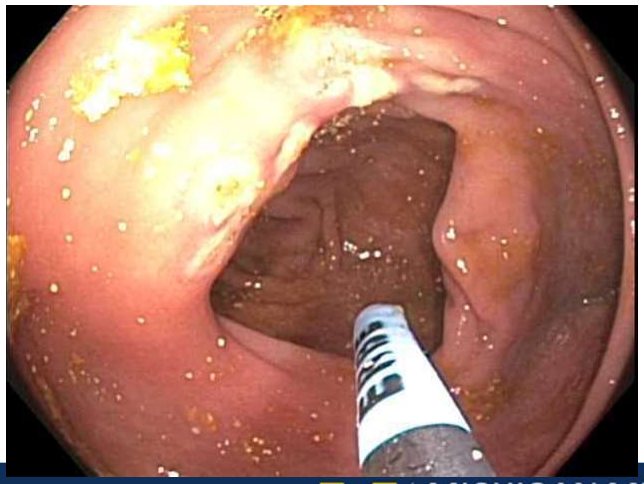
Finding of cecal AVM



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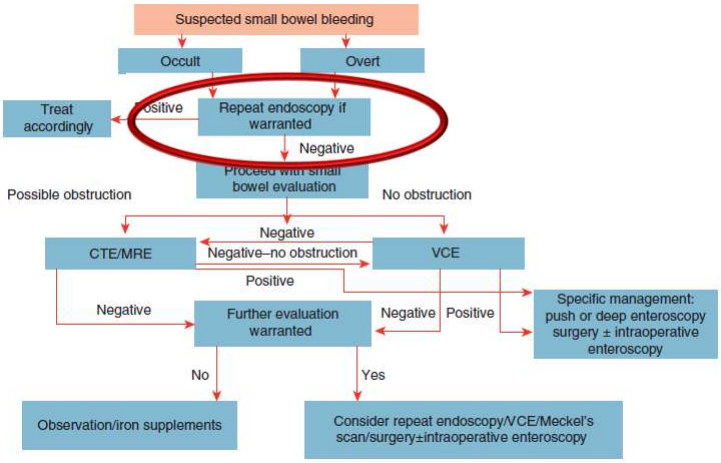
Role of Relook Endoscopy



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Role of Relook Endoscopy

- Def: OGIB have undergone EGD and colonoscopy
- Many have undergone several evaluations
- VCE shows bleeding lesions within reach
  - 3-17% in upper GI tract
  - 2-4% in lower GI tract

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Alimentary Pharmacology & Therapeutics

Incidence of bleeding lesions within reach of conventional upper and lower endoscopes in patients undergoing double-balloon enteroscopy for obscure gastrointestinal bleeding

L. C. FRY, M. BELLUTTI, H. NEUMANN, P. MALFERTHEINER & K. MÖNKEMÜLLER

- **Frequency of non-SB lesions definitely explaining the source of GIB in patients referred for DBE was 24.3%.**
- **Repeat EGD and ileo-colonoscopy should be considered before DBE.**

- N=107 OGIB patients
  - Obscure overt (n=85)
  - Obscure occult (n=22) GIB.
- Lesions outside SB as possible sources of GIB were found in 51 pts **(47.6%)**
- Definite source of bleeding outside the (SB) was detected in 26pts **(24.3%)**
  - gastric ulcer (n=3), duodenal ulcer (n=3), Cameron's lesions (n=2), gastric antral vascular ectasias (n=4), radiation proctitis (n=1), radiation ileitis (n=2), duodenal angiodysplasias (n=1), haemorrhoids with stigmata of recent bleed (n=1), colon angiodysplasias (n=3), colon diverticulosis (n=3), colonic Crohn's disease (n=1), anastomotic ulcers (n=1).

Fry et al. Aliment Pharmacol Ther. 2009 Feb 1;29(3):342-9

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Relook endoscopy

- Attempt to identify patients referred for VCE likely to harbor lesions within reach
  - Significant difference in rate of lesion outside the SB
    - patients referred from centers who do not perform VCE
    - EGD, colonoscopy at VCE at same center
  - (6.3% vs. 1.15% respectively, p = 0.026.)

Vlachogiannakos J, Papaxoinis K, Viazis N, et al. Bleeding lesions within reach ofreach of conventional endoscopy in capsule endoscopy examinations for obscure gastrointestinal bleeding: is repeating endoscopy economically feasible? Dig Dis Sci. 2011 Jun;56(6):1763-8.

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Case #2

- 71 yo female PMHx of HTN, GERD, OA presented to PCP for annual HME
- ASA 81mg, ibuprofen prn, Omeprazole 20mg
- PE: Rectal: **Brown stool, heme+**

Labs:

- Normal chemistries, Hgb 9.4 and MCV of 81

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Case #2

- **FOBT+**, UA negative, **low iron studies**

- Discontinue the NSAIDs and ASA
- Referred for screening colonoscopy and EGD
  - **Negative**

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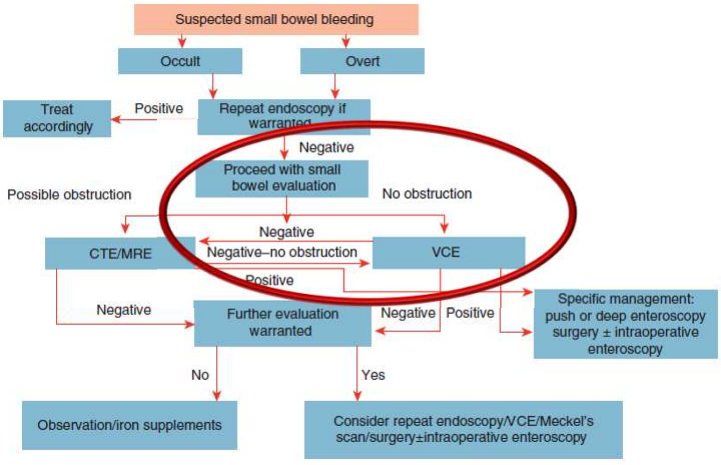
Algorithm for suspected small bowel bleeding



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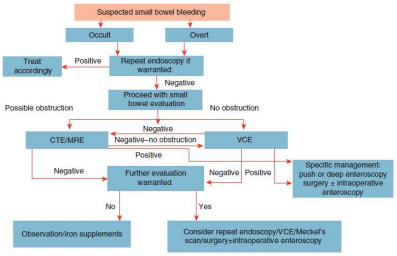
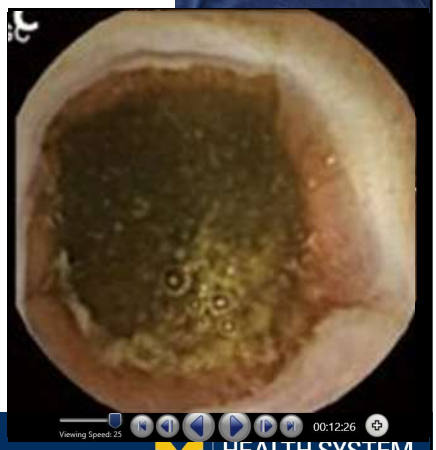
Case #2





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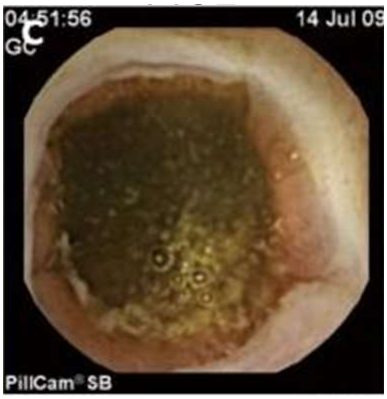

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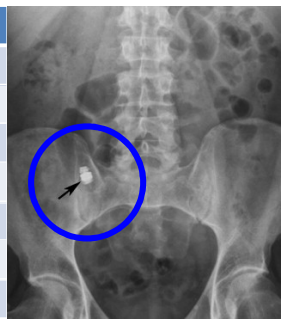
Capsule Retention Rates

Volunteers/Patients	Frequency
All	0.75%
Healthy Volunteers	0%
Suspected Crohn's	1.4%
Known Crohn's	5%
Obscure GIB	1.5% (up to 5%)
Neoplastic Lesions	2.1%
Suspected Bowel Obstruction	21%



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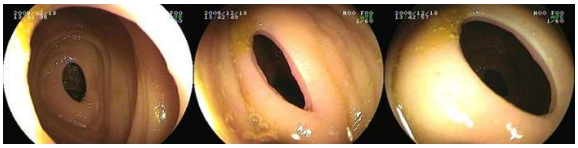

- NSAIDs are one of the most commonly used medications world wide
- Most aware of NSAID complications in the UGI
  - pill esophagitis and gastroduodenal ulceration and hemorrhage
- Significant potential for NSAID injury of the small intestine.

Maiden L, Thjodleifsson B, Theodors A, Gonzalez J, Bjarnason I. A quantitative analysis of NSAID-induced small bowel pathology by capsule enteroscopy. Gastroenterology. 2005; 128:1172-8.

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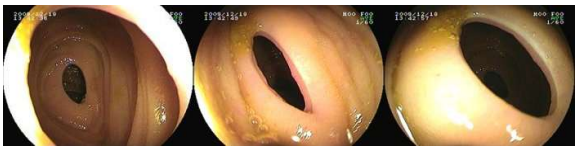

- NSAID enteropathy common in healthy and arthritic patients
  - multiple small bowel erosions or ulcers
  - >70% of subjects treated with NSAID vs. 10% among control subjects

- Spectrum of small intestinal injury from NSAIDs
  - macroscopically invisible→mild mucosal inflammation →ulceration →*diaphragmatic strictures*

- **Diaphragmatic strictures**
  - Multiple, 2-3 mm thick septae
    - can reduce the size of the intestinal lumen to a pinhole
  - Thin and easily missed on CTE
    - may resemble plicae circularis

Maiden L, Thjodleifsson B, Theodors A, Gonzalez J, Bjarnason I. A quantitative analysis of NSAID-induced small bowel pathology by capsule enteroscopy. Gastroenterology. 2005; 128:1172-8.

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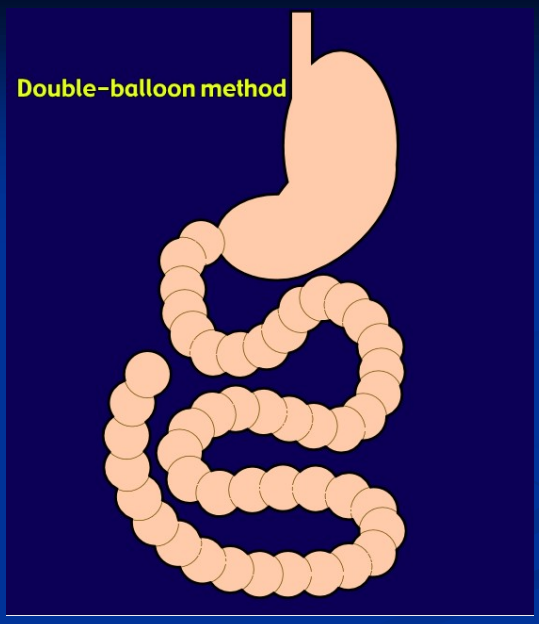
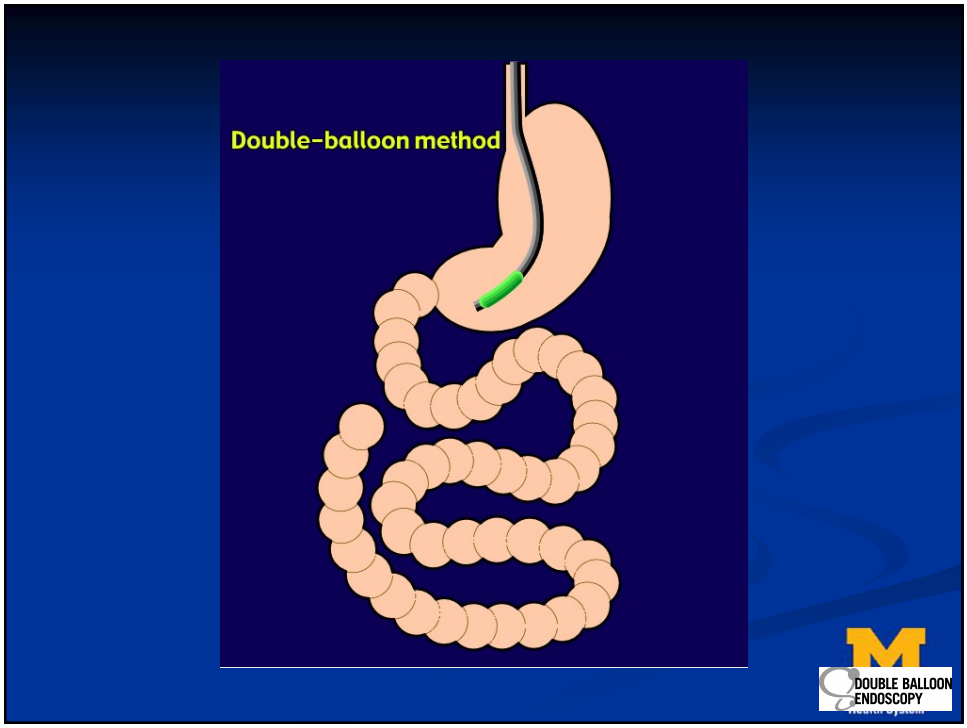
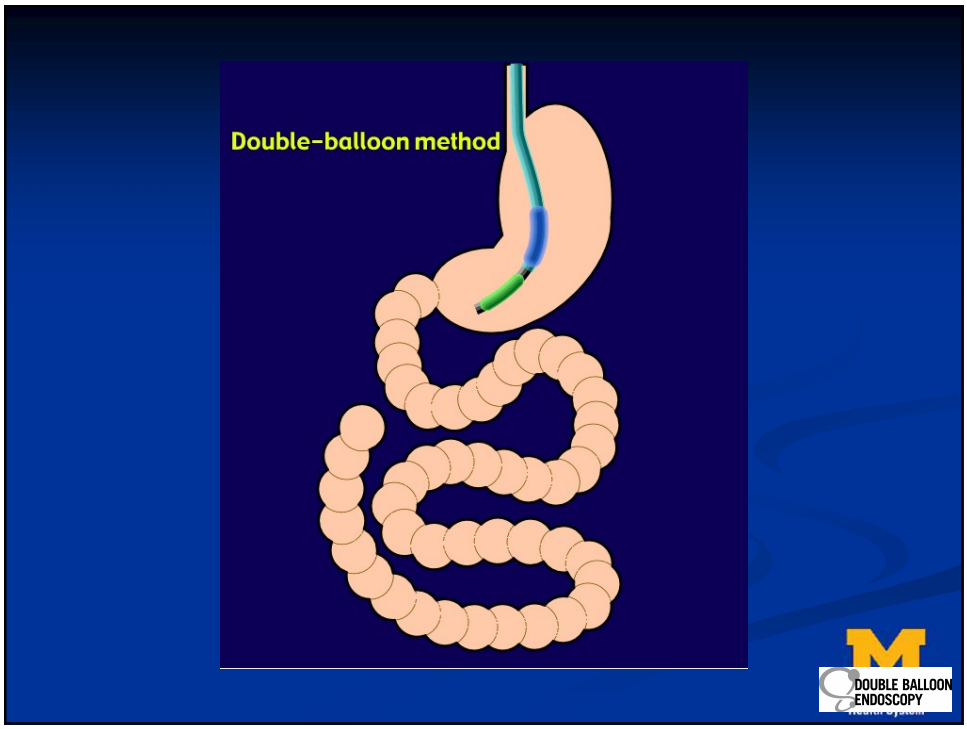


DOUBLE BALLOON ENDOSCOPY


Double-balloon method
DOUBLE BALLOON ENDOSCOPY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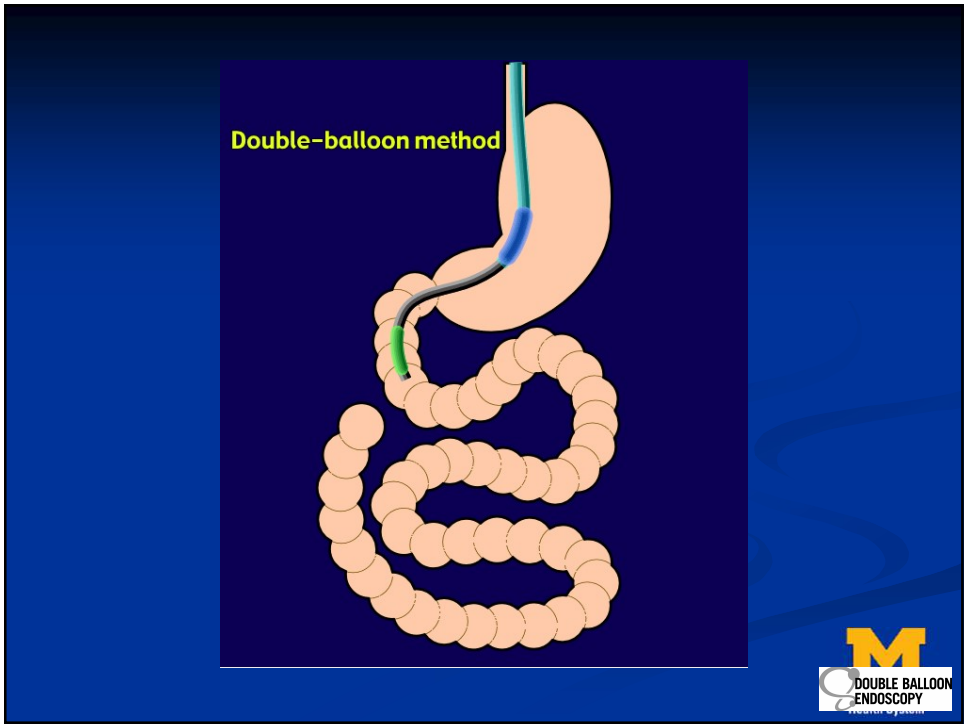
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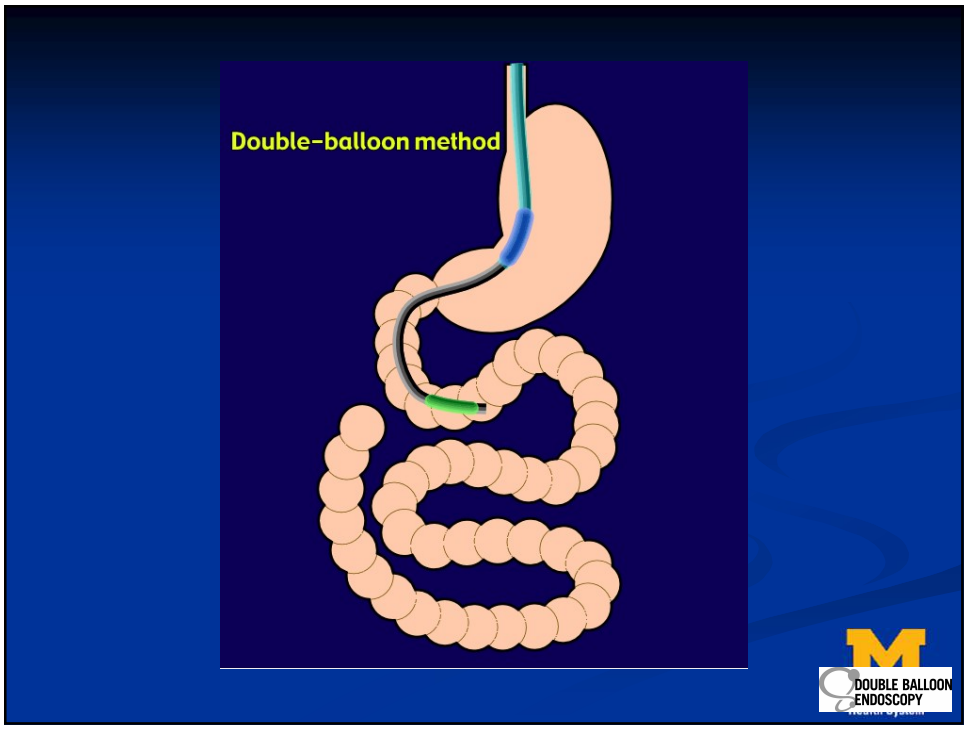
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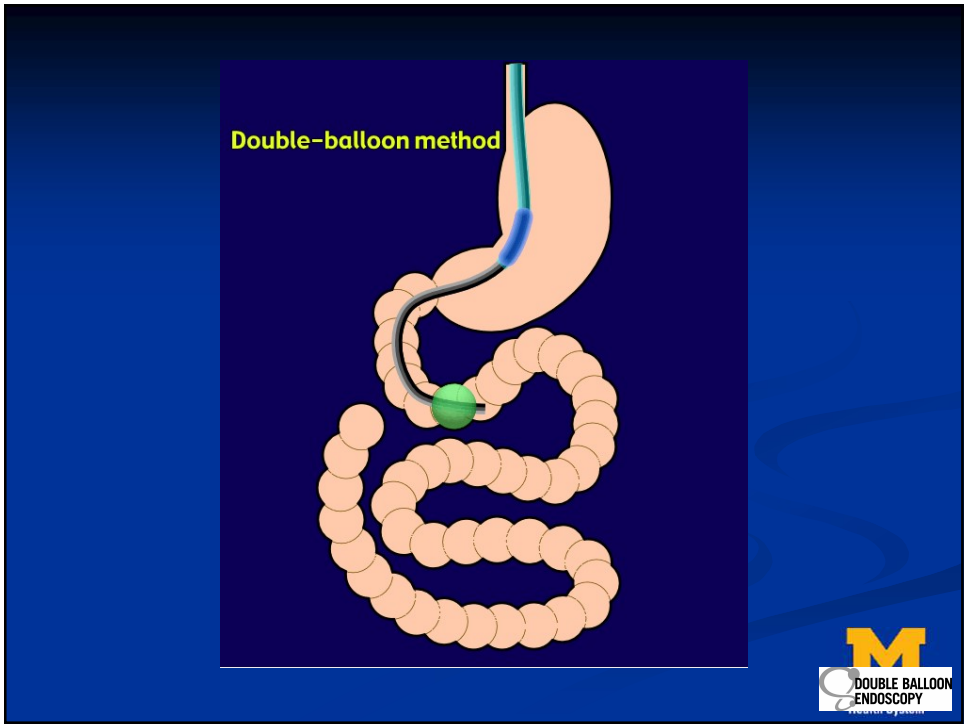
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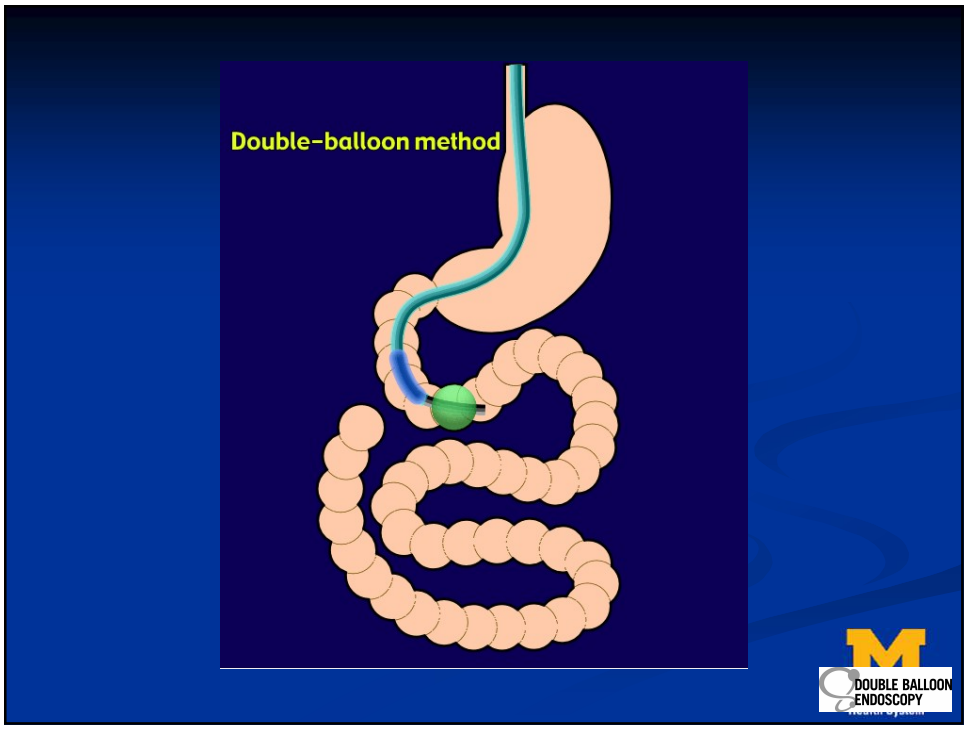
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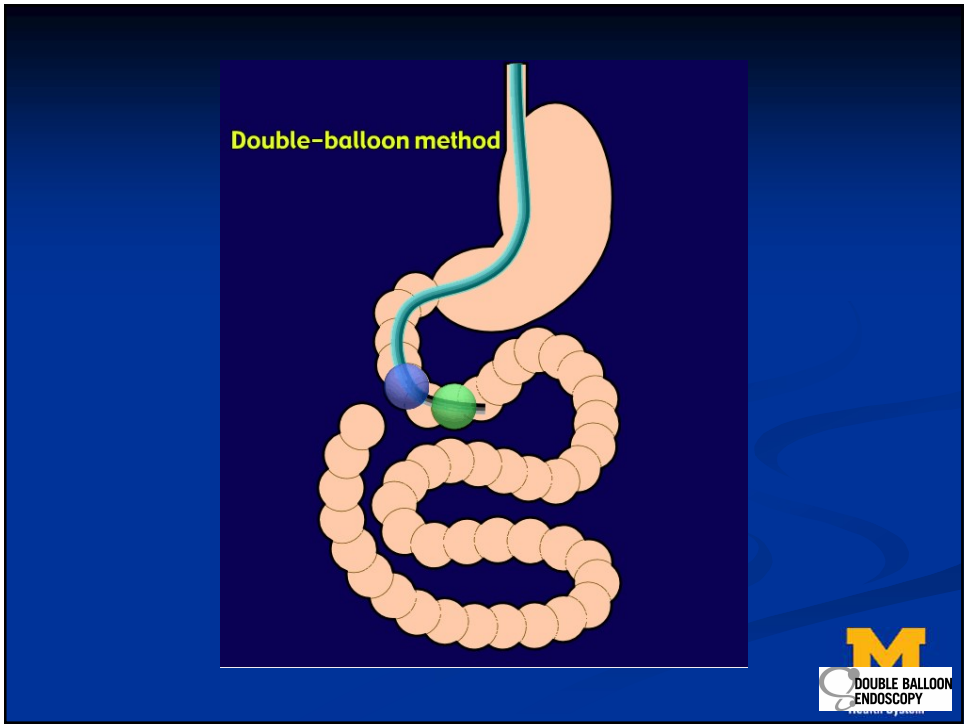
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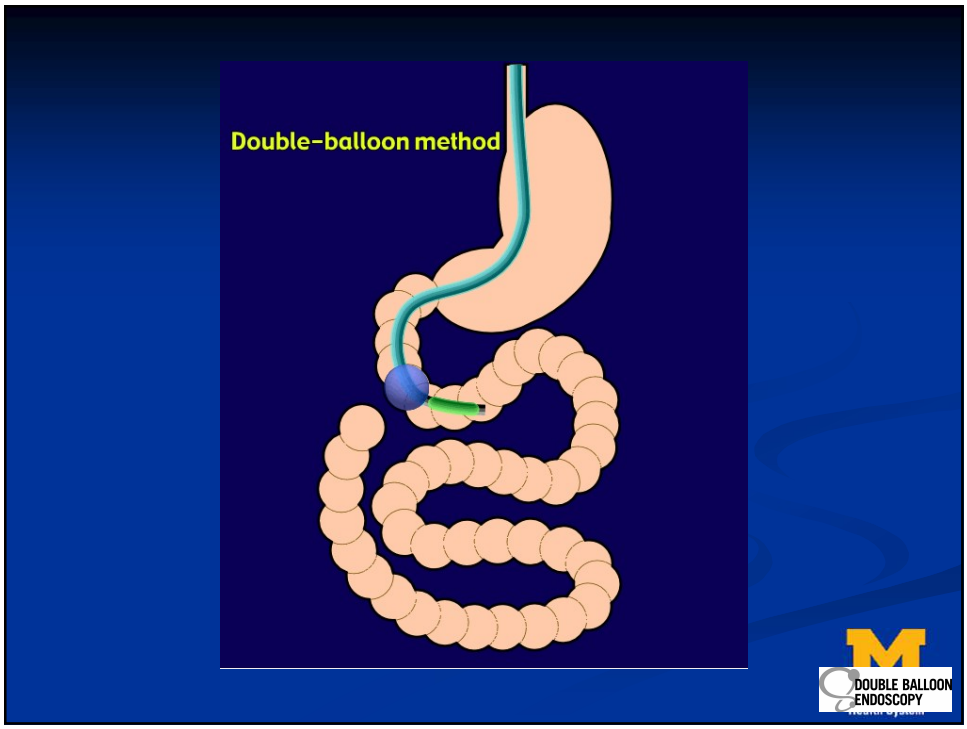
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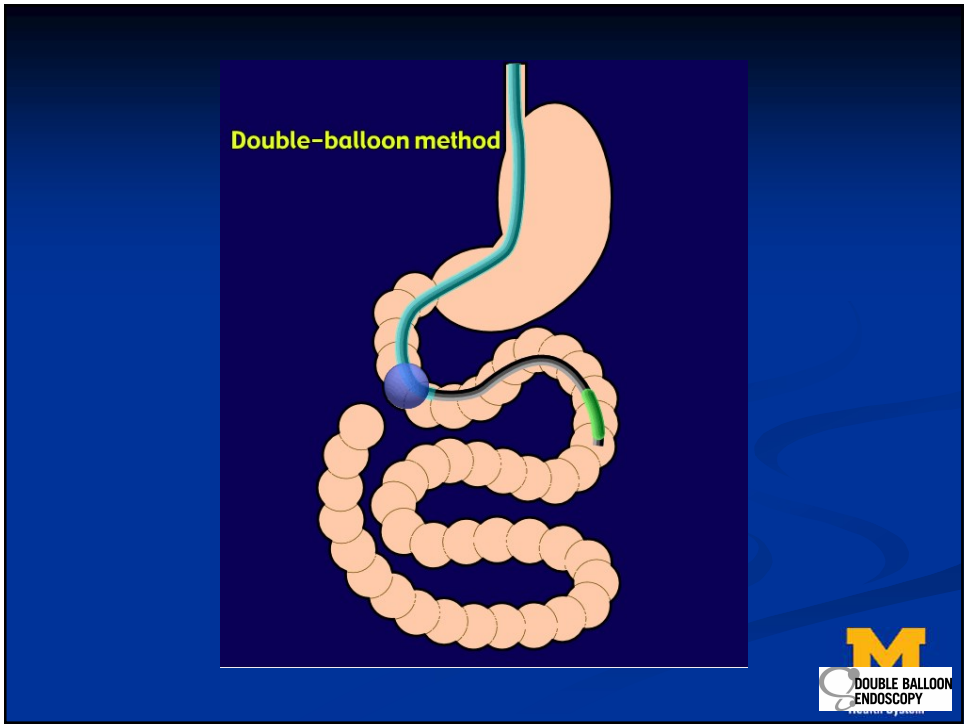
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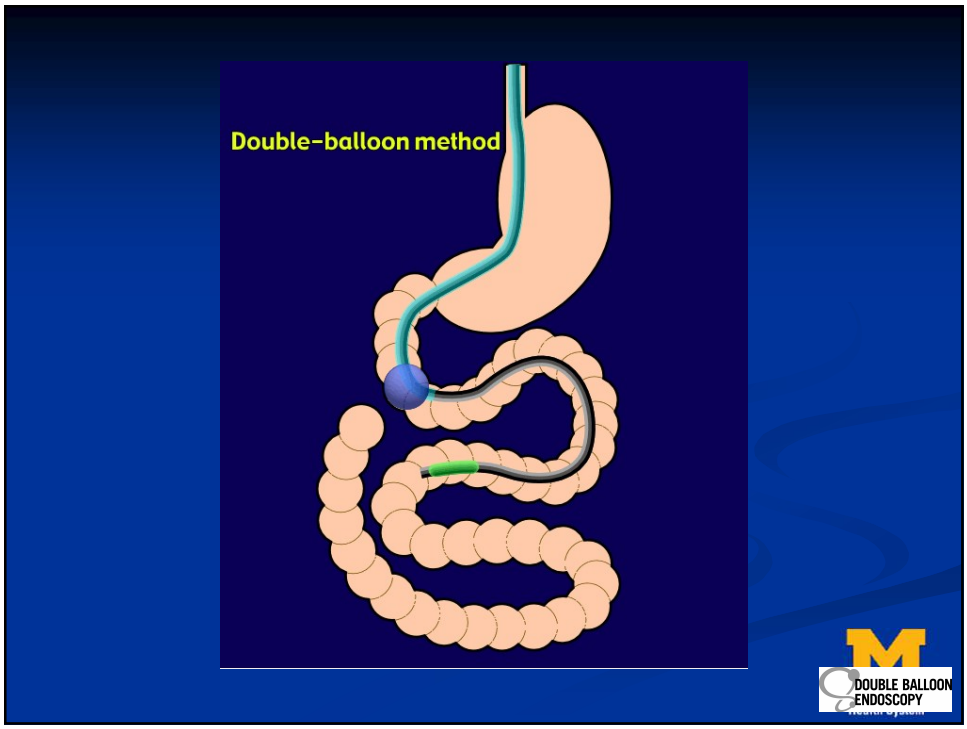
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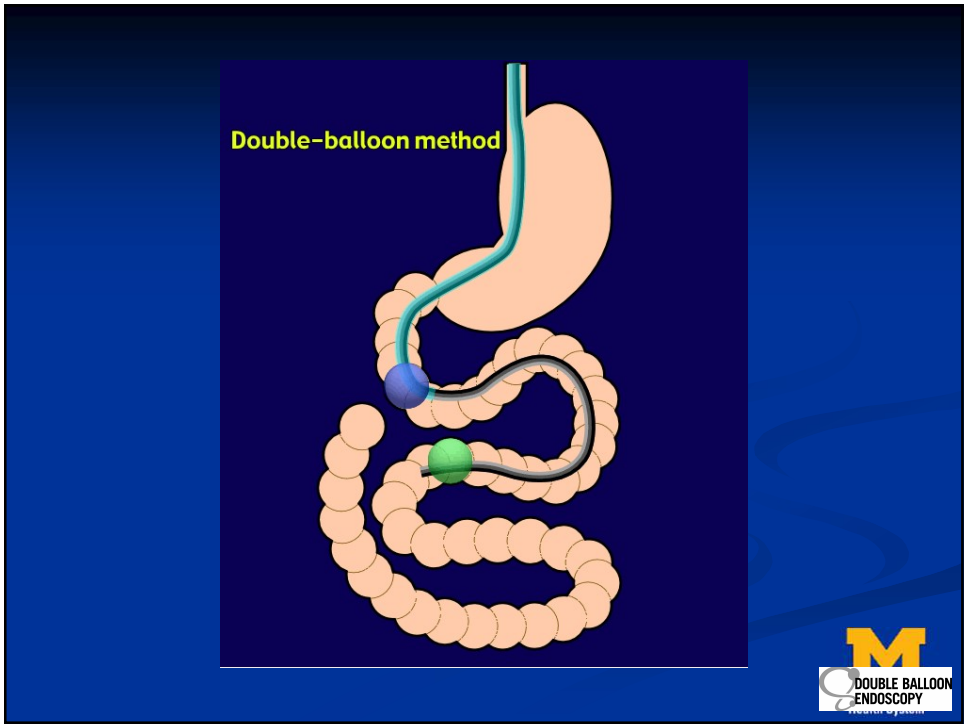
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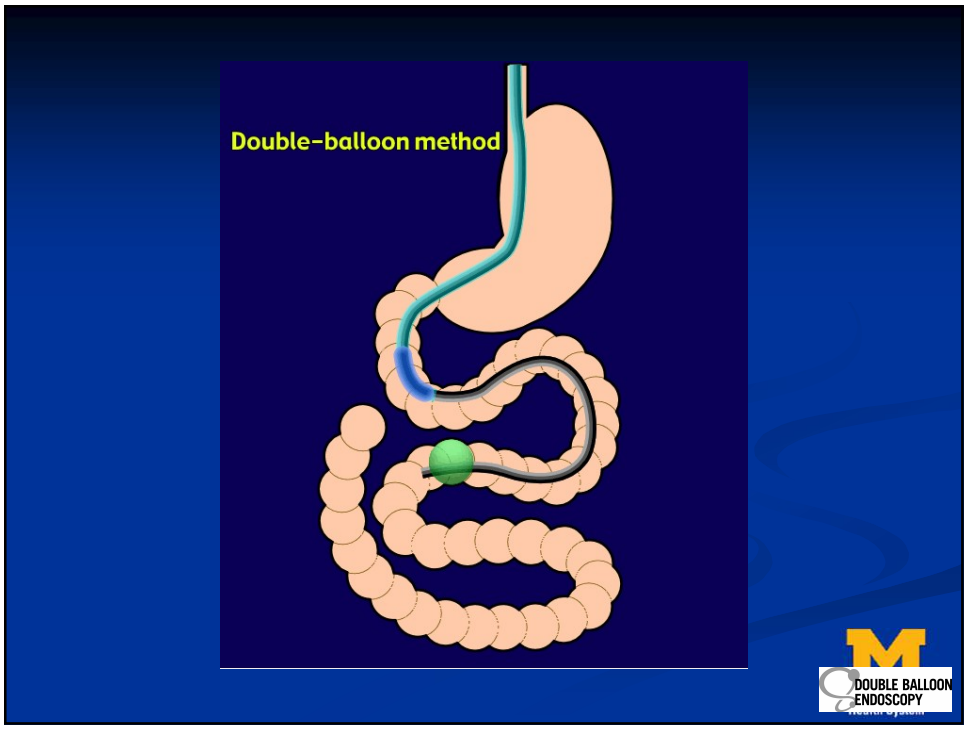
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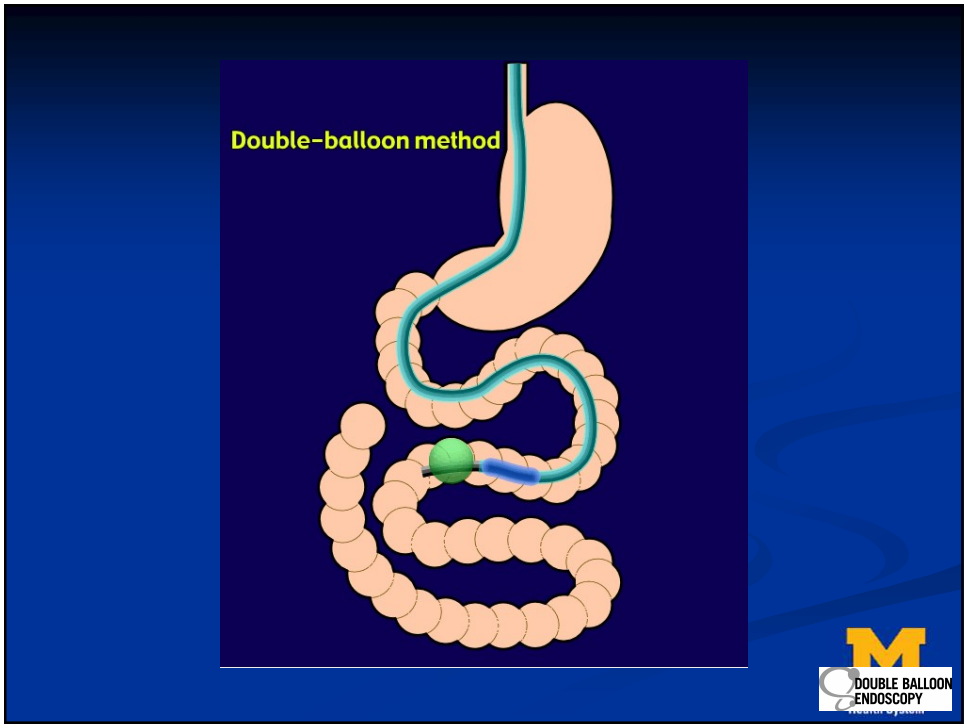
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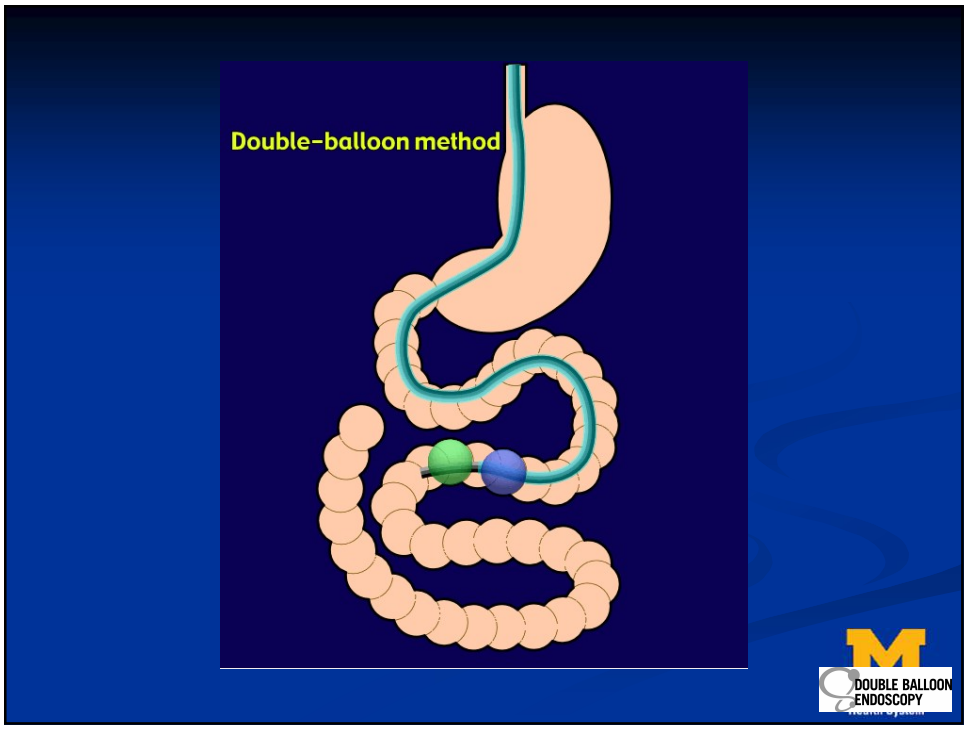
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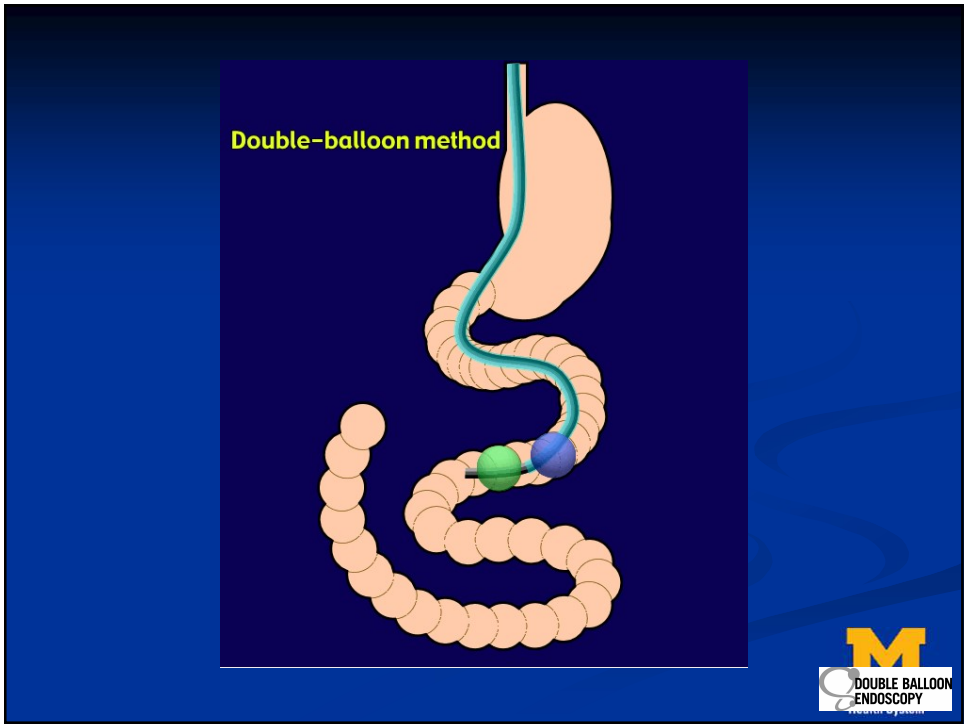
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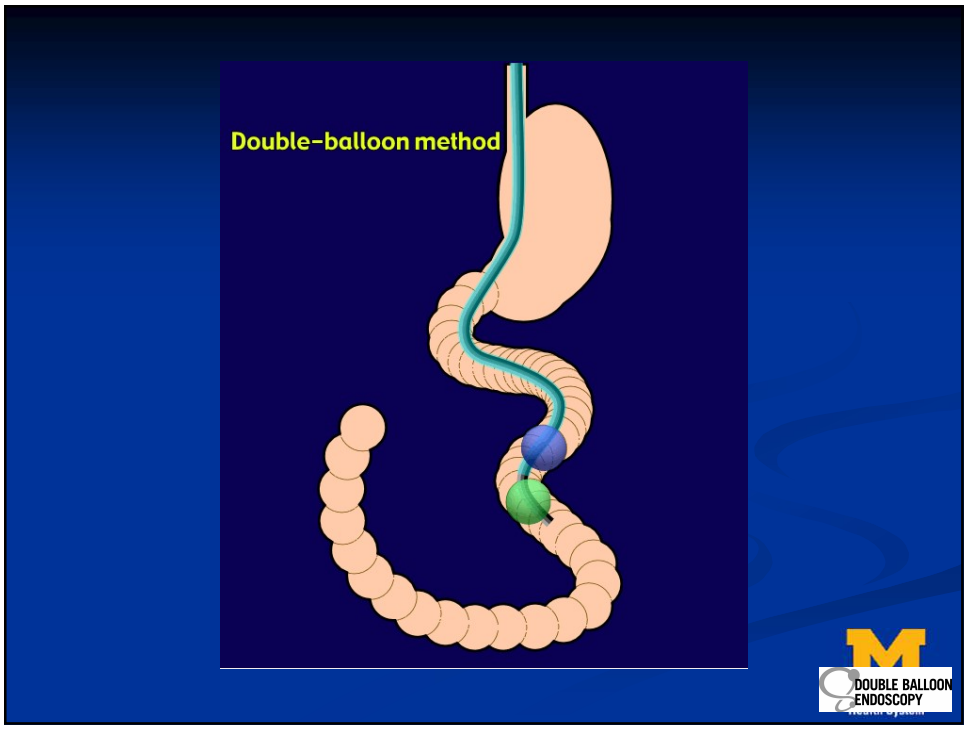
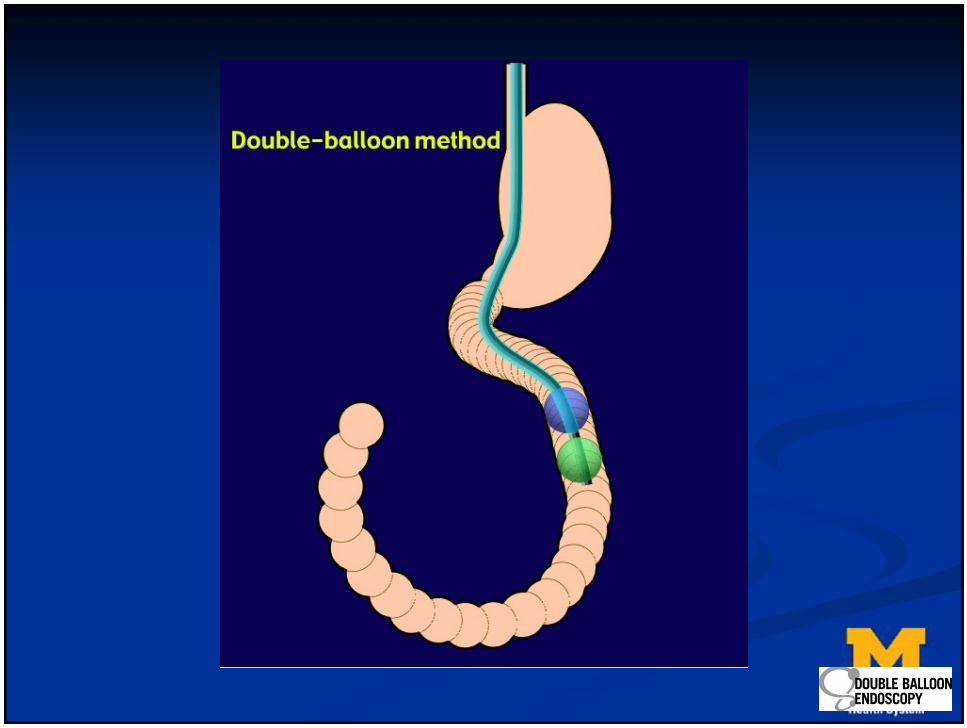
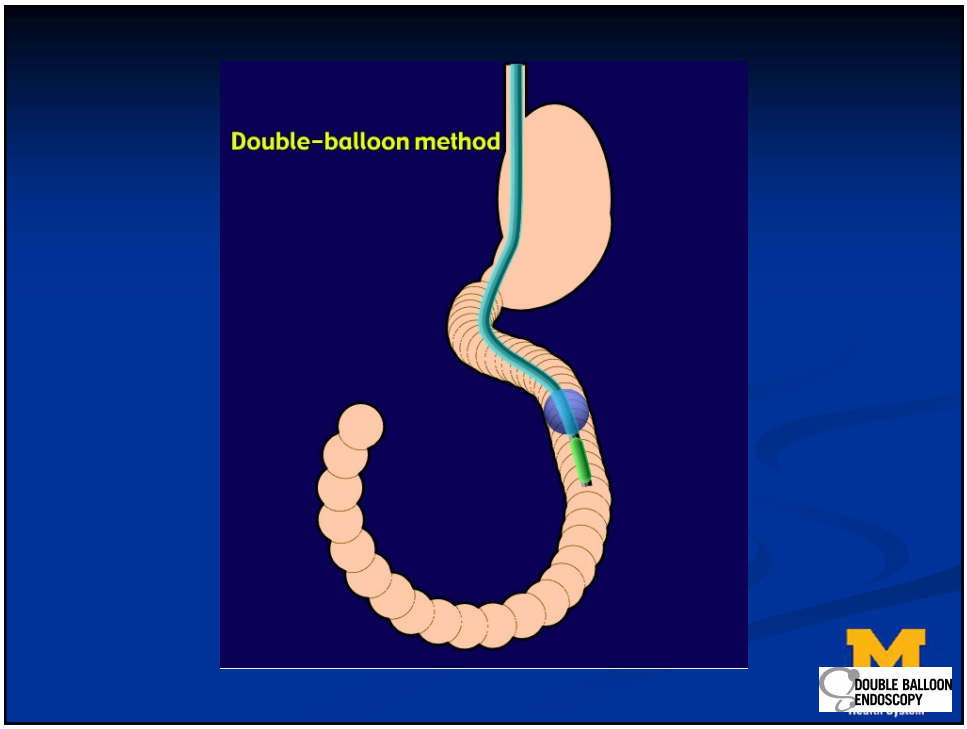

Double-balloon method
DOUBLE BALLOON ENDOSCOPY


Double-balloon method
DOUBLE BALLOON ENDOSCOPY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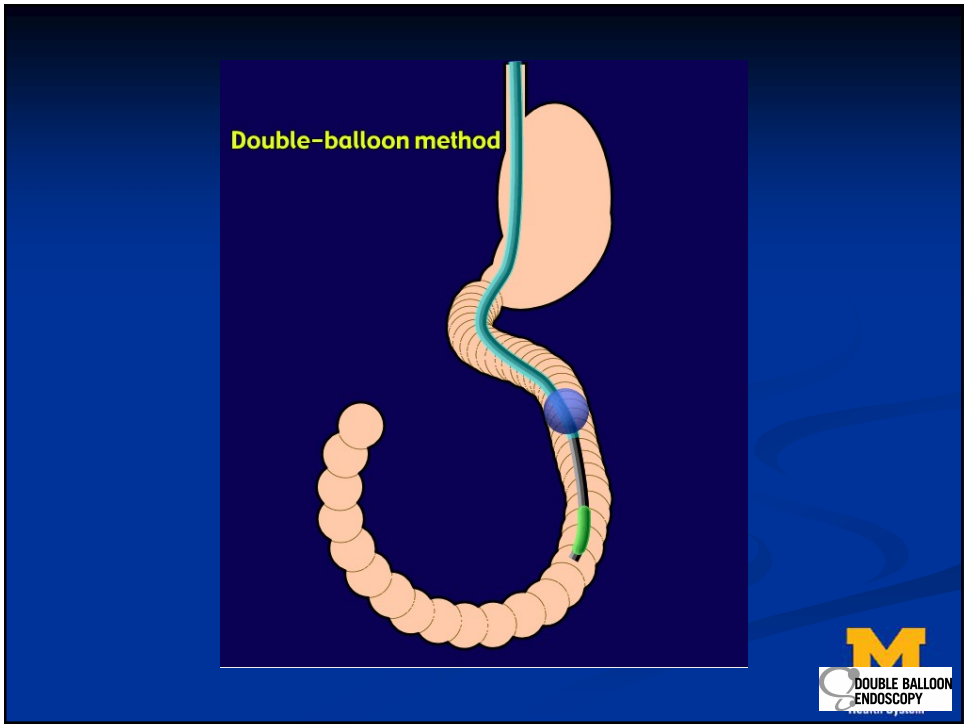
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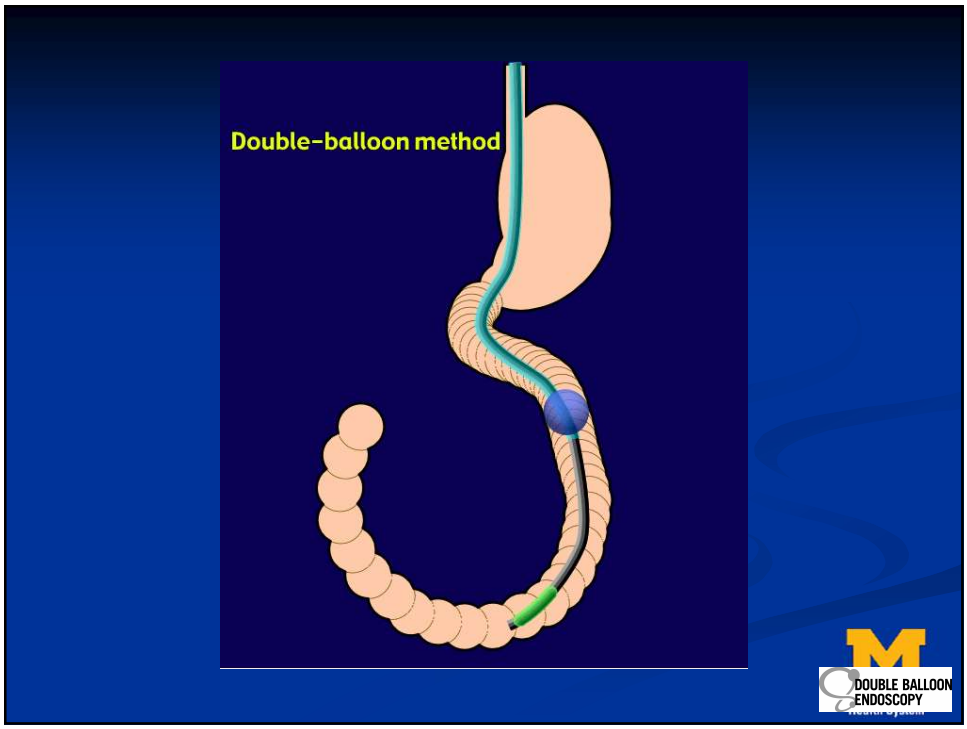
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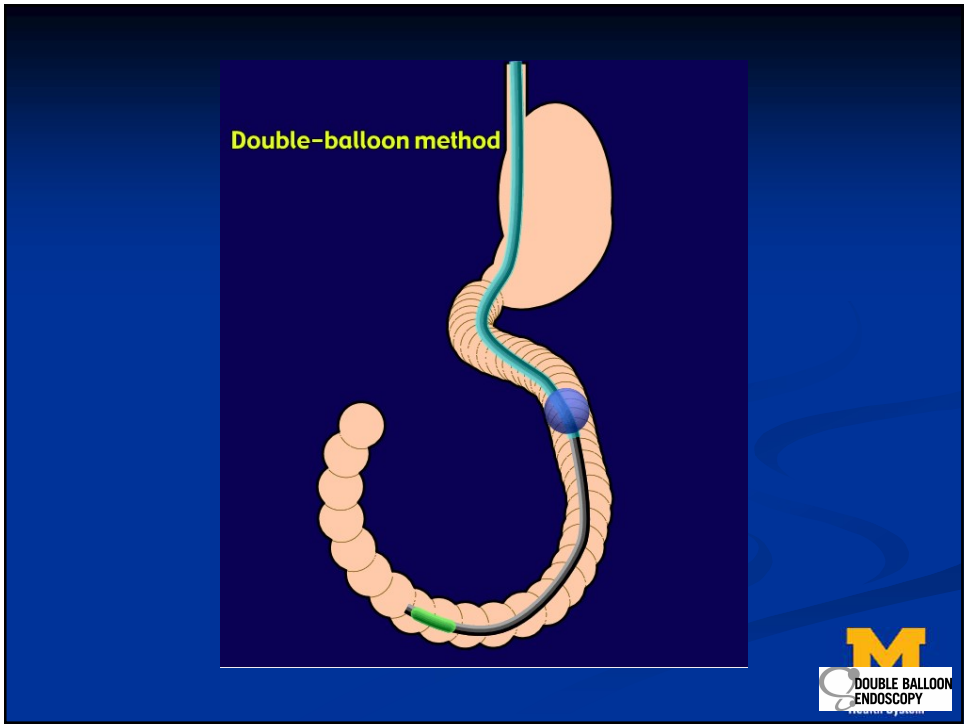
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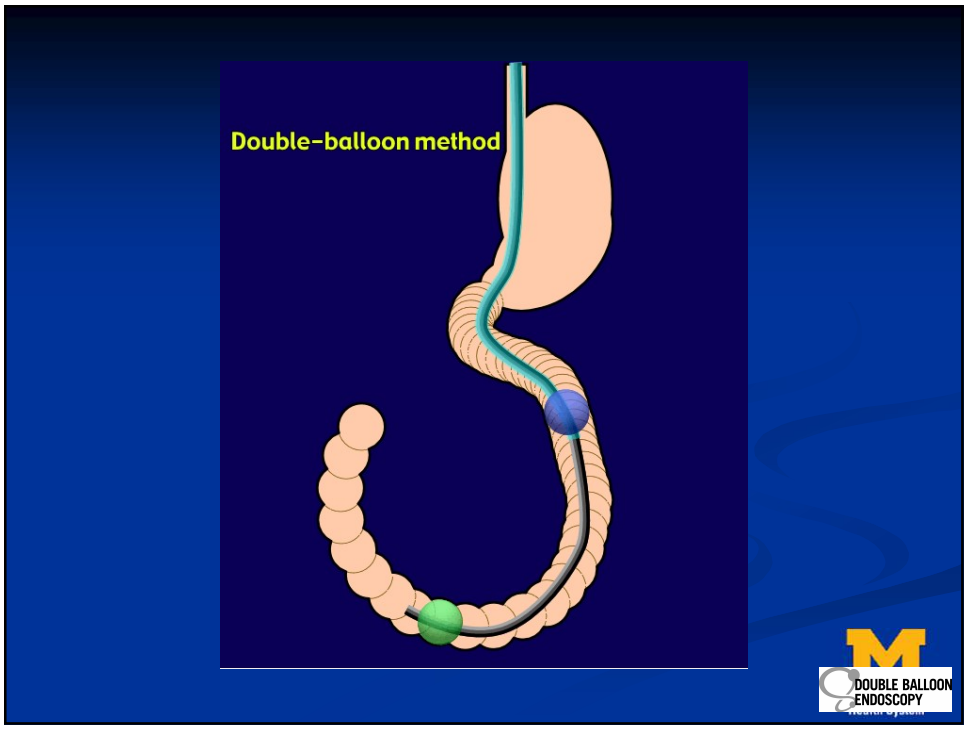
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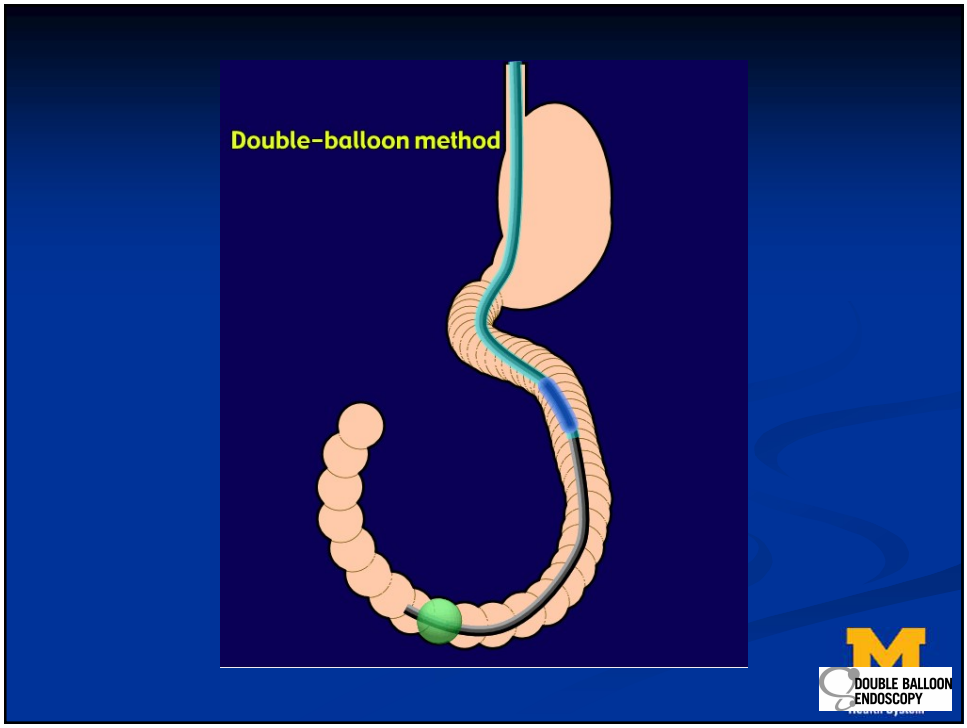
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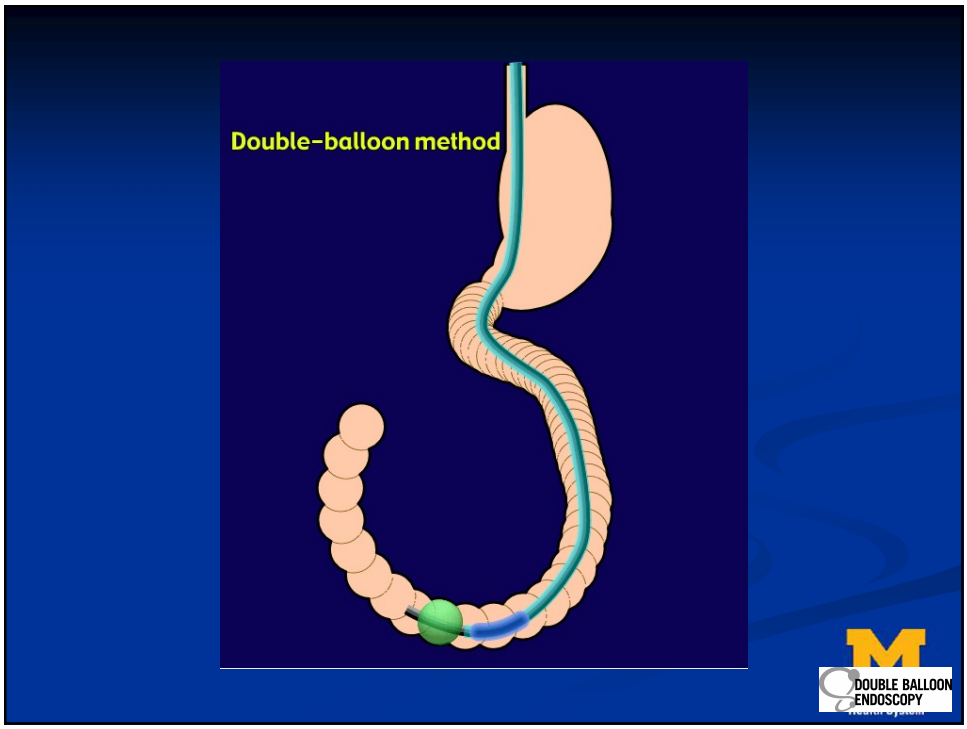
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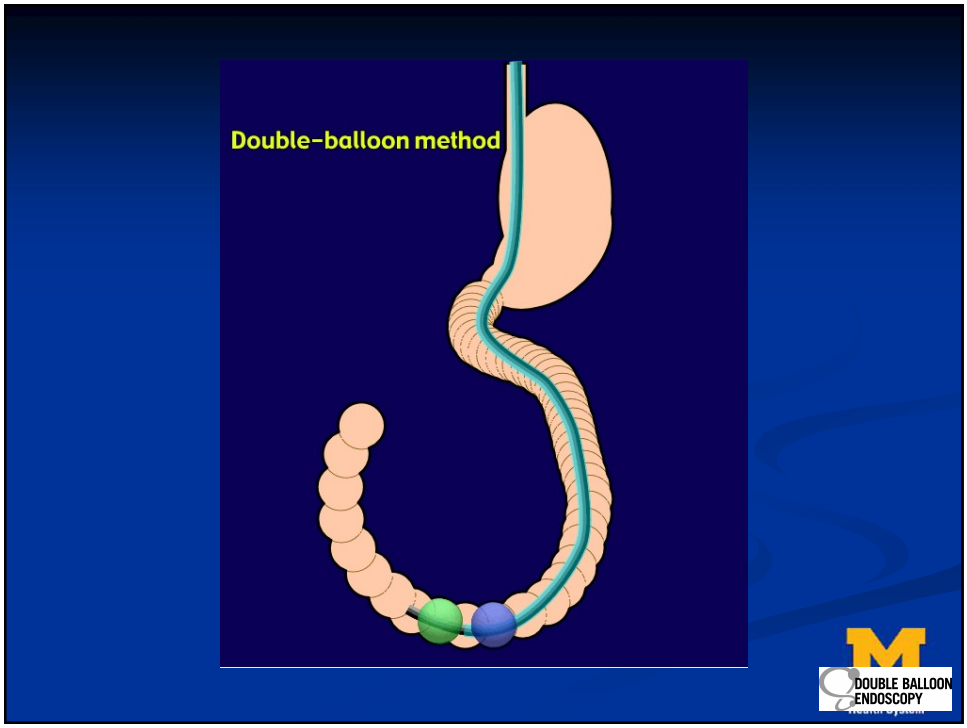
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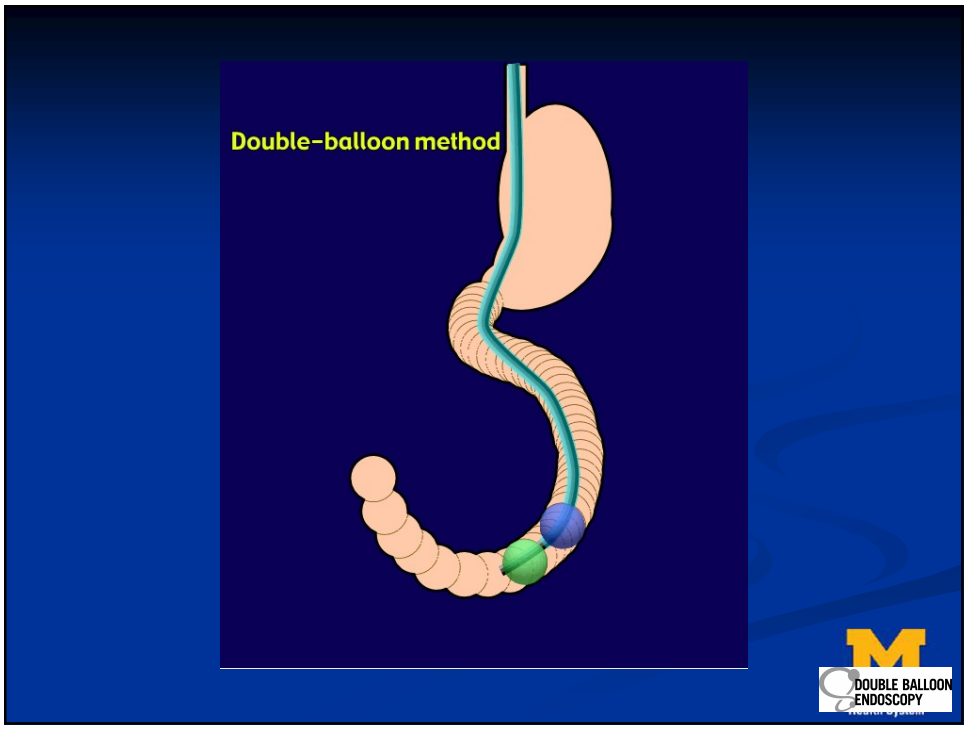
DOUBLE BALLOON ENDOSCOPY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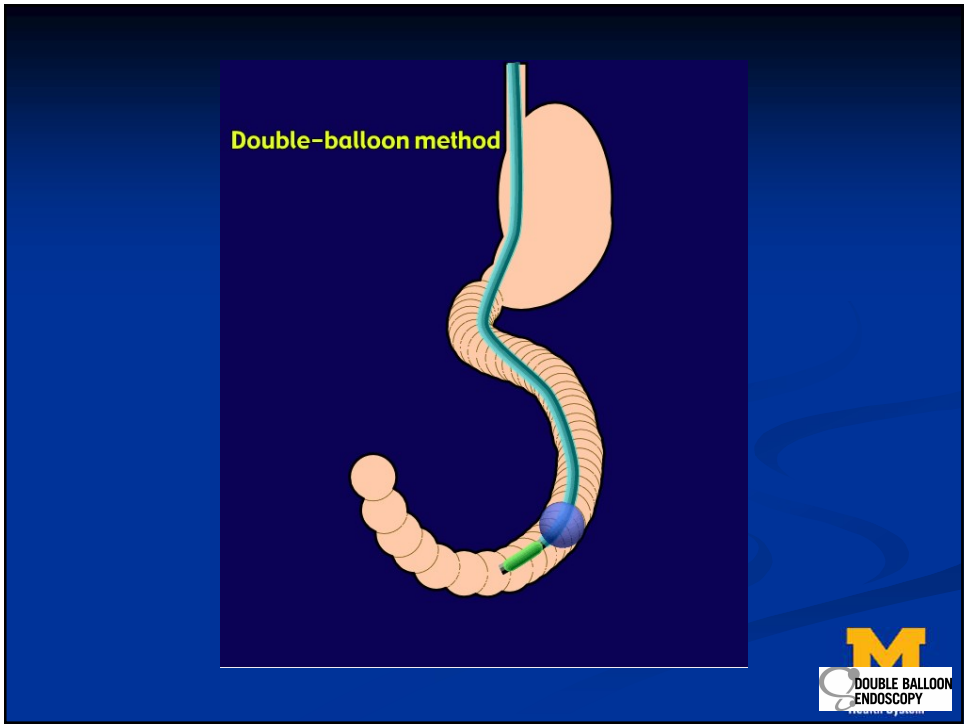
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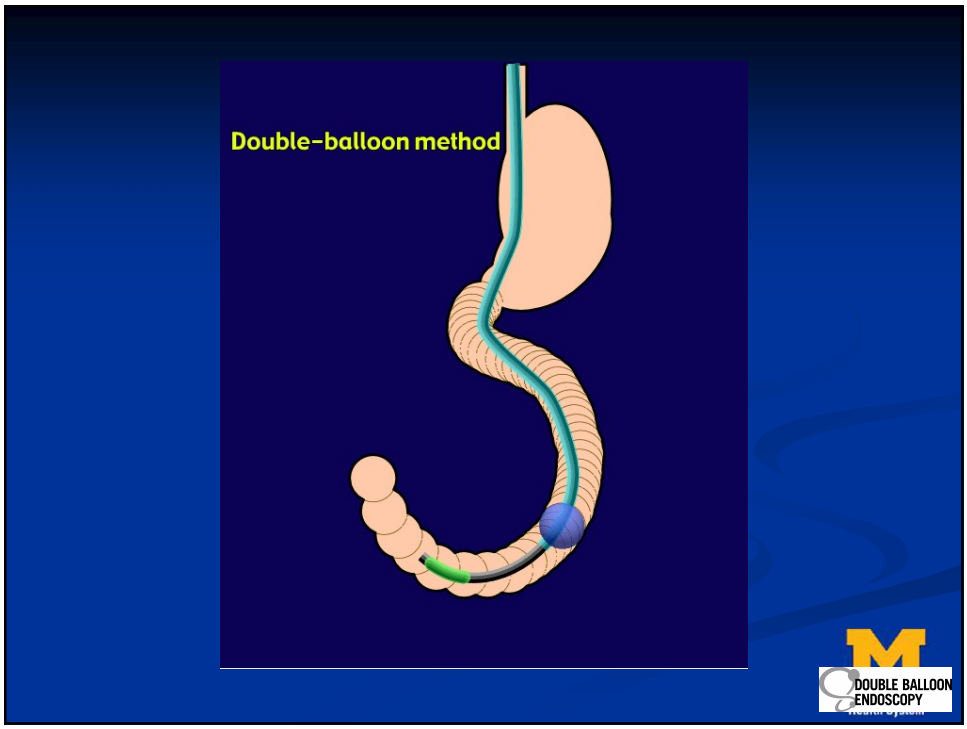
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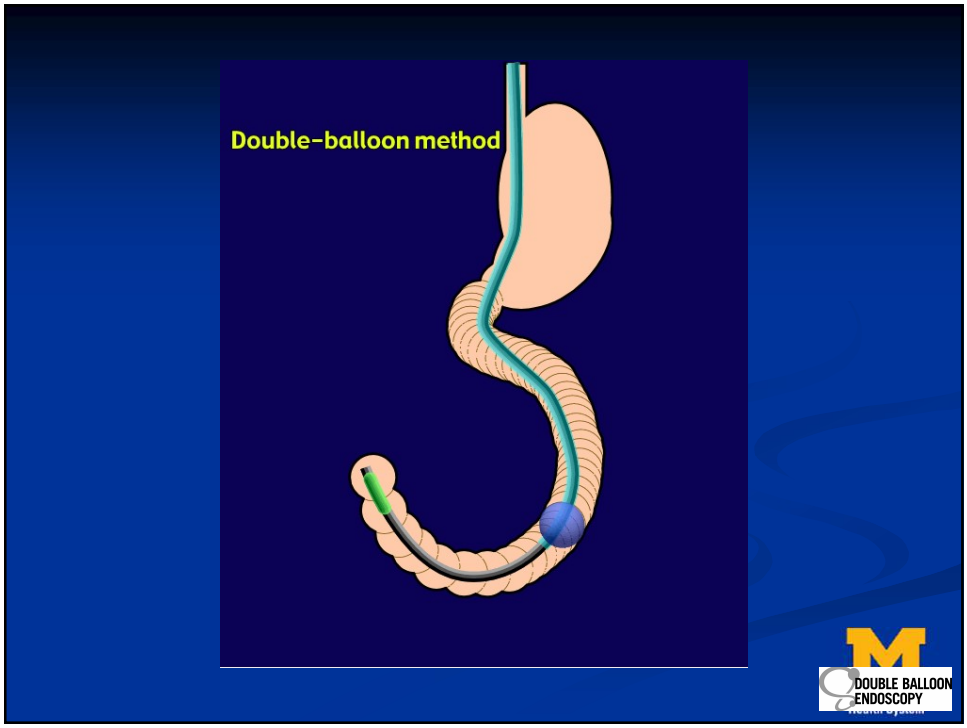
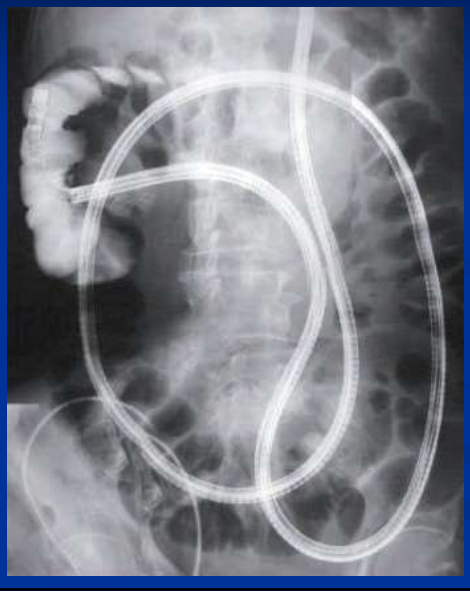
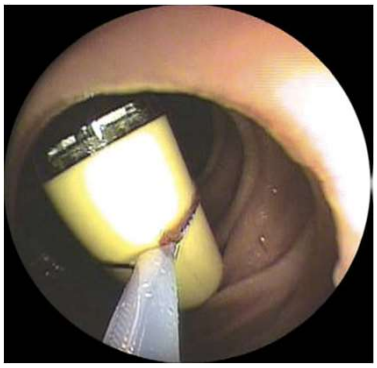


Antegrade (oral) DBE



Retained Capsule



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Causes of small bowel bleeding

Common causes		Rare causes
Under age 40 years	**Over age 40 years**	**Henoch–Schoenlein purpura**
Inflammatory bowel disease	Angioectasia	Small bowel varices and/or portal hypertensive enteropathy
Dieulafoy's lesions	Dieulafoy's lesions	Amyloidosis
Neoplasia	Neoplasia	Blue rubber bleb nevus syndrome
Meckel's diverticulum	NSAID ulcers	Pseudoxanthoma elasticum
Polyposis syndromes		Osler–Weber–Rendu syndrome
		Kaposi's sarcoma with AIDS
		Plummer–Vinson syndrome
		Ehlers–Danlos syndrome
		Inherited polyposis syndromes (FAP, Peutz–Jeghers)
		Malignant atrophic papulosis
		Hematobilia
		Aorto-enteric fistula
		Hemosuccus entericus

FAP, familial adenomatous polyposis; NSAID, nonsteroidal anti-inflammatory drug.

ACG Guidelines 2015 for Diagnosis and Management of Small Bowel Bleeding

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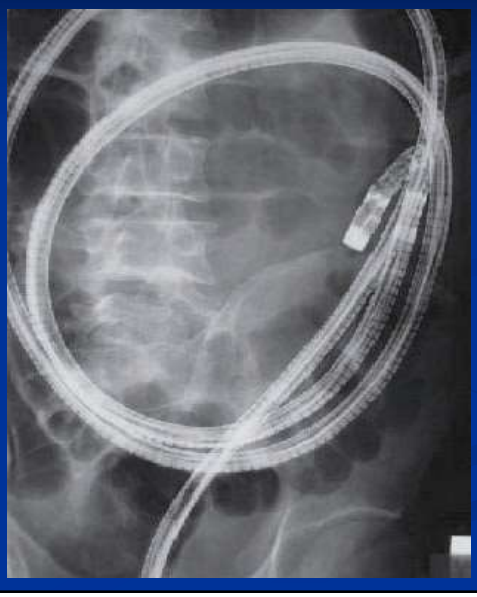
Retrograde (anal) DBE



University of Michigan Health System

Future Research/Development

- Improved technology for VCE localization of lesions
  - select the appropriate enteroscopy system/approach
- Technology development to enhance efficiency of DAE
  - reduce procedure times
  - may promote adoption in community settings
- Improved and newer therapeutic accessories
  - currently available DAE platforms

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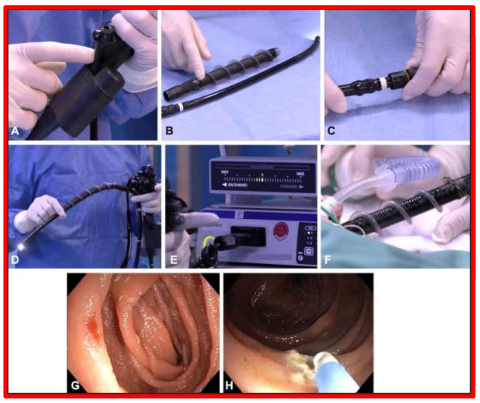
Motorized Spiral Enteroscopy

- Replaces manual clockwise rotation of spiral enteroscopy
- Reusable endoscope
  - integrated drive motor
  - rotational coupler
- Short spiral overtube
  - on end of enteroscope
- Motor control unit
  - foot pedal
- Preliminary reports: complete enteroscopy is possible (10%)
- Not yet FDA approved



Video GIE 2016

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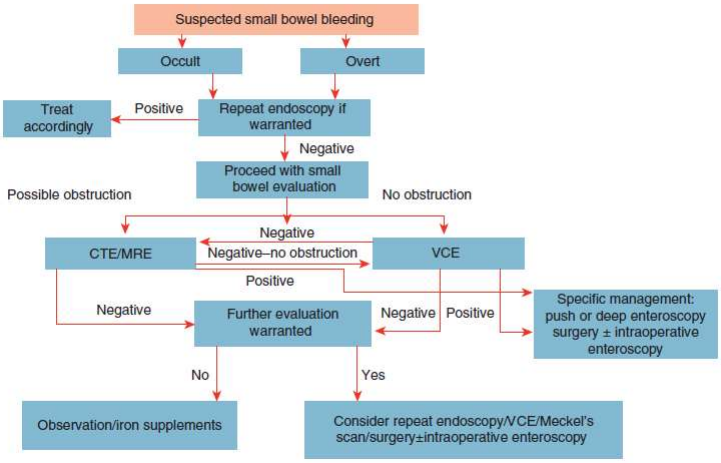
Algorithm for suspected small bowel bleeding



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Michigan Small Bowel Physicians


Mimi Takami, MD


Andrew Read, MD


Neil Sheth, MD


Michael Rice, MD

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Small Bowel Program

- DAE is typically performed in the Hospital Setting
- Most patients with acute GIB and OGIB/suspect SB start as inpatients
- Does not fit in traditional ASC business model
- ↑**Co$t** equipment/Time
  - Inpt VCE?

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Economics of Inpatient Small Bowel Evaluation

- Inpatient capsule endoscopy
  - Paid under a single DRG
  - Costs of not doing it

- 

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Inpatient VCE – costs of negative diagnostic tests

- Pennanzio et al.
- 100 consecutive pts with OGIB
  - Active Overt-Obscure GI: 26 pts
  - Occult-obscure: 43 pts
- 620 negative diagnostic tests performed prior to VCE
- VCE overall Diagnostic Yield: 50%
- Quality= (Appropriateness x Outcomes)/Waste

Pennanzio et al., Gastro 2004

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Summary

- Definition of Small Bowel Bleeding
- History of endoscopic eval of small bowel
- Algorithm for evaluation for obscure GIB

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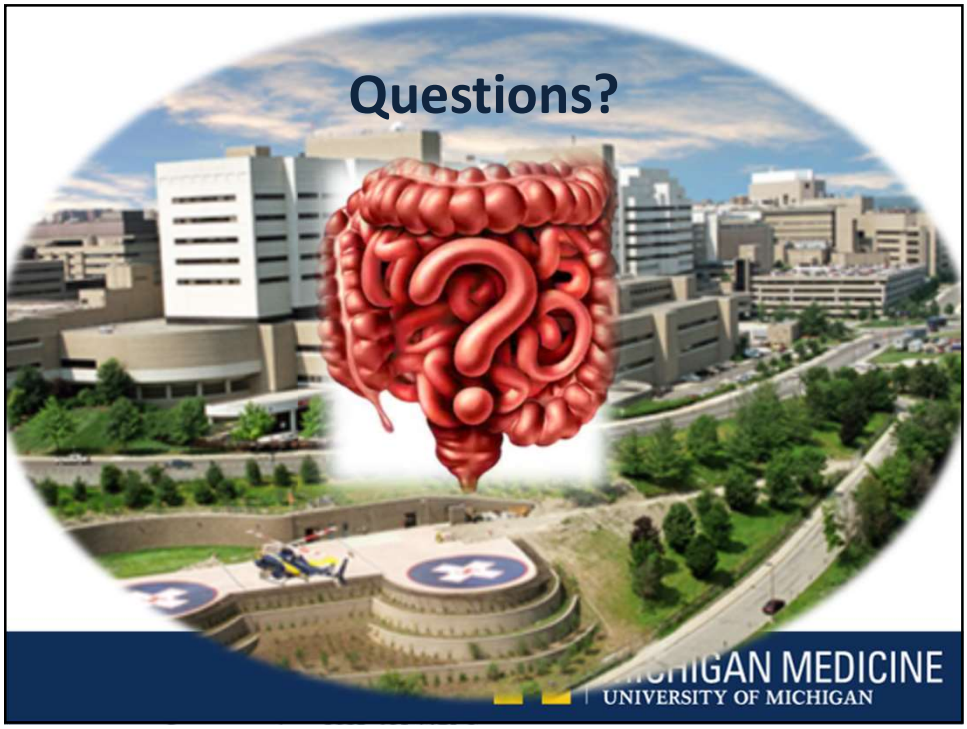
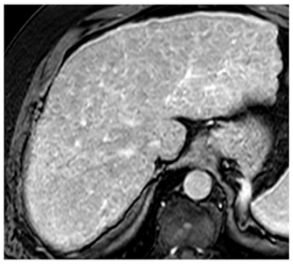


Diagnosis and Management of Hepatitis B



Robert J. Fontana, MD
Professor of Medicine
Medical Director of Liver Transplantation

Robert J. Fontana, MD

- Research support: Gilead, BMS, Abbvie.
  - Consultant: Sanofi
- NIH: HBRN

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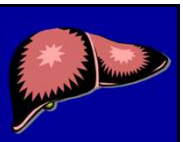
Hepatitis B

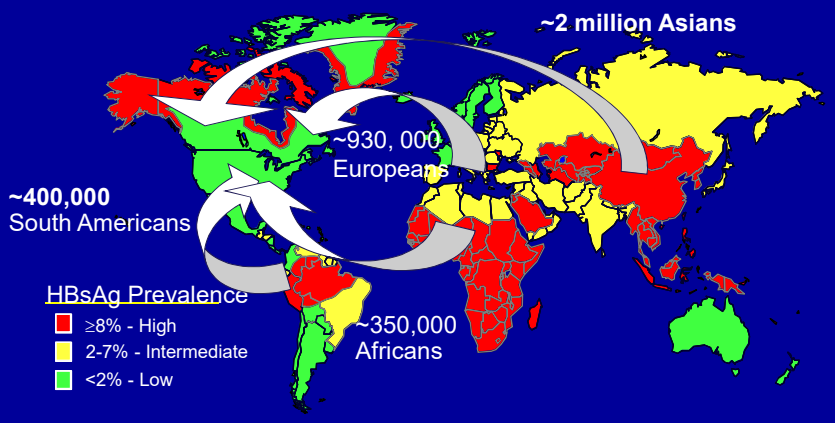


- **Diagnosis & staging**
  - **Serologies**
  - **Phases of infection**
  - **Biopsy & elastography**
- **Antiviral therapy**
  - **Long-term efficacy & safety**
  - **Endpoints of therapy**
- **Future therapies**
  - **Functional cure of HBV**

Hepatitis B Virus

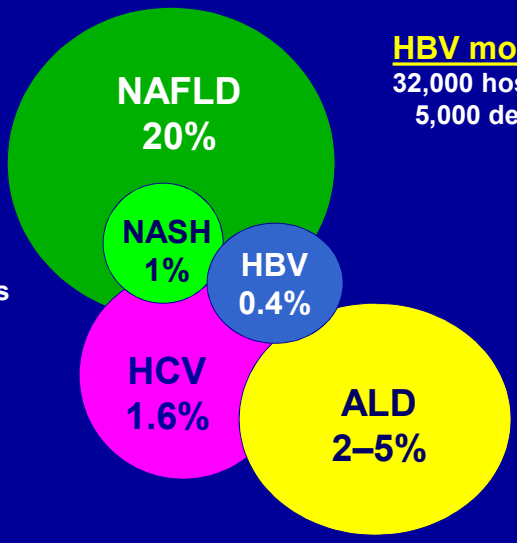
- **Double stranded DNA virus**
  - Replicates thru RNA intermediate (like HIV)
- Highly infectious **blood borne** pathogen
  - Preventable via vaccine
  - Horizontal transmission in adults (STD)
    - **< 5 %** chronic
  - Vertical transmission: Mother to infant
    - **> 90%** chronic

Geographic Prevalence of Chronic HBV



Immigration numbers by continent from 1996-2002

US Liver Disease



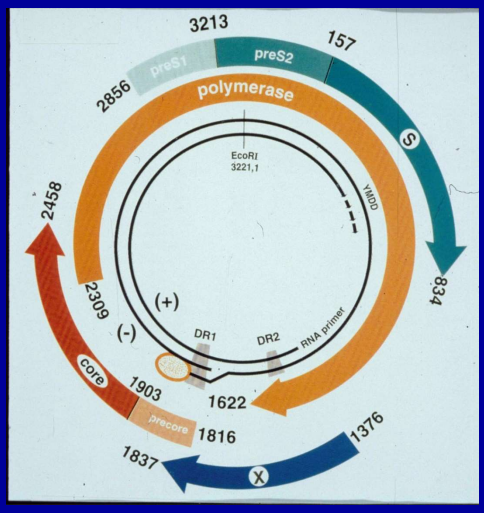
HBV morbidity
32,000 hospitalized
5,000 deaths/yr

Chronic HBV
1.1 million Americans
< 25% aware

IOM report 2010

Hepatitis B Virus

- 4 genes
  - HBsAg, HBcAg, HBV pol/ RT, HBx
- 10^{11} virions/ d
  - No proofreading
    - 3 x 10^{-4} sub/nt/yr
  - Not all mutants viable
- cccDNA
  - Covalently, closed circular DNA
  - Long half-life



Serologic and virologic assessment in Chronic HBV

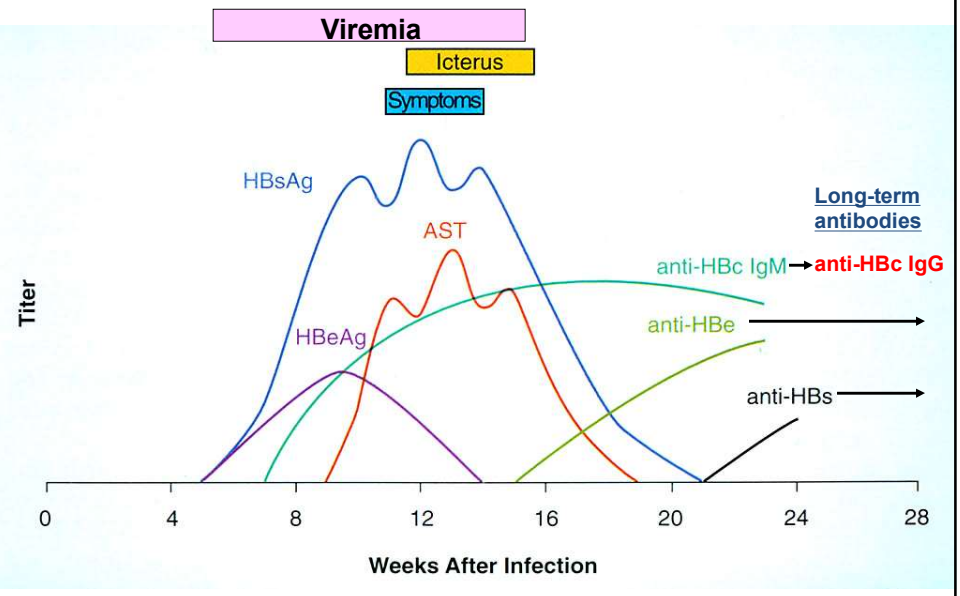
Serologic tests	
HBsAg	Infection
Anti-HBs	Exposure to HBV; immunity
Anti-HBc	Exposure to HBV
HBeAg	Marker of replication
Anti-HBe	Low replication or precore / core promoter variant infection
Virologic assessment	
HBV DNA	Quantitative assessment of degree of replication

1 IU/ml = 5 copies/ ml

Serological diagnosis of Hepatitis B infection

	Acute Hepatitis B	Chronic Hepatitis B	Prior Exposure	Prior Vaccination
HBsAg	+	+	-	-
Anti-HBc	+ (IgM)	+	+	-
Anti-HBs	-	-	+/-	+
Serum ALT	↑ to ↑↑↑	Normal to ↑↑	Normal	Normal
HBV DNA	+	++	-	-

Acute hepatitis B that resolves

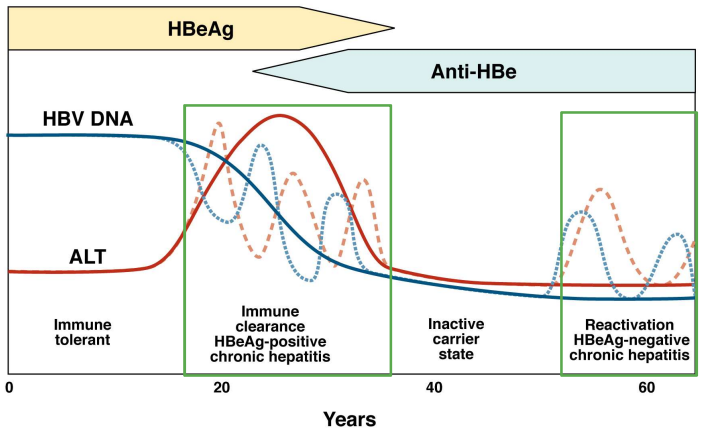


HBV is a Human Carcinogen

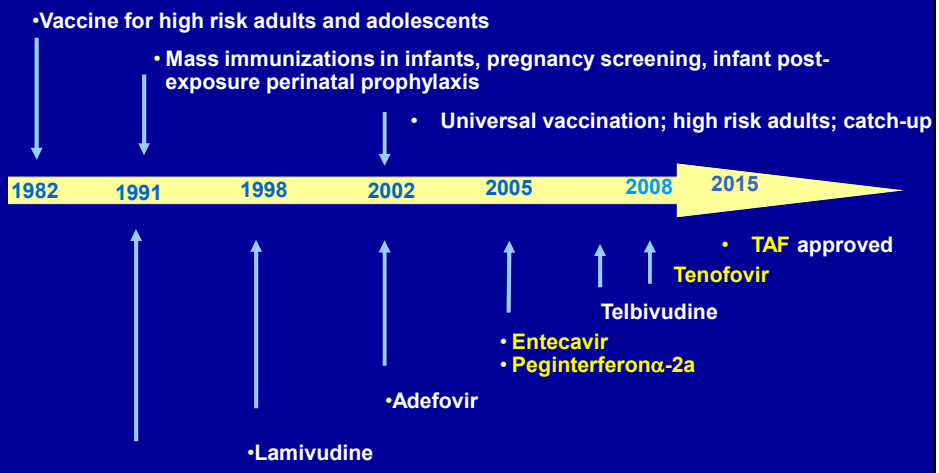
- **100 fold** HCC risk in HBsAg + *vs* non-infected
  - ↑ risk with age, men, alcohol, fibrosis
- Hepatocellular carcinoma screening
  - Liver USN and AFP q 6 months in all HBsAg +
    - Men > 40 years
    - Women > 50 years
    - Africans > 20 years
    - Cirrhosis
    - + Fam Hx HCC

Beasley et al, Cancer 1988; 61: 1942
McMahon et al, Ann Intern Med 2001; 135: 759
AASLD HBV Guidance Hepatology 2018

When to Initiate Treatment in Patients with Non-Cirrhotic Chronic Hepatitis B?



HBV Vaccination and Treatment



•α-interferon injection first approved treatment for HBV

Chronic HBV: Who to Treat

- **Chronic active HBV**
  - Serum ALT > 1.5- 2 × ULN

    and
    - HBeAg (+): HBV DNA > 20,000 IU/ml
    - HBeAg (-): HBV DNA > 2,000 IU/ ml

    or
  - Moderate inflammation/ fibrosis on biopsy

(AASLD HBV Guideline 2018)

Liver biopsy in chronic HBV

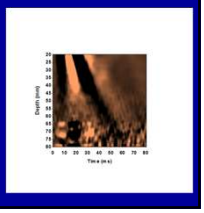
- **Assess disease severity**
  - Necroinflammatory grade/ fibrosis stage
  - If discordant ALT and HBV DNA levels (e.g. NAFLD)
- **Guide treatment decisions**
  - Antiviral therapy
  - Disease monitoring (Portal hypertension, HCC)
- **Limitations:** Sampling artifact, invasive

Clin Gastroenterol Hepatol. 2004;2:87-106.

Vibration Controlled Transient Elastography (VCTE)

- **Fibroscan a non-invasive estimate of hepatic fibrosis & steatosis severity**
- **Fibrosis** (Stiffness : 3 to 70 kPa)
  - Cirrhosis (> 12 kPa) vs no cirrhosis
    - False +: inflammation, bloodflow, alcohol

- **Steatosis** (CAP : 100 to 400 db/m)
  - Normal (< 10%) < 250 db/m
  - Mild (10-30%) 250-300 db/m
  - Mod/ severe (> 30%) > 300 db/m



MR Elastography

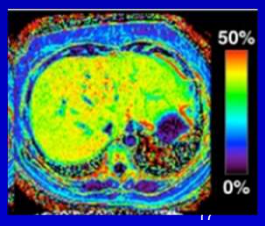
Liver stiffness

- < 2.5 (normal)
- 3-6 kPa mild-mod fibrosis
- > 6 kPa Cirrhosis

- **Steatosis (PDFF)**
  - < 5% normal
  - 5 to 10% mild
  - 10 to 20% moderate
  - > 20% severe

Limitations

Expensive
Needs validation
False +



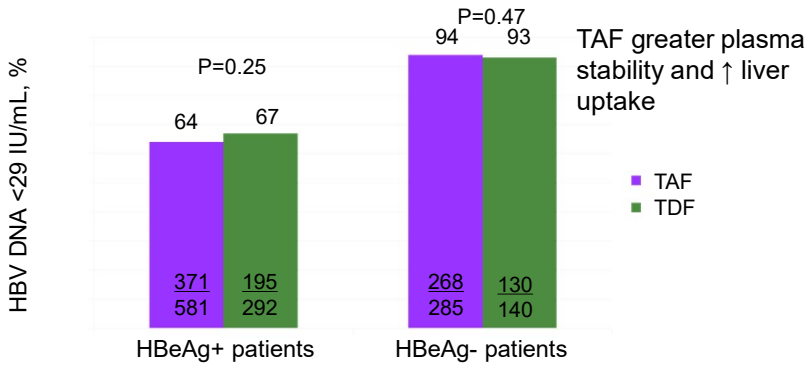
1st line agents Chronic HBV

	Entecavir	Tenofovir TAF	PEGIFN
Response yr 1 eAg + eAg -	 21% 90%	 21% 93%	 32% 70%
Side effects	-	-	++
Drug resistant (yr)	<1%(7) ^	< 1% (8)	None

^ In LAM-R, 57% at yr 6

(AASLD HBV Guideline 2018)

Tenofovir Alaflenamide (TAF) 25 mg vs. Tenofovir Disoproxil Fumarate (TDF) 300 mg Virologic Response at Week 48

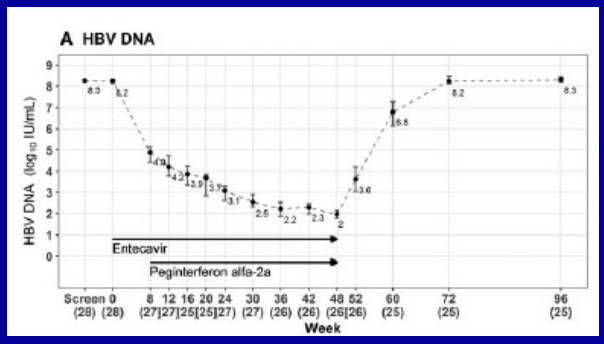


TAF has less impact than TDF on bone density and renal function

Chan H, Lancet Gastroenterol Hepatol 2016; 1: 185; Buti M, Lancet Gastroenterol Hepatol 2016; 1: 196

Immunetolerant Chronic HBV

HBeAg +, HBV DNA > 10^7 IU/ml ALT < 1.5 x ULN



- **1° Endpoint: HBeAg loss**
  - **3.3% of children (60) 0% of adults (28)**
- **DO NOT treat Immunetolerant chronic HBV**

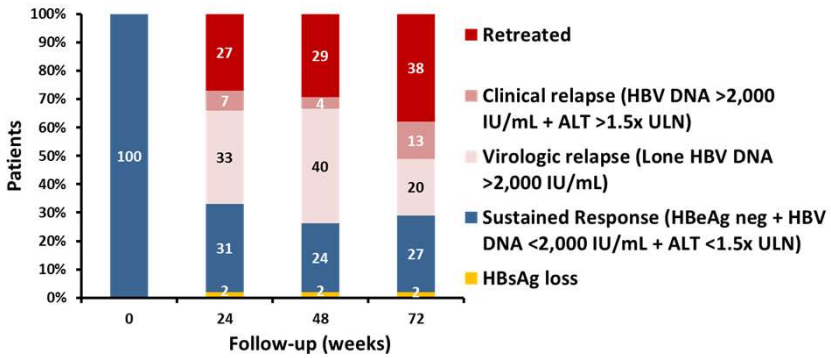
(Rosenthal, Feld Hepatology 2019)

Duration of NRTI's in chronic active HBV

- **HBeAg (+)**
  - Suppress HBV DNA to low/ undetectable
  - ALT normalization
  - Duration: HBeAg loss ± seroconv (+ 12 months)
- **HBeAg (-)**
  - Suppress HBV DNA to low / undetectable
  - ALT normalization
  - Duration= Indefinite
- **Functional cure of HBV**
  - Sustained HBsAg loss

Stopping NRTI in HBeAg (-)

Inc: > 3 yrs Rx or > 1 yr after HBeAg seroconversion
2:1 random; F/U x 72 wks n=67 Asians Toronto



Stopping NRTI's in chronic HBV is NOT effective

(Liem AASLD 2018: #268)

Guideline Recommendations on Stopping Nucleos(t)ide Analogues

	AASLD 2018	EASL 2017
HBeAg + (no cirrhosis)	HBeAg seroconversion, HBV DNA (-) for ≥12 mon	HBeAg seroconversion and HBV DNA (-) for ≥12 mon
HBeAg – (no cirrhosis)	HBsAg loss ?	HBsAg loss or selected pts, ≥3 year HBV DNA (-) and close post-Rx monitoring
Cirrhosis	DO NOT STOP	DO NOT STOP

Terrault N, Hepatology 2016; 63: 261; 2018; 67: 1560; Sarin SK, Hepatol Int 2016; 10: 1; EASL J Hepatol 2017; 67: 370

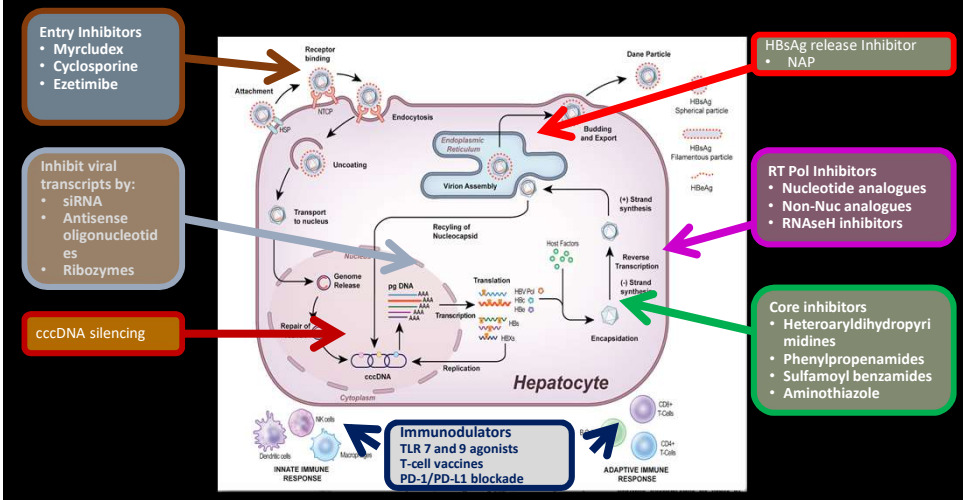
Functional cure of HBV

- **Definition:** Sustained loss of **HBsAg** for > 48 weeks after therapy discontinuation (+/- anti-HBs)
  - Improved natural history/ ↓ outcomes
  - Quantitative HBsAg assay in development
- WHO: worldwide elimination of HBV/ HCV by 2030

- Finite duration of antiviral/ immunomodulatory
  - ? Predictors of response
  - ? Safety of ALT flare
  - Efficacy: **20%** HBsAg loss 48 wks after d/c

(Chronic HBV : FDA Guidance for Industry Feb 2019)

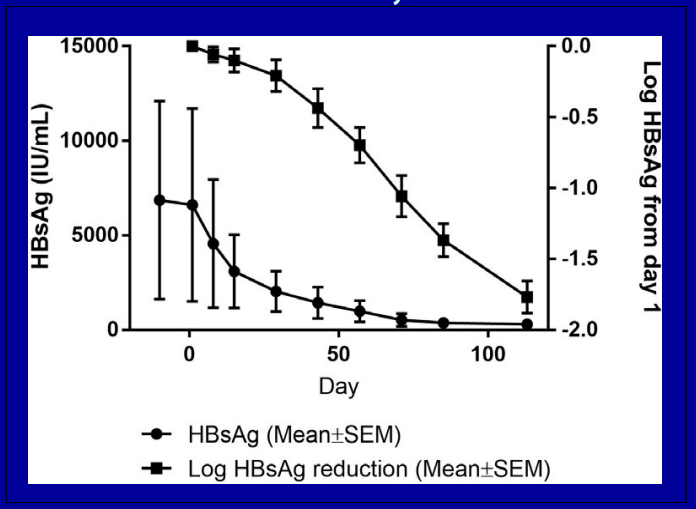
HBV Lifecycle and Drug Targets



Functional cure trials in HBV

- Antivirals (reduce or eliminate cccDNA)
  - NTCP inhibitors, Capsid assembly inhibitors
  - RNAi, HBX protein inhibitors
- Immunomodulatory
  - TLR-3 agonists
  - PD-1, CTLA-4 inhibitors
  - Therapeutic vaccines
- Patient groups: Naïve vs NRTI suppressed

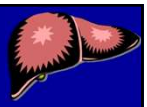
Combination RNAi, CAM and Nuc



Safety: 5 ALT flares (57 to 111 IU/L) ? Therapeutic flare

(Yuen AASLD 2019; LP4)

Chronic HBV in 2020



- **Chronic HBV is leading worldwide cause of cirrhosis and HCC despite safe and effective vaccine**
  - **Treatment: HBV-DNA, ALT, and severity (fibrosis)**
    - **Treat all cirrhotics**
    - **Do NOT treat Immunetolerant HBV**
- **Oral NRTI's safely suppress HBV DNA**
  - **Entecavir, Tenofovir, and TAF preferred**
    - **< 1% HBsAg loss/ year**
  - **NRTI discontinuation is NOT recommended**
- **Novel agents to achieve HBsAg loss**
  - **Antivirals +/- immunomodulatory**

Thank YOU !!!

rfontana@med.umich.edu

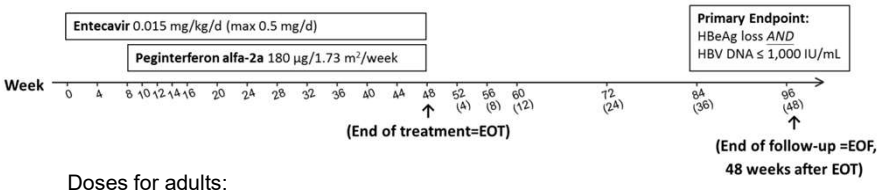
WHO and NAS
Worldwide elimination of HBV & HCV

- Widespread use of HBV vaccine along with development of safe and effective treatments can lead to worldwide elimination of chronic HBV

- Target Date: 2030

(National Acad Sciences 2016, WHO 2016)

Entecavir Lead-in Followed by Combination of Entecavir + Peg-Interferon in Immune Tolerant Children and Adults: HBRN Studies



Doses for adults:
Entecavir 0.5 mg/d, Peginterferon alfa-2a 180 ug/week

HBRN: NIH funded with clinical sites in United States and in Toronto Canada

Alcohol-Associated Liver Disease in the United States: Another "Disease of Despair"?

Jessica L. Mellinger, MD MSc

Advances in Gastroenterology & Hepatology
Bonita Springs, Florida
February 7-9, 2020

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Learning Objectives

- Epidemiology of ALD and AUD in the US
- Reasons for the rise in ALD
- Challenges and Opportunities in the fight against ALD

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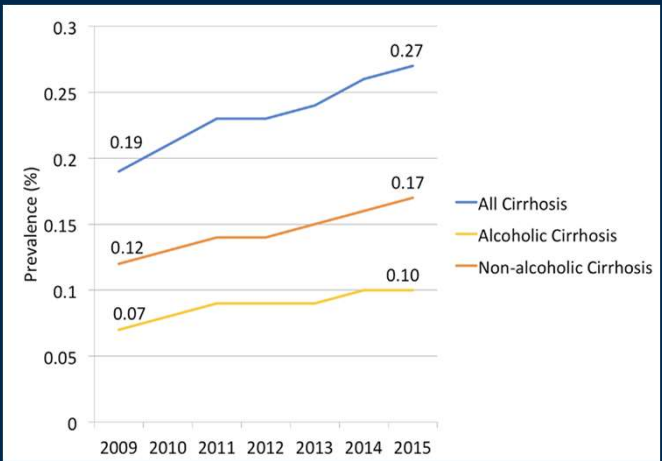
Alcohol-related Cirrhosis Prevalence

Privately insured US Adults, ages 18-64



1. Alcohol and non-alcohol cirrhosis prevalence rose 43%
1. Alcohol-related cirrhosis made up ~37% of the total burden
1. Enrollees age <45 had 3-fold increase (0.01% to 0.03%)
1. Women increased by 50%, men by 30%

Mellinger J. et al *Hepatology* 2018

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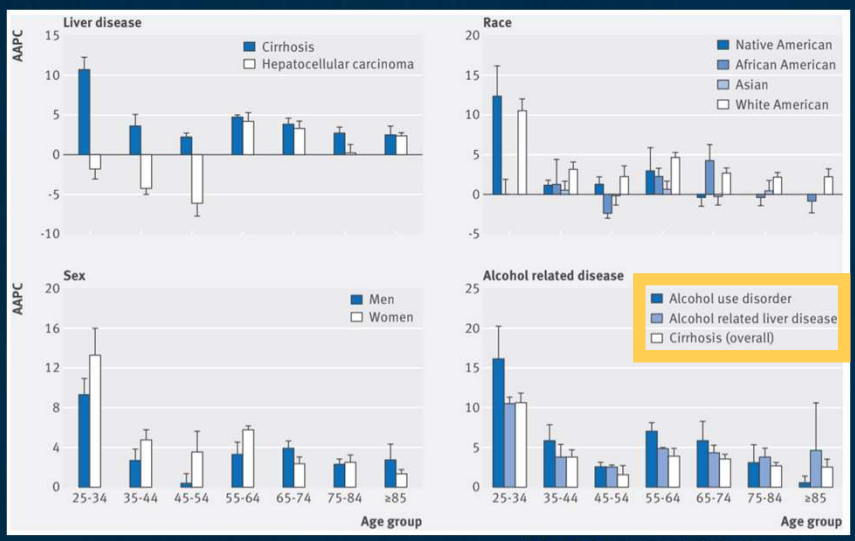
Alcoholic cirrhosis and AUD mortality has risen in young people

Annual percent change highest in ages 25-34, Native Americans, women



Tapper E & Parikh N *BMJ* 2018(362)

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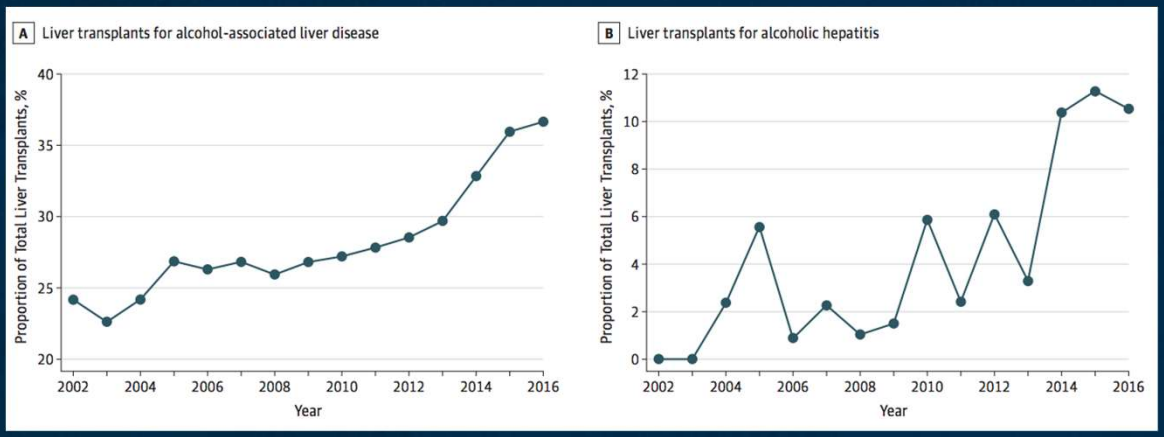
Changing Burden of ALD in Transplant: Now #1



Lee BP, et al *JAMA Int Medicine* 2019

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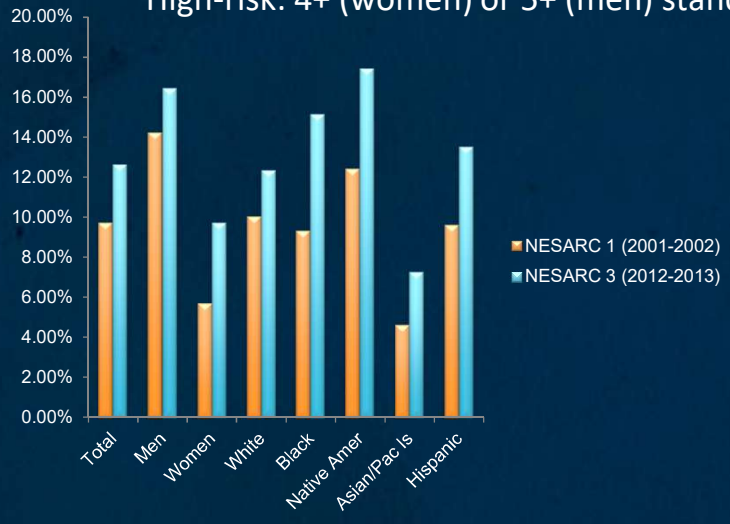
High-risk Drinking Also Rose

High-risk: 4+ (women) or 5+ (men) standard (US) drinks/day



- 30% overall increase
- More marked increases in women, minorities
- Greatest rate of increase for age was in >65 (65%) though overall prevalence low (3.8%)
- Age 18-29: 17→19.3%

Data from National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
Grant BF, et al *JAMA Psych* 2017

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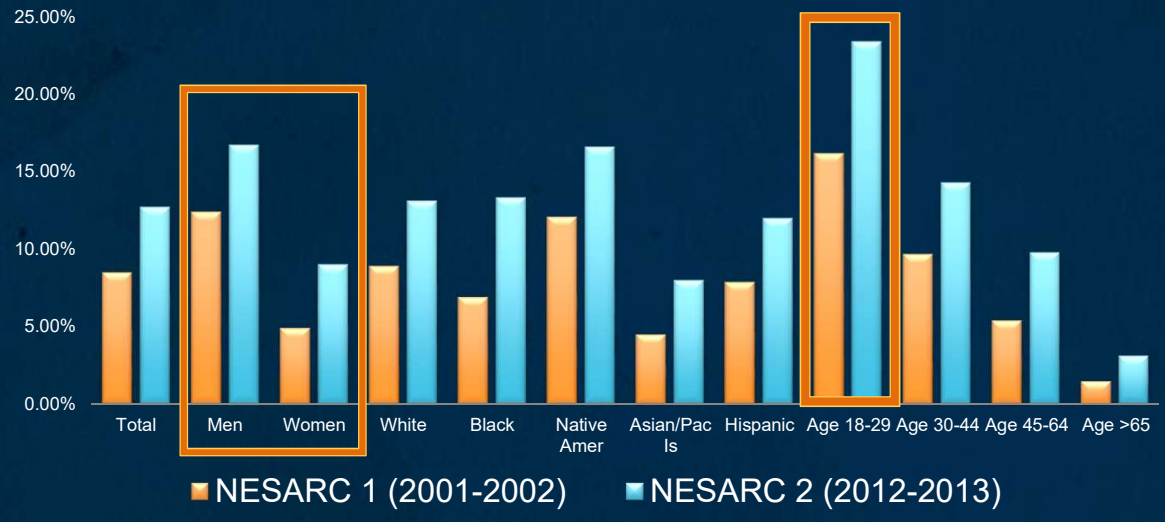
Alcohol Use Disorder in the US is Rising



Data from National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
Grant BF, et al *JAMA Psych* 2017

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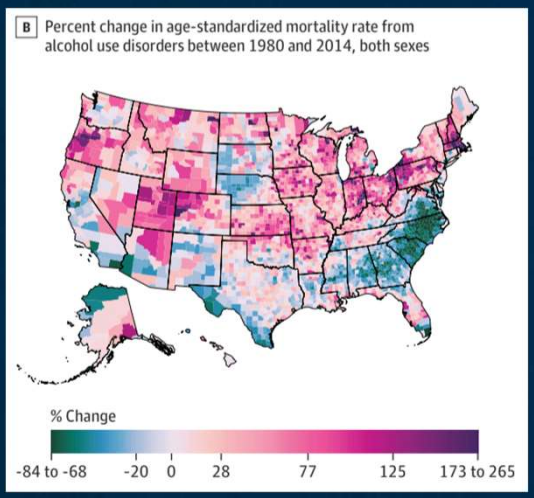
Alcohol Use Disorder Mortality Rising in the US



Dwyer-Lindgren L, et al *JAMA* 2018(319):1013-1023

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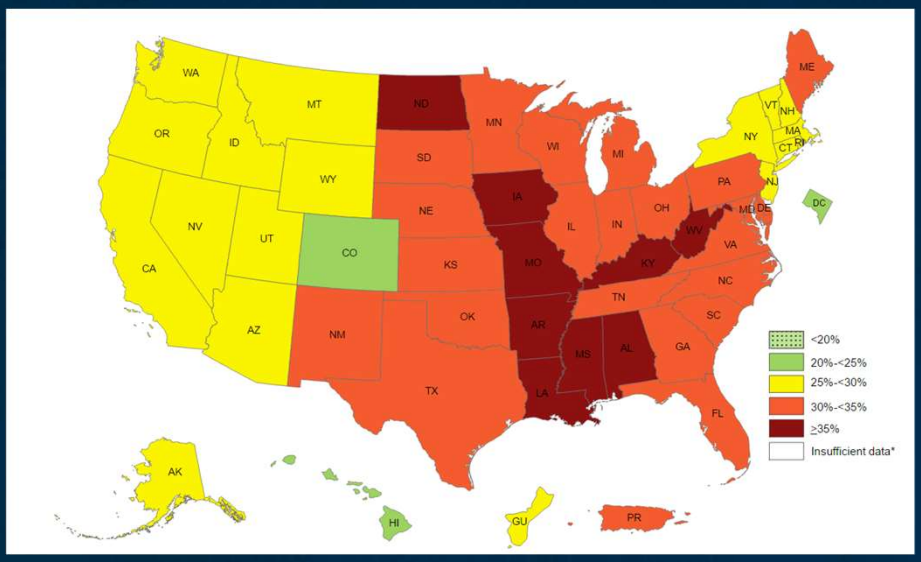
Why the rise in ALD: Obesity in the US is rising



https://www.cdc.gov/obesity/data/prevalence-maps.html

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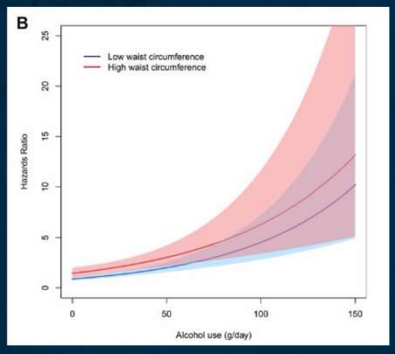
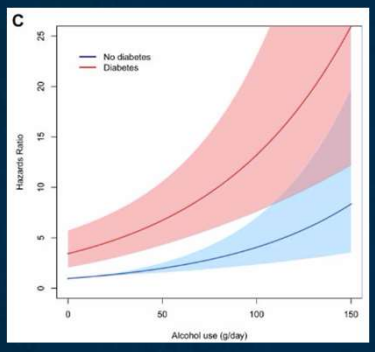
Alcohol Use + Central Adiposity/Diabetes = More Severe Liver Disease





- Rising rates of metabolic syndrome in the US
- 30.3 million people (9.4%) have diabetes
- 80 million (33.9%) have prediabetes

Aberg F, et al *Hepatology* 2018

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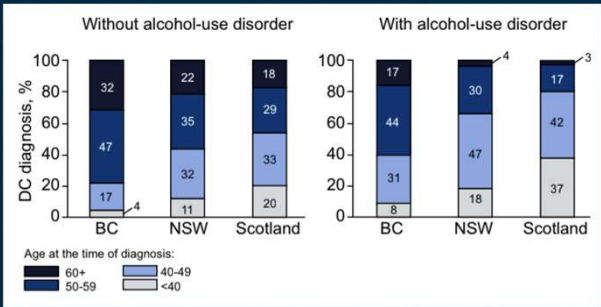
AUD + HCV = Earlier age at decompensated cirrhosis

Will rising AUD rates undo the successes of HCV treatment?

Comorbid AUD leads to younger age at decompensation



Population attributable fraction of decompensated cirrhosis in HCV patients due to AUD

Location	PAF (95% CI)
British Columbia	13% (11-15%)
NSW	25% (23-27%)
Scotland	40% (36-44%

Years assessed: 1995-2012

Alavi M, et al *J Hepatology* 2018 (68): 393-401

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Comorbid AUD + HCV may *undo* the advantages of DAA Therapy

Table 1. Adjusted analysis of factors associated with decompensated cirrhosis in people with HCV

AUD	Australia				Scotland			
	DC N=2,559	aHR	95%CI	P value	DC N=1,020	aHR	95%CI	P value
No	1,672	1.00	--	--	464	1.00	--	--
Yes	887	3.68	3.38-4.00	<0.001	556	3.88	3.42-4.40	<0.001

*Adjusted for birth cohort, gender, year of HCV diagnosis, Co-infection status (HIV, HBV) and AUD

Alavi M et al *J Hepatol* Oct 26, 2017

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AASLD ALD Guidance 2019: Alcohol Use in Comorbid Liver Disease

- Patients without liver disease should be educated about safe levels of alcohol consumption for men (no more than 2 standard drinks per 24 hours) and women (no more than 1 standard drink per 24 hours).
- Patients with ALD or other liver diseases, in particular NAFLD, NASH, viral hepatitis, and hemochromatosis, should be counseled that there is no safe level of drinking, and that they should abstain.

Crabb D, et al *AASLD Practice Guidance on ALD* 2019.

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The most important factor in long-term survival for patients with ALD is alcohol cessation

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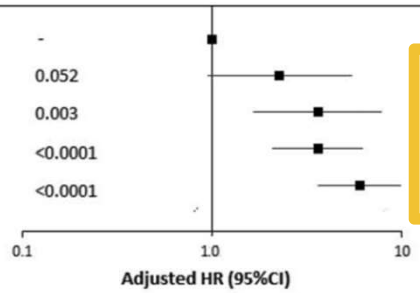
ALD patients need AUD treatment *urgently*

Alcohol consumption	Patients-months at risk	Death	Unadjusted HR (95%CI)	P	Adjusted HR * (95%CI)	P *
0 g/day	7389	38	1.00 (reference)	-		-
1-29 g/day	471	6	2.36 (0.99-5.60)	0.052	2.27 (0.96-5.40)	0.063
30-49 g/day	519	8	3.20 (1.48-6.90)	0.003	3.59 (1.66-7.79)	0.001
50-99 g/day	1106	20	3.51 (2.03-6.06)	<0.0001	3.59 (2.08-6.21)	<0.0001
≥ 100 g/day	928	27	5.61 (3.41-9.23)	<0.0001	6.01 (3.64-9.91)	<0.0001



*results adjusted for Lille model

Louvet A, et al *Hepatology* 2017;66(5)

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Cirrhosis Mortality Increases Dramatically with *Any* Drinking

Alcohol consumption (pure alcohol g day^{-1})	RR	*P*-value	(95% CI)
Women			
>0–12[b]	1.9	0.013	(1.1, 3.1)
>12–24[b]	5.6	<0.001	(4.5, 6.9)
>24–36[b]	7.7	<0.001	(6.3, 9.5)
>36–48[b]	10.1	<0.001	(7.5, 13.5)
>48–60[b]	14.7	<0.001	(11.0, 19.6)
>60[b]	22.7	<0.001	(17.2, 30.1)
Men			
>0–12[c]	1.0	0.991	(0.6, 1.6)
>12–24[c]	1.6	<0.001	(1.4, 2.0)
>24–36[c]	2.8	<0.001	(2.3, 3.4)
>36–48[c]	5.6	<0.001	(4.5, 7.0)
>48–60[c]	7.0	<0.001	(5.8, 8.5)
>60[c]	14	<0.001	(11.7, 16.7)

Rehm J, et al *Drug & Alcohol Review* 2010(29): 437-445

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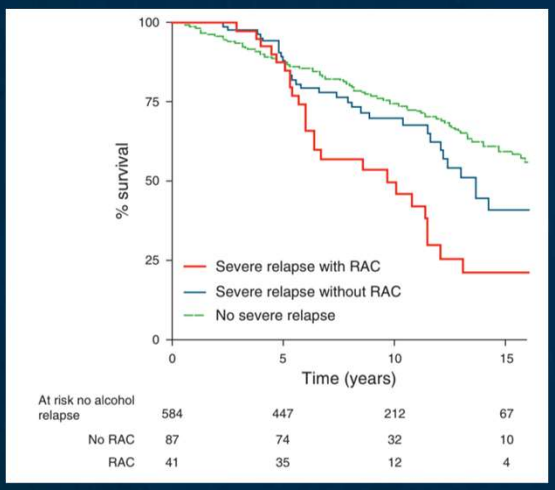
Post-transplant Alcohol Relapse Leads to Cirrhosis and Decreased Survival



Dumortier et al *Am Jnl Gastro* 2015

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What is a standard drink?

In the United States: 1 standard drink = 14 g EtOH

Amount of alcohol in a "standard drink" differs depending on where in the world you are.

Country	Grams EtOH in a standard drink	Daily Limits for:	
		Men	Women
United States	14	28 g	14 g
United Kingdom	8	16 g	16 g
Australia	10	<20 g	<20 g
Mexico	13	13-26 g	13 g
Argentina	14	28 g	14 g
Japan	20	40 g	20 g
India	8	16 g	8 g

www.iard.org/policy-tables/drinking-guidelines-general-population

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AASLD ALD Guidance 2019: Diagnosis of Drinking with Screening & Biomarkers

- All patients receiving care in primary care and gastroenterology/hepatology outpatient clinics, emergency departments, and inpatient admissions should be routinely screened for alcohol use using validated questionnaires.
- Brief intervention, pharmacotherapy, and referral to treatment should be offered to patients engaged in hazardous drinking (AUDIT-C ≥4, AUDIT >8, binge drinkers)
- Alcohol biomarkers can be used to aid in diagnosis and support recovery. Urine and hair ethyl glucuronide, urine ethyl sulfate, and PEth are not affected by liver disease, and therefore preferable.

Crabb D, et al *AASLD Practice Guidance on ALD* 2019.

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Available Alcohol Biomarkers

Biomarker	Sample	Time Frame
Blood Alcohol Level	Blood	12 hours
Ethyl Glucuronide	Urine	3-5 days
	Hair	Months
Ethyl sulfate	Urine	3-5 days
PETH	Blood	2-3 weeks

*GGT, LFTs alone less specific. %CDT (carbohydrate deficient transferrin) inaccurate in more advanced AALD so not preferred

Stewart S, et al *ACER* 2014;28. Cabezas J, *Clin Liv Dis* 2016.
Lowe JM, et al *ACER* 2015;39.

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Urine ethyl glucuronide (uEtG) and ethyl sulfate (uEtS)

- Direct alcohol metabolite by UDP-glucuronosyltransferase and UDP-sulfotransferase
- Found in urine, blood, and hair
- False positives can occur → reflex eEtS testing for + uEtG
- Not affected by liver disease→ can be prolonged in renal failure

Study	Patients	Cut-Off	Sensitivity (%)	Specificity(%)
Stewart 2013	N=120 CLD	EtG: 3 day drinking 7 day drinking EtS: 3 day drinking 7 day drinking	76 (62-91) 70 (57-84) 82 (70-95) 73 (60-86)	93 (88-98) 99 (96-100) 86 (78-93) 89 (83-96)
Andresen-Streichert 2017	N=112 (51 pre-liv txp 61 post-liv txp)	>0.5 mg/L	71 (41-91)	98 (94-100)
Staufer 2011	N=141 Pre/post liv txp with ALD	>0.5 mg/L	89	99

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Phosphatidylethanol (PETH)

- Phospholipid produced in red blood cell membrances
- Catalyzed by phospholipase D (PLD 1 and PLD 2)
- Direct alcohol biomarker
- Some validation in ALD patients in a “YES/NO” fashion
- Not influenced by liver disease

Study	Patients	Cut-Off	Sensitivity	Specificity
Stewart 2014	N=222, all ALD No post-liv txp 55% cirrhosis	Any: >8 ng/mL Any: >20 ng/mL >4 drinks/d: >20 ng/mL >4 drinks/d: >80 ng/mL	79 (71-88) 73 (65-80) 97 (92-100) 91 (82-100	90 (81-98) 96 (92-100) 66 (59-73) 77 (70-83)
Andresen-Streichert 2017	N=112 (51 pre-liv txp 61 post-liv txp)	20 ng/mL	100 (79-100)	96 (91-99)

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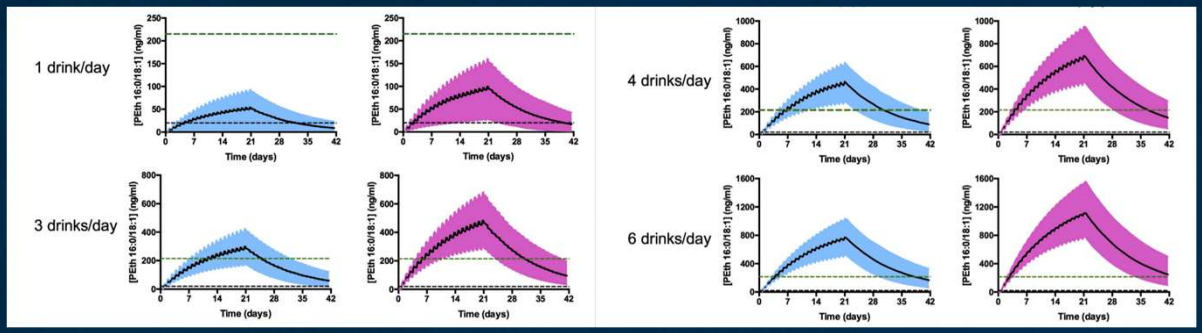
PETH Pharmacokinetics

- PK models show detection ability for chronic alcohol consumption at varying levels
- Cutoffs of 20 ng/mL vs 200 ng/ml (green dashed line: excessive drinking)
- Men and women vary in peak PETH and duration (men: blue, women: pink)



Simon TW et al *Reg Toxicology & Pharmac* 2018 (94)

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AASLD ALD Guidance 2019: What to Do About Drinking in ALD

- **Referral to AUD treatment professionals is recommended for patients with advanced ALD and/or AUD in order to ensure access to the full range of AUD treatment options.**
- **Multidisciplinary, integrated management of ALD and AUD is recommended and improves rates of alcohol abstinence amongst ALD patients.**
- **Based on limited data, the use of acamprosate or baclofen can be considered for the treatment of AUD in patients with ALD**

Crabb D, et al *AASLD Practice Guidance on ALD* 2019.

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Diseases of Despair: AUD and Mental Illness

	AUD, AOR (95% CI)							
	12-mo				Lifetime			
Other Psychiatric Disorder	Any	Mild	Moderate	Severe	Any	Mild	Moderate	Severe
Any drug use disorder	3.3 (2.88-3.76)	2.2 (1.79-2.77)	3.2 (2.56-4.00)	5.3 (4.52-6.27)	4.1 (3.72-4.57)	2.1 (1.72-2.66)	2.8 (2.35-3.32)	6.4 (5.76-7.22)
Nicotine use disorder	2.5 (2.24-2.69)	2.0 (1.75-2.25)	2.7 (2.26-3.32)	3.6 (3.07-4.24)[c]	3.2 (2.95-3.42)	2.2 (2.00-2.46)	3.0 (2.69-3.42)	4.3 (3.89-4.81)
Any mood disorder	1.3 (1.18-1.47)	1.1 (0.93-1.26)	1.4 (1.15-1.62)	1.8 (1.49-2.18)	1.5 (1.37-1.63)	1.2 (1.08-1.42)	1.4 (1.17-1.56)	1.8 (1.64-2.02)

- Associated drug and nicotine use disorders are common
- Mood disorders (depression, anxiety, bipolar disorder) less common
- Important implications for maintenance of abstinence, improving long-term outcomes, and potential transplant in ALD patients

Grant BF, et al *JAMA* 2015 (72), 5:757-766

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Mental Health Access: A Major US Challenge

Lack of Insurance Coverage	Logistics	Attitudinal
• Limited MHSA coverage • Medicaid restrictions • Limits on duration • High Copays	• Not enough MHSA providers • Transportation • Childcare • Lack of time off for appointments	• Don't feel need for treatment • Stigma • Concerns about privacy • Social anxiety

- For *all* substance-use disordered patients, access to SUD treatment rates are low at 11%
- Comorbid mental health and SUD require expert treatment

SAMSHA 2014; Mellinger et al *JSAT* 2018; Heyes CM et al *Transplant Direct* 2016

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AUD Treatment Access Rates are Low in ALD Patients

Table 1. Population Characteristics at Index Alcoholic Cirrhosis Diagnosis

Characteristics	Total AC patients *n* = 66,053 *N* (%)
Female	21,442 (32%)
Mean age (years)	53.5
Mental health/substance abuse treatment coverage	47,505 (72%)
Prescription drug coverage	57,632 (87%)
Mean Elixhauser	3.53
Hepatitis C	18,817 (28%)
Decompensation[a]	35,069 (53%)
Anxiety	7,642 (12%)
Depression	10,652 (16%)
Any FDA-approved alcohol relapse prevention medication	275 (0.4%)
Acamprosate	122 (0.2%)
Disulfiram	133 (0.2%)
Naltrexone	99 (0.1%)

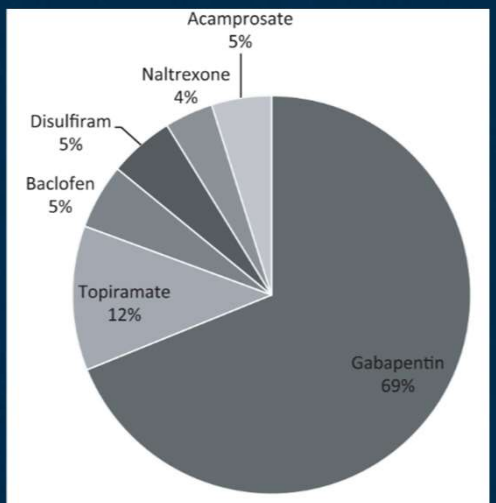

Fig. 1. Proportion of alcohol relapse prevention medication prescriptions at index diagnosis, by type of prescription.

Mellinger J et al *ACER* 2019

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AUD Treatment Access Rates are Low in ALD Patients

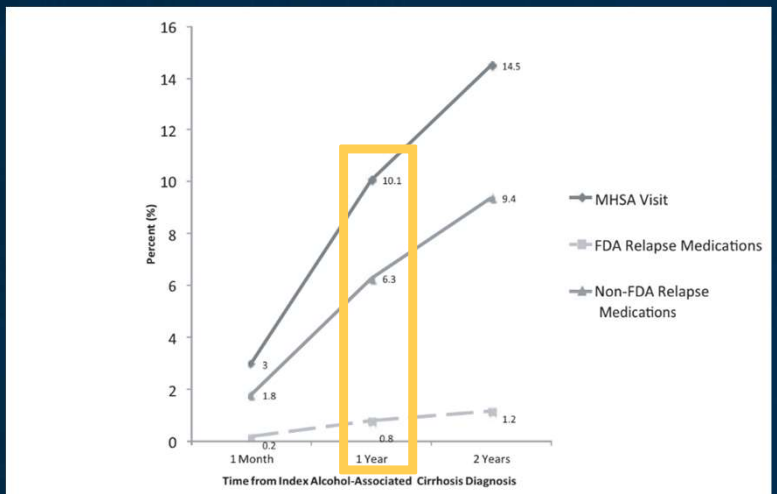

Fig. 2. Rates of MHSA treatment utilization at 1 month, 1, and 2 years postindex diagnosis.

Mellinger J et al *ACER* 2019

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How ALD Patients Differ from General AUD Patients

- Decision to stop drinking thrust upon them by medical event
- Medical health a priority (not psych health)
- Don't perceive need for treatment
- Preoccupied with medical/transplant management
- Don't think they have an addiction problem
- Are not addiction treatment seeking

*Courtesy of Andrea DiMartini MD (U Pittsburgh)

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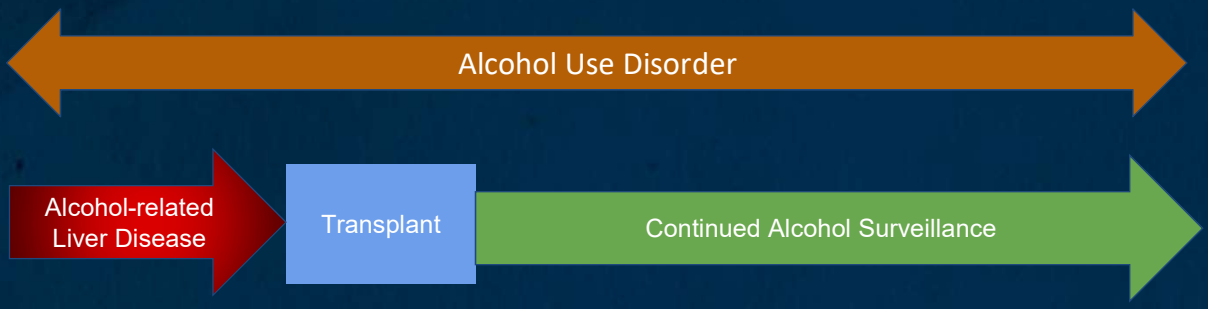
The New Model: Treat ***Both*** AUD and ALD Across the Life of the Liver



ALD patients who do not need or are not immediate candidates for transplant should have the same access to high-quality AUD treatment and mental health care as listed patients

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Multidisciplinary ALD Clinic: Filling the Gap for ALD Patients not Listed for Transplant

MAIN
Michigan Alcohol Improvement Network

Anne Fernandez PhD- Clinical Psychology
Scott Winder, MD MSc- Psychiatry
Kristin Klevering, LMSW- Social work
Amanda Johnson, RN- Nursing
Jack Buchanan- Medical Student Apprentice
Haila Asefah- Clinical Research Coordinator
Jessica Mellinger, MD MSc- Hepatology

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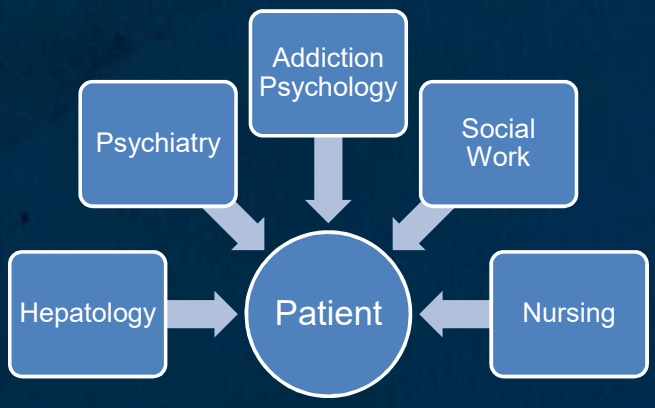
MAIN ALD Clinic Structure



- Every other Monday
- 3 NPs + RVs
- Pre-clinic phone call (SW)
- In-clinic ALD Education Packet with RN review
- See hepatology, psychiatry, either psychology or SW
- Tox screens each visit and in-between
- Commitment to 3 MET/CBT sessions with clinic staff

1st Year: 50 patients Outcomes: Liver, AUD, Cost/Value

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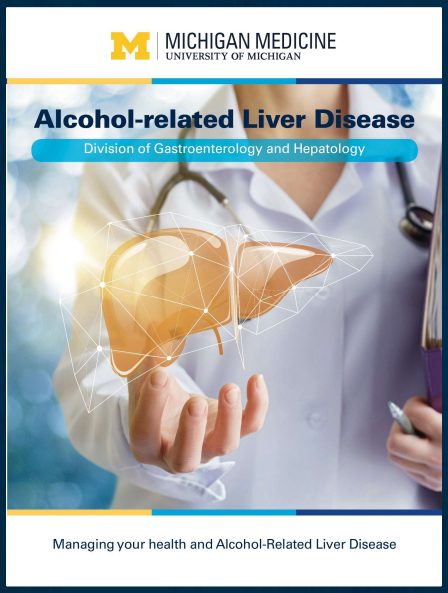
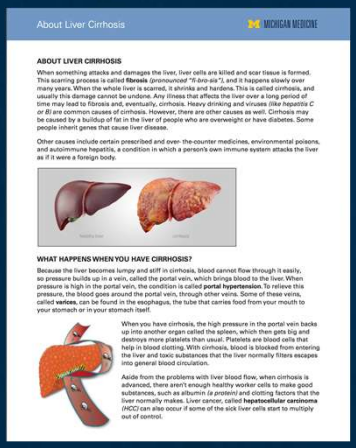
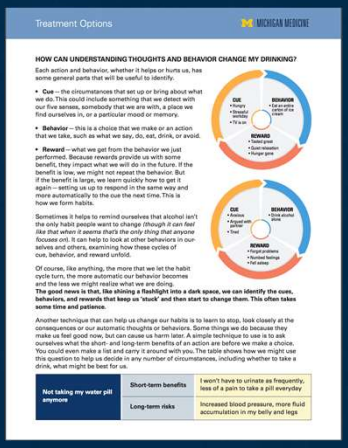
ALD Clinic Educational Materials







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Clinic Scheduling

Time	Patient 1	Patient 2	Patient 3
8:00 AM	Check-in & rooming	Check-in & rooming	Check-in & rooming
8:15 AM	Hepatology	Psychiatry	Psychology or social work
	Brief team discussion	Brief team discussion	Brief team discussion
9:15 AM	Psychology or social work	Hepatology	Psychiatry
	Brief team discussion	Brief team discussion	Brief team discussion
10:15 AM	Psychiatry	Psychology or social work	Hepatology
	Brief team discussion	Brief team discussion	Brief team discussion
11:15 AM	Wrap up and treatment planning	Wrap up and treatment planning	Wrap up and treatment planning
11:30 AM	Lab	Lab	Lab
12:00 PM	Discharge	Discharge	Discharge

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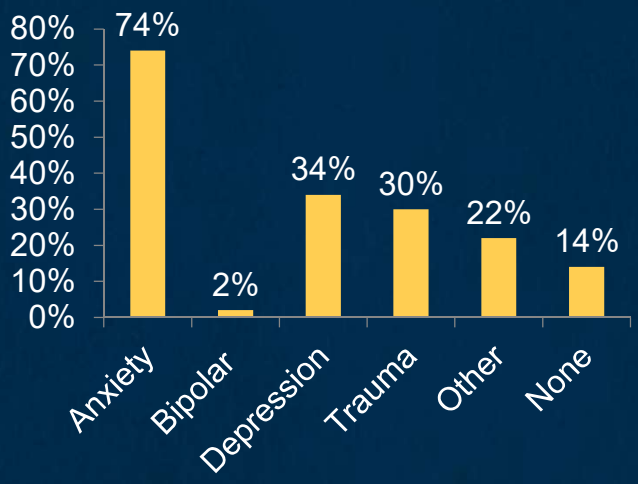
Clinic Demographics
N=50

- Mean age: 47 years
- 52% female, 46% male, 2% (1) declined to answer
- Race: White: 88%; Black 6%; Asian 2%; Unknown 4%
- Single 41%; Married 45%; Divorced 14%
- Medicare 12%; Medicaid 26%; Private insurance 60%



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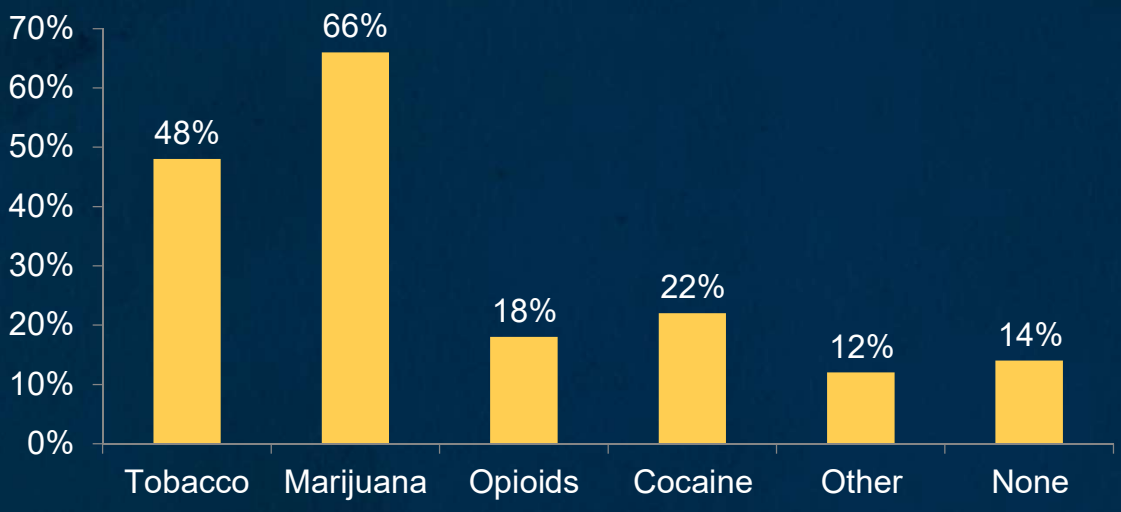
Comorbid Substance Use Rates are High



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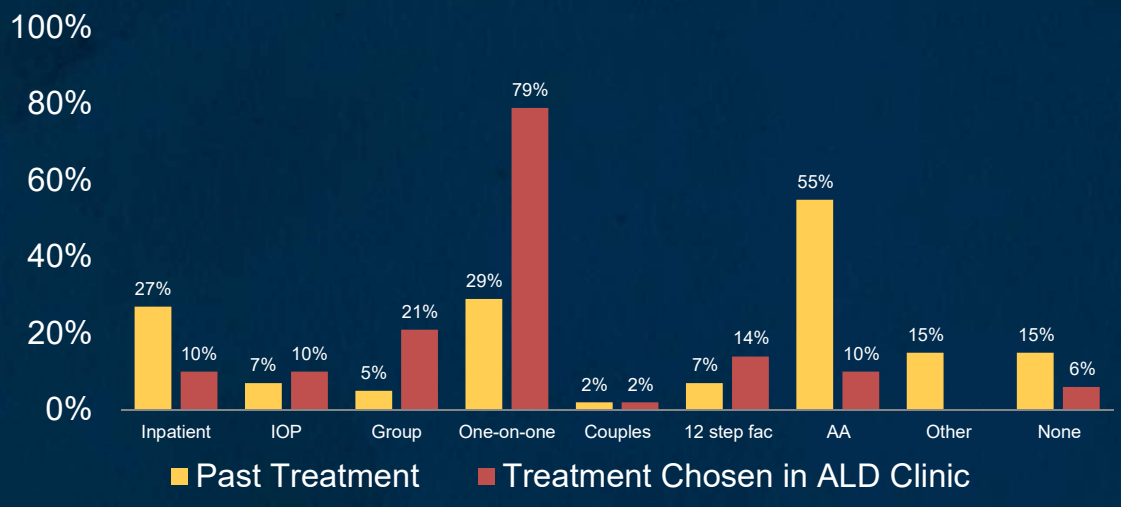
AUD Treatment Past & Present



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ALD Clinic: Lessons Learned 1 year In…

- No-shows/cancellations

Solution: Pre-visit calls, predictive overbooking, increase to 4 NPs

- Ensuring follow-up and connection to AUD Tx

Solution: Post-visit check-ins (1, 3 months or more frequent), requirement for 3 sessions, starting CBT curriculum specific to ALD, expansion of telepsych

- Medicaid coverage at UMATS

Solution: connections to policy/IHPI, research into cost-effectiveness of AUD treatment in ALD (Mellinger)

- Reliable data collection

Solution: automate surveys (MiChart, in-clinic tablets)

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More Consideration for Alc Hep Transplant?

ALD patients who do not need or are not immediate candidates for transplant should have the same access to high-quality AUD treatment and mental health care as listed patients

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The Dallas Consortium: Transplant for Alc Hep

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Existing US Published Experience in Alc Hep Txp

Study	Number of LT for AH	Age*	Male	Abstinence prior to LT*	MELD at time of LT*	1-year patient Survival	Return to harmful drinking
Mathurin[21]	26	47	58%	<90 days	34	77%	10%
Im[25]	9	41	56%	33 days	39	89%	12.5%
Weeks[27]	46	50	72%	50.5 days	33	97%	17%
Lee[28]	147	43	73%	55 days	38	94%	11%

Dallas consensus recommendation: Programs and UNOS should be collecting data on pre- and post-transplant outcomes *beyond just patient and graft survival.*

- *Standardized reporting, auditing, and transparency are key*

Opinion from Dallas: The 6 month rule should not be used as a criterion for transplant

Im G et al *J Hepatology* 2018

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Dallas *Suggested* Listing Criteria Under Discussion

1. First liver decompensating event
2. Failed/ineligible for prednisolone trial
3. Psych eval able to be performed
4. Acceptance of diagnosis/insight
5. Commitment of patient/family to sobriety
6. At least 2 close, supportive family members
7. Good psychosocial assessment
8. No more than 1 failed rehab attempt
9. No other substance use disorder
10. Absence of uncontrolled psych disorder

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Conclusions

- ALD and AUD rates are rising in the US
- Alcohol cessation saves lives
- Multidisciplinary integrated care is necessary

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Thank you

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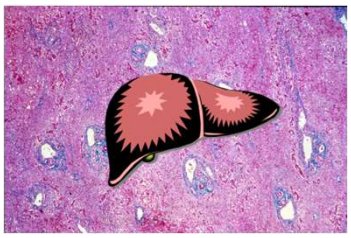
An Update on Drug and Herbal Hepatotoxicity



Robert J. Fontana, MD, FAASLD, FAGA
University of Michigan Medical Center

MICHIGAN MEDICINE
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RJ Fontana: Disclosures

- **Research support: Abbvie, Gilead, BMS**
  - **Consulting: Sanofi**
- **NIH: DILIN, US ALFSG**

MICHIGAN MEDICINE
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Acetaminophen: Friend or foe ?

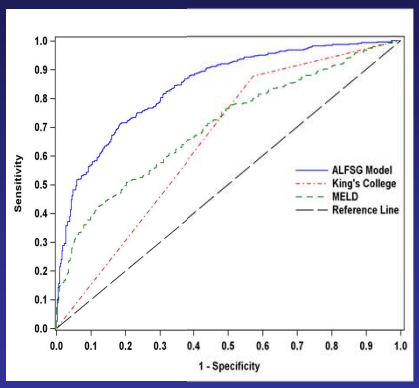
- **Safe & effective analgesic**
  - > 1 billion tabs / yr
    - Preferred to ASA in liver dz, children
  - 300 OTC products & > 20 Rx drugs
- **Hepatotoxicity**
  - Dose dependent (> 4 grams)
    - ↑ AST/ ALT +/- INR
  - > 60,000 overdose/ yr
    - Leading cause of ALF in US

APAP Hepatotoxicity: Management

- **Single time point ingestion**
  - < 4 hrs: NG tube +/- ipecac
  - Activated Charcoal 1 g/kg
  - N-acetylcysteine (oral or IV)
- **Injury severity/ prognosis**
  - Hospitalize if altered MS, suicidal, ↑ AST/ INR/ cre
- **Transfer high risk to LT center**

(Fontana Handbook of Liver Dis 2017)

ALFSG Prognostic Index *vs.* MELD and King's College Criteria



(Koch CGH 2017)

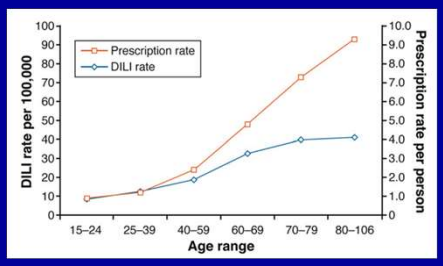
"Idiosyncratic" Drug Induced Liver Injury

- Most common reason for regulatory actions concerning drugs
  - Denial Withdrawal Restriction
- Significant morbidity & mortality
  - Leading cause of ALF in the US (13%) [1]
- No reliable means to predict/ prevent

(Ann Int Med 2016; 137)

Idiosyncratic DILI

- DILI is important but infrequent
  - < 1% acute liver injury [1]
  - 1 in 10,000 to 10^6 prescriptions



Iceland [2] 10-20 per 100,000

In US, ~60,000 DILI cases/ yr

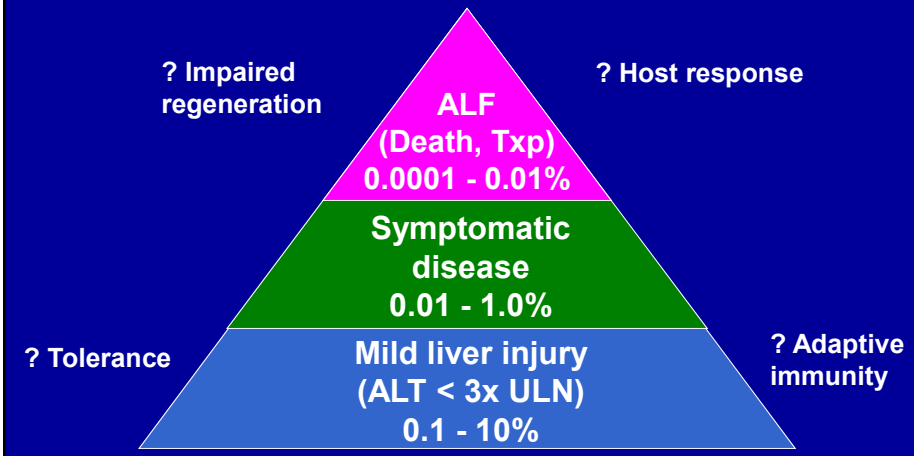
(1 J Clin Gastro 2005; 39: 64)
(2 Gastroenterology 2013;144:1419)

DILI: A Clinical diagnosis

Requires a high index of suspicion

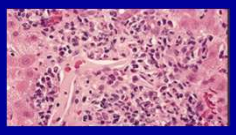
- Inclusion
  - Temporal association (most < 6 mon)
    - Dechallenge requires time
  - Drug latency, lab profile (R-value)
    - Polypharmacy common
  - Histology
- Exclude more common causes
  - HAV, HBV, HCV, pancreaticobiliary, ischemia, alcohol, AIH, NAFLD
- No objective/ confirmatory test

DILI Severity

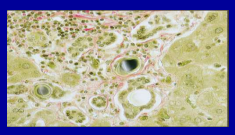


The Histology of DILI

- Immunoallergic hepatitis
- Autoimmune hepatitis-like
- Acute hepatic necrosis
- Acute liver failure
- Cholestatic hepatitis
- Bland cholestasis
- Acute fatty liver with lactic acidosis
- Sinusoidal obstruction syndrome
- Nodular regeneration
- Vanishing bile duct syndrome
- Cirrhosis
- Benign neoplasms

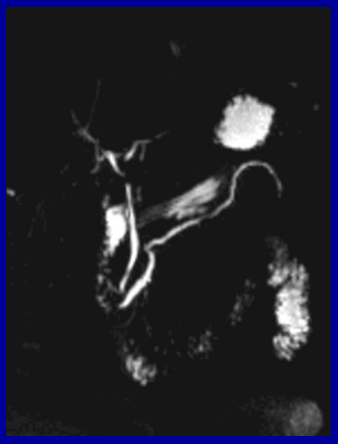


Minocycline (AIH-like)



Ceftriaxone (cholestasis)

Drug induced Sclerosing cholangitis



48 Black F with Moxifloxacin DILI
- MRCP (mon 6) : CHD and Left hepatic duct stricture
- Liver explant: collapse & ductopenia

4 of 56 (7%) DILIN pts had sclerosing cholangitis like changes on MRCP (blinded review)

(Ahmad CGH 2018 on line)

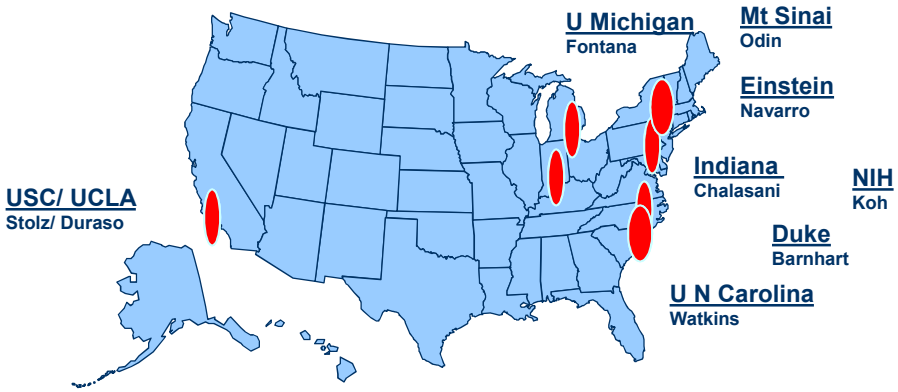
Idiosyncratic DILI Management

- Discontinue suspect medication
  - High index of suspicion
- Early referral of ALF DILI patients
  - 30% spontaneous survival
    - NAC (3 days) 58% vs 27% PBO [2]
- General supportive care
  - Fluids, bedrest, anti-emetics
  - Steroids if DRESS or hypersensitivity features

(1 ACG Practice Guideline 2014)
(2 Lee Gastroenterology 2009;)

NIH NIDDK

DILIN 2003- 2023



UO1 Cooperative Agreement NIDDK

J Hoofnagle, J Serrano, A Sherker

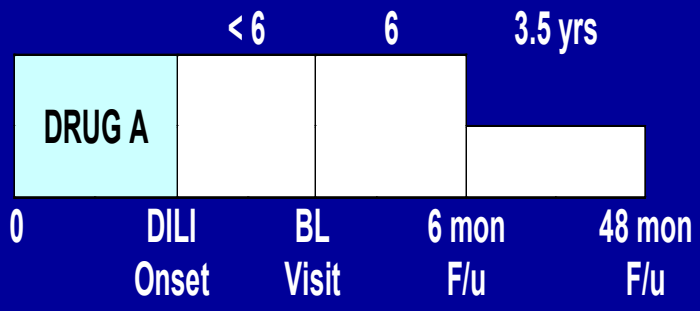
Inclusion criteria

- **Age > 2**
- **Within 6 months of DILI onset ***
  - **On 2 consecutive blood draws ***
    - **AST or ALT > 5 X ULN (baseline)**
    - **Alk phos > 2 X ULN (baseline)**
    - **T bilirubin > 2.5 mg/dl**
- **Chronic HBV, HCV, HIV allowed**

(Fontana Drug Safety 2009; 32: 55)

DILIN Prospective Study

Case



(Fontana Drug Safety 2009; 32: 55)

DILIN Prospective Study

(899 high causality cases) 9/04-5/13

Single prescription drug	62%
Herbal & dietary suppl (HDS)	16%
Multiple drugs	22%

(Gastroenterology 2015; 148; 1340)

DILIN Prospective Study

	N=899
Mean age *	49 + 17
% Female	59%
% Cau/ AA	79/ 12
Mean BMI (kg/m^2)	27 + 6
% Hep /mixed/ chol	54/ 23/ 23
Peak ALT (U/l)	1008 + 1221
Peak alk phos (U/l)	406 + 388
Peak bilirubin (mg/dL)	13 + 12
% Liver biopsy	52%

* 6% < 18 years old

(Gastroenterology 2015; 148; 1340)

Top 10 causes of DILI

Agent	No	Percent
Amoxicillin/ Clavulanate	91	12 %
Isoniazid	48	6.5%
Nitrofurantoin	42	5.6%
TMP/SMZ	31	4.1%
Minocycline	28	3.7%
Cefazolin	20	2.7%
Azithromycin	18	2.4%
Ciprofloxacin	16	2.1%
Diclofenac	15	2.0%
Levofloxacin	13	1.7%

(Gastroenterology 2015; 148; 1340)

DILIN Causality Scores

3 reviewers: Clinical narratives and lab/ diagnostic data

	Likelihood	'04-'07 N=210
Definite (1)	> 95%	32%
Highly likely (2)	75-95%	41%
Probable (3)	50-75%	13%
Possible (4)	25-50%	10%
Unlikely (5)	< 25%	4%

(Rockey Hepatology 2010; 51: 2117)

DILI Imitators in the US

- Acute HEV infection [1]
  - 9 of 318 (2.8%) anti-HEV IgM +
    - 4 HEV RNA + (genotype 3)
  - Mean age =67
    - 89% male
- Unlikely adjudicated cases (n=50) [2]
  - 18% Acute Hepatitis C
  - 14% Pancreaticobiliary

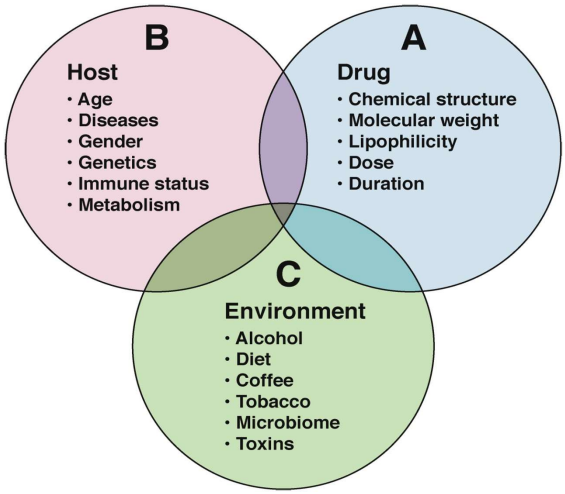
(1 Gastroenterology 2011;141:1665)
(2 Rockey et al, AASLD 2015: Abstract)

DILI Natural History

- ~ 10% die or liver transplant within 6 mon
  - ++ severe dz, underlying liver dz, ? Asian
- ~ 20% residual liver injury 6 mon after onset
  - + cholestatic, blacks [2]

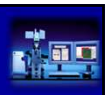
(1 Gastroenterology 2014)
(2 Am J Gastroenterol 2016;)

DILI Pathogenesis



(Fontana Gastroenterology 2014; 146: 914)

GWAS with individual drugs



Series	Cases	Controls	Locus	OR	MAF
Lumiracoxcib	41	176 treat controls	DRB1*15:01 DQB1*06:02	5.0	15%
Ximelagatran	74	130 treat controls	DRB1*07 DQA1*02	4.4 4.4	8.5%
Lapatanib	37	286 treat controls	DQA1*02	9.0	21%
Amoxicillin-clavulanate	201	532 Pop controls	DRB1*15:01 A*02:01	3.1 2.3	14% 28%
Flucloxacillin	51	282 pop controls	B* 57:01	80	6%
Minocycline	25	6835 pop controls	B* 35:02	29	0.6%

(Daly Nat Genet 2009; 41: 816)
(Kindmark Pharmacogenomics; 2008:8: 186)

(Lucena Gastroenterology 2011; 141)
(Urban J Hepatology 2017)

AASLD

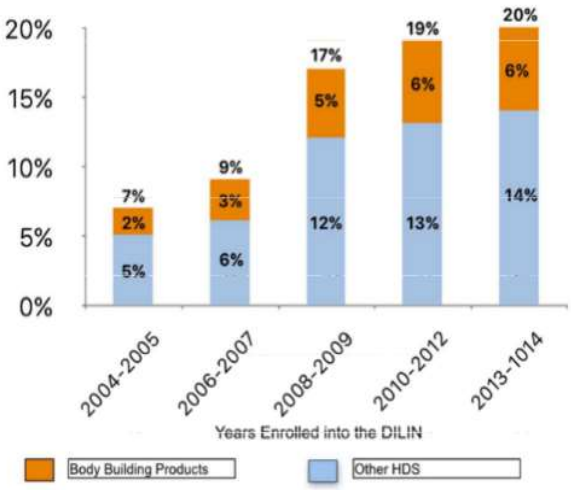
Herbal and Dietary Supplements

- Herbal and dietary supplements (HDS) used to enrich diet and improve health/ function
  - Herbal and botanicals (ginseng, black cohash, turmeric)
  - Vitamins (Niacin, folate)
  - Minerals & elements (Calcium, iron)
  - Amino acids/ powder (Whey protein)
  - Performance enhancing products (OxyELITE Pro, Hydroxycut)
  - Synthetic compounds (Aegeline)
- HDS obtained without a prescription or medical advice/ monitoring

(Navarro Hepatology 2017; 65: 363-373)

"Proprietary Blends"

Figure 1. Proportion of DILIN Cases due to HDS



(Navarro Hepatology 2017)

HDS products in the US

- **40-50%** report HDS use [1]
  - Improve well-being, relief of symptoms
    - Medical claims to treat disease prohibited
  - "Natural is safer" "More is better"

- **HDS** regulated by FDA as **foods** (not drugs)
  - **DSHEA** 1994- "Safe till proven otherwise"
    - No requirement for safety or efficacy testing
    - Register only if new ingredient since 1994
  - **4,000** vs **80,000** HDS products ('94) vs ('14)

(1 Clarke NHSR 2015)
(2 Nut Bus J 2015: 67)

Outcomes in HDS DILI

	Body Building N=45	Non-body building N=85 *
Age	31	47
% Male	100%	35%
Latency (days)	43	30
% Hospitalized	71%	68%
% Liver Transplant	0%	13%
% Death	0%	4%

* 58% multi-ingredient nutritional supplements
(3 to 20 ingredients/ product)

(Navarro Hepatology 2014; 60)

DILIN Repository for HDS

NIDDK DILIN FNIH, December 2013 Page 28

Analysis of HDS Products

Category	Samples with Labels n	Inaccurate Labels n (%) *
General Health	53	26 (49%)
Bodybuilding	46	37 (80%)
Weight Loss	36	26 (72%)
GI Symptoms	22	9 (41%)
Energy Boosters	5	3 (60%)
Sexual Enhancers	4	4 (100%)
Misc or Unknown	106	35 (33%)
TOTAL	272	140 (51%)

* Labelled ingredients not detected

(Hepatology Communic 2019)

29

United States National Library of Medicine
NIDDK National Institute of Diabetes and Digestive and Kidney Diseases

LiverTox
Clinical and Research Information on Drug-Induced Liver Injury

- A comprehensive, authoratative e-textbook culled from the world's literature
  - > 900 drugs with hepatotoxicity pattern, mechanism, management; case examples, annotated references, links to product insert
    - Exemplary cases (pathology) from DILIN
    - Likelihood scale (A to D)
    - 50 HDS products catalogued
- PUBMED availability worldwide
  - http://livertox.nih.gov

Drugs, Herbs and the Liver 2020

- Acetaminophen OD is leading cause of ALF
  - Prognosis: ALFSG App
- DILI is uncommon with most drugs/ HDS
  - High index of suspicion
    - LiverTox (latency, phenotypes)
  - Management: Discontinue drug (NAC if severe)
- HDS hepatotoxicity is increasing
  - ↑ HDS use (perceived safety & marketing)
  - Multi-ingredient supplements frequently mislabeled
  - Potentially severe hepatotoxicity

Thank YOU !!!

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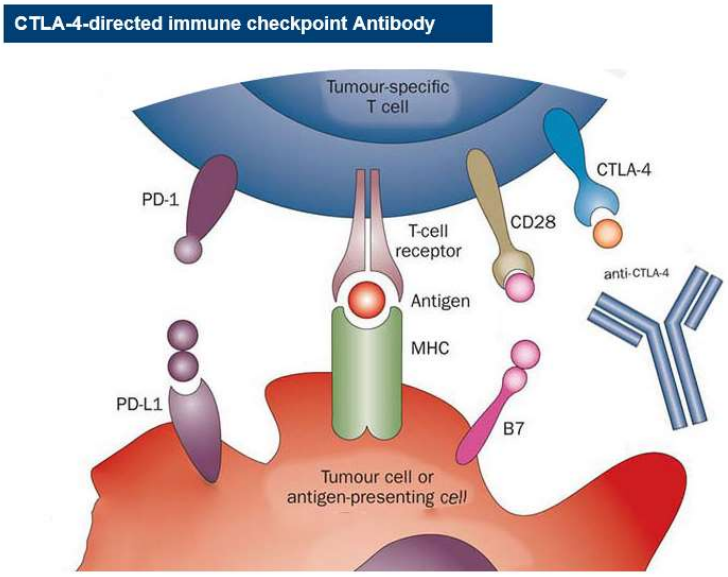
Acknowledgments: NIDDK, DILIN investigators, and DCRI



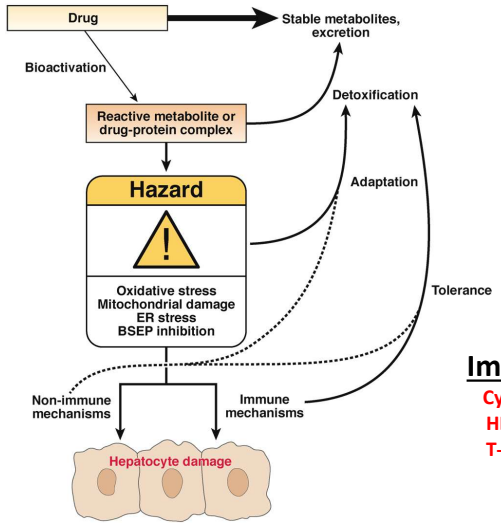
Immunotherapy related Hepatotoxicity

- Monoclonal Ab to CTLA-4 and PD-1
  - ↓ host tolerance to tumor antigens
- Autoimmune ADR
  - Colitis 10-40%
  - Hepatitis 10-15%
    - Onset: 1 to 6 mon
    - Bx: plasma cells vs granuloma vs steatosis
  - Risk: Ipilimumab > Pembrolizumab/ nivolibumab
    - ? Host genetics, immune status, predictors

ADME genes

Cytochrome P-450

Transporters



Immune genes

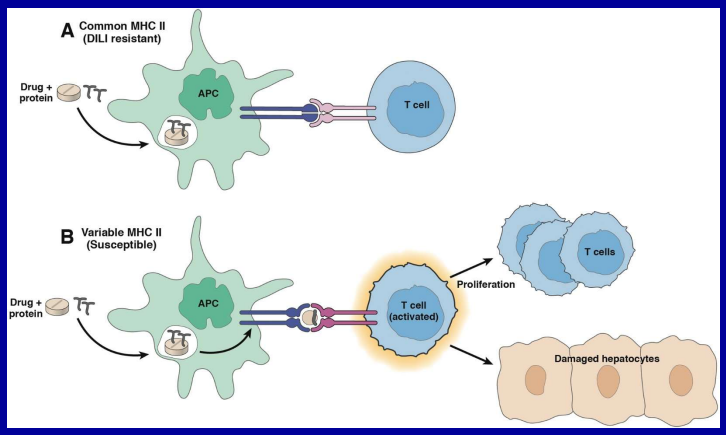
Cytokine SNP's

HLA Class 1 & 2

T-cells

(Gastroenterology 2014; 146: 914)

Adaptive Immunity in DILI



(Fontana Gastroenterology 2014; 146: 914)

Unlabeled Hepatotoxins in 96 HDS that caused Liver Injury in 71 Patients

HDS	n	Anabolic steroids*	Pyrrolizidine Alkaloids*	Pharma-ceuticals *
Bodybuilding	26	13	0	1
Weight Loss	19	0	0	0
General Health	10	0	0	0
GI symptoms	11	0	0	0
Bones/Joints	3	0	0	1
Sexual Enhancers	1	0	0	0
Unknown, Misc.	26	0	1	0
TOTAL	96	13	1	2

* Identification Standards

38

(Hepatol Comm 2019)

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Current Management of Crohn's Disease

Peter DR Higgins

Management of Crohn's Disease

- Early diagnosis
- Stratifying severity vs. activity
- Assessing and treating flares
- Durability of maintenance therapy
- The assess and adjust feedback loop
- Adverse effects of therapy
- Recognizing and treating EIMs
- Health maintenance and vaccinations
- Emotional care

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Early Diagnosis in Crohn's Disease

- Most CD diagnoses are delayed 9-18 months, often more if GI referral is delayed
- Presentation can be protean – fatigue, low-grade fevers, and weight loss
- Longer delays – more obstruction and surgery
- Up to 30% present with complications
  - Strictures, abscesses, fistulas
- Up to 5-10% of patients post UC/IPAA will develop CD, usually within 5 years
- Best screening test – Fecal Calprotectin
  - Scan/scope for repeated FCP >100

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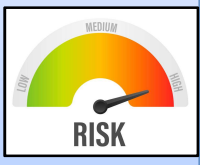
Separating Activity vs. Severity

- Activity – current level of inflammation 
  - From quiescent to severe
- Severity – the risk for future complications
  - Low – mild colonic inflammation
  - High - risk factors
    - Early age at diagnosis
    - Upper GI disease > Small bowel > colon
    - Smoking
    - Prior penetrating complication or surgery
    - Deep ulcers
    - Perianal involvement



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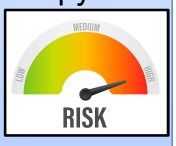
Stratifying Severity

- Most patients with CD = High severity
  - More than 60% will require intestinal resection
  - About 30% moderate severity
  - Only ~ 10% truly have mild severity
    - Often dx as short TI CD on screening colonoscopy
- High severity –
  - Start with Top Down
  - Rapid, early control of inflammation
  - Prevent bowel damage
  - Prevent complications and cancer



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Assessing and Treating Flares

- Worsening of Symptoms
  - Rule out infection – C diff, GI PCR
  - Measure inflammatory activity
    - FCP, CRP, Scope, Scan
  - Based on activity, decide on intensity of intervention
    - Adjust current med (dose/interval)
    - Add budesonide & adjust
    - Add prednisone & adjust
    - Consider inpatient IV steroids / new Rx?

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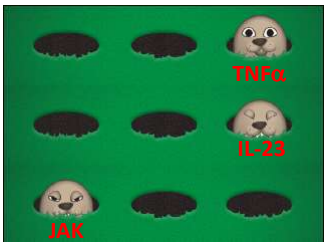
The Durability of Maintenance Therapy

- What makes an IBD Therapy Stop Working?
  - Rapid Clearance – Antibodies to biologics
  - Change in Mechanism – Whack-A-Mole



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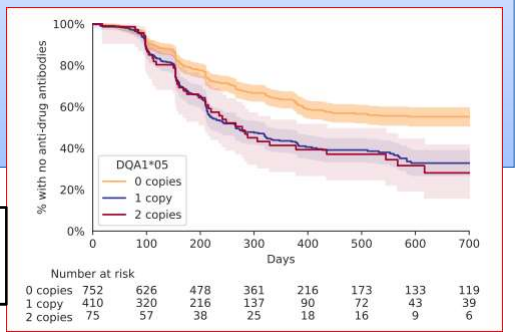
The Durability of Maintenance Therapy

- Antibodies to Biologics – Risk Factors
  - High inflammatory burden – CRP, FCP
  - Low Albumin – intestinal leak
  - HLA-DQA1*05
  - High BMI
  - Male

Having the HLA DQA1*05 variant increases the risk for anti-biologic antibodies



Gastro Jan 2020;158:189–199

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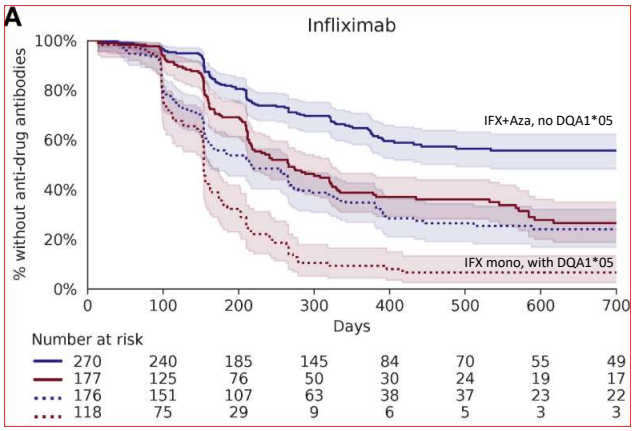
The Durability of Maintenance Therapy

- Aza combo reduces the effect of DQA1*05



Blue – no DQA1*05
Red – has DQA1*05
Dotted lines - monotherapy
Solid lines – combo with Aza

For IFX, everyone benefits from combo Rx, but DQA1*05 highest risk

Gastro Jan 2020;158:189–199

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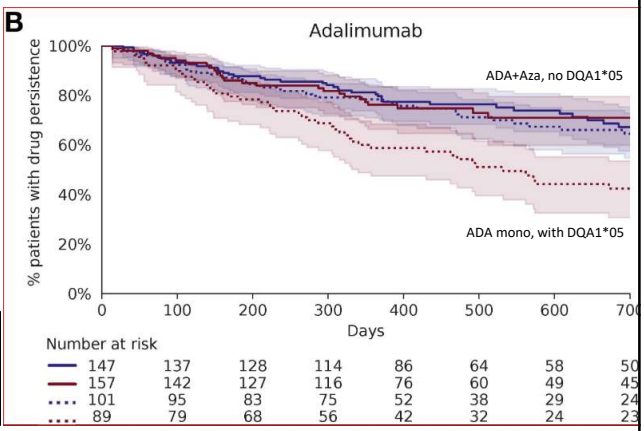
The Durability of Maintenance Therapy

- Similar, smaller effect with ADA: combo reduces effect of DQA1*05



Blue – no DQA1*05
Red – has DQA1*05
Dotted lines - monotherapy
Solid lines – combo with Aza

For ADA, only patients with DQA1*05 get clear benefit from combo Rx

Gastro Jan 2020;158:189–199

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Reactive Therapeutic Drug Monitoring

- Bob does well on IFX for 2 years, but starts developing recurrent symptoms at week 7
- CRP drifting upward, 12 mg/L before infusions
- IFX level at trough (morning of infusion): 1.7 mcg/mL, no anti-biologic antibodies
- Bowel symptoms OK after infusions – but gradually return
- IFX increased to 10 mg/kg q 6 weeks – recurrent symptoms resolve
- Reactive Therapeutic Drug Monitoring – R-TDM
  - REACTIVE therapeutic drug monitoring is supported by evidence and AGA Guideline
  - PROACTIVE TDM (when patient is feeling fine, normal inflammatory markers) is NOT supported by RCTs or Guidelines.

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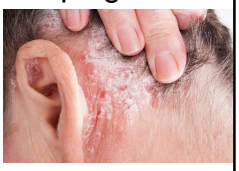
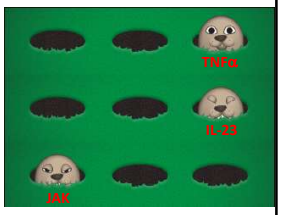
What About Change in Mechanism?



- Bob does well on IFX for 2 years, but starts developing psoriasis in and behind his ears
- CRP drifting upward from 2, now 11 mg/L
- Symptoms gradually worsening
  - More abdominal pain after meals
  - More fatigue, up to 5 BM daily



- IFX level at trough (morning of infusion): 11.2 mcg/mL, no anti-biologic antibodies
- Adequate drug level, but losing benefit
  - Symptoms not quickly responsive to infusions
  - Less TNFα effect – likely more IL-23 pathway
- Switch to Ustekinumab (anti-IL12/23) – back into remission, ears improve

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The Assess and Adjust Feedback Loop

- Proactive Assessment of Inflammation 
  - Recent flare or change in therapy: q12w after normalized
  - ≥1 year of deep remission, on biologic: q6m
  - Multiple years of remission, not on biologic: annually
- How to assess:
  - CRP in 70% - easy, cheap
  - FCP in 20% - if willing to provide stool
  - Small bowel CD – rotate in imaging (MR if <35), scope if within reach in TI, or capsule/DBE
    - Get multiple views of inflammation

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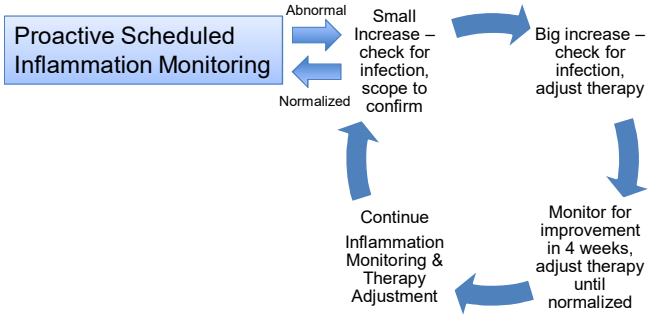
The Assess and Adjust Feedback Loop

- Watch closely for worsening
  - CRP can be noisy – sometimes just a URI
  - FCP / scan can be C diff/norovirus/E coli.
  - Rule out infection, scope to confirm if borderline



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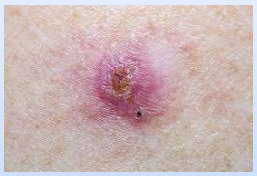
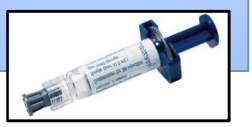
The Adverse Effects of Therapy

- Skin cancer in IBD
  - Baseline 64% increase NMSC in CD
  - NMSC increased 85% by thiopurines
  - Risk increased by JAKi
  - Melanoma risk increased 88% by αTNFs



- Pneumonia in IBD
  - Baseline risk increased 54%
  - Steroids increase another 226% ~ 4 fold baseline
  - TNF increase by another 28% ~ 2 fold baseline
  - PPIs increase by 14%
  - Prevnar 13 & Pneumovax 23



Gastroenterology. 2012; 143: 390–399.
AJG 2013; 108: 240-248.

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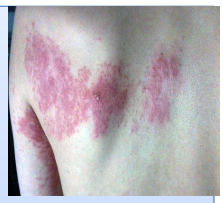
The Adverse Effects of Therapy

- Shingles in IBD
  - Baseline increase 49% vs. non-IBD
  - More with IS – steroids 73% more, TNF 81%, thiopurines 85%
    - About 2.5x risk of non-IBD
    - Tofacitinib – 5% per year @ 10mg bid
  - Shingrix recombinant vaccine at age 50 for all
    - Earlier for these meds (but cash pay?)
    - CDC website supports vaccination for the immunosuppressed
    - Risk starts ~ age 30-35 if on IS
      - 25-30 years after chicken pox



APT 2013; 37: 10.1111

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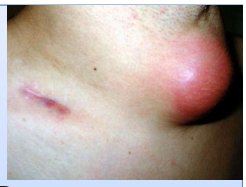
The Adverse Effects of Therapy



- Tuberculosis risk
  - Assess travel and exposure risk
  - QFTB, PPD are *not* 100% sensitive
  - Also at risk of other mycobacteria (MAI !)
- Increased risk *Clostridium difficile* in IBD
  - Vancomycin first line, use long (28-42d) tapers
- Osteoporosis risk
  - Chronic inflammation, low vitamin D
  - Corticosteroids >3m in lifetime
    - Screen with DEXA

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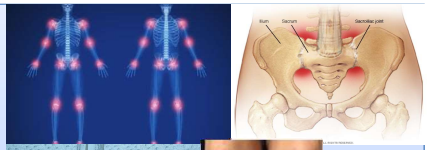
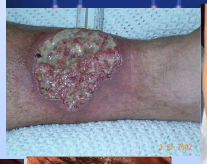
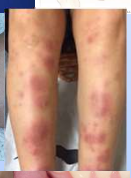
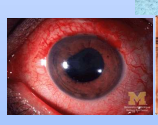
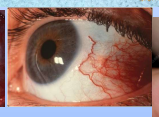
Recognizing and Treating EIMs

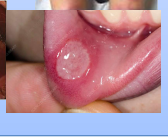












- Enteropathic arthritis
- Sacroiliitis
- Pyoderma gangrenosum
- Erythema nodosum
- Uveitis/Iritis
- Episcleritis
- Mouth Ulcers
- PSC$_{(AlkPh \rightarrow MRCP)}$

Rheumatology, Dermatology, and Ophthalmology can often help.
Triamcinolone dental paste for deep mouth ulcers.
Do *not* let a well-meaning surgeon debride PG ‘infection’.

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Health Maintenance and Vaccinations

- If > 1/3 of the colon involved → Surveillance
- Work on smoking cessation in CD
- Bones – DEXA if >3m steroids
- Vaccinations
  - Prevnar 13 & Pneumovax 23
  - Shingrix
  - Annual Influenza
  - Tdap q10y

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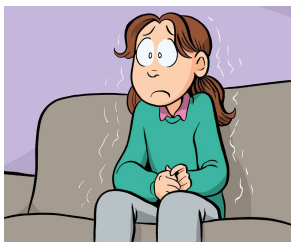
Emotional Care in Crohn's Disease

- Anxiety and Depression are Highly Prevalent
  - Up to 30% of CD
  - Worse during flares (~4 fold more frequent)
  - Adversely affects adherence
- Screen, Recognize, and Refer



Can J Gastro Hep 2017: 6496727

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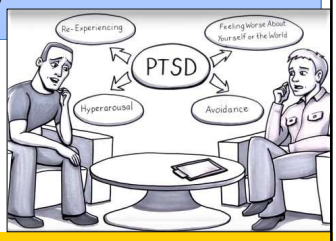
Emotional Care in Crohn's Disease

- PTSD is more common than previously thought
  - Up to 38% of CD in one referral center
  - More common after hospitalizations, surgery
  - Can result in avoidant behavior, flat affect
    - Avoidance of physician visits, testing, adherence
    - Refusal to go to ER, refusal to be hospitalized
- Screen, Recognize, and Refer

Hypervigilance	Difficulty Concentrating
Nightmares	Irritability
Easily startled	Foreshortened Future
Sleep Disturbance	Blunted Emotions
Intrusive thoughts	Detached feeling
Flashbacks	Anhedonia

IBD Sep 2019;25:1577-1585



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Take Home Points

- Most CD patients high-risk for complications – severity
- Monitor and achieve tight control of inflammation – activity
- For flares, objectively measure inflammation
  - Rule out infection (Cdiff, EPEC, Norovirus)
  - Intervene to control inflammation to deep remission
  - Reactive TDM
- Recognize high risk for anti-biologic antibodies – combo
- Recognize and prevent infections with vaccination
- Recognize anxiety, depression, and PTSD
  - Screen and refer

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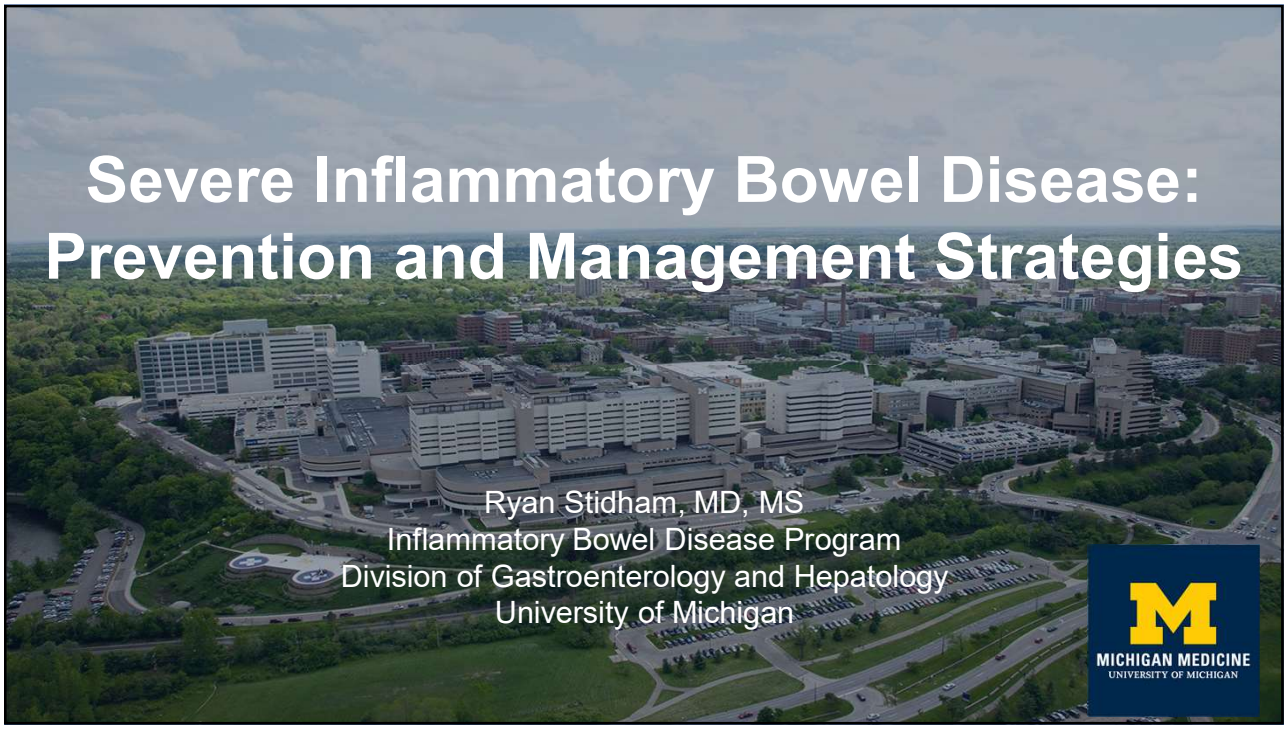

Relationship Disclosures

Outside Relationships

I have served as a consultant for the following:

- Abbvie
- Janssen
- Merck
- Takada

I have received research funding from:

- Abbvie
- Janssen

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Discussion Topics

Risk Stratification of Future Poor Outcomes in IBD

Strategies for Managing Severe IBD Scenarios/Cases

- Severe Disease Activity Management and Thiopurine Dosing
- Managing symptomatic strictures in CD – therapeutic decision making
- Severe UC – when to escalate, when to operate

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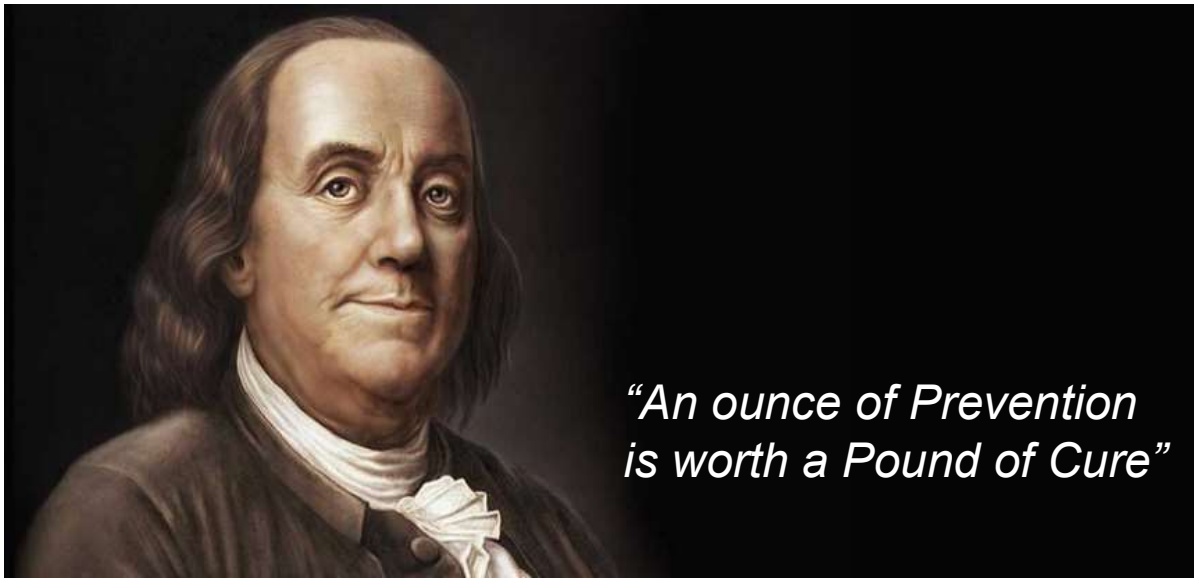
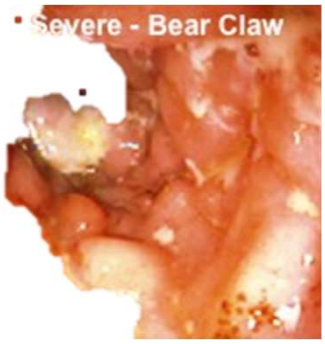
Preventing Complications in IBD



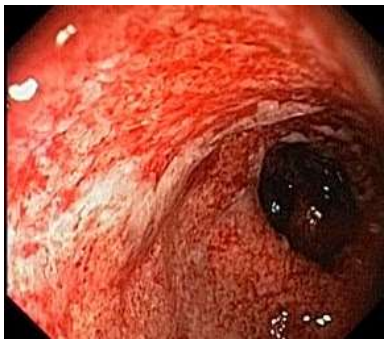
Avoiding Complications and Poor Outcomes are Long Term Goals of IBD Care

- Surgery
- Hospitalizations
- Fistulas/Strictures
- Disability
- Future Flares

Crohn's Disease



Ulcerative Colitis



You'd Think Little Argument for Using High-Intensity Therapy when Disease is Obviously Severe

2008: 'TOP-DOWN'

Early High Intensity Tx Superior to Sequential Tx (Step-Up)

	Outcomes at 1 year	
	Top-down therapy	Step-up therapy
How many patients were in remission?	62%	42%
How many patients received the combination of azathioprine plus infliximab?	100%	14%
How many patients took prednisone?	0%	100%
How many patients had mucosal healing?*	73%	30%
How many patients had a bowel resection?	9%	13%

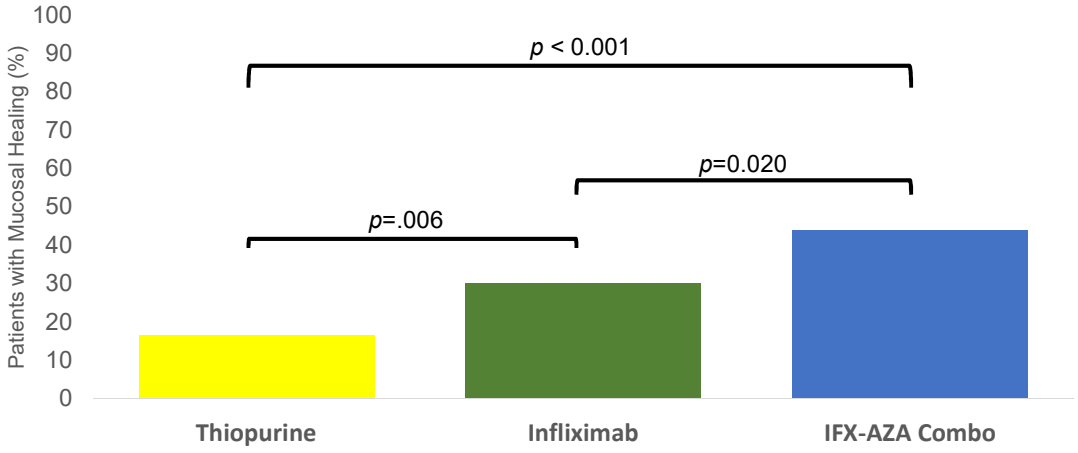
*2-year outcome
Study assessing the effectiveness of early use of combined immunosuppression with conventional management in patients with active Crohn's disease (n=133) who had not previously received glucocorticoids, antimetabolites, or infliximab.

D'Haens, et al. *Lancet* 2008

6

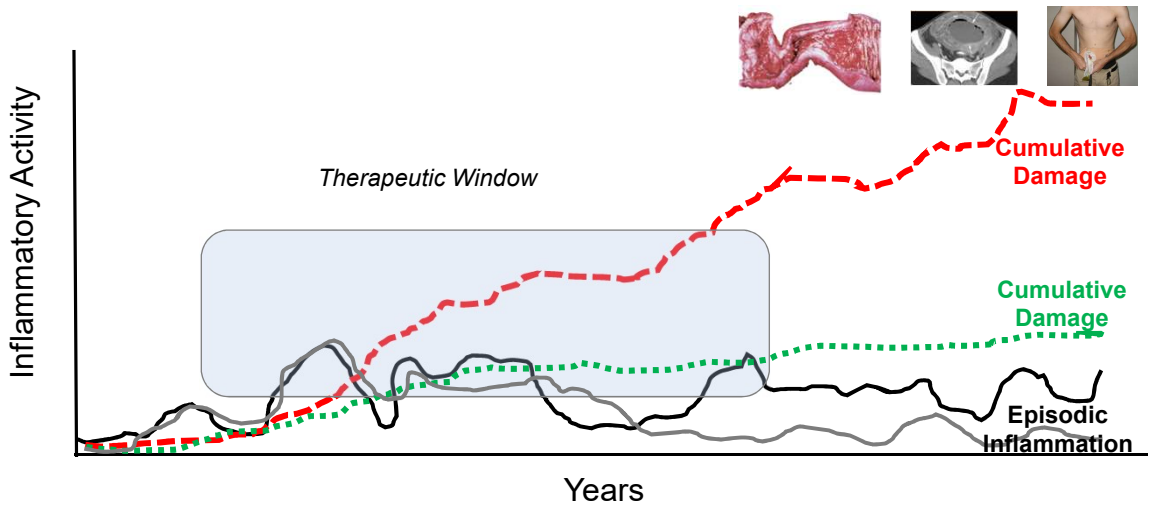
2010: SONIC Boom!

Combination Therapy Proven Better than Monotherapy in CD



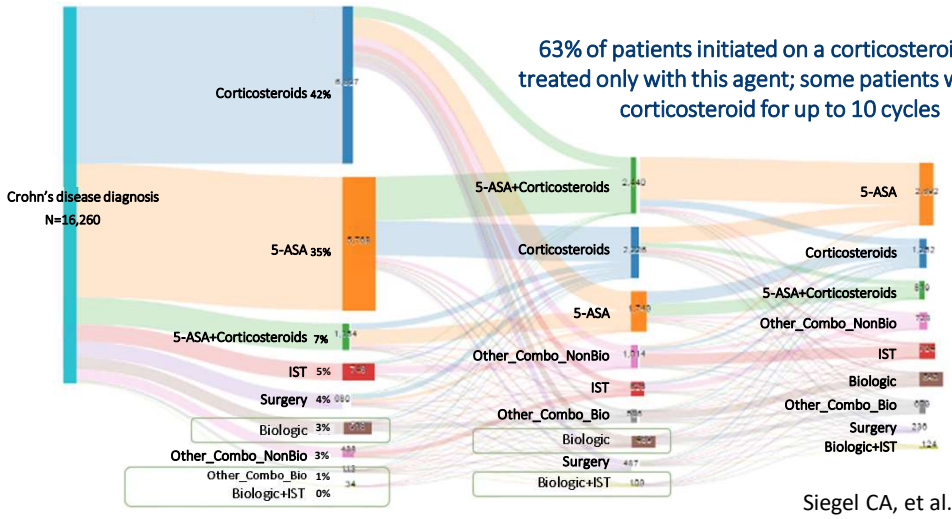
Colombel et al, NEJM 2010

Improving CD Natural History Requires Early Intervention



We're not acting on what we've learned!

Treatment Flows For Patients with Crohn's Disease Using National Insurance Data (Truven)



63% of patients initiated on a corticosteroid were treated only with this agent; some patients were on a corticosteroid for up to 10 cycles

Siegel CA, et al. *J Crohns Colitis* 2017

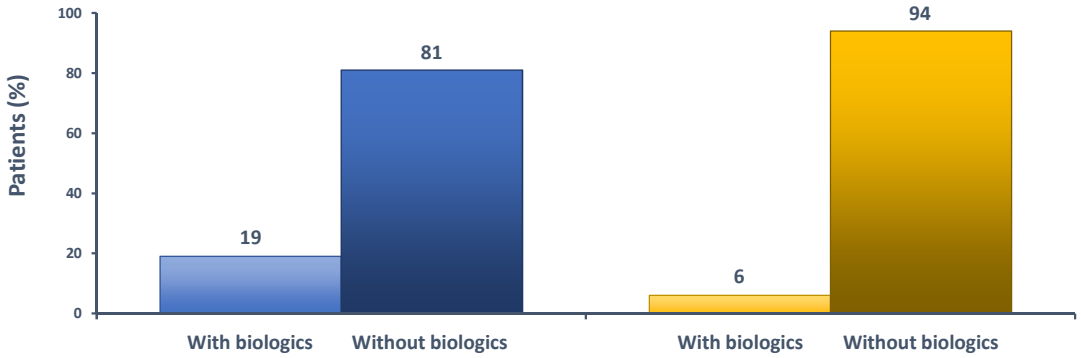
We're Still Not Using Biologics Very Often

Crohn's disease

CD pathways-based patient counts (N=16,260)

Ulcerative colitis

UC pathways-based patient counts (N=28,119)



Siegel CA, et al. *J Crohns Colitis* 2017

Determining High Risk vs. Low Risk IBD Patients to PROACTIVELY Prevent Poor Outcomes

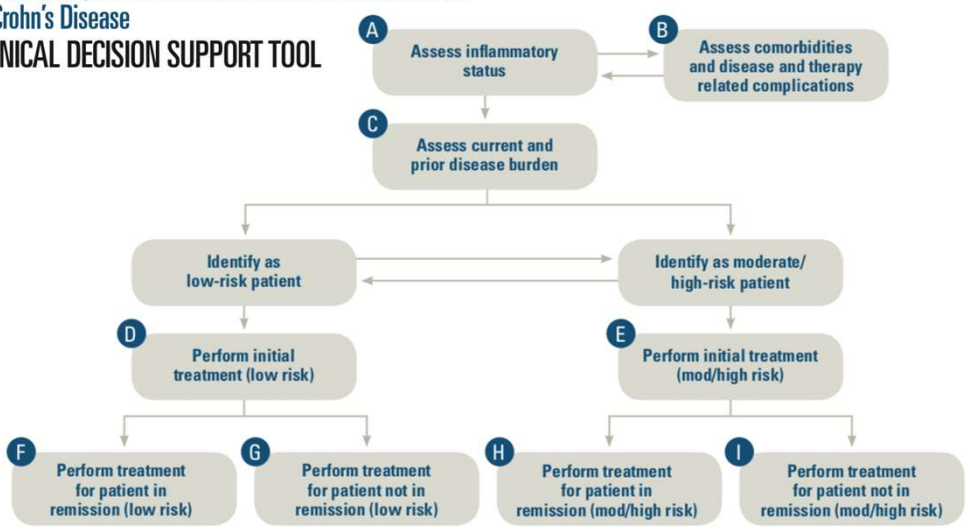
- Systemic Steroids at Dx
- >5kg Weight Loss
- Presence of Stricturing
- History of Perianal Disease
- Upper GI Tract Distribution

Likely More Severe Future Course (CD)

Peyrin-Biroulet L et al, CGH 2016

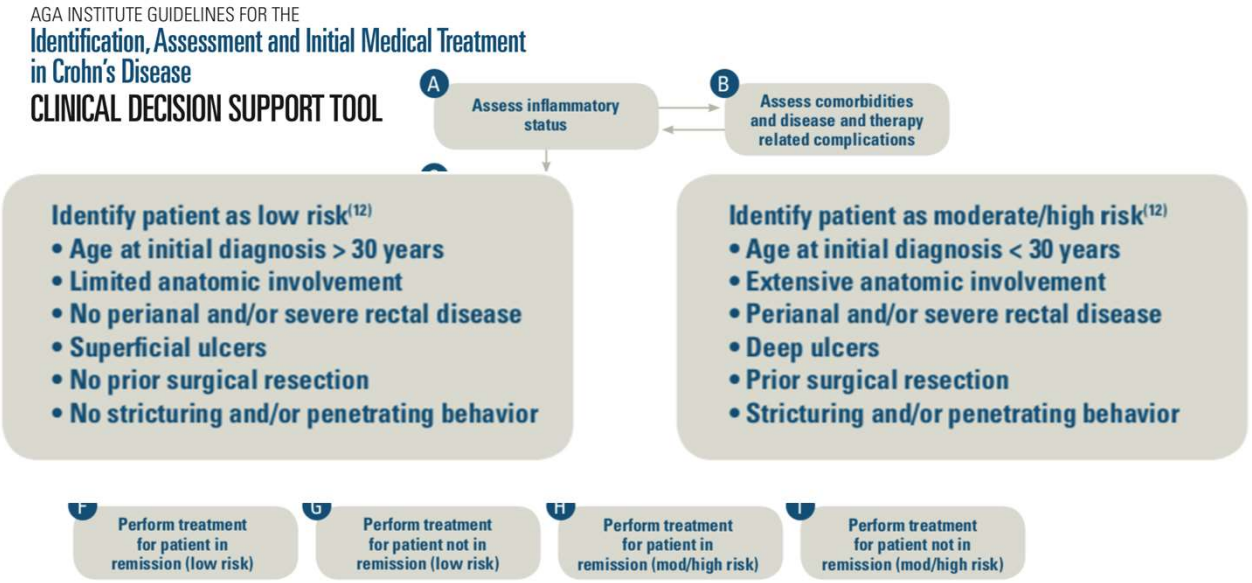
Risk Stratifying CD for Treatment Decisions

AGA INSTITUTE GUIDELINES FOR THE
Identification, Assessment and Initial Medical Treatment in Crohn's Disease
CLINICAL DECISION SUPPORT TOOL



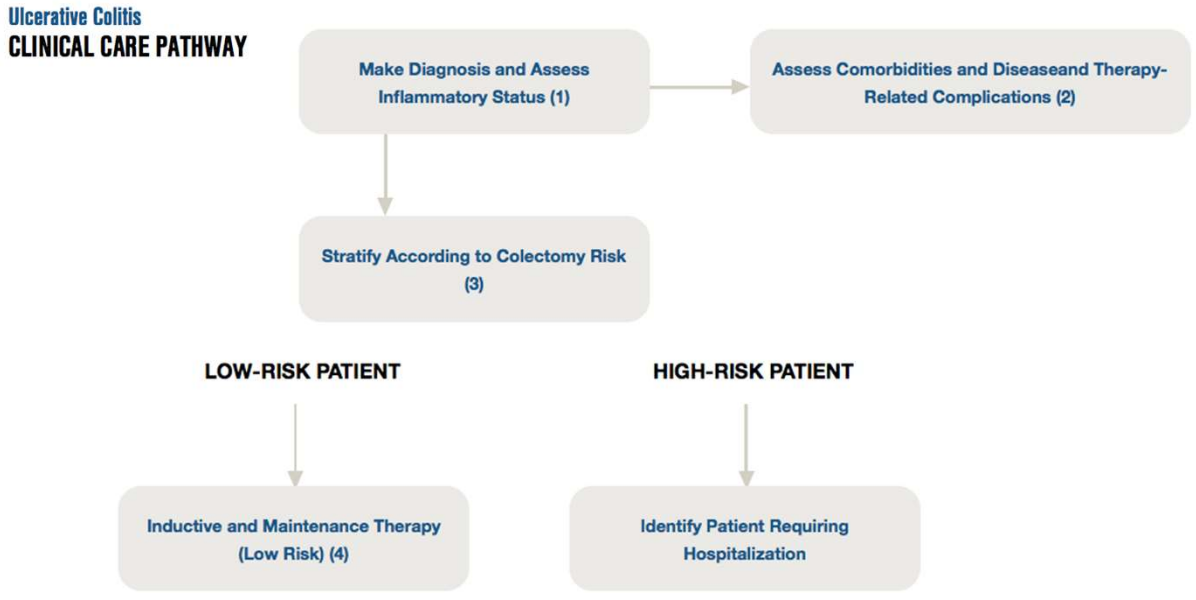
Sandborn et al, Gastro 2015

Risk Stratifying CD for Treatment Decisions



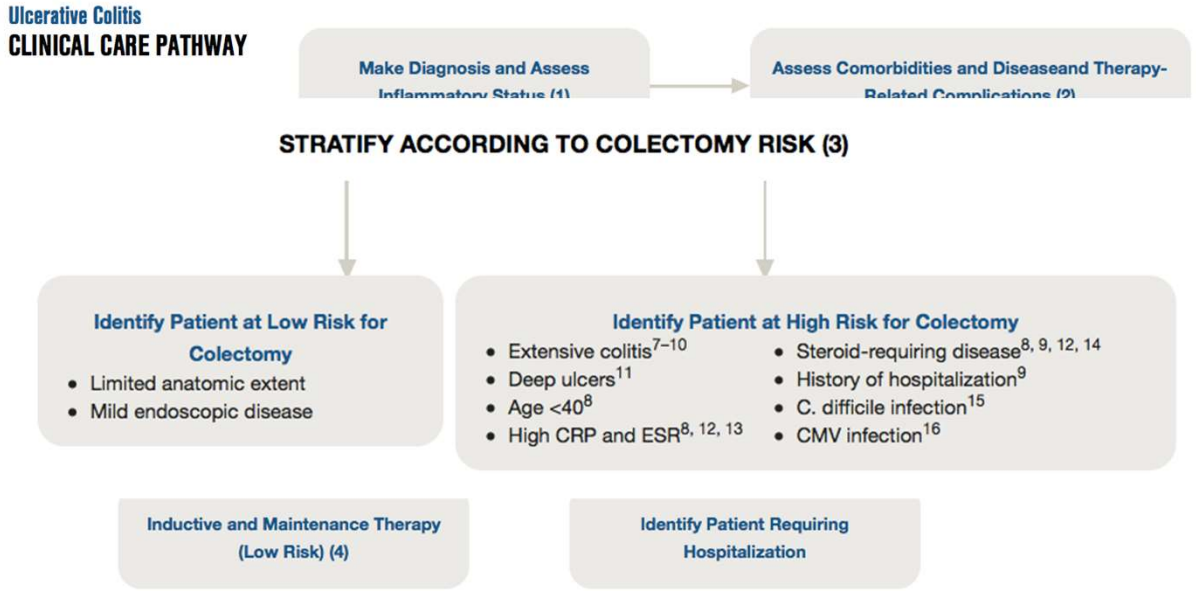
Sandborn et al, Gastro 2015

Risk Stratifying UC for Treatment Decisions



AGA, Gastro 2015

Risk Stratifying UC for Treatment Decisions



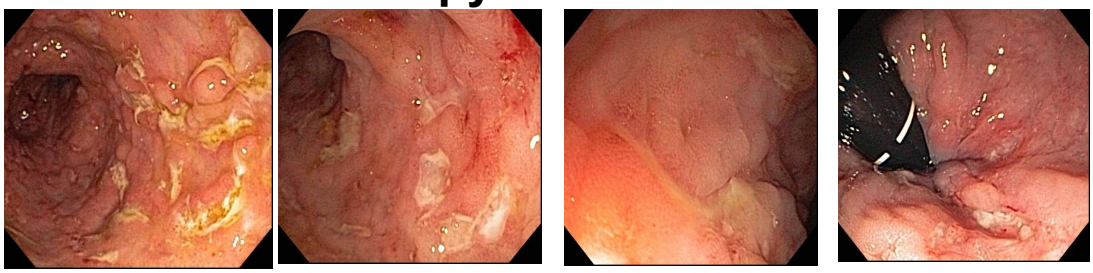
AGA, Gastro 2015

Severe Disease Activity Management in IBD

Case 1: Severe Crohn's Disease Activity

- 25 yo male with 2 yr Hx of CD: ileocolonic with perianal fistula
- Current Symptoms: diarrhea, RLQ pain (RLQ), draining fistula
  - Prior Treatments: 5-ASA, antibiotics
  - Frequent corticosteroids
  - 3-4 "flares" per year

Current Colonoscopy



Case 1: Severe Crohn's Disease Activity

Start Infliximab 5mg/kg – standard induction/maintenance

- Very good clinical response immediately !

4 Months Later

- Symptoms return: Diarrhea, abdominal and perianal pain
- Symptoms occurring about 3 weeks after infliximab dose.

Neutralizing Anti-Drug Antibodies (Change Biologic)	**Insufficient Level (Increase IFX Dose)**	**Wrong Mechanism? (Change Biologic)**	**Effective Biologic Severe Activity (Add Therapy)**

Approach to Loss of Response

- ❑ Rule out Infection
- ❑ Objective Inflammation assessment
- ❑ Rule out strictures if obstructive symptoms or atypical abdominal pain
- ❑ Confirm adherence

Therapeutic drug monitoring
- ❑ Detectible levels of drug
- ❑ Antibody levels

Infection Evaluation

C. Diff: PCR Negative
GI PCR: Negative

Inflammation Assessment

CRP: **3.1** mg/dL
Fecal Cal Pro: **390** ug/mg

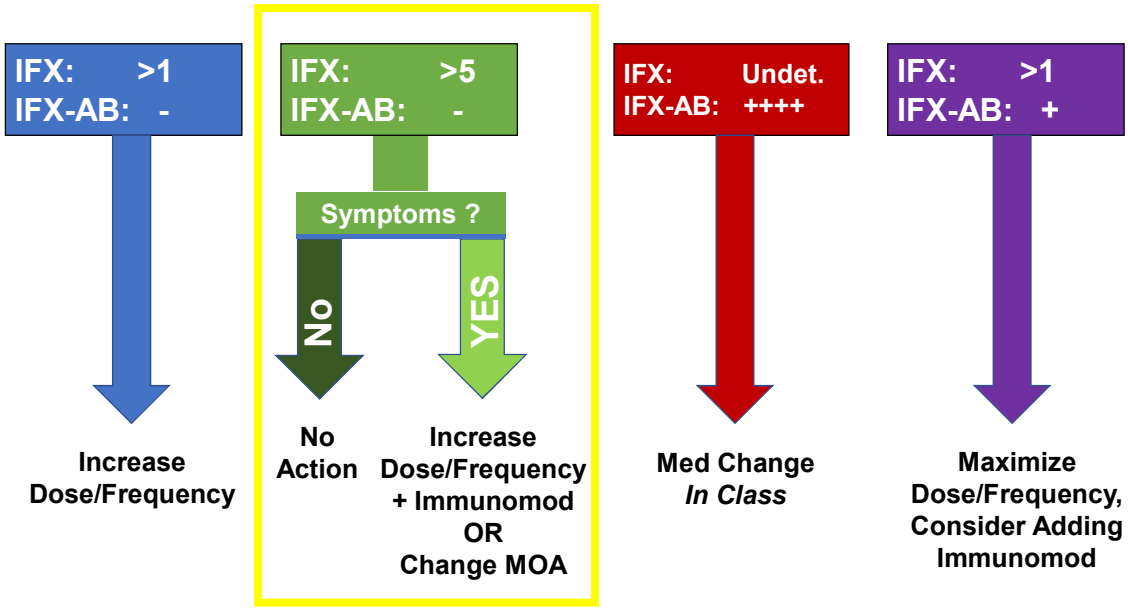
Structural Disease Suspicion

No obstructive symptoms

Therapeutic Drug Monitoring

IFX Level: **4.5** ug/mL
IFX-Antibody Level: **neg** ng/mL
(normal <25ng/mL)

Anti-TNF Drug Level Interpretation



Thiopurine Combination Therapy: *Dose for Efficacy*

Metabolite Levels Are Minimally Helpful for Predicting Efficacy

6-TGN HIGH
6-MMP low
Excellent Drug Effect
May be too much bone marrow suppression

Low — TPMT Activity — High

6-TGN low
6-MMP HIGH
Minimal therapeutic effect
Risk of hepatotoxicity

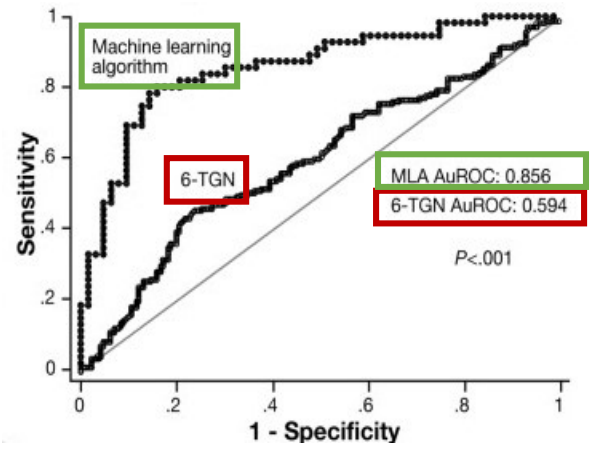
Using 6-TGN > 235
for clinical response
Sensitivity: 62%
Specificity: 64%

Two RCTs **FAILED** to Show Benefit Using
6-TGN vs. Weight-Based Dosing for Clinical Response

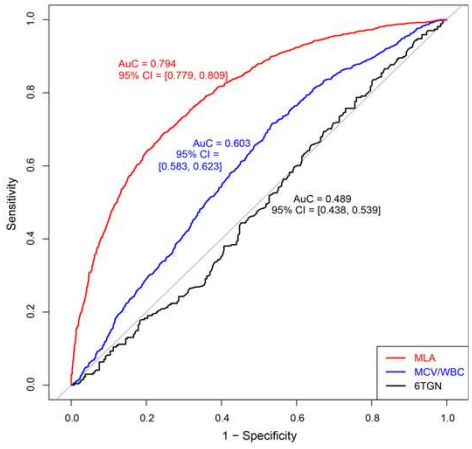
Reinshagen, et al. Clin Chem 2007
Dassopoulos, et al. APT 2014

ThioMon: Machine Learning Analysis of CBC and COMP Superior to Thiopurine Metabolites for Predicting Response

*ThioMon vs. 6-TGN for **Clinical Response***



*ThioMon vs. 6-TGN for **Biologic Response***



Waljee, Higgins, et al. JCC. 2017

Dosing Thiopurines for Efficacy: Often Underdosed

Check TPMT

NORMAL

- 2.5 mg/kg start
- Increase by 50mg q4 weeks, max 300mg

LOW

- Start with 50mg
- Slow Increase by 25mg q2-4 weeks

HIGH

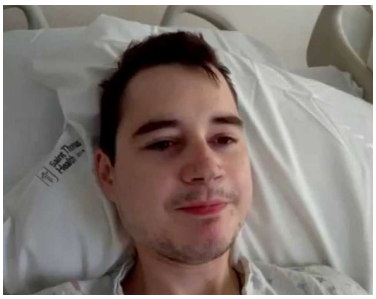
- Allopurinol 100mg + Azathioprine 50mg
- Slow Increase by 25-50mg q4 weeks
- Max allopruinol 200 + aza 100mg
- ***ALLOPURINOL COMBINATION CAN RESULT IN SUPRA-THERAPEUTIC EFFECTS OF THIOPURINES***

Goals & Monitoring

- Reduction in WBC count to near 4.0 k/mL
  OR clear trend of WBC reduction
- Laboratory (CBC & LFT) Monitoring Schedule
  Every 2 weeks during dose optimization, THEN
  Every 4 weeks for 3 months, THEN
  Every 4 months
- If WBC not reduced OR no clinical improvements check Thiopurine Metabolites for evidence of shunting (MMP>>>6TG).
  IF evidence of shunting-> REDUCE AZA to 50mg and add ALLOPURINOL 100mg.

Managing Crohn's Disease When Strictures Already Exist

New Admission: Crohn's disease



Wes: 23, Crohn's Disease

- History of Crohn's Disease
- Uncontrolled Abdominal Pain
- Nausea, Vomiting, Bloating for 2 days
- Not Much Diarrhea (1-3 BM daily)
- Using Azathioprine for 6 Months

- 2nd Hospitalization in Last Year
- Lots of Prednisone Use
- Leave of Absence from Grad School

Testing Indicates Active Crohn's Disease With Stricture

Laboratory

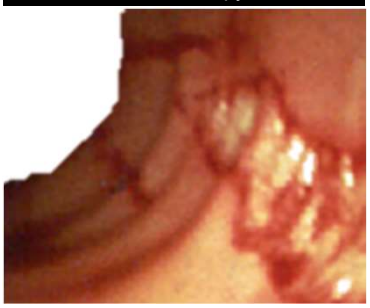
WBC: 12.1 k/mm^3
HGB: 10.9 g/dL

Albumin: 3.4g/dL

CRP: 1.9 mg/dL
Fecal Calprotecin: 550

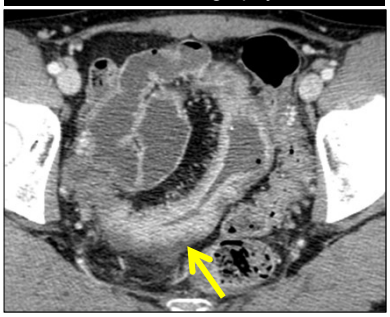
Positive Biomarkers of Inflammation

Colonoscopy



Active Endoscopic Inflammation Detected

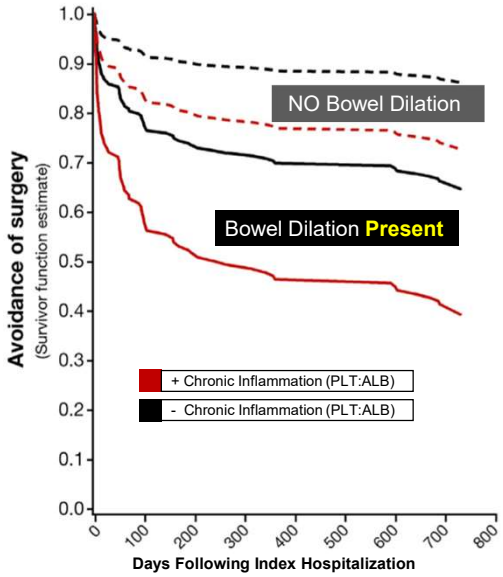
CT-Enterography



Active Disease with Stricturing on Imaging

Active Inflammatory Target and Stricture Both Are Present

CD with Pre-Stenotic Bowel Dilation + Chronic Inflammation Less Likely to Respond to Treatment



Probability of Surgery Over 2 Years

Dilation (+) & Inflammation (+): 61.8%

Dilation (+) & Inflammation (-): 32.1%

Dilation (-) & Inflammation (+): 23.7%

Dilation (-) & Inflammation (-): 10.4%

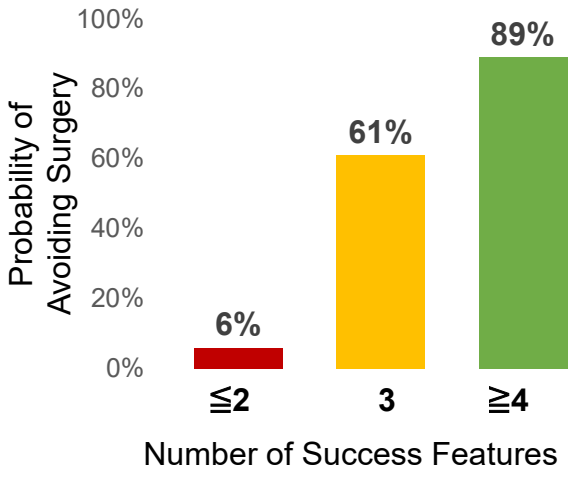
Stidham et. al CGH 2016

CREOLE: Predicting Anti-TNF Success in Stricturing Crohn's Disease

Prospective multicenter observational cohort (N=97)
Small bowel strictures, failure of immunomodulators, new anti-TNF start

Treatment Success Features

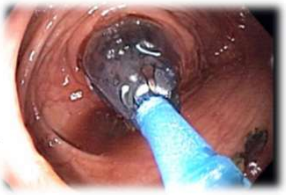
- Use of Immunosuppressive Treatment
- CD Obstructive Score <4
- Duration Obstructive Symptoms
- *<5 Weeks*
- Stricture **Length** <12cm
- Small Bowel **Diameter** <30mm
- **Delayed Enhancement** T1W Images
- Fistula (not present)

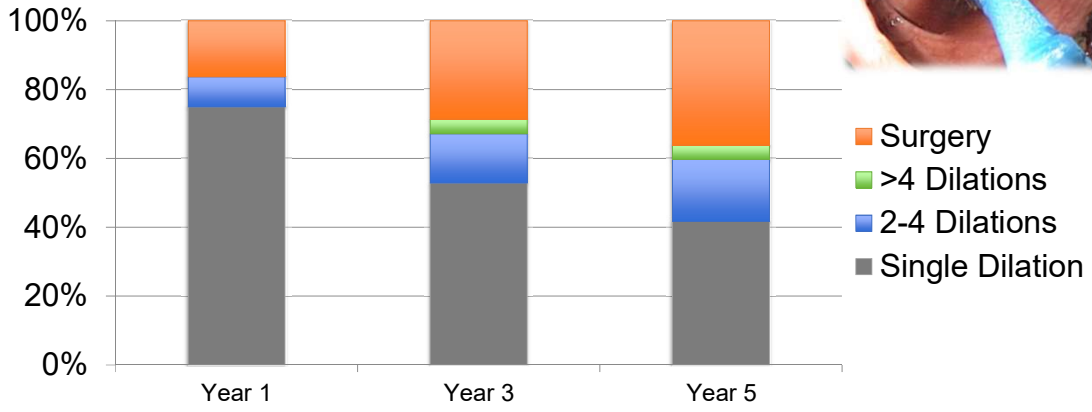


Bouhnik et al. Gut 2017

Endoscopic Balloon Dilation Can Result in Sustained Relief

At 5 years Single Dilation **~40%** sustained response
Serial Dilation: **~60%** sustained response





Dilation follow up over 5 years
Adapted from Gustavsson et al 2012

Gustavsson et al. APT 2012

Who is a Good Candidate for Stricture Dilation?

Short: Stricture length <5cm Best

Simple: Absence of abscess fistula near stricture

Straight: Absence of high angulation at stricture

Recent Imaging in Necessary Prior to Dilation

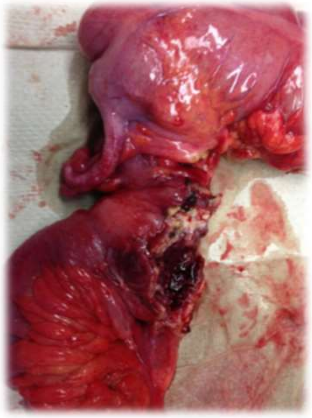
Does stricture location/type impact success? NO

Reutermann, Stidham et al, IBD 2017
Bettenwerth et al. IBD 2018

Endoscopic Balloon Dilation – Complications

Overall complication rate reported at ~5% (per dilation)[1,2]

- Severe Abdominal Pain/Fever 1.0%
- Bleeding 1.0-3.0%
- Bowel Perforation 1.5-2.5%



Factors ***Not Associated*** with Complications

- Anastomotic Activity
- Total endoscopic disease activity
- Stricture ulceration
- CRP

Van Assche et al. Gut 2010:320–324

Managing Acute Severe Ulcerative Colitis

Severe Ulcerative Colitis

- 43 yo F, Pancolitis Diagnosis in 2014
- 2017 flare(s) – outpatient steroids x 2
- On Azathioprine, tolerating well
- BM: 1-3 daily without blood

Another Flare

- BM: 10-12 watery BM daily
- URGENCY: ~ 60 seconds
- BLOOD: 50% of BMs
- Cramping LLQ pain, Thirsty

Lab	Value
WBC	9.8
Hgb	11.4
Plt	409
CRP	12.6 mg/dL
Alb	3.7

Michigan Medicine Severe UC Protocol

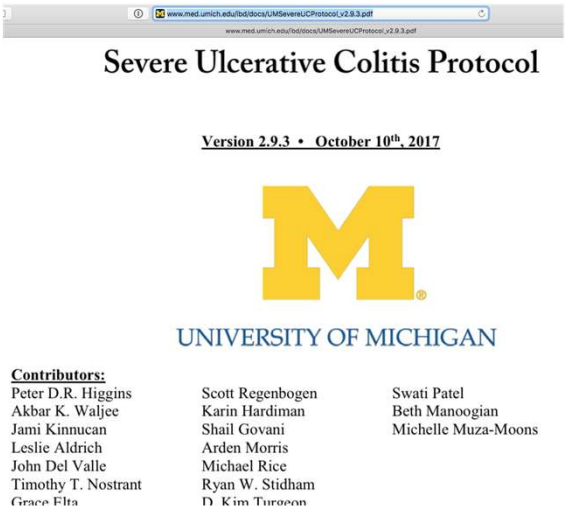
http://www.med.umich.edu/ibd/docs/UMSevereUCProtocol_v2.9.3.pdf

Day 0: IV Steroid Start
Baseline Assessment

Day 3: Assess Response
- CRP
- BM
- Frequency
- Endoscopy

Initiate Outpatient Treatment

Rescue Therapy
Anti-TNF vs. Cyclosporine
OR
Colectomy



Severe Ulcerative Colitis Protocol

Version 2.9.3 • October 10th, 2017

UNIVERSITY OF MICHIGAN

Contributors:

Peter D.R. Higgins, Akbar K. Waljee, Jami Kinnucan, Leslie Aldrich, John Del Valle, Timothy T. Nostrant, Grace Elta, Scott Regenbogen, Karin Hardiman, Shail Govani, Arden Morris, Michael Rice, Ryan W. Stidham, D. Kim Turgeon, Swati Patel, Beth Manoogian, Michelle Muza-Moons

UC Severe Flare Management: Checklist

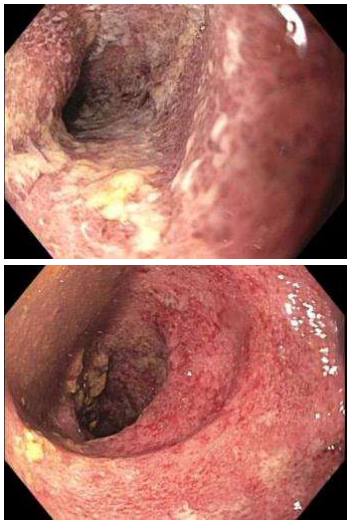
	Key Item	Detail
✓	Volume Resuscitation	500cc/hr x12h, then 250cc/hr
✓	Infectious Colitis Evaluation	C. diff, CMV, GI PCR (BioFire)
✓	Abdominal X-ray - Admit	Rule Out Toxic Megacolon
✓	IV Corticosteroids	Solumedrol 15mg q6h +/- Rectal Steroids for Urgency
✓	NPO	Until Pain Resolves, then full liquids
✓	DVT Prophylaxis	Lovenox 40mg SC daily
✓	Daily Labs	CBC, COMP, CRP, Albumin
✓	Prep for Anti-TNF	Tb (Quantiferon/PPD), HBV Serologies

Decision Point: DAY 3 Data

- On IV steroids, minimal improvement
- Added Canasa 1 g PR bid
- 9 bloody/mucoid BM daily
- Not hungry, staying NPO

Lab	Initial Value	24h	72h
WBC	9.8	9.4	8.6
Hgb	11.4	9.8	10.2
Plt	409	411	396
CRP	12.6 mg/dL	13.3	8.6
Alb	3.7	3.1	2.9

Sigmoidoscopy



CMV Negative

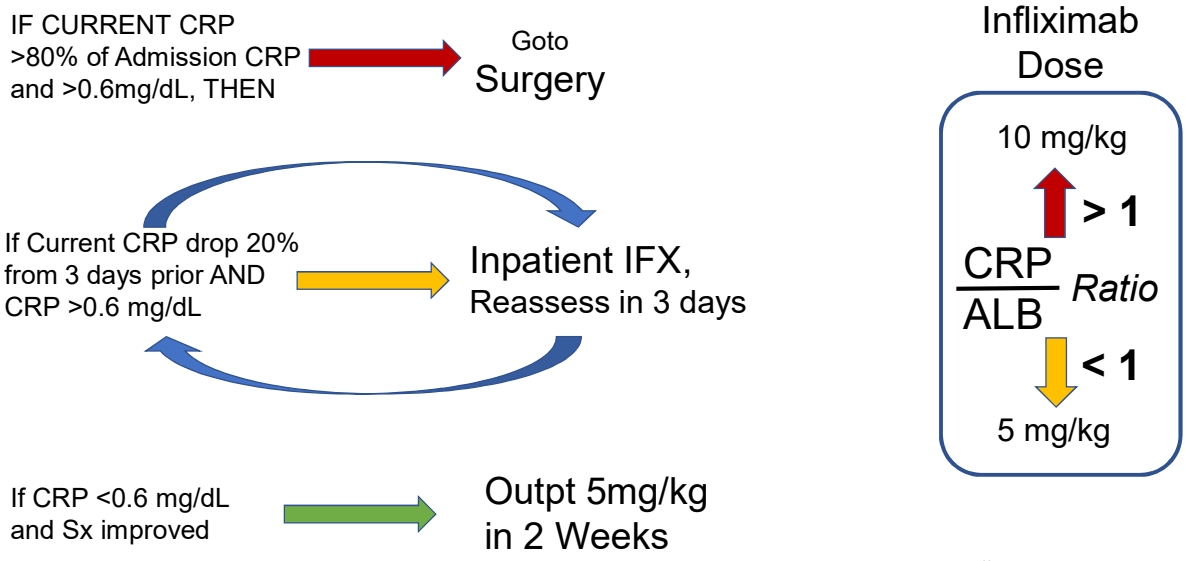
DAY 3: Will Steroids Be Enough?

Predictive Models for Steroid Failure

Scoring System	Data Types Used	Formulas	Probability Steroid Failure
Travis	BM, CRP	>8 BM/day OR (>2 BM's & CRP>4.5 mg/dL)	TRUE = PPV 85%
Ho	BM, Albumin, X-Ray	colonic dil> 5.5 cm = 4 pts albumin < 3.0 = 1 point BM/day: <4=0pts, 4-6=1pts, 6-9=2pts, >9=4pts	>5pts = PPV 85%
Lindgren	BM, CRP	stool frequency/d + 0.14 × CRP (mg/dL)	>10.2 = PPV 72%

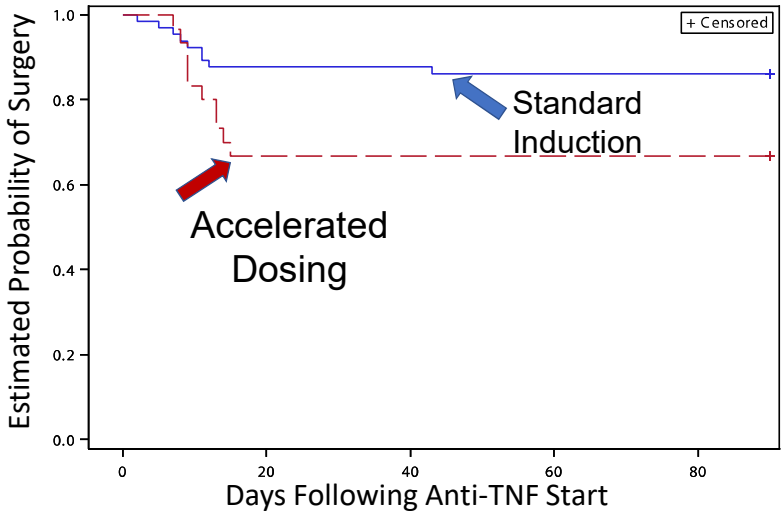
1. Travis SP, et al. Gut. 1996;38(6):905-10.
2. Lindgren SC, et al. Eur J Gastroenterol Hepatol. 1998;10(10):831-5.
3. Ho, GT. Aliment Pharmacol Ther. 2004;19(10):1079-87.

Initiation of Rescue anti-TNF for UC at Hospital Day 3



Govani, Stidham, Higgins. DDS 2019

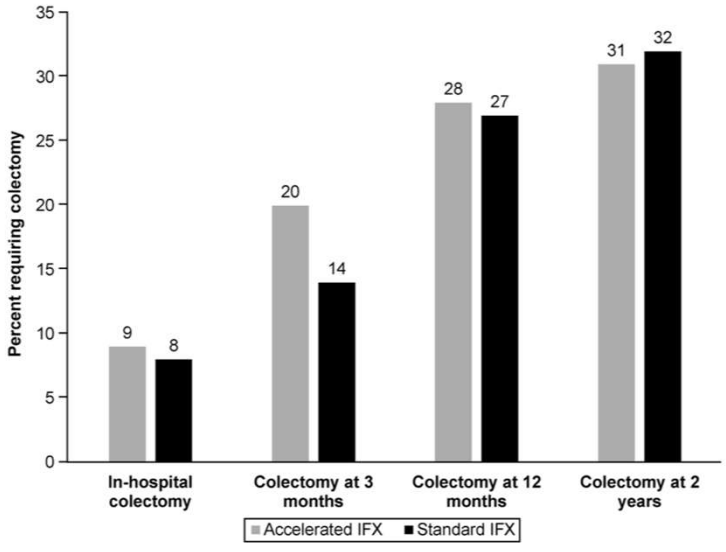
90 Day Colectomy Risk Lower Among With Accelerated Michigan IFX Induction Protocol



Govani, Stidham, Higgins. DDS 2019

Benefits of Accelerated IFX Dosing Remain Unclear

- Retrospective study of steroid Refractory Acute Severe Ulcerative Colitis
- 3 Centers, 216 Patients
- 2005-2017 Timeframe
- Only Testing 5 vs >5mg/kg Dosing
- Protocols not standardized for IFX dosing or decision making

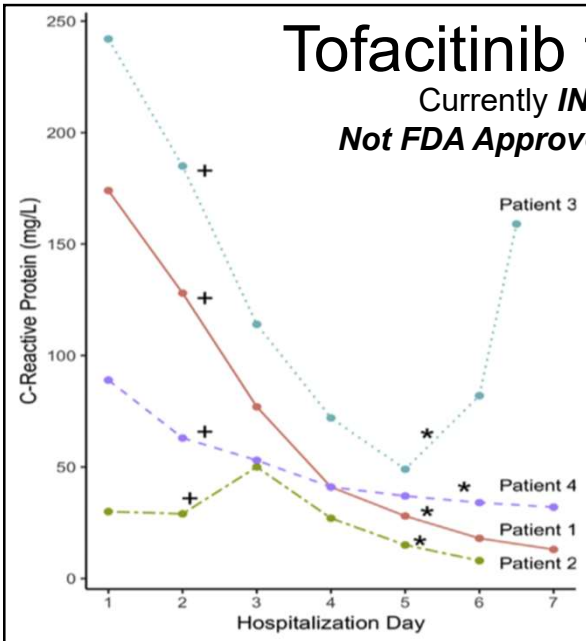


Nalagatla N et al. CGH 2019

Tofacitinib for Acute UC?

Currently ***INVESTIGATIONAL***

Not FDA Approved for Use at High Dose



Small experience using high-dose tofacitinib in:

- Hospitalized UC
- Failed high dose steroids
- Failed anti-TNF

Used 10mg TID for 3 days, then 10mg BID

Rapid symptom improvement for Patients 1,2,4 (days)

Sustained clinical remission for Patient 1,4 at 6 months

Patient 3 underwent inpatient colectomy.

Patient 4 had detection of dysplasia at 6 month - colectomy

Formal Clinical Studies to Begin Soon (Higgins)

Berinstein, Stidham, Higgins. AJG 2019

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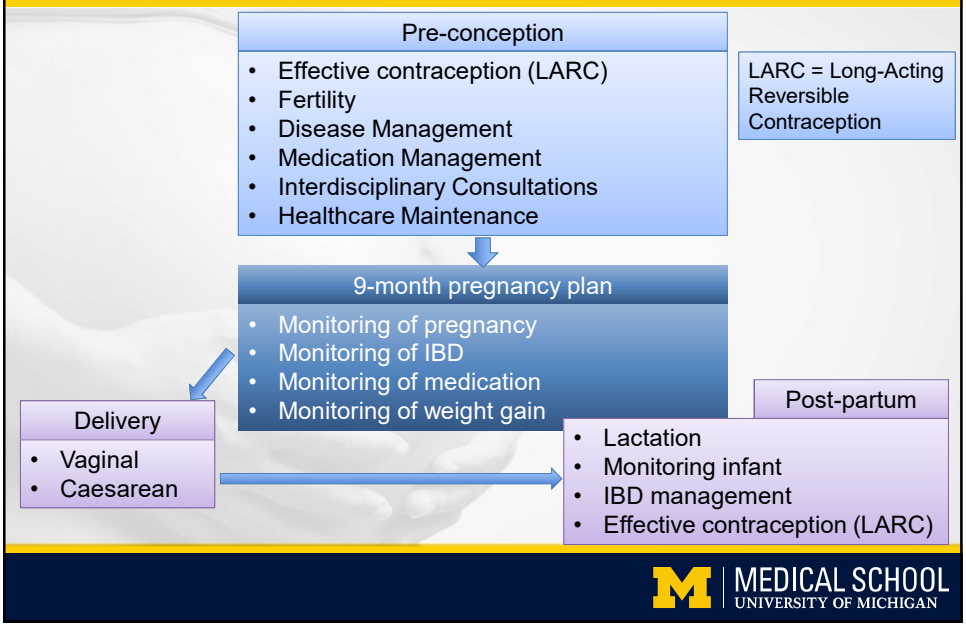
Pregnancy in IBD

Peter DR Higgins

AGA Pregnancy Pathway



AGA Clinical Decision Support Tool

Pre-conception

- Effective Long-Acting Reversible Contraception (LARC)
- Disease Management
- Fertility
- Interdisciplinary Consultations
- Medication Management
- Healthcare Maintenance

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AGA Clinical Decision Support Tool

Pre-conception

- Start the conversation early
  - Every woman between 14-49 with IBD
  - Are you sexually active?
  - Are you planning a pregnancy?
  - Establish that outcomes are much better with ***planned*** pregnancies in IBD
- Effective contraception (LARC)

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AGA Clinical Decision Support Tool: Pre-conception

Disease Management

- Minimum 3-month steroid-free remission before conception
- Confirm remission with endoscopy or other objective markers before stopping contraception

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AGA Clinical Decision Support Tool: Pre-conception

Fertility

- Decreased fertility after IPAA and other pelvic surgery
- Active IBD decreases fertility
- Refer to reproductive endocrinologist for infertility treatment if lack of conception after 6 months of timed intercourse.

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AGA Clinical Decision Support Tool: Pre-conception

Interdisciplinary Consultations

- Nutrition – ensure adequate caloric intake and vitamin levels
- MFM (Maternal Fetal Medicine) – refer if history of prior pregnancy complication
- Colorectal surgeon – refer if history of IPAA or ostomy

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AGA Clinical Decision Support Tool: Pre-conception

Medication Management

- Stop methotrexate or leflunomide ≧ 3 months before conception
- Continue mesalamine
  - Sulfasalazine requires 2mg folic acid daily
- Taper off steroids
- Continue Aza or 6MP therapy
- Continue biologic therapy
  - Measure serum drug levels, optimize
  - Consider risk/benefit of stopping thiopurine combo
  - Tofacitinib – avoid or use with great caution

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AGA Clinical Decision Support Tool: Pre-conception

Healthcare Maintenance

- Up to date pap smear
- Up to date vaccines for mom
- Cessation of drugs, alcohol, and tobacco
- Taper off opioids
- Colon cancer surveillance
- Achieve healthy weight
- Start a prenatal vitamin
- Standard preconception health care (per ACOG)
- Effective contraception (LARC) until ready

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Complete 9-month Pregnancy Plan

- Overview of Issues
- IBD Remission vs. IBD flare
  - IBD Monitoring
  - Maternal/fetal monitoring
- Medication plan
- Nutrition and Weight gain

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9-month Pregnancy Plan with IBD in Remission

- IBD Monitoring in Remission
  - GI visit in trimester 1 or 2, then as needed
  - Labs at least every trimester
    - CBC, liver, Albumin (combine with OB labs)
- Maternal/Fetal Monitoring
  - Routine antepartum care
  - Trimester 3 fetal growth ultrasound
  - Examine perineum for evidence of active IBD
  - Counseling on mode of delivery

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9-month Pregnancy Plan with IBD in Flare

- IBD Monitoring in Flare
  - GI follow-up every 2 weeks – in person or video/portal
  - Acutely manage flare
  - Adjust medication
  - Monitor labs, calprotectin

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9-month Pregnancy Plan with IBD in Flare

- Maternal/fetal Monitoring (OB)
  - Rec Fetal growth surveillance q4weeks after week 24
  - Recommend antepartum surveillance if active IBD in T3
  - Rec ultrasound cervical length screening at 18-22 wks
    - If short cervix (<25mm), close followup
  - Nutrition counseling
  - Nonstress test and Biophysical Profiling per usual OB indications
  - Early glucose screen for patients on steroids
  - Counseling on mode of delivery

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Medication Management in Pregnancy

- Stool softeners as needed
- Appropriate antimicrobials if needed
- Can continue 5-ASA, thiopurines throughout
- Steroids are NOT maintenance therapy – only for flares
- Biologics should continue throughout pregnancy without interruptions
  - ***Can consider*** 'timing' the last dose in T3 (giving it early) to deliver infant at presumed trough
  - But *no proven benefit* to this effort.

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Nutrition and Weight Gain in Pregnancy

- Prenatal vitamins daily
  - Iron may worsen abdominal pain
- Trimester 1 – check iron and B12 levels
- Confirm adequate folate supplementation
- Monitor gestational weight gain (often too low in IBD)
- Nutrition consult if needed, especially for:
  - Surgical changes – short bowel, ostomy
  - Inadequate weight gain
  - Active disease

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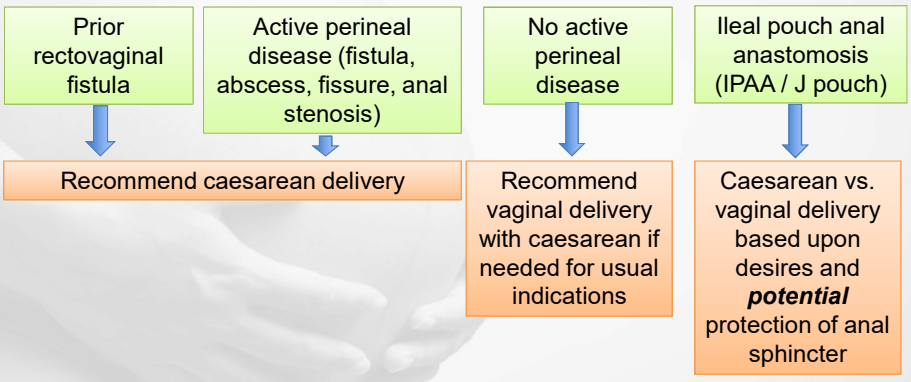
Approaching Delivery – Week 35

- Group B Strep culture at week 35
- Serial perineal inspection for perineal disease



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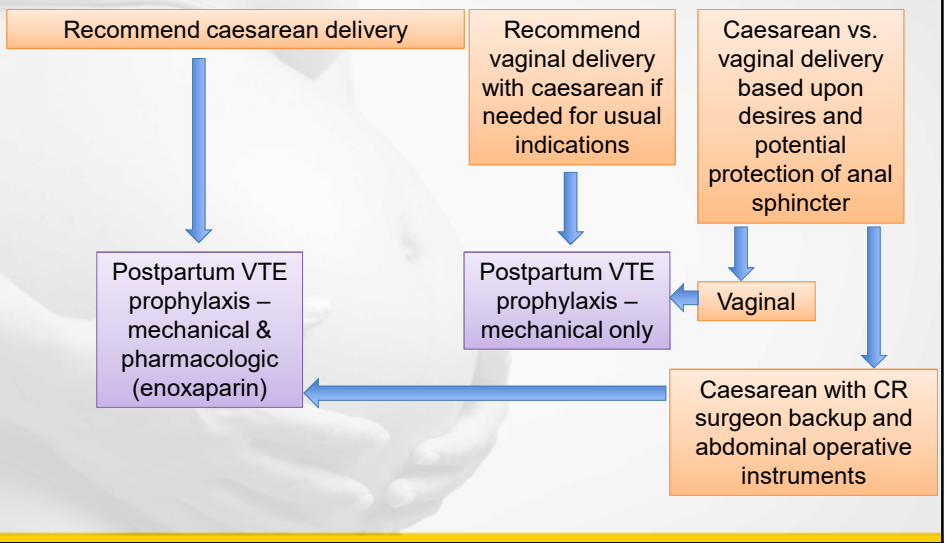
Delivery and Postpartum VTE Prophylaxis



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Mode of Delivery

Caesarean

- Can resume biologics 48 hours post-delivery if no infection
- Measures to prevent ileus and wound infection
- Mechanical & Anticoagulant prophylaxis for VTE

Vaginal

- Can resume biologics post-delivery if no infection

- Continue other IBD-specific medications
- Can use short (~3d) course of NSAID or narcotics if needed for post-partum or post-caesarean pain
- Ostomy care – wound ostomy continence nurse (WOCN) consult to evaluate change in shape of abdomen – may need a wafer adjustment to prevent leakage

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Post-partum General Considerations

- Maintain adequate hydration, especially while breastfeeding
- Well balanced diet and weight maintenance
- Effective contraception (LARC) early!
- Preconception planning before next pregnancy
  - Time to heal, get into good rhythm with current baby first

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Post-partum Lactation and Breastfeeding

- Do not breastfeed on tofacitinib or methotrexate
- Mesalamine is preferred over sulfasalazine
- Thiopurines can be continued
- Biologics can be continued
- Avoid fenugreek for ‘milk stimulation’
- ‘Pumping and dumping’ discouraged

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Post-partum Infant Vaccines

- All vaccines should be given on schedule
- Exception: avoid live vaccines in first 6 months after *in utero* exposure to biologics (except certolizumab)
- Live vaccines scheduled at 1 year (MMR, varicella) can be given even in breastfeeding infants of mothers on biologics

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Post-partum Infant Developmental Milestones

- Normal developmental milestones are to be expected with thiopurine and biologic exposure *in utero*.
- Standard Ages and Stages (ASQ-3) monitoring of infant development / milestones
- Methods to monitor childhood developmental milestones can be found on AAP/CDC websites
- Effects of inflammation *in utero* on the developing brain are currently being studied.

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Post-partum IBD Management: Ostomy

- Stomal problems often occur with changes in abdominal contour: displacement, enlargement, retraction, stenosis, prolapse
- Post-partum care may require coordination with a wound ostomy continence nurse (WOCN) and a colorectal surgeon
- No special changes needed for caesarean or vaginal delivery

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Take Home Points

- Start the conversation early
  - Plan and prepare for pregnancy
  - Achieve and document remission
- Pregnancy
  - Continue medications through pregnancy
  - Monitor closely during pregnancy
  - Call in consultants when needed
  - Most deliveries can be vaginal
- Post-partum: DVT prophylaxis, contraception, vaccination, no live vaccines if mom was on biologics, and be prepared to fine-tune ostomies after delivery

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Take Home Points

- Post-partum
  - DVT prophylaxis
  - Contraception for mom
  - Vaccination for infant
    - No ***live*** vaccines if mom was on biologics
  - Fine-tune ostomies after delivery

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Gastroparesis

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Gastroparesis: Definition, Etiologies, and Epidemiology

- Definition: Syndrome with symptoms of gastric retention with evidence of delayed gastric emptying

Etiologies
Idiopathic (65%) Diabetes (31%) Post-surgical (mainly postfundoplication)(3%) Miscellaneous (1%)

Factor	Epidemiology
Prevalence	9.6/100,000 men, 37.8 women Community: 5% type 1 vs. 1% type 2 diabetes
Incidence	2.4/100,000 years men, 9.8 women 5.2% over 11 yr type 1 vs. 1.0% type 2 diabetes (33 and 7.5 x control) Gastroparesis 1st DM complication in 39%

Hasler et al., Neurogastroenterol Motil 2013
Jung et al., Gastroenterology 2009
Choung et al., Am J Gastroenterol 2012
Kofod-Andersen, Tarnow, J Diabetes Comp 2012
Parkman et al., Am J Gastroenterol 2019

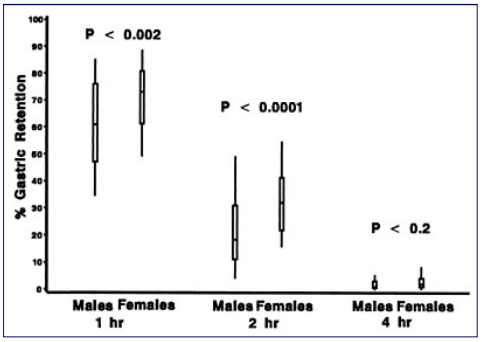
Symptoms in Gastroparesis

- Nausea and vomiting:
  - Nausea in 96% (severe in 40%); meal related in 71%
  - Vomiting 81% in diabetics, 59% in idiopathics
- Early satiety/postprandial fullness:
  - 60% report severe early satiety/fullness
  - May contribute to decreased BMI
- Abdominal pain:
  - Two thirds report severe pain (more common in idiopathics)
  - Leads to opiate use in 40%
- Bloating:
  - 75% report bloating (more severe in women)
  - ?Relation to bacterial overgrowth

Parkman et al., Neurogastroenterol Motil 2017
Parkman et al., Neurogastroenterol Motil 2017
Hasler et al., Neurogastroenterol Motil 2013
Hasler et al., Am J Gastroenterol 2011
Reddymasu, McCallum, J Clin Gastroenterol 2010

Standardized Scintigraphy Method

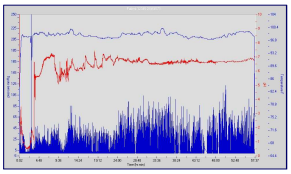
- 123 volunteers given ^{99}Tc EggBeaters, toast, jam, water (2% fat, 255 kcal). Assess emptying at 1, 2, and 4 hours
- Delayed: Retention >60% at 2 hr, >10% at 4 hours for diagnosis of gastroparesis
- Recommended by US motility and nuclear medicine societies in 2008
- Inconsistently adopted

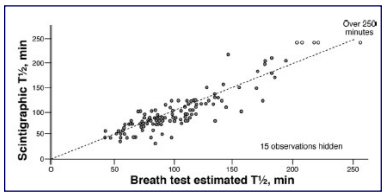


Tougas et al., Am J Gastroenterol 2000
Abell et al., Am J Gastroenterol 2008
Abell et al., J Nucl Med Tech 2008

Other Methods to Measure Gastric Emptying

- Wireless Motility Capsule:
  - Measures pH (transit) and contractions
  - 3 prospective studies validating to measure gastric emptying
  - Measures small bowel and colon transit (detects extragastric and generalized delays in ~40%)
- ^{13}C-gastric emptying breath test:
  - FDA approved in 2015 but delayed to market
  - Non-radioactive ^{13}C-labelled food emptied into the intestine; digested to liberate $^{13}CO_2$ over time
  - Closely correlates with scintigraphy





Kuo et al., Aliment Pharmacol Ther 2008
Hasler et al., Neurogastroenterol Motil 2017
Lee et al., Clin Gastroenterol Hepatol 2019
Szarka et al., Clin Gastroenterol Hepatol 2008

Case 1: Diet/Medication Management

- CS is 47 year old woman with refractory gastroparesis.
- 4 years of meal-induced nausea and vomiting with postprandial fullness and early satiety. Associated constipation with 2 BM/wk. Minimal pain, no weight loss.
- PMH: 28 years of type 1 diabetes, peripheral neuropathy, A1c 9.2% (as high as 14%), wide glycemic excursions, depression, HTN
- Current meds: Lantus, Humalog, venlafaxine, ondansetron, lisinopril
- Prior med trials: Some relief with metoclopramide but associated with suicidal thoughts, no effect with erythromycin
- Other therapy: No recent diabetic teaching or dietician
- Evaluation: Normal labs, EGD normal except for small amount retained food
- Gastric emptying: 22% 4 hour retention of solid meal

Diet in Gastroparesis

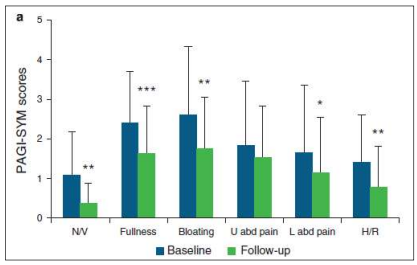
- Standard diet recommendations based on physiology:
  - Frequent small meals (soft to liquid consistency)
  - Low fat, low fiber, low residue
- Patient tolerance:
  - Improved symptoms—crackers, gelatin
  - Tolerated—bland, salty, sweet, and starchy
  - Worsened symptoms—fatty, acidic, spicy, high roughage foods
- Actual patient compliance:
  - 1.4±1.0 meals/d; 37% small portions
  - 10% on low fat diet; 67% on low fiber diet
  - 2% follow "gastroparesis diet"

Wytiaz et al., Dig Dis Sci 2015
Parkman et al., Gastroenterology 2011

RCT of Small Particle Diet in Gastroparesis

- Methods: 56 diabetics with gastroparesis given "small particle size" diet vs. standard diet for 20 weeks
  - Small particle —"easy to mash with fork"; did not include foods with husks/peels, membranes, stringy foods, seeds/grains
  - Control—allowed almonds, nuts, brown rice, grated vegetables, raw vegetable salad, fresh fruit, bread with whole grain/sourdough

SMALL PARTICLE DIET



Olausson et al., Am J Gastroenterol 2014

Safety/Efficacy of Insulin Pump Plus Continuous Glucose Monitoring in Diabetic Gastroparesis

- Methods: 24 week open label study of CGM plus insulin pump in diabetic gastroparesis
- Safety: 10 hypoglycemic events in 9 of 45 patients
- Efficacy:
  - CGM plus insulin pump reduced A1c from baseline 9.3% by 1.1% at 12 and 24 weeks (P<0.01)
  - CGM plus insulin pump decreased time in hypo-, hyperglycemia on CGM

Measure		Baseline vs. 12 Weeks	Baseline vs. 24 Weeks
Symptoms	Total symptom score	-26% (P<0.0001)	-23% (P<0.0001)
	Nausea/vomiting subscore	-36% (P<0.0001)	-35% (P<0.0001)
	Fullness/early satiety subscore	-22% (P<0.0001)	-17% (P=0.002)
	Bloating/distention subscore	-18% (P=0.0009)	-21% (P=0.0007)

Calles-Escandon et al., PLOS ONE 2018

Medications to Treat Gastroparesis

- Prokinetics - medications that accelerate stomach emptying
- Antiemetics - drugs that reduce vomiting (and to lesser extent nausea)
- Sensory neuromodulators - therapies that reduce sensation in the stomach

Prokinetic Agents to Stimulate Gastric Emptying

Drug(s)	Mechanism	Evidence
Metoclopramide	5-HT_4 agonist D_2 antagonist 5-HT_3 antagonist	13 trials (9 RCT)—benefits > placebo in most studies
Erythromycin, azithromycin	Motilin agonist	10 trials (3 RCT)—small samples, can cause N/V, tachyphylaxis, probably better for acute flares
Domperidone	Peripheral D_2 antagonist	Benefits in 2/3 of 27 reports—low quality, not US approved FDA IND advocated

Sugumar et al., Clin Gastroenterol Hepatol 2008

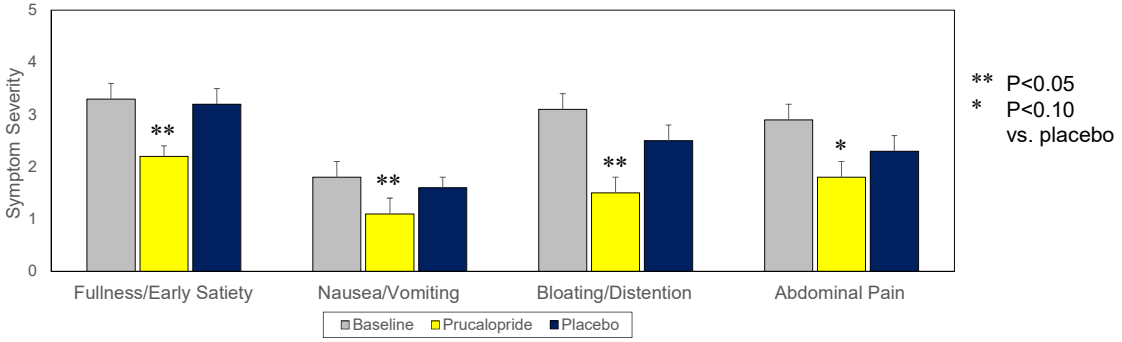
Prokinetic Safety in Gastroparesis

- Metoclopramide:
  - FDA warning (2009) for tardive dyskinesia reduced prescription from 70% to 24%
  - Tardive dyskinesia 1 per ~2000 treatment years (2nd most common after haloperidol); risk groups—age >70 yr, daily dose >30 mg, treatment >20 months
- Domperidone:
  - Netherlands (1304 pts): Sudden death risk increased OR 3.72 (95% CI 1.72-8.08); dose >30 mg/d (OR 11.4, 95% CI 1.99-65.2)
  - Canada (1559 pts): Sudden death increased age >60 yr OR 1.64 (95% CI 1.31-2.05)
  - EKG monitoring every 2 mo x 1 yr then every 6 mo; stop for QTc >470 msec in women and >450 msec in men
  - Cardiac arrhythmias also with erythromycin, TCAs, 5-HT_3 antagonists, other antiemetics

Lee and Kuo, Exp Rev Endo Metab 2010
Ehrenpreis et al., Am J Gastroenterol 2013
Van Noord et al., Neth Drug S 2010
Johannes et al., Pharmacoepidemiol Drug Saf 2010
Hill et al., Pharmacoepidemiol Drug Saf 2015

RCT of Prucalopride (5-HT_4 Agonist) for Gastroparesis

- Methods: 28 idiopathic gastroparesis patients in crossover trial of placebo and prucalopride 2 mg x 4 wk each arm; used ^{13}C-breath test
- Results:
  - Accelerated gastric emptying half time (86±13 min) on prucalopride vs. placebo (128±20 min)(P<0.05) and baseline (141±17 min)(P<0.005)



Carbone et al., Am J Gastroenterol 2019

Antiemetics for Gastroparesis

Drug class	Examples	Published data
H_1 antagonists	Dimenhydrinate, meclizine, promethazine	None
M_1 antagonists	Transdermal scopolamine	None
D_2 antagonists	Thiethylperazine, prochlorperazine	1 case report (thiethylperazine)
5-HT_3 antagonists	Ondansetron, granisetron	1 case report of intraperitoneal ondansetron in diabetics 2 case series of 36 and 54 pts with transdermal granisetron (50% and 76% responders)
NK_1 antagonists	Aprepitant	2 case reports
CB_1 agonists	Dronabinol	None
Benzodiazepines	Lorazepam	None

Simmons and Parkman, Dig Dis Sci 2014
Midani et al., J Neurogastroenterol Motil 2016

RCT of Aprepitant (NK_1 Antagonist) for Gastroparesis Symptoms

- Methods: 126 pts (57% delayed gastric emptying) with gastroparesis symptoms treated with aprepitant 125 mg/d vs. placebo x 4 wk
- Results—Primary Outcome:
  - >25 mm reduction in VAS nausea score or nausea score <25 mm
  - No difference between aprepitant (46%) vs. placebo (40%)—RR 1.2 (95% CI 0.8-1.7, P=0.43)
- Results—Secondary Outcomes:
  - Aprepitant reduced daily hrs of nausea vs. placebo (-2.5 vs. -1.2, P=0.03)
  - Aprepitant reduced overall gastroparesis symptom score vs. placebo (-1.3 vs. -0.7, P=0.001)
  - Aprepitant reduced scores for nausea, vomiting, fullness, bloating, distention, upper pain and discomfort, GERD (P<0.05)

Pasricha et al., Gastroenterology 2018

Cannabinoid Use in Gastroparesis

- Of 197 gastroparesis patients, 92 (47%) were cannabinoid users:
  - 36% current vs. 11% past users
  - Most often smoked (50%)
  - Use included tetrahydrocannabinol (THC)(68%), cannabidiol (CBD)(17%), dronabinol (39%)
- Cannabinoid users were younger (41±15 vs. 48±16 yrs) with higher symptom scores (3.4±1.0 vs. 2.8±1.3)
- Benefits reported by 94% on THC, 81% on CBD, and 47% on dronabinol

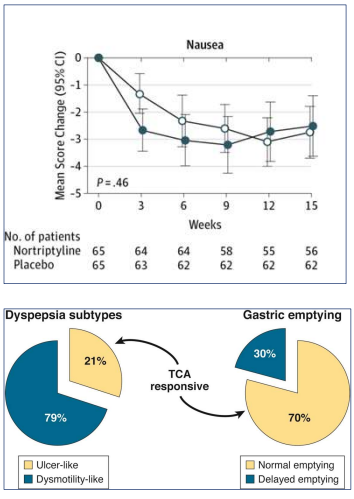
Jehangir and Parkman, Am J Gastroenterol 2019

Neuromodulators With Theoretical Benefit in Gastroparesis

Drug(s)	Mechanisms of Action	Reported Clinical Utility
Tricyclics (amitriptyline, nortriptyline)	Norepinephrine reuptake inhibition with variable serotonin (and dopamine) reuptake inhibition	Functional dyspepsia Cyclic vomiting syndrome Functional vomiting
Mirtazapine	5-HT_{1A} agonism, 5-HT_2 antagonism, 5-HT_{2C} inverse agonism, 5-HT_3 antagonism, α_2 antagonism, H_1 inverse agonism	Functional dyspepsia Postoperative nausea and vomiting Chemotherapy-induced nausea and vomiting
Olanzapine	5-HT_2 inverse agonism, 5-HT_3 antagonism, M_1 antagonism, M_3 antagonism, D_2 antagonism, H_1 inverse agonism	Chemotherapy-induced nausea and vomiting
Buspirone	5-HT_{1A} partial agonist	Functional dyspepsia Increases gastric volume after meals Improved early satiety and meal induced pain

RCT of Tricyclic Agent in Gastroparesis

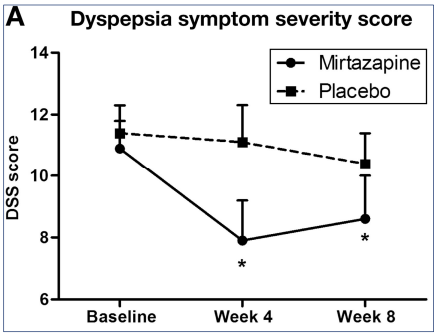
- Methods:
  - Nortriptyline to 75 mg qhs vs. placebo x 15 wk in 130 idiopathic gastroparetics
  - Primary outcome $\geq$50% decrease from baseline on 2 visits
- Results:
  - 23% response on nortriptyline vs. 21% on placebo (RR 1.06, 95% CI 0.56,2.00, P=0.86)
- In functional dyspepsia:
  - Amitriptyline superior to escitalopram and placebo (P=0.05)
  - Benefits only with normal gastric emptying



Parkman et al., JAMA 2013
Talley et al., Gastroenterology 2015
Hasler, Koch, Gastroenterology 2015

RCT of Mirtazapine in Functional Dyspepsia

- 34 functional dyspeptics with >10% weight loss treated with mirtazapine 15 mg/d vs. placebo x 8 weeks
- Mirtazapine reduced dyspepsia scores at 4 wk (P=0.003) and 8 wk (P=0.02)
- Mirtazapine produced ~4 kg wt gain over 8 wk; placebo produced no change
- Case reports show benefits in gastroparesis



Tack et al., Clin Gastroenterol Hepatol 2016

Case 1: Clinical Course

- Referred to dietician:
  - Initiated low fat, low fiber, low residue diet
- Referred back to endocrinology:
  - Reinforced frequent fingerstick monitoring and continued combined long and short acting insulin
  - Considering insulin pump and CGH
  - Repeat A1c 8.1%
- Medications for gastroparesis:
  - Reduced venlafaxine dose (goal to discontinue)
  - Started low dose mirtazapine
  - Started prucalopride for constipation with additional benefit to stimulate gastric emptying
  - On demand antiemetics for breakthrough nausea
- Current clinical status:
  - Improved GI symptoms

Case 2: Endoscopic/Surgical Management

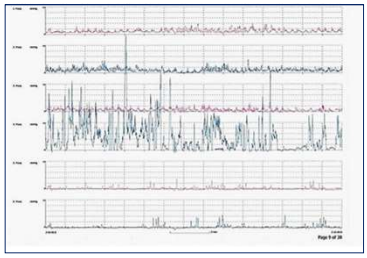
- SC is a 62 year old woman with refractory gastroparesis.
- Longstanding nausea, vomiting, fullness, bloating, and epigastric pain. Multiple hospitalizations for dehydration and IV therapy. Considered for GJ tube placement—patient refused. Relies on cannabis ~1/2 gram 3 days/wk and CBD oil.
- PMH: Type 2 DM (A1c 6.4%), restless legs
- Current meds: Liraglutide, pramipexole, ondansetron
- Evaluation: EGD negative, gastric emptying rate 47% 4 hour solid food retention
- Failed gastroparesis therapies: Metoclopramide, domperidone, prochlorperazine, dronabinol, aprepitant, mirtazapine, buspirone

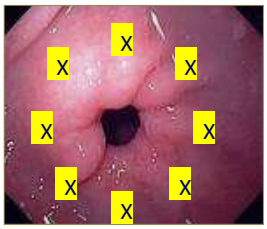
Non-Medication Treatment of Gastroparesis

- Pyloric therapies:
  - Botulinum toxin
  - Gastric Per-Oral Endoscopic Myotomy (G-POEM)
  - Pyloroplasty—accelerated gastric emptying in ~80% in uncontrolled studies
- Other surgeries:
  - Gastric electrical stimulation
  - Gastric resection—~60-70% improved with gastric bypass or subtotal gastrectomy
  - Pancreas transplant (diabetic gastroparesis)—no benefits
- Supplemental nutrition:
  - Improved health with J-tube feeds in 83%

Hibbard et al., J Gastro Surg 2011
Mancini et al., Am Surg 2015
Zehetner et al., Surg Endo 2013
Papsavas et al., Surg Obes Rel Dis 2014
Bhayani et al., J GI Surg 2015
Fontana, Barnett, Am J Gastroenterol 1996

Pyloric Botulinum Toxin for Pylorospasm in Gastroparesis



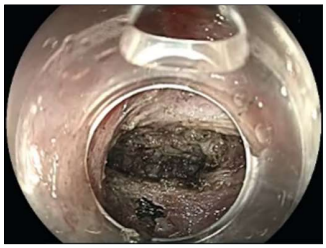


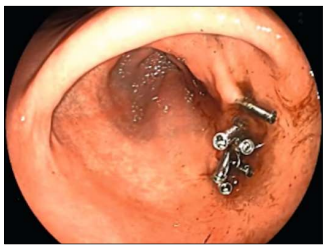
- >20 articles report reduced symptoms or improved stomach emptying
- Largest study (179 patients) showed higher doses (200 units) work better than lower doses (100 units)
- 2 low powered trials compared botulinum toxin to placebo—no symptom benefits or consistent acceleration of gastric emptying

Coleski et al., Dig Dis Sci 2009
Friedenberg et al., Am J Gastroenterol 2008
Arts et al., Aliment Pharmacol Ther 2007

G-POEM for Gastroparesis

- Gastric POEM (per oral endoscopic myotomy):
  - Injection of 10mL of saline/methylene blue to create a submucosal bleb
  - Scope passed thru the submucosal tunnel to the pylorus-dissected away
  - Myotomy performed with endocut through pylorus and 2-3 cm proximally
  - Close tunnel with endoclips





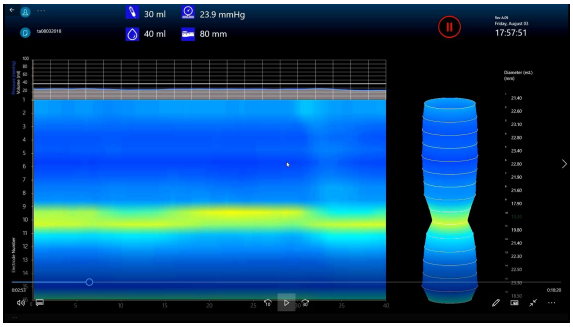
Benefits of G-POEM in Gastroparesis

- Largest single center study of 177 patients:
  - Intra-procedure time 30±20 minutes; 1.2 day mean length of stay
  - Mean improvement in symptom score 1.29 points (out of 5)
  - Gastric emptying improved from 46% to 18% 4 hour retention
- Systematic review of 14 studies of 276 patients:
  - 61% normalized gastric emptying
  - Symptom improvements in 90% at 1 month and 57% at 18 months
  - Complications in 3.2%
- Comparison of response to G-POEM vs. surgical pyloroplasty in 18 studies of 707 patients:
  - Symptoms improved in 76% with G-POEM vs. 77% with surgery
  - Gastric emptying improved in 85% with G-POEM vs. 84% with surgery
  - Predictors of response: idiopathic gastroparesis, prior botulinum toxin injection

Strong et al., J Gastrointest Surg 2019
Zhang et al., Gastroenterol Hepatol 2019
Mohan et al. Surg Endosc 2019

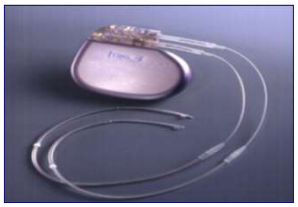
EndoFLIP to Measure Pyloric Compliance/Distensibility

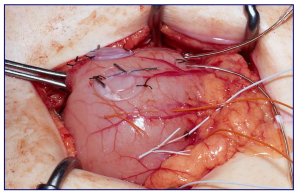
- Using EndoFLIP to measure pyloric stiffness, 19/35 (54%) gastroparesis patients had decreased distensibility:
  - In patients with low distensibility, symptoms reduced after botulinum toxin (13.5 to 10.5, P<0.01)
  - In patients with normal distensibility, no symptom benefits



Desprez et al., Gastrointest Endosc 2019

Gastric Electric Stimulator for Gastroparesis

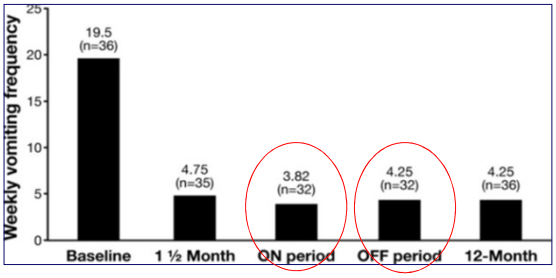




- Misconceptions:
  - Not a true pacemaker
  - Does not improve gastric emptying
- Helps 50-90% of patients in 25 articles (1 to 221 patients):
  - Reduced symptoms and improved nutrition
  - Less health care usage
  - More effective for diabetic vs. idiopathic patients
  - Less useful for pain or with opioid dependence
- FDA approved as a humanitarian device:
  - Restricted access

Concerns Raised About Gastric Stimulator

- In 3 trials, no differences in symptoms when device turned ON or OFF



- Many centers discontinued performance or never started because of lesser responses/skepticism about data
- All controlled trials used lowest current settings; mean ON time 8 x these settings in UM patients

Abell et al., Gastroenterology 2003
McCallum et al., Clin Gastroenterol Hepatol 2010
McCallum et al., Neurogastroenterol Motil 2013

Update on Gastric Stimulation for Gastroparesis

- Observational study:
  - Studied 319 gastroparesis pts (238 without stimulation, 81 with gastric stimulation) over 48 wk
  - After propensity score adjustment, only nausea improved to greater degrees with stimulation vs. no stimulation
- Sham-controlled study:
  - Double-blind sham vs. active stimulation with crossover x 4 mo in 172 pts from 17 French centers (133 delayed emptying, 39 normal emptying, 72 diabetics)
  - During ON period, 31% reported 1 point improvement in vomiting score vs. 16% during OFF period ($P<0.05$); no impact on QOL or gastric emptying

Abell et al., Neurogastroenterol Motil 2019
Ducrotte et al., Gastroenterology 2019

Case 2: Clinical Course

- Referred for gastric stimulator surgery:
  - Initial settings produced little benefit
  - Increased settings with partial symptom control
- Received pyloric botulinum toxin 200 units x 3 with additional symptom benefits
- EndoFLIP performed showing narrow pylorus (8.7 mm; normal >12 mm) and reduced distensibility (4.2 mm^2/mmHg; normal >10 mm^2/mmHg)
- Underwent G-POEM earlier this year with similar symptom responses as botulinum toxin:
  - Improved gastric emptying from 47% to 21% 4 hour solid food retention

The Problem of Patient Access to Gastroparesis Therapy

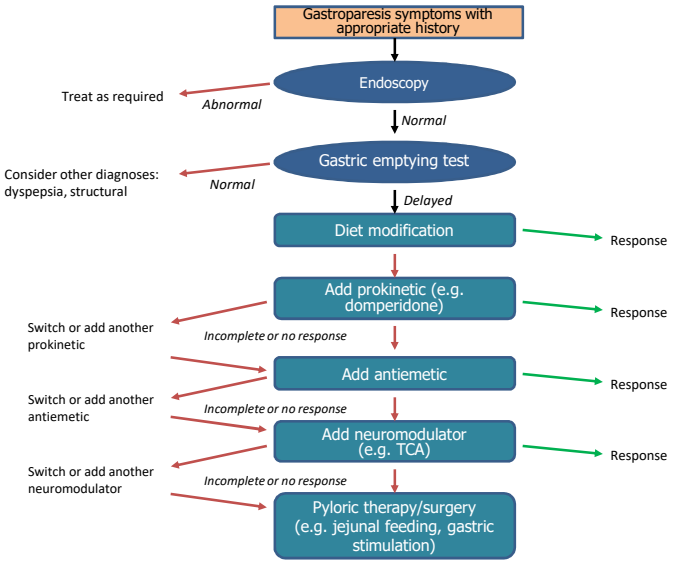
NOT SO BAD

Therapy	Monthly Cost
Metoclopramide	$6
Erythromycin	$7
Prochlorperazine	$30
Promethazine	$15
Ondansetron	$35

CHALLENGING

Therapy	Cost	Coverage by Payers
Prucalopride	$150-450 monthly	Approved for chronic constipation in US; can obtain from Canadian pharmacies
Dronabinol	$200-1000 monthly	Only covers chemotherapy induced vomiting
Aprepitant	$5,700 monthly	Only covers chemotherapy induced vomiting
Transdermal granisetron	$2,500 monthly	Only covers chemotherapy induced vomiting
Pyloric botulinum toxin	$5,000/3-6 months	Not covered by Medicaid/Medicare, some 3rd parties cover
Gastric stimulator	$50-75,000	Covered by Medicaid/Medicare, many 3rd parties do not cover

Is There a Right Way to Treat Gastroparesis?



Adapted from Vanormelingen et al., Br Med J 2013

Need for Tertiary Referral for Gastroparesis Care?

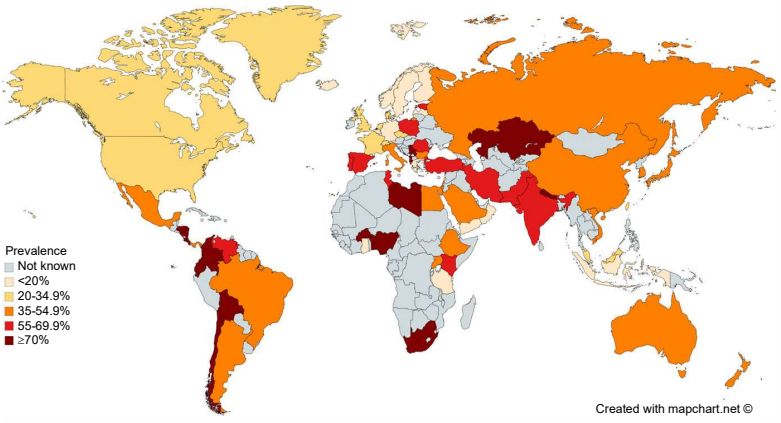
- Desire for advanced diagnostics:
  - Wireless motility capsule to measure transit in small bowel and colon
  - Use of EndoFLIP to assess pyloric dysfunction (when considering pyloric therapies)
- Consideration of alternate diet/medication therapies:
  - Dietician referral
  - Concern about metoclopramide toxicity
  - Access to domperidone
  - Use of neuromodulators, high-end antiemetics (aprepitant) and prokinetics (prucalopride)
- Availability of non-medication therapies:
  - Pyloric therapies (botulinum toxin, G-POEM)
  - Gastric stimulation
  - Enteral/parenteral nutrition

Primary and Salvage Therapies for H. pylori

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

William D. Chey, MD, AGAF
Professor of Medicine
University of Michigan

Worldwide prevalence of *H. pylori*

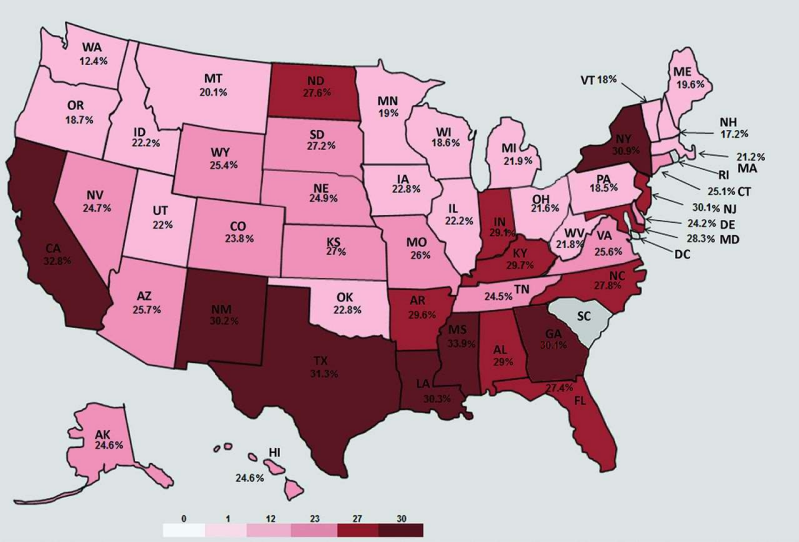


Zamani et al Aliment Pharmacol Ther 2018;47:868

H. pylori: Regional Prevalence

Race/Ethnicity	Prevalence
United States	35%
Caucasian	26%
African American	54%
Hispanic	60%
Alaska Native/ Native American	75%
Elderly >60 years	50%
Asian*	70%

*NYC-based Asian population (Perez-Perez, Guillermo Ignacio, et al. *Journal of Urban Health* 2005;82(3):510-516).



Everhart JE, et al. Journal of Infectious Disease. 2000:181(4):1359-1363.
Hooi JKY et al. Gastroenterology, 2017;53:420-429;
Kamboj AK, et al. In Mayo Clinic Proceedings, 2017;92(4):599-604.
Jalaly JB, et al. The Journal of Applied Laboratory Medicine, 2018;2(6), 904-913.

Indications for *H. pylori* Testing & Treating: Absolute

- **PUD or a history of PUD**
- **MALToma**
- **Early gastric cancer**

Chey et al. Am J Gastroenterol 2017;112:212

Indications for *H. pylori* Testing & Treating

- **Uninvestigated dyspepsia**
- **Functional dyspepsia**
- **Aspirin or NSAIDs**
- **Unexplained iron deficiency**
- **Idiopathic thrombocytopenic purpura**

Chey et al. Am J Gastroenterol 2017;112:212

WHO: Urgent Need for New Antibiotic Treatments

World Health Organization

GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

- February 2017 - WHO published a global priority pathogens list of antibiotic-resistant bacteria to help in prioritizing the R&D of new and effective antibiotic treatments
- The purpose was to identify the most important resistant bacteria at a global level for which there is an urgent need for new treatments
- Pathogens prioritized in 3 categories - Critical, High and Medium
- ***H. pylori*** **(clarithromycin-resistant) was categorized as a pathogen for which there is a High Priority need to develop new treatments**

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Diagnostic Tests

Nonendoscopic

- Antibody detection
- Urease tests
- Fecal antigen detection

Endoscopic

- Rapid urease test
- Histology
- Culture/Molecular

Current US Treatment Paradigm for *H. pylori*

First Line
Triple Therapy

↓

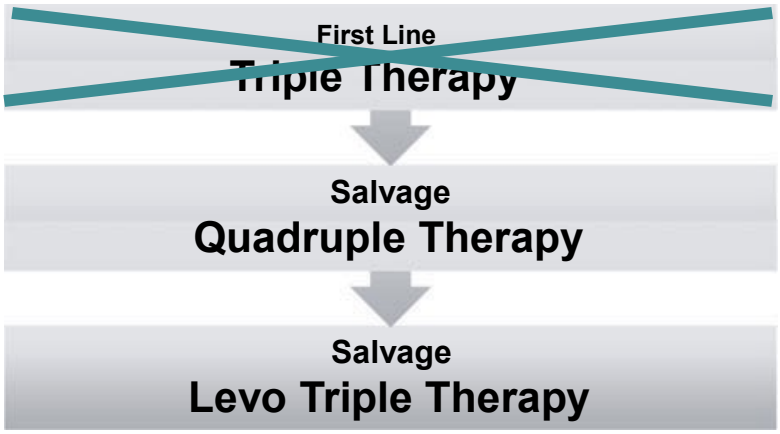
Salvage
Quadruple Therapy

↓

Salvage
Levo Triple Therapy

Vakil & Vaira, J Clin Gastroenterol 2013;47:383–388

Current US Treatment Paradigm for *H. pylori*



Vakil & Vaira, J Clin Gastroenterol 2013;47:383–388

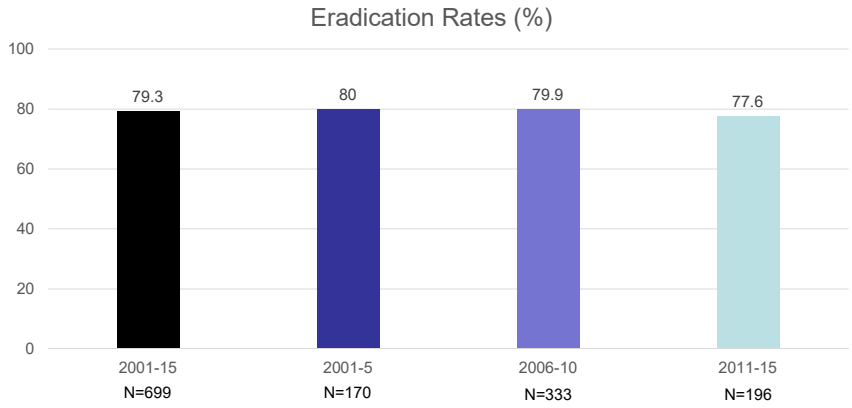
First-line *H. pylori* Therapies

First-line Therapies for *H. pylori*

Recommended First-Line Therapies for H pylori Infection				
Regimen	Drugs (doses)	Dosing Frequency	Duration (Days)	FDA approval
Clarithromycin Triple	PPI (standard or double dose) Clarithromycin (500 mg) Amoxicillin (1 grm) or Metronidazole (500 mg TID)	BID	14	Yes*
Bismuth Quadruple	PPI (standard dose) Bismuth subcitrate (120-300 mg) or subsalicylate (300 mg) Tetracycline (500 mg) Metronidazole (250-500 mg)	BID TID or QID	10-14	No**
Concomitant	PPI (standard dose) Clarithromycin (500 mg) Amoxicillin (1 grm) Nitroimidazole (500 mg)^	BID	10-14	No

Chey et al. Am J Gastroenterol, 2017;112:212

15 year US, single center experience with Triple Therapy for H. pylori



All pts referred for post-treatment UBT at UMHS

Baker JR, Chey SW, Saad R, Chey WD. ACG 2016

First-line Therapies for *H. pylori*

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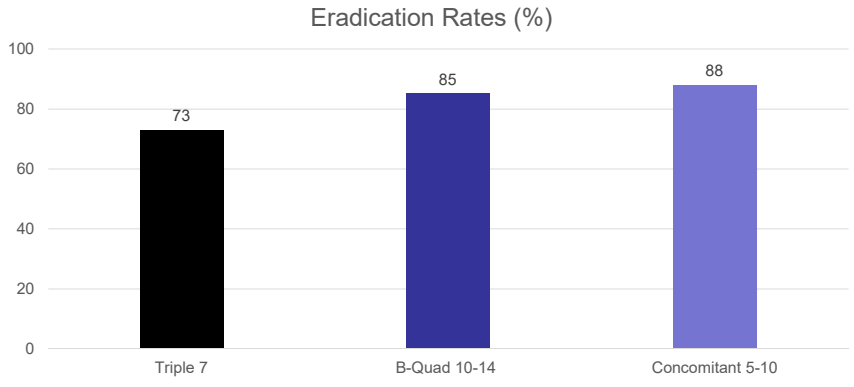
Chey et al. Am J Gastroenterol, 2017;112:212

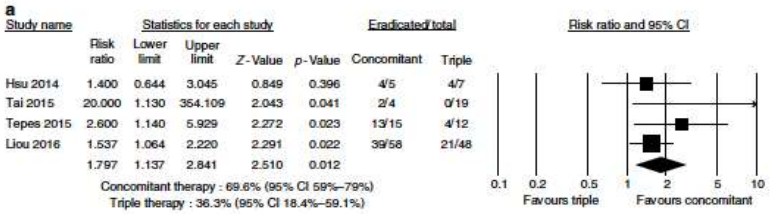
Meta-analysis of First-line *H. pylori* Therapies



Li et al. BMJ 2015;351:h4052
Gisbert Clin Exp Gastroenterol 2012;5:23-34

Concomitant vs. Triple Therapy: A meta-analysis

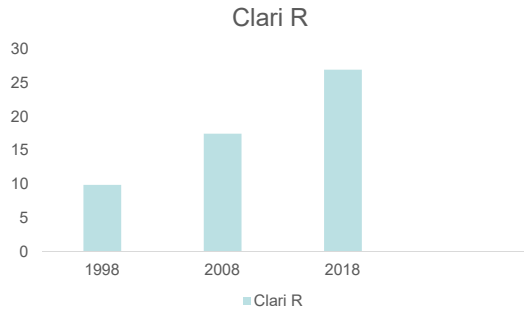
- 23 RCTs including 3305 patients in the concomitant & 3327 in triple groups.
  - Overall, Concomitant therapy superior to triple therapy [RR: 1.15; 95% CI: 1.09–1.21; p < 0.001]
  - Significant heterogeneity (I^2 = 74.0%, p < 0.001)
  - More AEs with Concomitant [RR: 1.2]
  - Subgroup analyses: Concomitant for 5 or 10 days superior to 7- or 10-day triple therapy but NOT 14-day triple therapy



Chen et al. Am J Gastroenterol 2018;113:1444

Increasing Clarithromycin Resistance in Europe

- 1,393 *H. pylori (+)* patients from 25 centers in 19 European countries



- **<u>Take Home Point:</u> In Europe, there has been a progressive 1% rise per year in primary *H. pylori* clarithromycin resistance**

Megraud F, et al UEG 19

H. pylori resistance over time:

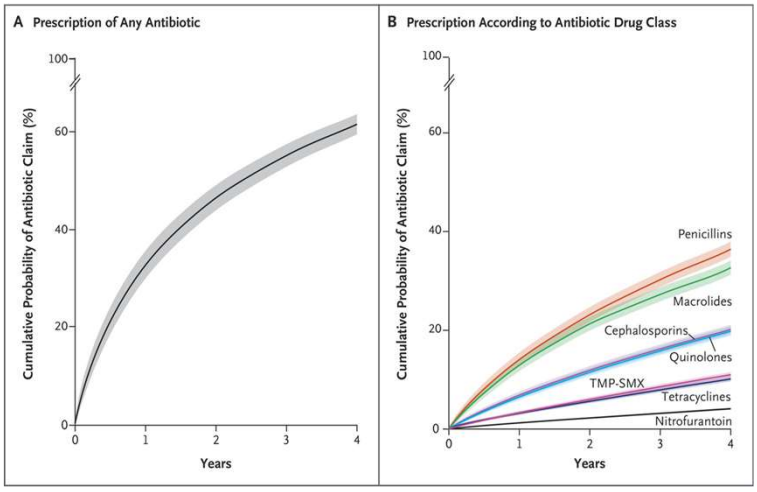
Results of a meta-analysis

WHO region, time period	Pooled prevalence of antibiotic resistance, % (95% CI)			
Americas region	Clarithromycin	Metronidazole	Levofloxacin	Cla+Met
2006–2008	11 (3–19)	26 (10–42)	—	—
2009–2011	9 (2–15)[a]	21 (13–33)	11 (5–16)	—
2012–2016	20 (12–28)	29 (0–59)	19 (11–27)	—
Eastern Mediterranean region	Clarithromycin	Metronidazole	Levofloxacin	Cla+Met[b]
2006–2008	29 (18–39)	57 (47–68)	12 (4–20)	2 (0–5)
2009–2011	25 (12–38)	67 (56–68)	32 (12–51)	20 (4–37)
2012–2016	32 (24–41)	60 (49–71)	24 (6–41)	14 (8–21)[a]
European region	Clarithromycin[b]	Metronidazole	Levofloxacin	Cla+Met
2006–2008	28 (24–32)	38 (33–43)	15 (12–18)	15 (10–20)
2009–2011	23 (20–27)	33 (25–40)	13 (9–17)	12 (8–15)
2012–2016	28 (25–31)	46 (34–58)	12 (8–15)	23 (11–36)

178 studies, 66K isolates, 65 countries

Savoldi et al. Gastroenterol 2018;156:1372

Cumulative Probability of Antibiotic Use



- Growing potential of having an antibiotic prescription over the 4 year period
  - >60% for any antibiotic
- Potential for prior exposure to antibiotics used for H. pylori therapy
  - Macrolides >30%

Data Capture 2010-2014

Olesen et al. N Engl J Med 2019;380:1872-1873

Effect of Previous Antibiotic Use on *H. pylori* Resistance

		No. of patients & % resistant				
Antibiotic course	**Antibiotic sensitivity tested**	**0 courses**	**1 course**	**2+courses**	**RR**	**95% CI**
Quinolone	Levofloxacin	114 (4%)	7 (14%)	11 (27%)	1.8	1.24-2.49
Metronidazole	Metronidazole	114 (28%)	13 (38%)	5 (100%)	1.6	1.46-1.75
Clarithromycin	Clarithromycin	103 (7%)	21 (19%)	8 (25%)	1.5	0.92-2.41
Erythromycin	Clarithromycin	104 (8%)	15 (20%)	13 (15%)	1.1	0.82-1.59

*This is the ratio of the risk of being resistant per unit increase in number of courses

McNulty CAM, et al. Aliment Pharmacol Ther 2012;35:1221

Other First-line Therapies

			Duration	FDA approved
Sequential	PPI (standard dose) + Amoxicillin (1 grm) PPI, Clarithromycin (500 mg) + Nitroimidazole (500 mg)^	BID BID	5-7 5-7	No
Hybrid	PPI (standard dose) + Amox (1 grm) PPI, Amox, Clarithromycin (500 mg), Nitroimidazole (500 mg)^	BID BID	7 7	No
Levofloxacin Triple	PPI (standard dose) Levofloxacin (500 mg) Amox (1 grm)	BID QD BID	10-14	No
Levofloxacin Sequential	PPI (standard or double dose) + Amox (1 grm) PPI, Amox, Levofloxacin (500 mg QD), Nitroimidazole (500 mg)^	BID BID	5-7 5-7	No
LOAD	Levofloxacin (250 mg) PPI (double dose) Nitazoxanide (500 mg) Doxycycline (100 mg)	QD QD BID QD	7-10	No

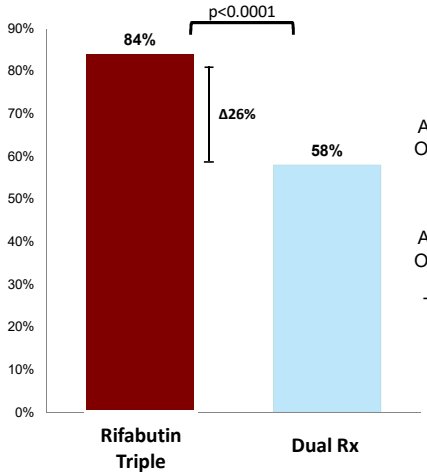
Chey et al. Am J Gastroenterol, 2017;112:212

Rifabutin Triple Therapy for *H. pylori* - Phase 3 Study Primary Endpoint Results

455 pts randomized to rifabutin triple or dual therapy

Analysis*	Phase 3 Results - Talicia vs. Active Comparator	p-value
ITT Population	84% vs. 58%	p<0.0001
mITT Population	84% vs. 58%	p<0.0001
PK population (evidence of drug exposure)	90% vs. 65%	P<0.0001

No safety issues were reported in the study; Both treatments found to be well-tolerated



Rif 50 mg
Amox 1 grm
Omep 40 mg

Vs.

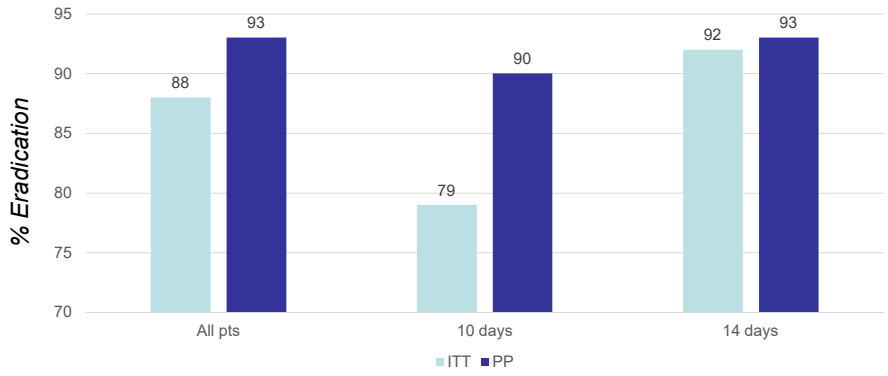
Amox 1 grm
Omep 40 mg

TID dosing

* ITT population included all randomized patients who received at least one dose of study drug; PK population included those subjects in the ITT population who had demonstrated presence of any component of investigational drug at Visit 3 (approx. day 13) or had undetected levels drawn >250 hours after the last dose.
Graham DY, et al. ACG 2019

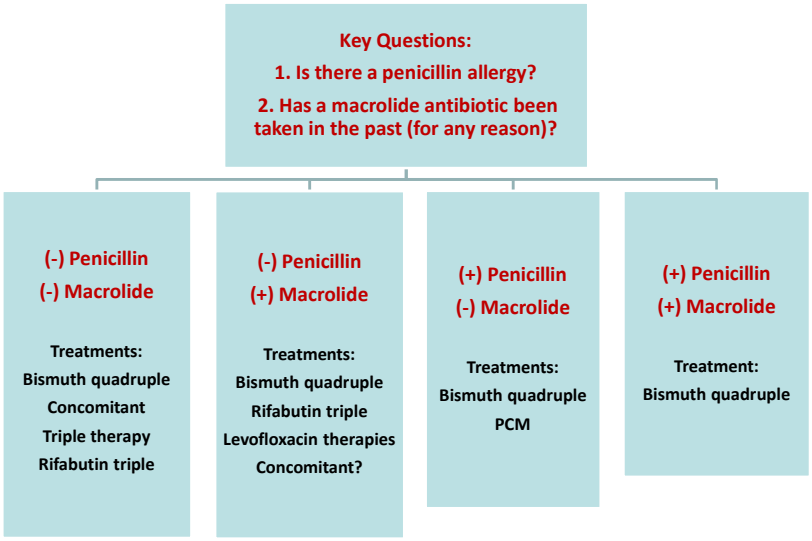
Bismuth AND Triple Therapy for *H. pylori*

- European Resistry on *Hp* Management
- 1141 treatment naïve pts with *Hp* infection
- Open label treatment with ***Bismuth 240 mg, PPI, Amox 1 gram, Clari 500 mg bid x 10-14 days***
- AEs 36%, Predictors of eradication: Compliance, High-dose PPI, 14 days therapy



McNicholl et al. Clin Gastroenterol Hepatol 2020;18:89-98

First Line *H. pylori* Therapy



Modified: Chey et al. Am J Gastroenterol, 2017;112:212

Post-Treatment *H. pylori* Testing

Post-Therapy *H. pylori* Testing

- *Whenever H. pylori infection is identified and treated, testing to prove eradication should be performed using a urea breath test, fecal antigen test or biopsy based testing at least 4 weeks after the completion of antibiotic therapy and after PPI therapy has been withheld for 1-2 weeks*

- There may be infrequent situations which make eradication testing impractical or unnecessary

Chey et al. Am J Gastroenterol, 2017;112:212

Post-Therapy *H. pylori* Testing

- **Urea breath test**
  - **Perform >4 wks after completion of therapy**
  - **May be accurate when done 2 weeks after therapy**
- **Fecal antigen test**
  - **Perform >4 wks after completion of therapy**
  - **Monoclonal test perferred**
- **Biopsy-based testing**
  - **histology ± RUT**
  - **requires multiple biopsies**

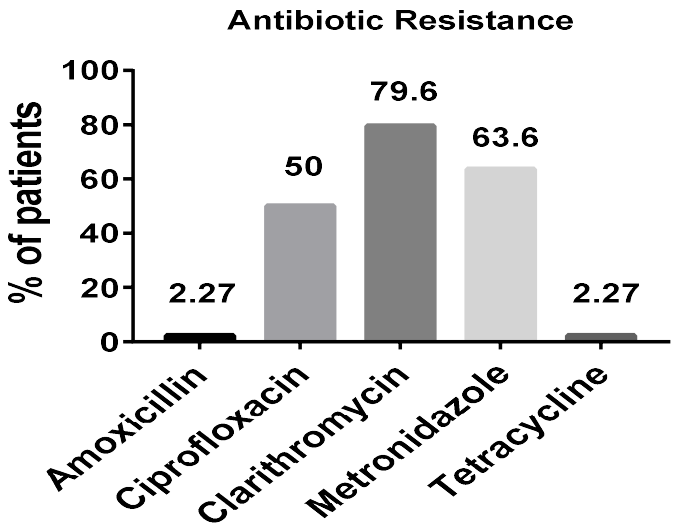
Chey et al. Am J Gastroenterol, 2017;112:212

Antibiotic Sensitivity Testing

- Traditional Culture & Sensitivity
  - Cumbersome
  - Technically challenging
  - Expensive
  - Not widely available
- Molecular Testing
  - fresh, frozen, paraffin embedded gastric bxs
  - PCR, fluorescently-labeled nucleic acid hybridization
  - Identify mutations associated with resistance to specific antibiotics
  - More scalable & less costly than culture & sensitivity

Chey et al. Am J Gastroenterol 2017;112:212
Nishizawa et al Front Mol Biosci 2014;1:19

Antibiotic resistance after >2 failed courses of *Hp* Rx



Amox = 3%
L^R = 21%
C^R = 82%
M^R = 52.1%

Yang CGH 2015

Fradkov et al. DDW 2019

Salvage Therapy for Persistent or Recurrent *H. pylori* Infection

Salvage Therapy for *H. pylori*

- Do not use the same antibiotics
- Stress the importance of compliance and review possible side effects
- Treat for 10-14 days
- Use high dose PPI BID
- Consider culture and sensitivity testing after 2 failed attempts at empiric treatment

Chey, et al. Am J Gastroenterol 2017;112:212
Song M, Ang TL World J Gastroenterol 2014;20(6): 1517

Salvage Regimens for Persistent H. pylori

Salvage Therapies for H pylori Infection				
Regimen	Drugs (doses)	Dosing Frequency	Duration (Days)	FDA approval
Bismuth Quadruple	PPI (standard dose) Bismuth subcitrate (120-300 mg) or subsalicylate (300 mg) Tetracycline (500 mg) Metronidazole (500 mg)	BID QID QID TID or QID	14	No**
Levofloxacin Triple	PPI (standard dose) Levofloxacin (500 mg) Amox (1 grm)	BID QD BID	14	No
Concomitant	PPI (standard dose) Clarithromycin (500 mg) Amoxicillin (1 grm) Nitroimidazole (500 mg)	BID BID BID BID or TID	10-14	No
Rifabutin triple	PPI (standard dose) Rifabutin (300 mg) Amox (1 grm)	BID QD BID	10	No
High-dose dual	PPI (standard to double dose) Amox (1 grm TID or 750 mg QID)	TID or QID TID or QID	14	No

Chey et al. Am J Gastroenterol, 2017;112:212

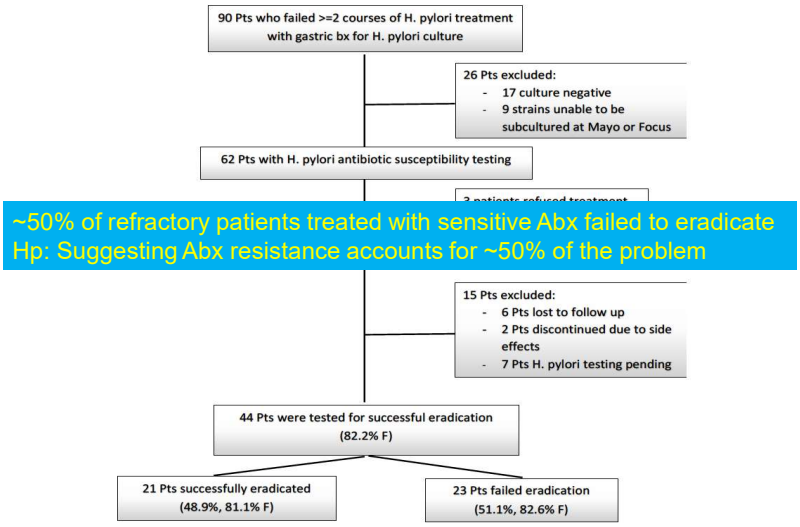
ACG Guideline Recommendations

- ***Bismuth quadruple* or *levofloxacin salvage regimens*** *are the preferred treatment options if a patient received a first-line treatment containing clarithromycin.*
- ***Clarithromycin-* or *levofloxacin salvage regimens*** *are the preferred treatment options if a patient received first-line bismuth quadruple therapy.*
- *Selection of the best salvage regimen should be directed by local antimicrobial resistance data and the patient's previous exposure to antibiotics*

Chey et al. Am J Gastroenterol, 2017;112:212

UM experience using *H. pylori* Cx/Sens Based *Hp* Rx

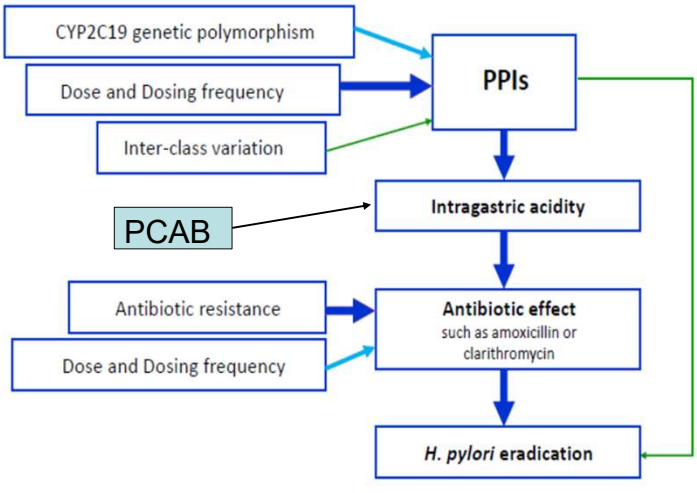
Diagram 1. Patient enrollment flowchart.



~50% of refractory patients treated with sensitive Abx failed to eradicate Hp: Suggesting Abx resistance accounts for ~50% of the problem

Fradkov et al. DDW 2019

Parameters influencing the efficacy of PPIs and antibiotics in the treatment of *H. pylori* infection



Yang JC, et al. Expert Opin Drug Metab Toxicol, 2010

Take Home Points:

- **Key factors to consider when choosing *primary therapy* for *Hp*:**
  - **PCN allergy?**
  - **Previous macrolide (or quinolone) exposure?**
  - **Quadruple therapies are replacing traditional triple therapy**
- **Key Factors to consider when choosing *salvage therapy*:**
  - **Avoid drugs used previously**
  - **Treat for 14 days**
  - **Quadruple therapies and Levofloxacin therapies are preferred**
  - **HD PPI & Amoxicillin and Rifabutin Triple therapies are other considerations**
  - **Optomize PPI therapy, PCAB therapy in the future?**

Disclosures

Received industry grant support for investigator initiated studies from the following:

Abbvie, Lycera, Pfizer, UCB

I have served as a consultant or advisory board for the following:

Abbvie, Janssen, Merck, Takeda

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Outline

- Telemedicine Vocabulary
- Types of Telemedicine
- Infrastructure Needs
- Reimbursement and Compliance
- Patient and Physician Experiences
- Case Use Examples

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TeleMedicine has Arrived and is Growing

Many Services **Provide Infrastructure** or
Increasing Connecting Patients to **Employed Providers**

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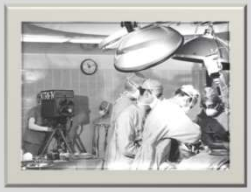
Telemedicine has been here for decades

1906:
transmission of EKG via telegraph

1962:
Videoconferencing of operations



1970s:
Remote monitoring of Kaiser patients

Evans et al. Updates in Surgery. 2018.

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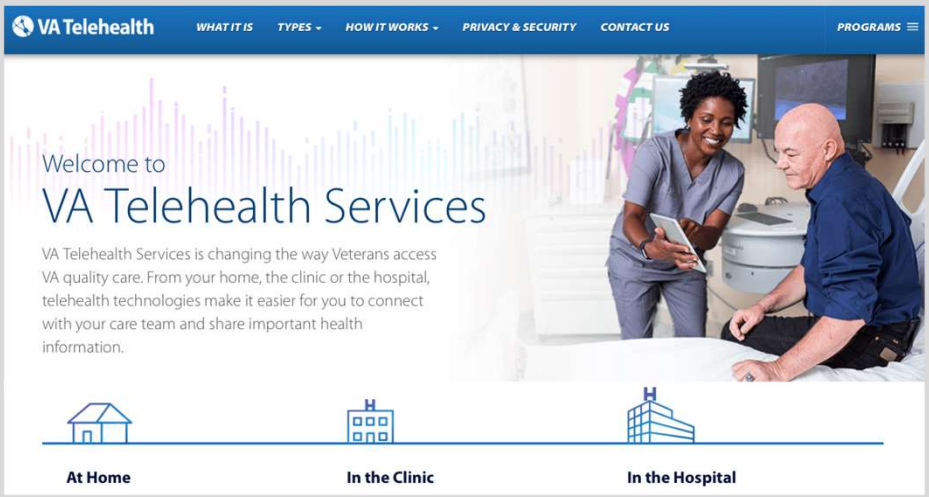
Telemedicine has been here for decades



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Telemedicine Vocabulary is Unstandardized

TeleMedicine

eHealth

TeleHealth

Remote Care

Virtual Consults

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Types of Telemedicine Based on Time and Space

Synchronous Care: Real Time Interaction

Asynchronous Care:

Medical Information Provided by The Patient

Saved and Reviewed at Different Times

(Store & Forward)

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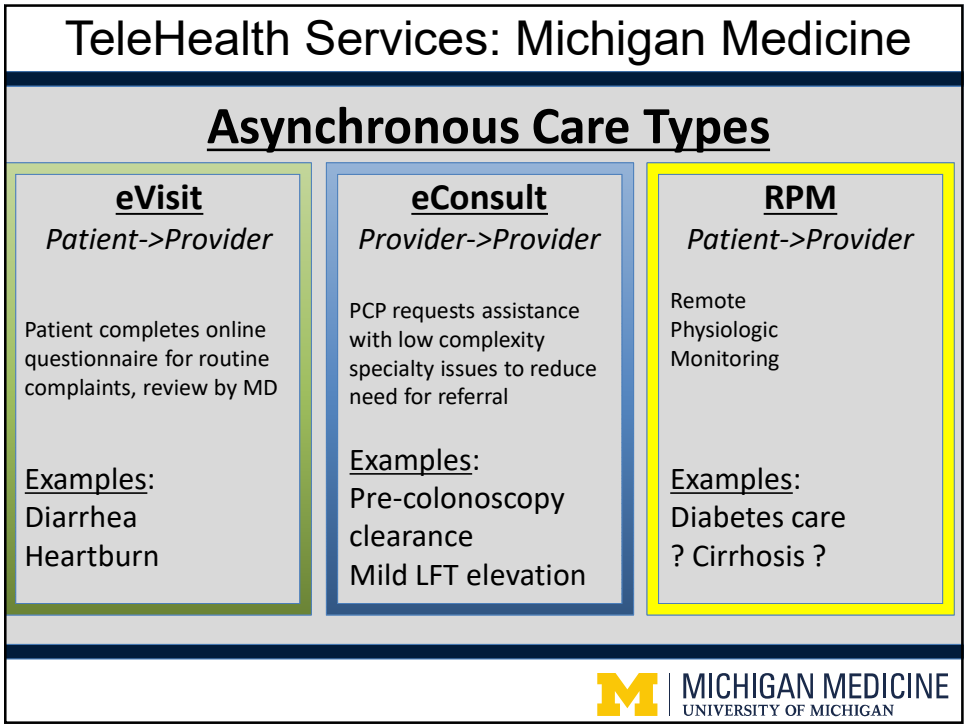
TeleHealth Services: Michigan Medicine
Asynchronous Care Types
eVisit
Patient->Provider
Patient completes online questionnaire for routine complaints, review by MD
Examples:
Diarrhea
Heartburn
eConsult
Provider->Provider
PCP requests assistance with low complexity specialty issues to reduce need for referral
Examples:
Pre-colonoscopy clearance
Mild LFT elevation
RPM
Patient->Provider
Remote Physiologic Monitoring
Examples:
Diabetes care
? Cirrhosis ?
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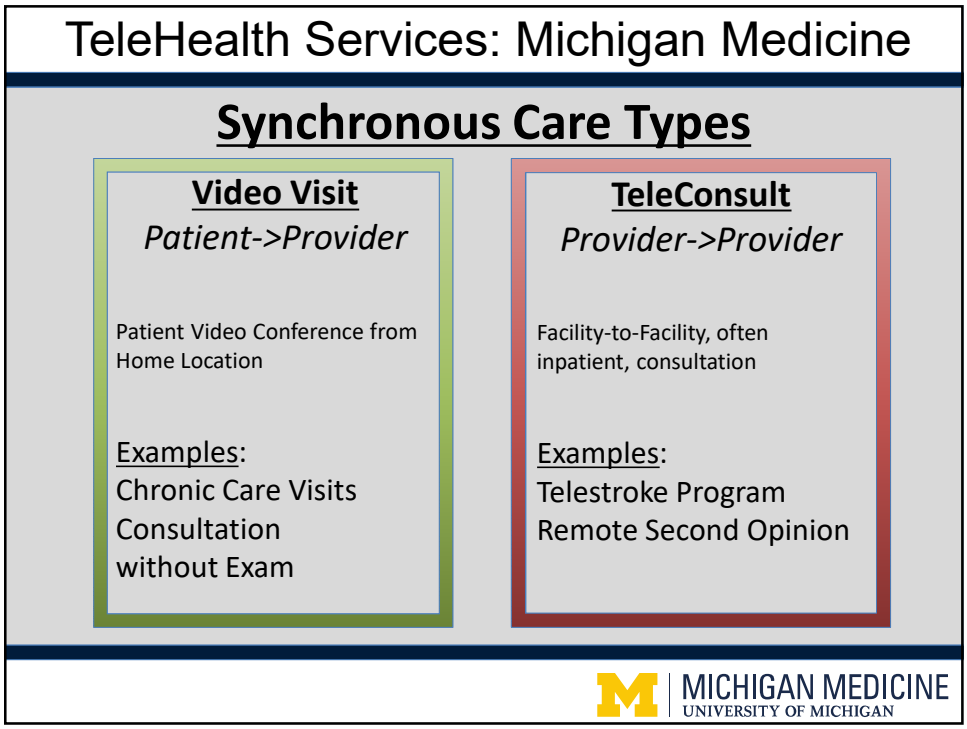
TeleHealth Services: Michigan Medicine
Synchronous Care Types
Video Visit
Patient->Provider
Patient Video Conference from Home Location
Examples:
Chronic Care Visits
Consultation without Exam
TeleConsult
Provider->Provider
Facility-to-Facility, often inpatient, consultation
Examples:
Telestroke Program
Remote Second Opinion
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Lots of Uncertainty Over Telemedicine

Reimbursement and Legal?

Will patients accept this?

How do I implement ?

What are the best applications?

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Video Visits Replace *In Person* Clinic Visits

Provider in Office

Not using clinic room
Comfortable in Office

Patient at Home

Did not need to travel
Did not need to park
Took Less Time Off Work
Kept appointment despite snow
Comfortable in home

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Video Visit Benefits

Patient	Institution
Patient only travels for the procedure	Extended Geographic Reach
Reduced Travel Cost	Improved Patient Retention at Distance
Reduced Time Off Work	Improved New Patient Access
High value for short check ups	Reduced Physical Space Needs & Costs
Convenience, Comfort, Satisfaction	Option to Reduce Weather/Distance Cancels

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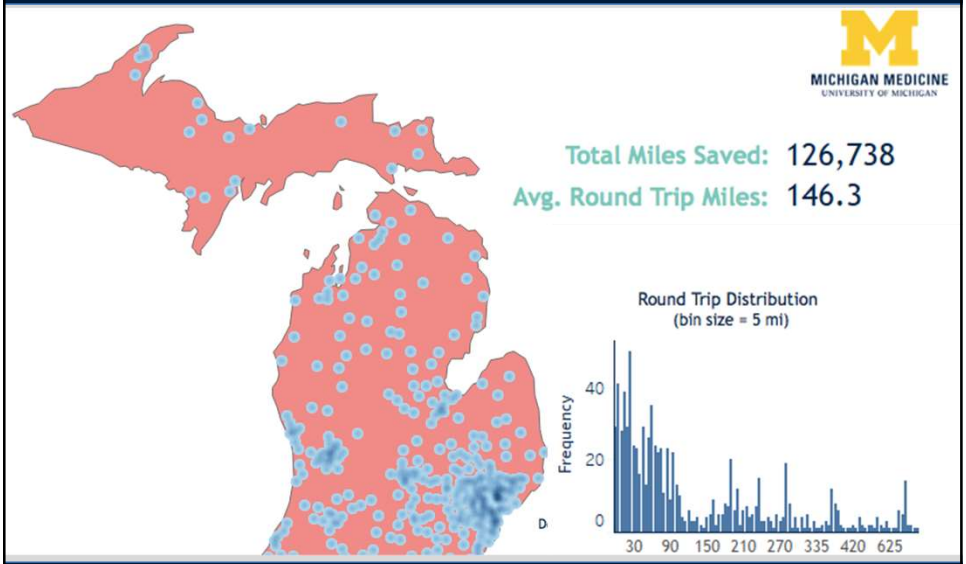
Michigan Medicine Video Visit 2020 Data



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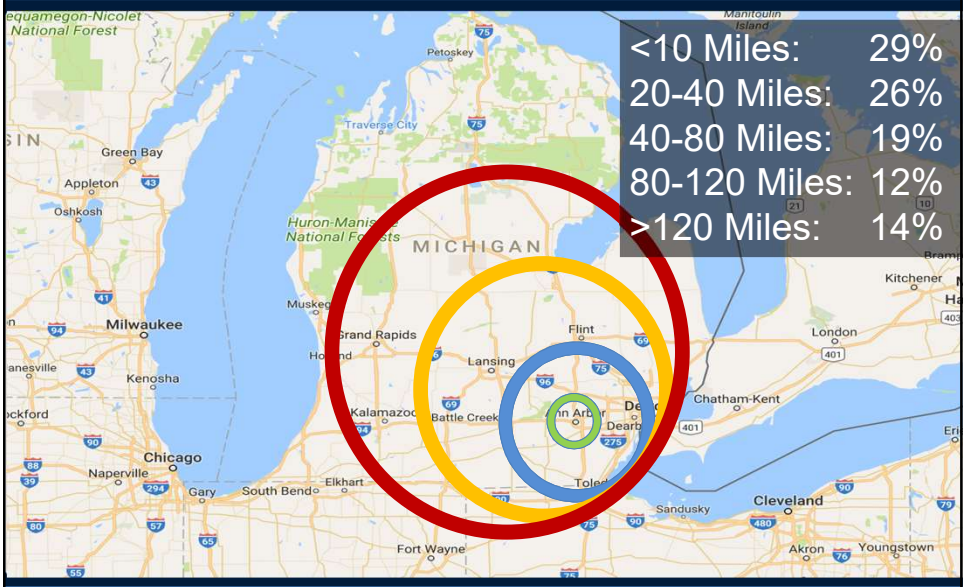
IBD Population: Patients Distance from UM



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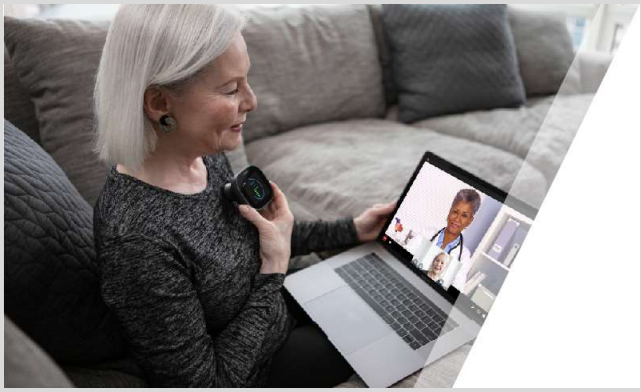
Many Popular EHRs Now Have Video Visits Capabilities

Cerner
Epic
athenahealth
eClinicalWorks
ORION HEALTH
McKESSON
Allscripts
Greenway



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Making a Video Visit Happen: *the easy parts*

Patients Need Internet Access/Technology

<u>Use a HIPPA-secure Video Client</u>

- Common EMRs Have This Functionality
- Stand Alone Examples:
  Cisco, BlueJeans, Vidyo, HIPPA Chat

Have Tech Support Available for Patients and back up plan if they can't connect
(Written Instructions and Telephone)

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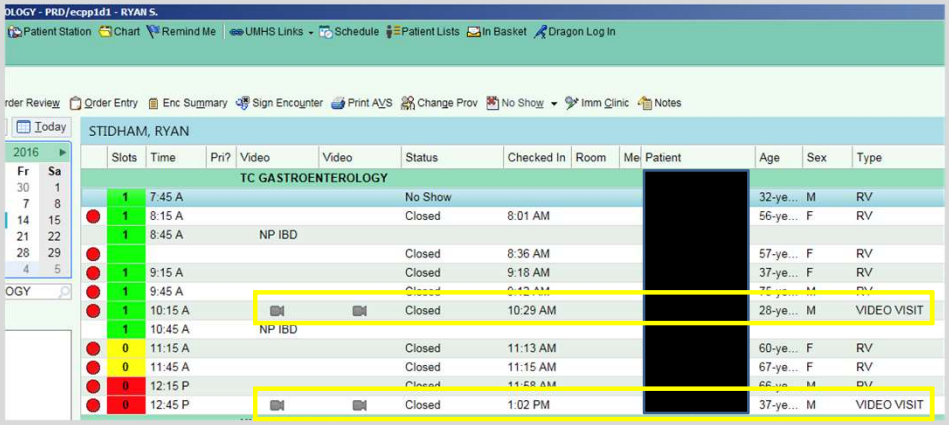
End-to-End EHR Integration



Visit Experience and Workflow
Very Similar to In Person Visit for Providers

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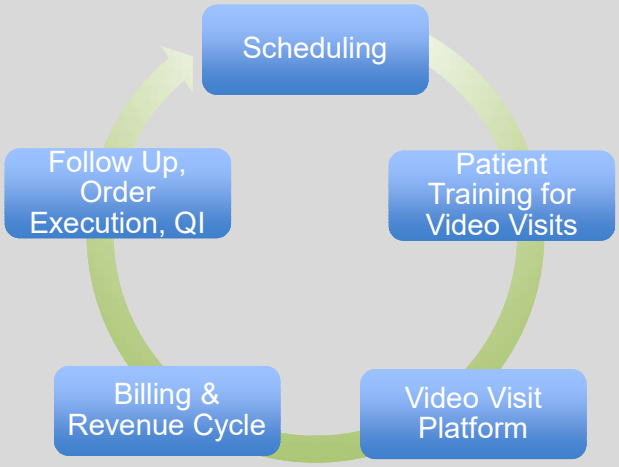
Setting Up a TeleHealth Program



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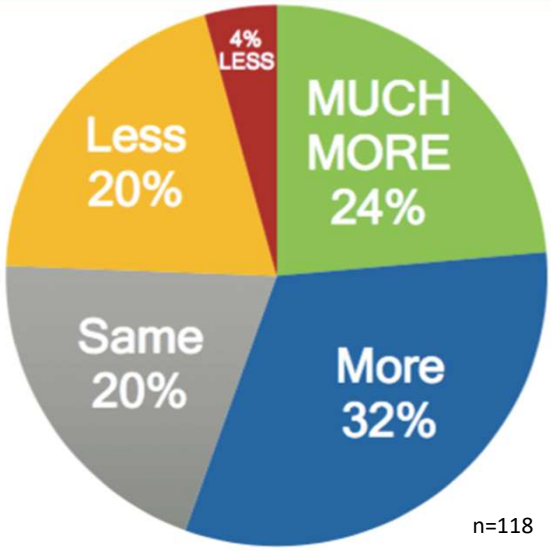
Patients Believe Video Visits Are a Better VALUE



76% of Patients Believe

Video Visits

are SAME or BETTER VALUE compared to

traditional office visits

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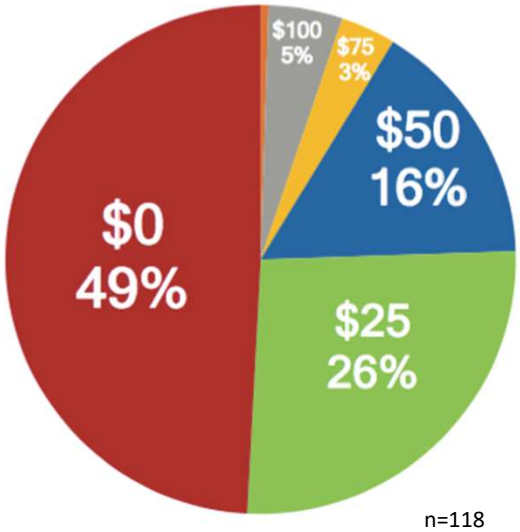
BUT, Patients Unwilling to Pay More Out of Pocket



<25% of Patients Would Pay More than in Office Copay

Primary Reason: Expect the service is less expensive for provider/institution

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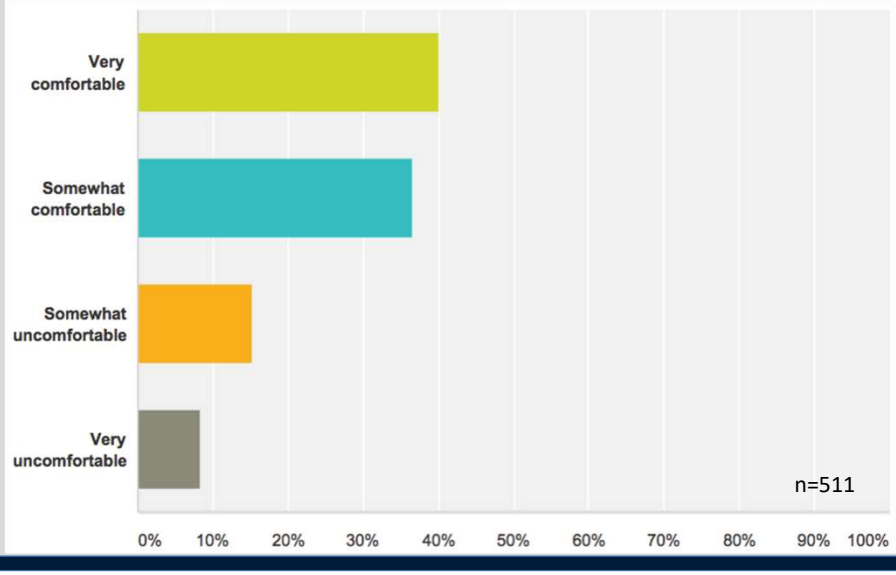
IBD Survey: Replace *In-Office* with Video Visit



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IBD Clinic: Complex Consultations Done from Home

- Seeing distant (and local) IBD Patients
- Can manage complex medications at distance
- Patient satisfaction very good to excellent
- Visits (surprisingly) shorter than in office
- Opportunities for complex results review by face-to-face visit (99212/99213) rather than telephone

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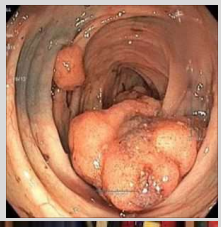
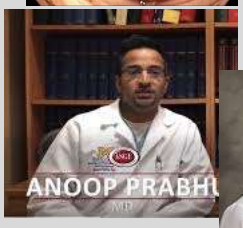
GI Applications: Remote Complex Polyp Clinic



- 6cm Polyp Ascending Colon
- Considering Endoscopic Mucosal Resection
- Using Anti-Coagulation for Atrial Fibrillation
- Lives 90 miles away, disability



Video Visit

Face-to-Face Visit with Dr. Prabu & PA Morisi

Good candidate for EMR

Anti-coagulation instructions given

Patient able to have all questions answered

Conducted Visit from Patient's Living Room

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Example of TeleHealth + Bariatric Interface

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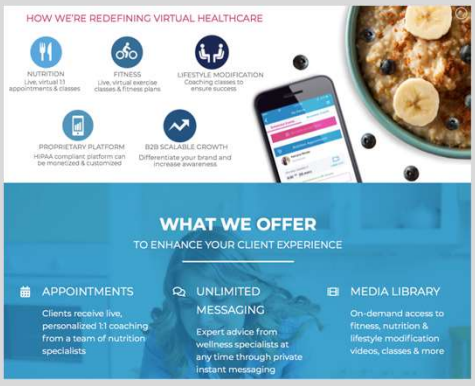
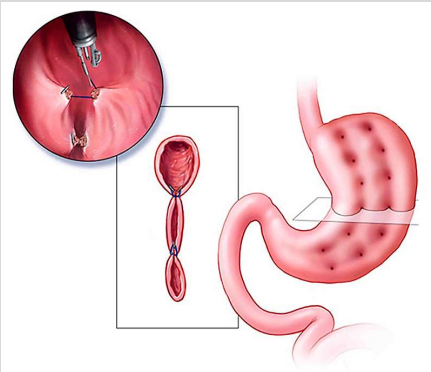
Case Study: Virtual Health Partners, LLC

Linking Support Services + Procedures





To Provide Useful *Support* BEFORE and AFTER Surgery/Endoscopy

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Reimbursement and Compliance

Its still the Wild West

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Reimbursement

- Nationally, Medicare/Medicade Will NOT Reimburse for Patient Home->Physician Office.
- State Level Legislation for CMS Coverage of Home Visits

  Texas, Iowa, California, **Michigan**, Minnesota, Georgia, Virginia, and Kentucky.
- In Michigan nearly all commercial payers cover Professional Fees for Visit
- Variation State to State
- Many sites have transitioned to flat-fee billing

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Reimbursement and Billing

Typically bill level 4 (99214) for IBD RV follow up

Same in office billing code but add the GT or GQ MODIFIER

In MICHIGAN Advanced Practice Providers Can Bill Visits.

CPT Code	Description	wRVU	Charge (Pro Fee Only)	Medicare (Self-Pay)	Commercial
99212	Video Visit in the home level 2	0.48	$49.00	$19.60	$29.40
99213	Video Visit in the home level 3	0.97	$81.00	$32.40	$48.60
99214	Video Visit in the home level 4	1.50	$119.00	$47.60	$71.40
99215	Video Visit in the home level 5	2.11	$172.00	$68.80	$103.20

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Compliance and Legal

Consent

Patients need to consent for Video Visits and its limitations
- electronic forms at the start of video visit
- modified global patient consent (we're moving to this) singed once

Documentation

Document that patient consented to video visit limitations and that two-way audio-video communications were used (this is a must)

License Reciprocity

In Michigan, can only render care to patient physically in the state of Michigan at the time of visit.

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Video Visits Do Not Solve Everything

1. Does not Dramatically Reduce Provider Time
2. Once Advertised, Patients Are Less Interested in Office Visits
3. Uncertain if Reimbursement Will Continue at Scale
4. Anticipate Patients Will Expect Reduction of Costs
5. Telecom Glitches Still Occur

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eConsults in Gastroenterology

- Non-Urgent Consultation from PCP
- Prespecified Questions/Problems for eConsults
- **<u>Currently Using in Michigan Hepatology</u>**
  1. Elevated LFTs
  2. Incidental mass on imaging
- Reduces unneeded specialist utilization
- Increases access for other new consultations

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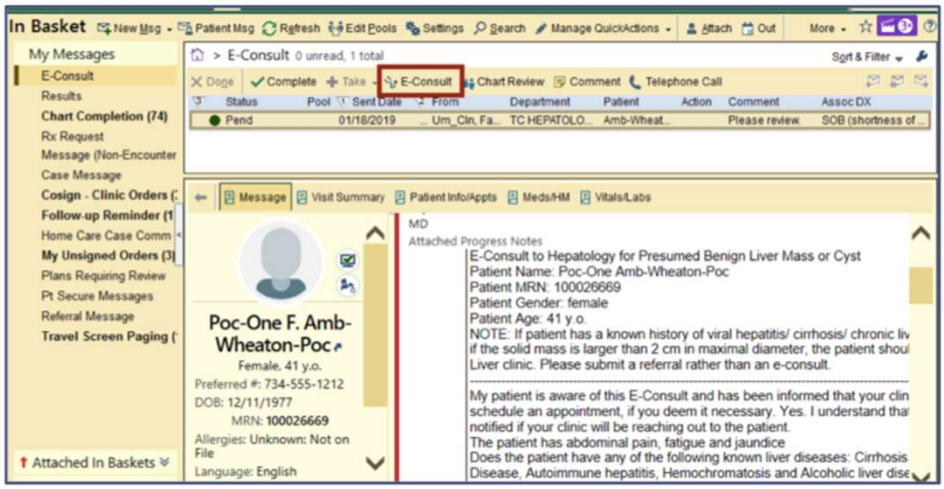
eConsults in Gastroenterology



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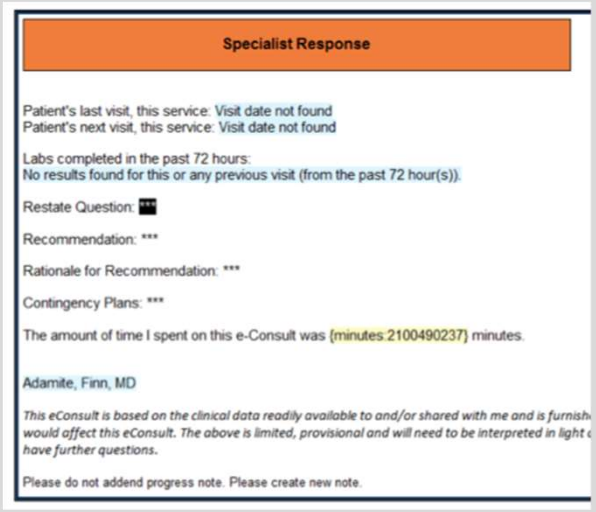
eConsults in Gastroenterology

Reply through EHR

Billable to 99451

Criteria:
"Interprofessional health record assessment and management service provided by a **consultative physician** including a written report to the patient's treating/requesting physician, 5 or more minutes of medical consultative time (99451)"

At Michigan Medicine
0.7 wRVU, Charge $116.00



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eConsults in at Michigan Medicine

Michigan Medicine eConsult Data

Approximately 15% of Visits Convert to Office Visit

Majority of Issues handled by eConsult

Only 4% of consults rejected by Specialist

All Wave Specialties				
Mo/Yr	Clinical Questions Answered	Converted to Visit	Rejected	Percent Converted
Aug-16	48	6		11.1%
Sep-16	55	16		22.5%
Oct-16	63	14		18.2%
Nov-16	47	9		16.1%
Dec-16	55	12	1	17.6%
Jan-17	50	4	3	7.0%
Feb-17	94	27	2	22.0%
Mar-17	110	18	1	14.0%
Apr-17	92	17	2	15.3%
May-17	107	15	2	12.1%
Jun-17	119	28	15	17.3%
Jul-17	120	21	6	14.3%
Aug-17	155	24	3	13.2%
Sep-17	117	19	5	13.5%
Oct-17	156	23	7	12.4%
Nov-17	112	14	5	10.7%
Dec-17	124	22	9	14.2%
Jan-18	155	32	6	16.6%
Feb-18	140	29	12	16.0%
Mar-18	161	29	6	14.8%
Apr-18	128	29	4	18.0%
May-18	129	23	5	14.6%
Jun-18	131	30	7	17.9%
TOTALS	2337	431	94	15.6%

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Other TeleHealth Technologies

Remote Patient Engagement RFP

Supplier	Mode
Population Health Outreach Tools	
Medumo (Phillips)	SMS texting, Email, Paper, IVR/robo Calls
CipherHealth	IVR/robo calls, email and text
Emmi	Interactive Automated Video, IVR/robo Calls
Twistle	IVR/robo calls, SMS texting, mobile app, web app
Epharmix	IVR/robo calls and SMS texting
Conversa	Chat Bot – Device Agnostic
Fully Managed Device Kits	
Vivify	Fully Managed Device Kit and BYOD App
Health Recovery Solutions	Fully Managed Device Kit, Bring Your Own Device (BYOD) solution
L365	Fully Managed Device Kit, Bring Your Own Device (BYOD) solution

Third Party Vendors for Asynchronous Data Collection

Cirrhosis: Functional Status Monitoring

IBD: Symptom Activity

IBS: Symptoms and QOL

Endoscopy: Bowel Prep management

Endoscopy: Post Procedural Monitoring

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Re-Imagining Patient-HealthTeam Interaction

Merge Synchronous and Asynchronous Care

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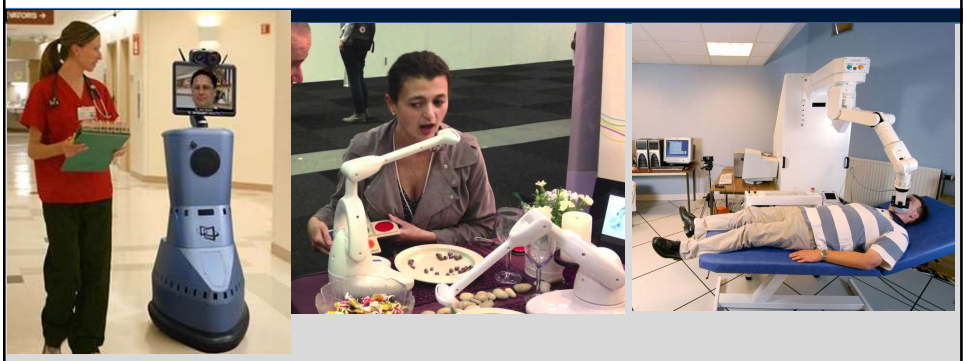

Thank You

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