MICHIGAN MEDICINE

GASTROENTEROLOGY UPDATE:

A Case-Based Approach to Common GI Problems

STATE OF THE ART LECTURE SERIES

October 18-19, 2019

The Inn at St. John's, Plymouth, MI

michmed.org/intmedcme

MICHIGAN MEDICINE

DEPARTMENT OF INTERNAL MEDICINE CME COURSE CALENDAR

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.

We offer a variety of courses each year. The content of our activities includes primary care, specialty and subspecialty topics in the broad field of medicine. We target and welcome all physicians and other healthcare professionals, locally, nationally, and globally.

UPCOMING COURSES

32nd Annual Update in Pulmonary and Critical Care Medicine
Friday - Saturday, November 1-2, 2019
The Inn at St. John's, Plymouth, MI

22nd Annual Liver Disease Wrap-Up
Saturday, December 7, 2019
The Inn at St. John's, Plymouth, MI

SAVE THE DATE!

Advances in Gastroenterology & Hepatology
Friday - Sunday, February 7-9, 2020
Hyatt Regency Coconut Point Resort and Spa,
Bonita Springs, FL

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

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

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

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

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

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

FOR MORE INFORMATION AND TO REGISTER:
michmed.org/intmedcme • (734) 232-3469 • intmedcme@umich.edu

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PROGRAM SCHEDULE

FRIDAY, OCTOBER 18, 2019

7:30 am Registration & Continental Breakfast

8:00 **Welcome and Announcements**
Michael Rice, MD
Richard Saad, MD, MS, FACG

SESSION 1: UPPER GI

8:10 **Eosinophilic Esophagitis**
Joy Chang, MD

8:45 **Heartburn with a Normal EGD**
Joan Chen, MD, MSCI

9:20 **Gastroparesis**
William Hasler, MD

9:55 Questions & Answers

10:10 Break

SESSION 2: IBD

10:25 **Health Maintenance in IBD**
Jami Kinnucan, MD

11:00 **Current Landscape for the Treatment of Crohns**
Ryan Stidham, MD, MSc

11:35 **Role of Diet in IBD**
Emily Haller, MS, RDN

12:10 pm Questions and Answers

12:25 Lunch

SESSION 3: LOWER GI

1:30 **Small Bowel Bleeding**
Michael Rice, MD

2:05 **FMT: Present and the Future**
Michelle Muza-Moons, MD, PhD

2:40 **Pelvic Floor Dyssynergia**
Stacy Menees, MD, MS

3:15 Questions and Answers

3:30 Session Adjourns

SATURDAY, OCTOBER 19, 2019

7:30 am Registration & Continental Breakfast

8:00 **Welcome and Announcements**
Michael Rice, MD
Richard Saad, MD, MS, FACG

SESSION 4: PANCREAS / BILIARY

8:10 **Exocrine Pancreatic Insufficiency**
Matthew DiMagno, MD

8:45 **Gall Bladder Disease**
Erik Wamsteker, MD

9:20 Question and Answers

SESSION 5: LIVER

9:30 **HCC Surveillance**
Neehar Parikh, MD

10:05 **Hepatitis B**
Andrew Tai, MD, PhD

10:40 Questions and Answers

10:50 Break

SESSION 6: FUNCTIONAL GI

11:05 **Functional Diarrhea**
Richard Saad, MD, MS, FACG

11:40 **Avoidant Restrictive Food Intake Disorder**
Kimberly Harer, MD

12:15 pm **Role in Trauma in GI Disorders**
Christina Jagielski, PhD

12:50 Questions and Answers

1:00 Course Adjourns

PROGRAM PLANNING COMMITTEE / PROGRAM FACULTY

PROGRAM FACULTY

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Kimberly Harer, MD
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William Hasler, MD
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Department of Internal Medicine
DIVISION OF GASTROENTEROLOGY

www.med.umich.edu/gi

The Division of Gastroenterology and Hepatology is one of the largest gastroenterology and hepatology practices in the country and is a leader in the prevention, diagnosis, and treatment of diseases of the gastrointestinal tract and liver. Our 60-plus physicians are experts in the diagnosis and treatment of all diseases of the gastrointestinal system, from simple to complex, including those of the esophagus, stomach, small intestine, colon, rectum, liver, gallbladder, pancreas, and biliary tract.

In addition to being leaders in clinical care, our faculty are also leaders in their respective areas of research, which span such varied interests as the role of peptides in the brain-gut interactions in functional bowel diseases to innovative treatments of viral hepatitis and liver cancer.

The Gastroenterology and Hepatology Division has created the following subspecialty clinics to better direct our clinical expertise to meet the needs of referring physicians and their patients:

CLINIC LOCATIONS

A. Alfred Taubman Health Care Center
(888) 229-7408

Briarwood Health Associates
Building 5 - Ann Arbor
(888) 229-7408

Brighton Health Center
(888) 229-7408

Canton Health Center
(888) 229-7408

Dexter Health Center
(888) 229-7408

East Ann Arbor Health and Geriatrics Center
(888) 229-7408

Northville Health Center
(888) 229-7408

Saline Health Center
(888) 229-7408

Veterans Affairs Ann Arbor Healthcare System
(734) 845-4341

M-LINE

M-LINE is a toll-free number for referring physicians and their staff seeking access to clinical services and faculty at the Health System. M-LINE physician representatives work closely with personnel across the Health System to provide efficient, personalized service and will stay on the line with your call until your request is met to your satisfaction.

One number, 24 hours a day, 7 days a week, providing:

- Physician-to-physician consultation
- Appointment scheduling
- Hospital-to-hospital transfer requests
- Inpatient status update
- Laboratory, test, and procedure results

M-LINE (800) 962-3555

Activity Information

Gastroenterology Update: A Case-Based Approached to Common GI Problems

October 18-19, 2019

Accreditation and Credit Designation:

The University of Michigan Medical School is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The University of Michigan Medical School designates this live activity for a maximum of 11 AMA PRA Category 1 Credit(s) ™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 11 Medical Knowledge MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Evaluation and Certificate:

Attendance must be registered within 6 months to be awarded credit. Please complete the following steps to fill out the course evaluation and print your certificate:

- Login to your account at MiCME at http://micme.medicine.umich.edu/

  Don't have an account? Click on the "Login or Create a MiCME Account" link at the top of the page and follow the instructions. ***Note: You must have a MiCME account to claim credit for any University of Michigan Medical School (UMMS) CME activity.*** On the Credit Center card on your Dashboard, click on *Claim Credits and View Certificates*.

- Locate the activity in the *Activities Available for Credit Claiming* section.
- Under Action, click on *Claim*.
- Under Action, click on *Add Credit*.
- Enter the number of credits you're claiming and the the "I Attest" button. *(Note: This number should reflect credits claimed for the entire course, not just a single day.)*
- Complete the evaluation form to provide feedback on the activity.
- Click the *Submit* button.
- Scroll down to the *Awarded Credits* section to view or print your certificate and/or comprehensive University of Michigan CME transcript.

For more information about this activity, contact Emily Vandervoort at vaemily@umich.edu, or visit www.micme.medicine.umich.edu.

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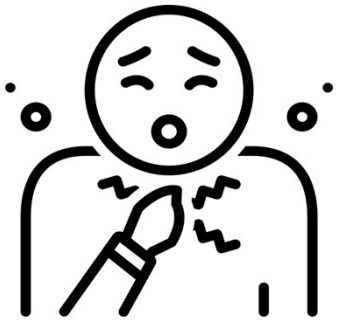
One number, unlimited assistance. M-LINE. With it, referring physicians and their staff can reach more than 3,000 doctors and 26 departments, 24 hours a day, 7 days a week. Services include:

- Physician-to-physician consultation
- Appointment scheduling
- Hospital-to-hospital transfer requests
- Inpatient status update
- Laboratory, test, and procedure results

800-962-3555

Everyday Eosinophilic Esophagitis



Joy Chang, MD, MS
Gastroenterology Update
October 18, 2019

MICHIGAN MEDICINE
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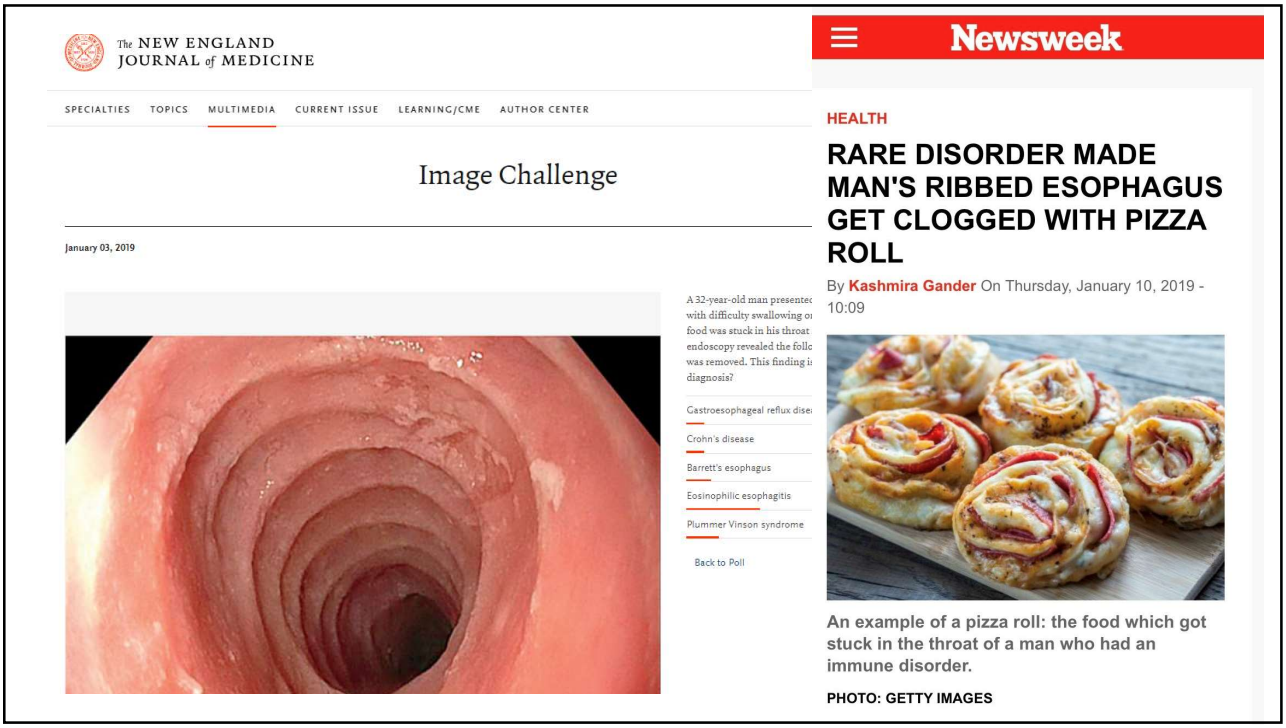


The NEW ENGLAND JOURNAL of MEDICINE

SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER

Image Challenge

January 03, 2019

A 32-year-old man presented with difficulty swallowing of food was stuck in his throat. endoscopy revealed the follc was removed. This finding is diagnosis?

Gastroesophageal reflux dise
Crohn's disease
Barrett's esophagus
Eosinophilic esophagitis
Plummer Vinson syndrome

Back to Poll

Newsweek

HEALTH

RARE DISORDER MADE MAN'S RIBBED ESOPHAGUS GET CLOGGED WITH PIZZA ROLL

By Kashmira Gander On Thursday, January 10, 2019 - 10:09

An example of a pizza roll: the food which got stuck in the throat of a man who had an immune disorder.

PHOTO: GETTY IMAGES

Eosinophilic Esophagitis (EoE)

- A chronic, allergy and immune-mediated inflammatory disease.
- Eosinophilic inflammation → fibrosis and esophageal strictures

- Clinical presentation:
  - Dysphagia, food impaction, and reflux
  - Less commonly: globus, chest pain, N/V

- One of the most common causes of dysphagia and food impaction in adults
  - 12-23% of adults undergoing endoscopy for dysphagia
  - Up to 50% of adults who present with food impaction (up to 63% of children)

Clinical Case 1

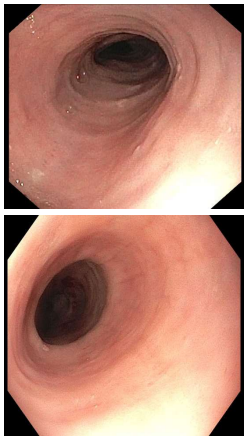
21yo male college student presents to clinic with dysphagia

- 10 year history of dysphagia to solids
- Uses compensatory mechanisms with all meals
- 3 prior food impactions – 1 resolved after 2 hours, 2 required endoscopic therapy
- Forcefully regurgitates after meals 3x/month
- Prescribed PPI in past, but did not use
- No prior follow-up with GI
- "Slow eater" all of his life
- No prior anaphylactic reactions, but he suspects food allergies to sunflower seeds and legumes.

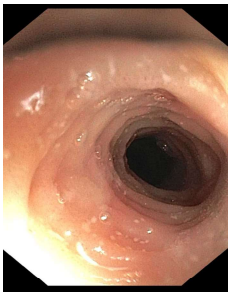
→ Endoscopy!

EoE: Endoscopic Features

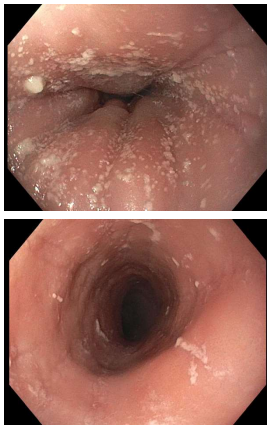
EDEMA
(loss of vascular markings)



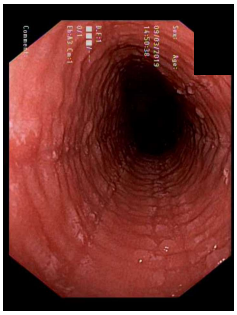
RINGS
(trachealization)



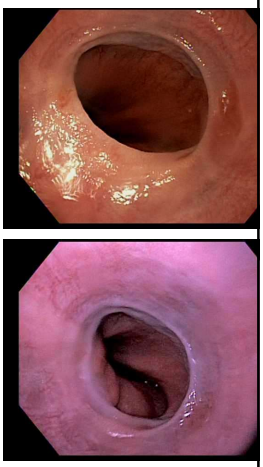
EXUDATES
(white plaques)



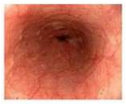
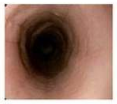
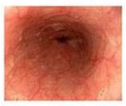
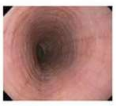
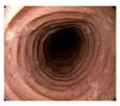
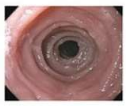
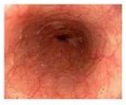
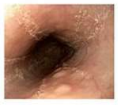
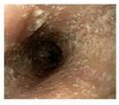
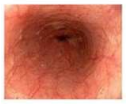
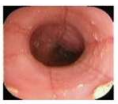
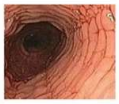
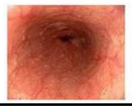
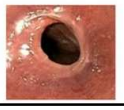
FURROWS
(vertical lines)



STRICTURE



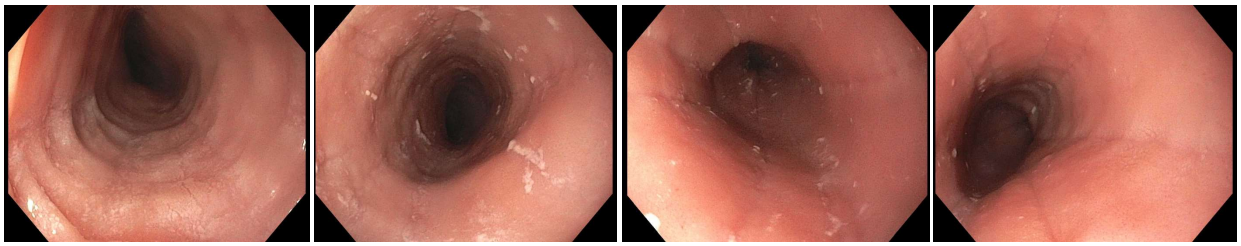
Endoscopic Features: EREFS Score

	Grade 0	Grade 1	Grade 2	Grade 3	
EDEMA (loss of vascular markings)					0: Distinct vascularity 1: Decreased 2: Absent
RINGS (trachealization)					0: None 1: Mild (ridges) 2: Moderate (distinct rings) 3: Severe (scope can't pass)
EXUDATES (white plaques)					0: None 1: Mild (≤ 10% surface) 2: Severe (> 10% surface)
FURROWS (vertical lines)					0: None 1: Mild 2: Severe (depth)
STRICTURE					0: Absent 1: Present (+ luminal diameter)

Hirano et al. Gut. 2013;62(4):489-95.

Clinical Case 1

- Upper endoscopy shows exudates, mucosal rings, furrows, no stricture.



Ed ___ R ___ Ex ___ F ___ S ___

Clinical Case 1

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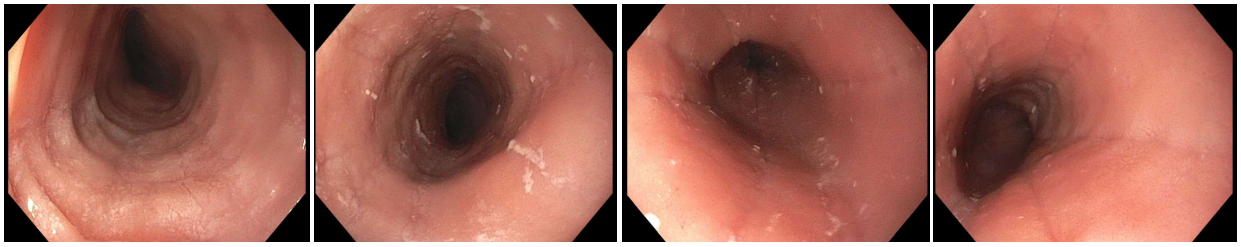


Ed **1** R **1** Ex **1** F **1** S **0**

Biopsies of esophagus show: **proximal <u>55</u>** Eos/hpf, **distal <u>72</u>** Eos/hpf

Diagnosis

- Clinical symptoms of esophageal dysfunction **AND**
- Histology: presence of ≥ 15 Eos/hpf within the esophageal epithelium

Should I biopsy every esophagus for Dysphagia? **YES**

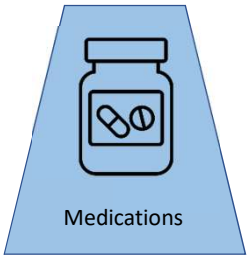
How should I biopsy?

- ✓ 4 biopsies from proximal + 4 bx from distal
- ✓ Target lesions (exudates, furrows) increases diagnostic yield

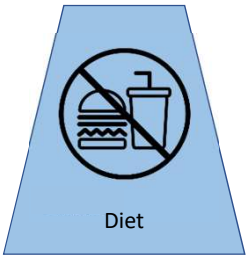
Other causes of/associations with esophageal eosinophilia

- Gastroesophageal reflux disease
- Eosinophilic gastrointestinal disease
- Achalasia
- Hypereosinophilic syndrome
- Esophageal Crohn's disease
- Celiac disease
- Infections (fungal, viral)
- Drug hypersensitivity reacitons
- Pill esophagitis
- GVHD
- CTD, autoimmune disorders, vasculitis

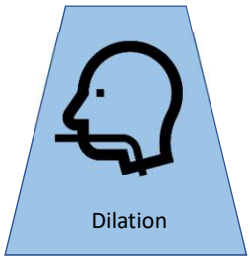
Treatments



Proton-pump inhibitor (PPI)
Topical corticosteroids (TCS)



Elimination Diet
- Wheat
- Eggs
- Soy
- Dairy
- Shellfish
- Tree nuts



What would you recommend as initial treatment?

Proton pump inhibitor

Swallowed topical steroids

Elimination diet

Endoscopic dilation

20mg BID? 40mg BID?

Swallowed fluticasone inhaler?

Oral viscous budesonide?

Oral prednisone?

PPIs and EoE

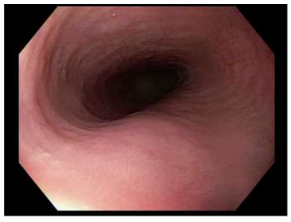
- Guidelines regarding PPI's role in EoE has changed over last 10 years
  - PPI to rule out GERD
  - PPI to rule out "PPI-responsive esophageal eosinophilia" (PPI-REE)
  - We used to call "PPI trial"

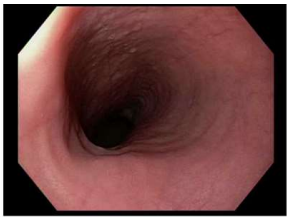
Current guidelines: PPI can be a **first-line treatment** too

- ✓ PPI dual function = anti-acid + anti-inflammatory
- ✓ About 30-40% of EoE patients will respond to PPI alone
- ✓ Start with omeprazole 20mg BID
- ✓ Goal: continue PPI at lowest minimum dose to maintain disease control

Clinical Case 1

- After using a 6-week course of omeprazole 20mg twice daily, the patient undergoes a repeat upper endoscopy.



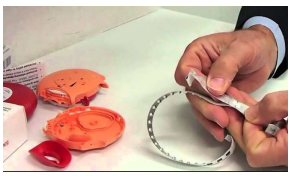


Ed 1 R 1 Ex 0 F 1 S 0

- Biopsies of the esophagus:
  - **proximal 55 → 40** Eos/hpf
  - **distal 72 → 35** Eos/hpf

Topical Corticosteroids for EoE

- **Fluticasone inhaler**
  - Swallowed dose from MDI
  - 440mcg BID
  - Consider high induction dose (880mcg BID)
- **Fluticasone diskus/powder**
  - $$$$
  - 250mcg BID or 500mcg BID



- **Budesonide**
  - Oral viscous budesonide (OVB) aka "slurry"
  - Dispensed as respules
  - OVB 1mg BID
  - Mix in 5 packets of Splenda. Or honey, maple syrup, applesauce.

Clinical Case 1

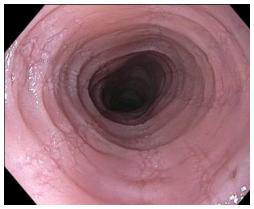
- After failing PPI, an 8-week course of fluticasone 440mcg twice daily is started. He reports complete resolution of his dysphagia on this regimen.

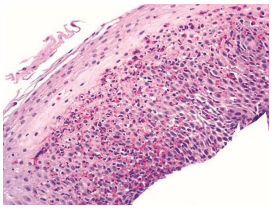
What now? We have symptomatic response…

Repeat endoscopy + biopsy to document response to therapy

Therapeutic Endpoints

- Improvements in both clinical **<u>symptoms</u>** + **<u>histology</u>**





- Monitor response to treatment (meds or diet) 6-8 weeks after change
- Histologic response is important
  - Symptoms alone <u>do not</u> predict histologic or endoscopic activity.
  - Without histologic remission, symptoms <u>will recur</u> over time.

Clinical Case 2

48yo woman with HTN, referred to you for new EoE diagnosis

- 2 year history of intermittent dysphagia
- No prior impactions
- Has done Internet research and lots of questions
- Would rather pursue a “natural treatment”

Diet Therapy for EoE

- Empiric elimination
  - **6**-food elimination = wheat, dairy, egg, soy, treenuts, shellfish **70-80% response**
  - **4**-food elimination = wheat, dairy, egg, soy **50-60% response**
  - **2**-food elimination = wheat, dairy **40% response**
  - **2-4-6** step up
  - Single food elimination (milk)

- Allergy testing directed
- Elemental formula

Diet Therapy for EoE

- Empiric elimination
  - Refer to GI nutrition
  - Remove all food groups → (6-8 weeks) → Endoscopy with biopsies
  - Add 1-2 food groups back → (6-8 weeks) → Endoscopy with biopsies
  - Add back 1 more food group back → (6-8 weeks) → Endoscopy with biopsies

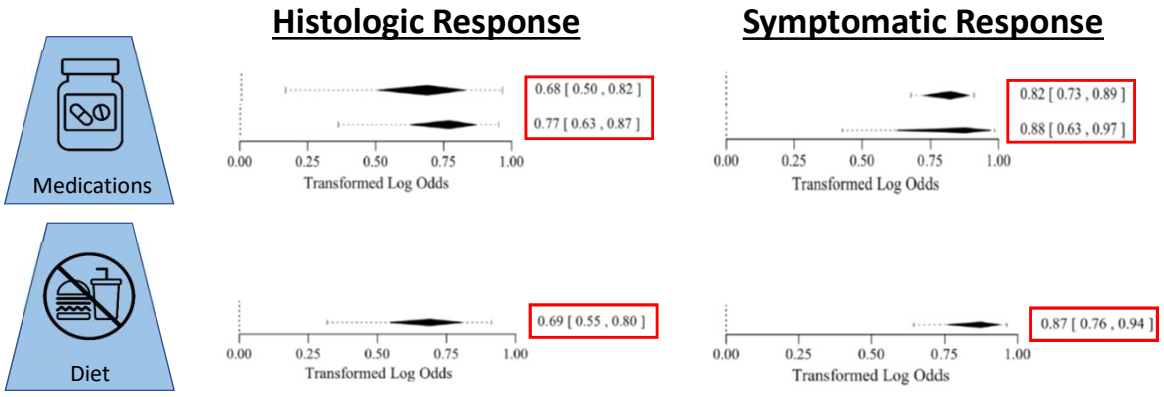
✓ Goal: Identify the 1-2 trigger foods to avoid for long term disease control
✓ Repeat Endoscopy with biopsies after any change to monitor response to treatment

Diet Therapy for EoE

- Empiric elimination
- Allergy testing directed
  - Atopy patch testing and IgE-based testing is poorly predictive of identifying dietary triggers in adults
- Elemental formula (70-80% response)

✓ Most common triggers = wheat, dairy
✓ Empiric elimination > allergy testing-directed strategies

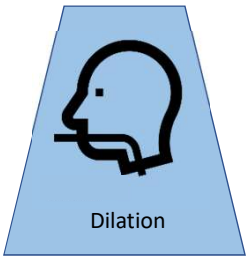
Treatment Response



Medications and diet are effective treatments to:
- Decrease eosinophilic inflammation and
- Improve symptoms

Cotton et al. DDS. 2017;62:2408-20.

Dilation for EoE



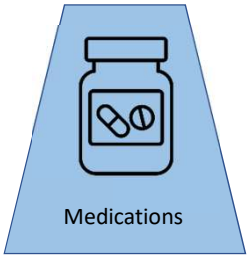
✓ Dilation is a safe and effective method for symptom improvement

Table 2. Efficacy and safety of dilation

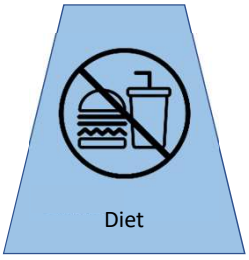
	Any dilation (*n*=164)
Total number of dilations	486
Number of dilations per patient (mean±s.d.)	3.0±3.7
Dilation method, n (%)	
Savary	91 (19)
Balloon	395 (81)
Esophageal diameter (mm) before dilation (mean±s.d.)	12.5±3.0
Esophageal diameter (mm) after final dilation (mean±s.d.)	15.2±2.9
Increase in esophageal diameter (mean mm±s.d.)	2.6±1.4
Symptom response, *n* (%)[a]	108 (87)
Complications, n (%)	
Any complication	25 (5.1)
Pain	21 (4.3)
Bleeding	0 (0)
ER visit	5 (1.0)
Hospitalization	2 (0.4)
Perforation	0 (0)
Death	0 (0)

Runge TM et al. Am J Gastroenterol. 2016;111:206-13.

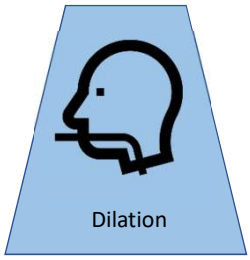
Treatments



Proton-pump inhibitor (PPI)
Topical corticosteroids (TCS)



Elimination Diet



Should I combine TCS + elimination diet?

NO – for the large majority of EoE cases, choose medications OR diet.

	Medications	Diet	Dilation
Advantages	Histologic & symptom improvement	Histologic & symptom improvement	Symptom improvement
	Short response time	Drug-free remission	Periodic treatment
	Ease of use		
Disadvantages	Expensive without insurance coverage	Adherence to strict diet	Uncontrolled eosinophilic inflammation
	Inconvenience of daily or BID dosing	Several endoscopies to identify trigger foods	Repeat dilations
	Potential side effects of systemic exposure	6-18 months to complete	Potential complications (pain, perforation)

Clinical Case 3

37yo man with history of allergic rhinitis, eczema, ?food allergies, and long-standing EoE.

- Diagnosed in 20s
- Intermittently compliant before, now strictly uses budesonide
- Worsening symptoms in the spring with allergies
- Experiencing dysphagia daily

For worsening symptoms, what's your next step in management?

- ❑ Empirically ↑ dose of OVB
- ❑ Switch from OVB to swallowed Fluticasone
- ❑ Add on elimination diet to the topical steroid
- ❑ Switch from OVB to diet therapy
- ❑ EGD with biopsies +/- dilation
- ❑ EGD with dilation only (no bx)

For worsening symptoms, what's your next step in management?

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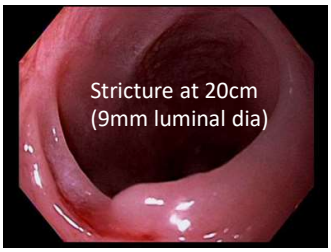
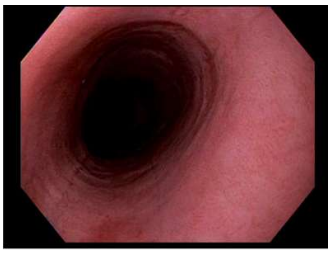
- ❑ Switch from OVB to swallowed Fluticasone
- ❑ Add on elimination diet to the topical steroid
- ❑ Switch from OVB to diet therapy
- ✓ **EGD with biopsies +/- dilation**
- ❑ EGD with dilation only (no bx)

Clinical Case 3





Biopsies of the esophagus: **proximal 15** Eos/hpf, **distal 35** Eos/hpf

- ✓ Persistent symptoms due to fibrostenotic disease (stricture)
- ✓ Treat with dilation in addition to targeting histology

Common EoE Myths

1) Symptoms alone are a good way to track disease activity and inflammation.

FALSE

- ✓ Symptoms DO NOT correlate with histologic response in EoE.
- ✓ Cannot rely on symptoms to make assumptions about disease activity in adults with EoE.
- ✓ Especially if dilation is performed!

Common EoE Myths

2) EoE can be treated with 1 course of steroids (like Lymphocytic colitis)

FALSE

- ✓ Symptoms and eosinophilic inflammation **will recur** after discontinuation of medical or diet treatment.
- ✓ A maintenance strategy should be offered to all patients with EoE.

Questions?

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MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Heartburn with a Normal EGD

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Department of Internal Medicine
University of Michigan

Disclosure

I have no personal or financial conflict of interest in relation to this presentation.

Outline

- Diagnostic tests for GERD
- Ambulatory reflux testing
- Lyon Consensus
- Functional esophageal disorders
- Treatment

Case

54 y/o male with 2-years of chronic heartburn

- Postprandial heartburn ≥3 times a week
- Frequent belching and lump in throat sensation
- Prilosec 20mg QD with ~50% improvement after 3 months

Case

- + work-related stress and poor sleep
- ROS negative
- No significant GI FHx
- Divorced, bar owner, non-smoker

5’7”, 96.7 kg (213 lbs, BMI 33)

Central obesity, exam normal otherwise

Labs (CBC, BMP, LFTs) unremarkable

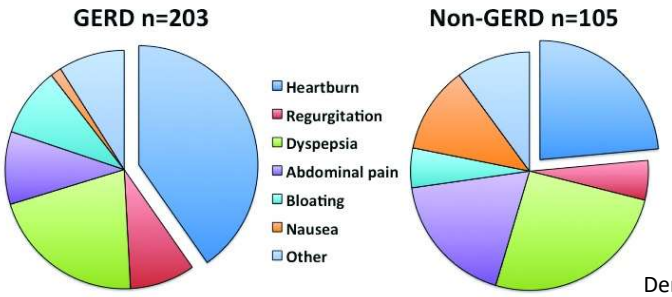
Diagnostic testing for GERD

- Symptom-based
- The PPI test
- Endoscopy
- Ambulatory reflux testing
  - pH-only monitoring: catheter or wireless
  - Impedance-pH testing

Symptom-based

- Typical symptoms are neither sensitive nor specific for GERD

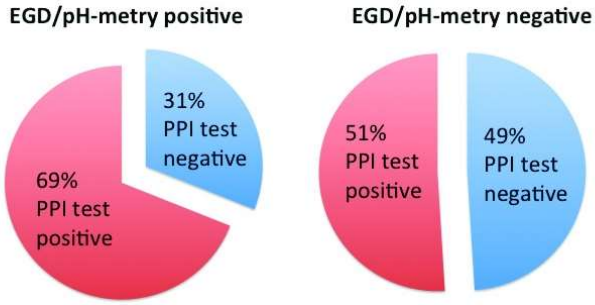
Most troublesome UGI symptom in the Diamond study
GERD diagnosis by EGD and pH-metry, n=308



Dent J, Gut 2010

PPI Test

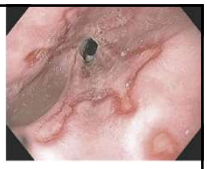
- Short course of high-dose PPI as a diagnostic test



- 80% sensitivity and 57% specificity in another study
- But simple and likely cost effective

Bytzer P, Clin Gastroenterol Hepatol 2014

Endoscopy



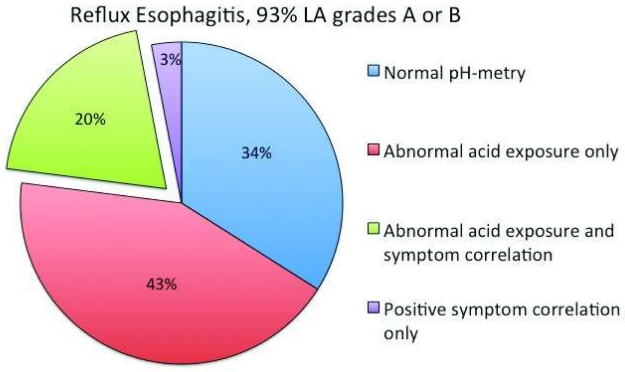
- R/o major potential GERD-related morbidities e.g. Barrett's, stricture, cancer
- Findings to direct management: reflux esophagitis, eosinophilic esophagitis, hiatal hernia, peptic ulcer, bleeding
- Poor sensitivity for diagnosis of GERD
  - Esophagitis absent in 70% of cases (NERD)
  - <10% show esophagitis if on PPI
  - 79% of esophagitis are mild (LA A or B)

Savarino E, Dis Esophagus 2017, Wang A, Dig Dis Sci 2009

Endoscopy

Esophagitis vs pH-metry in the Diamond study

116/308 (38%) EGD positive patients



Bytzer P, Clin Gastroenterol Hepatol 2014

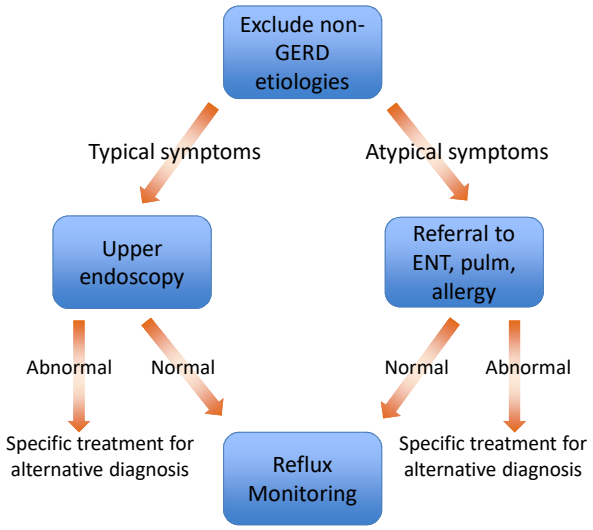
Indications for Endoscopy

Red flag/alarm symptoms

- Dysphagia, weight loss, bleeding, anemia, early satiety

Persistent symptoms despite adequate PPI therapy

Management for persistent reflux symptoms



Katz. Am J Gastroenterol. 2013

Ambulatory reflux testing

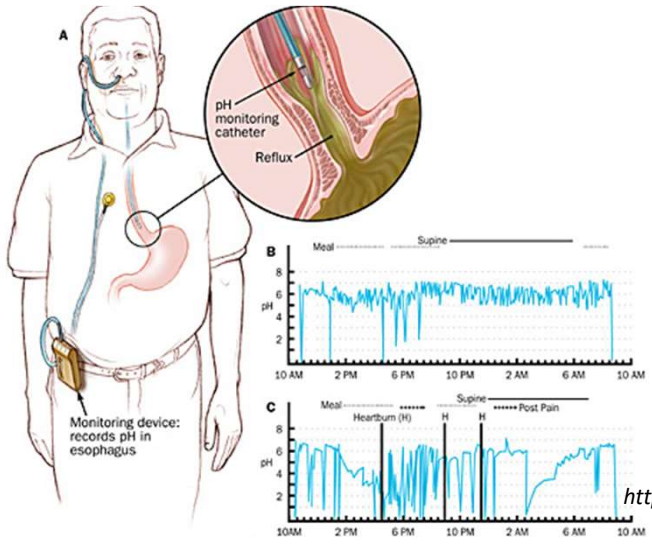
- pH and pH impedance monitoring reported sensitivity and specificity of pH-metry for differentiating controls from patients with esophagitis are 77-100% and 85-100%.
- Yield is increased by testing the relationship between reflux and patient reported symptoms

Kahrilas PK, F100Res. 2017

Ambulatory reflux testing

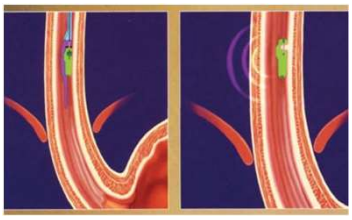
- pH-only testing
  - 24 hour catheter based
  - 48-96 hour wireless
- Combined impedance-pH monitoring (MII-pH)

24-hour pH monitoring



https://gi.jhsps.org

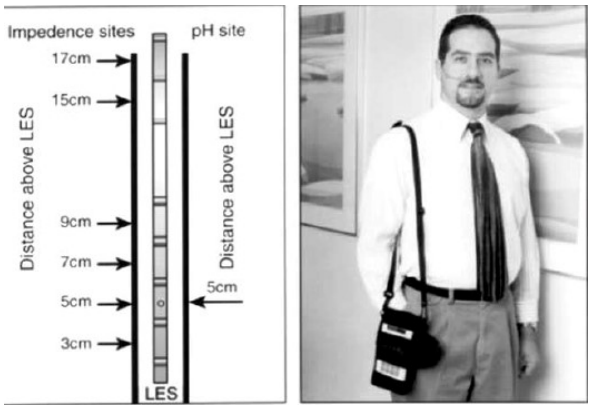
Wireless (Bravo) pH study



- Wireless capsule attached endoscopically to the mucosa 6 cm above the squamocolumnar junction.
- Monitoring beyond 24 hours is feasible and well tolerated (2-day or 4-day studies).
- Greater sensitivity to distinguish day-to-day variability.
- Increases potential number of symptoms available for association with reflux events.

Wong et al, Aliment Pharmacol Ther 2005
http://gjgastro.com/Education/Bravo-pH.html

Combined Multichannel Intraluminal Impedance-pH Monitoring



Shay S, et al. Am J Gastroenterol 2004

Combined Impedance-pH monitoring

- Majority of patients will have normal or low acid exposure while taking PPI
- In PPI-refractory patients, nonacid reflux may play an important role
- Impedance measurement allows for monitoring of nonacid reflux

Karamanolis G, et al. J Neurogastroenterol Motil 2011

The Lyon Consensus

Multinational group of GERD experts developed GERD consensus statements over a 2-year period.

Aim:

- To determine modern indications for esophageal testing in GERD
- To define criteria for a clinical diagnosis of GERD

Lyon Consensus

Ambulatory reflux monitoring

- **Indications:** patients with normal endoscopy, atypical symptoms and/or contemplating surgery.
- "*Proven GERD*" (prior LA C or D esophagitis, long segment Barrett's, or prior abnormal pH-metry) should be evaluated with *pH-impedance monitoring on BID PPI*.
- "*Unproven GERD*" should have *pH monitoring off therapy.*

On versus Off PPI Testing

- Low pretest probability for GERD: pH-only monitoring OFF PPI
- High pretest probability for GERD: pH-impedance monitoring ON PPI

"If pre-test prob is **LOW**, go Brav**O**! (and say **NO** to PPI!)

If **HIGH**, shoot for the **I** (impedance)!"

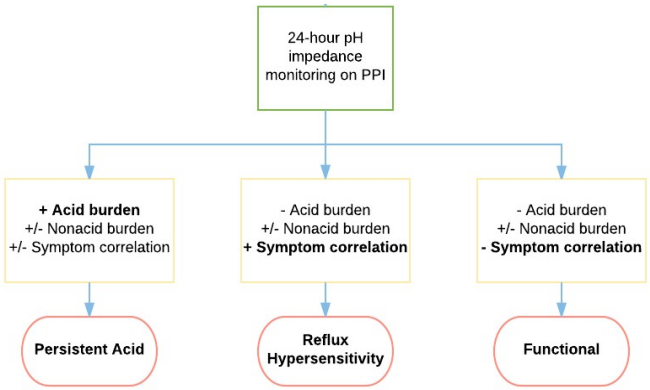
- Justin Brandler (1st year GI fellow)

Lyon Consensus

Interpretation of reflux monitoring

- Lyon consensus proposes that AET<4% be considered definitively normal and >6% definitively abnormal.
- Number of reflux episodes based on impedance: >80 reflux episodes per 24 hours are definitively abnormal, while <40 is physiological.

MII-pH monitoring for phenotyping of refractory GERD

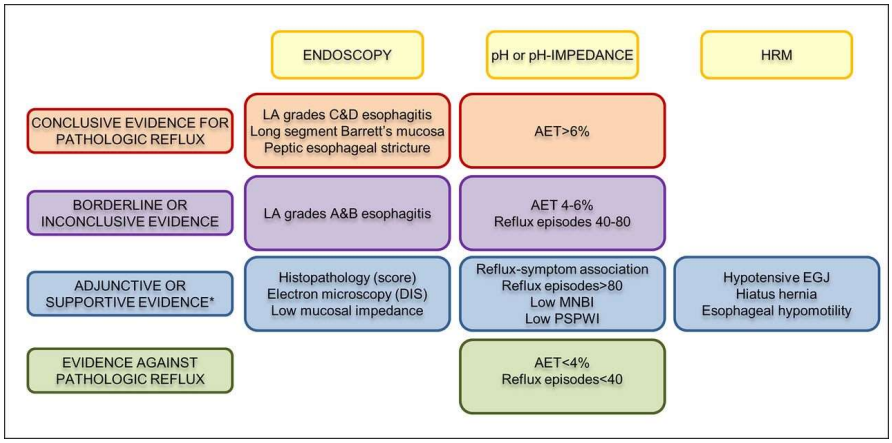


Chen, Gastroenterol Suppl 2012
Patel, Neurogastroenterol Motility 2016
Roman, Neurogastroenterol Motility 2017

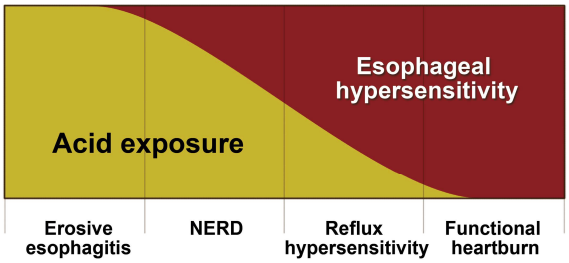
Lyon Consensus
Novel Metrics on pH-imp testing

- Post-reflux swallow-induced peristaltic wave (PSPW) index: proportion of reflux episodes on pH-imp monitoring that are followed, within 30 seconds, by a swallow
- Mean nocturnal baseline impedance (MNBI): average impedance from three 10 minutes periods spaced an hour apart while asleep
- Potentially helpful reflux metrics but outcome data are limited.

Lyon Consensus



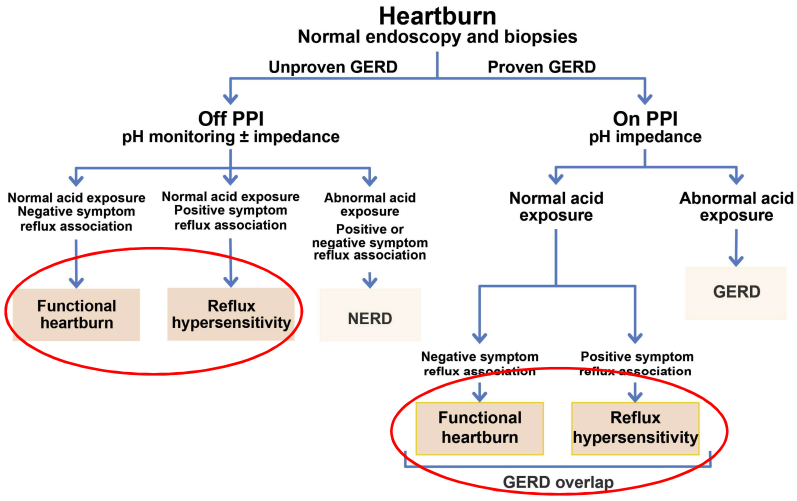
If not acid reflux, what is it?



- Rome IV introduced two separate functional esophageal disorders with heartburn as predominant symptom: **Functional Heartburn** and **Reflux Hypersensitivity**
- FH and RH may overlap with GERD

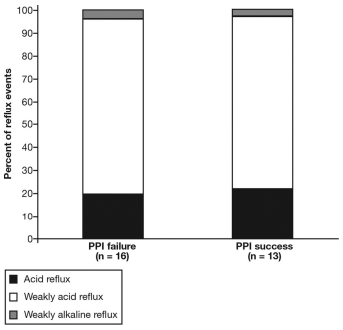
Aziz Q, Gastroenterology 2016

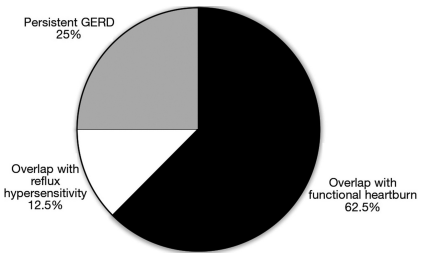
REFLUX SUBTYPES



Functional-GERD Overlap

- GERD subjects, separated into PPI success and PPI failure groups, underwent impedance-pH on PPI





Abdallah J, Clin Gastroenterol Hepatol 2019

Case:
PPI-partial responder

EGD negative

pH impedance on 20mg BID esomeprazole:

- Total AET 2.3% (3.9% upright, 0.3% recumbent)
- DeMeester Score 8.3
- Reflux events by impedance **85** (normal <73)
- **+ association between heartburn and reflux**

Treatment beyond PPI

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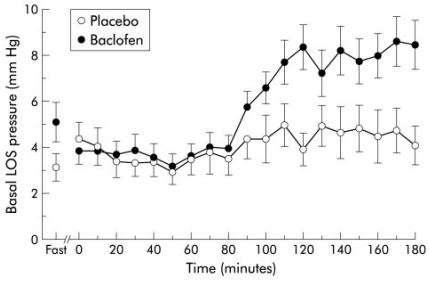
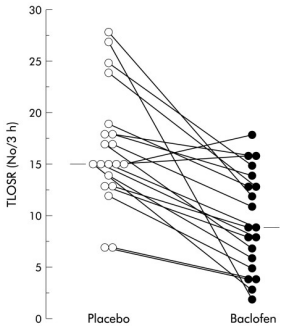
Reflux Inhibitor

Baclofen ($GABA_B$ agonist)

- Increase postprandial sphincter pressure
- Decrease frequency of transient lower esophageal sphincter relaxation
- Crosses blood brain barrier = frequent side effects



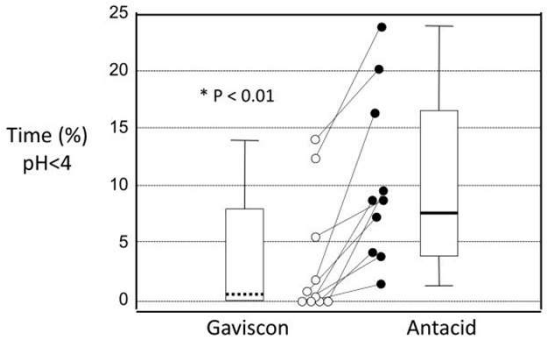


Zhang, GUT 2002

Postprandial heartburn

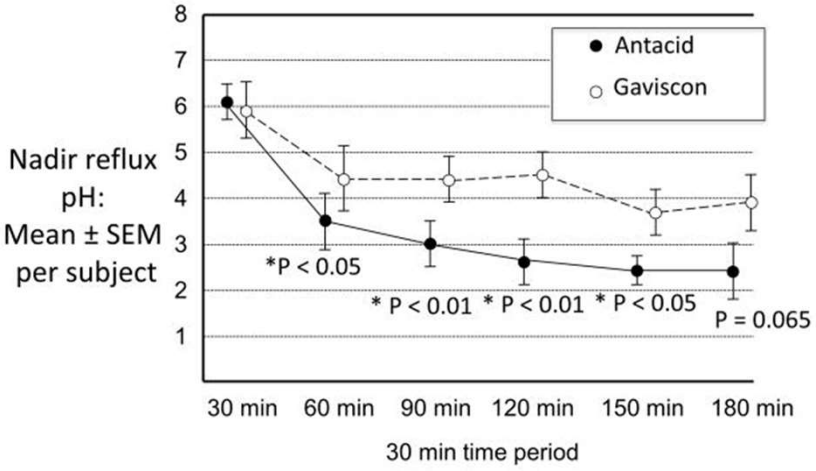
Alginate therapy

- Targeting the postprandial "acid pocket"



Chen, Aliment Pharmacol Ther 2015

Postprandial heartburn



Chen, Aliment Pharmacol Ther 2015

Treatment of Functional Esophageal Disorders

For **functional-GERD overlap:** optimize medical and lifestyle therapy for GERD as the first step

For **functional component**:

- Medications for neuromodulation
- Psychological/behavioral interventions

Neuromodulators for Functional Esophageal Disorders

- Modulate central (+/- peripheral) hyperalgesia

Drug classes and drug names	Typical dose for esophageal d/o	Typical dose for depression	Disorder	Response rate
TCAs				
Imipramine	25-50 mg/day	25-200 mg/day	NCCP	57%
Amitriptyline	10-20 mg/day	25-300 mg/day	NCCP, globus	52%
SSRIs				
Sertraline	50-200 mg/day	50-200 mg/day	NCCP	57%
Paroxetine	50-75 mg/day	20-50 mg/day	NCCP	Very limited
Citalopram	20 mg/day	20-40 mg/day	EH	Significant
Fluoxetine	20 mg/day	20-80 mg/day		
SNRI				
Venlafaxine	75 mg/day	37.5-225 mg/day	NCCP	52%
Trazodone	100-150 mg/day	50-400 mg/day	NCCP	Very limited
Theophylline	200 mg 2x/day	NA	NCCP	58%
Gabapentin	300 mg 3x/day	NA	Globus	66%

Riehl ME and Chen JW Curr Gastroenterol Rep 2018
Hoff DA, Brock C, Farmer AD, Ann NY Acad Sci 2016

Psychological Considerations

- Psychiatric comorbidity
- Esophageal Hypersensitivity
- Esophageal hypervigilance

The field of **psychogastroenterology** focuses on the application of scientifically-based psychological principles and techniques to alleviate digestive symptoms.

Psychological Interventions – Brain-Gut Psychotherapies

- Psychoeducation
- Modification of arousal
  - Diaphragmatic breathing
  - Guided imagery or progressive muscle relaxation
  - Esophageal-directed hypnotherapy
- Cognitive behavioral therapy

Riehl ME, Dis Esophagus 2016
Roman S, Neurogastroenterol Motil. 2015


AGA Clinical Practice Update: Expert Review

Best Practice Update: Incorporating Psychogastroenterology Into Management of Digestive Disorders

Laurie Keefer [1], Olafur S. Palsson [2], John E. Pandolfino [3]

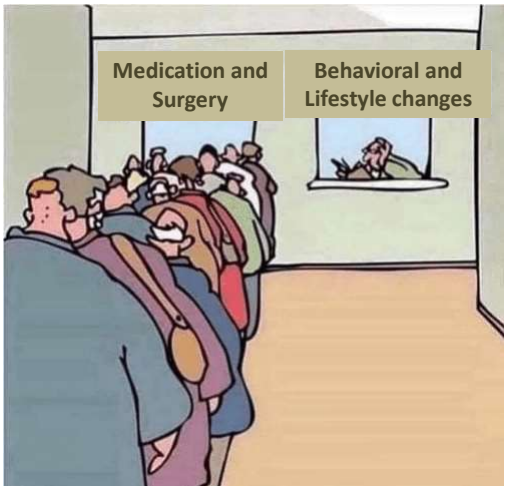
Best practice advice for gastroenterologists:

- Patient assessment
- Communication/education
- Knowledge in brain-gut psychotherapies
- Referral to mental health professional
- Neuromodulators

SUMMARY

- Not all heartburn is reflux; reflux does not always cause heartburn
- Look for alarm symptoms → EGD
- Consider ambulatory reflux testing to assess GERD phenotype/GERD-functional overlap
- Treatment for reflux symptoms should be individualized
- Consider role of esophageal hypersensitivity/hypervigilance

Questions?



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Gastroparesis

William L. Hasler
Professor, Division of Gastroenterology and Hepatology
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Gastroparesis: Definition, Etiologies, and Epidemiology

- Definition: Syndrome characterized by symptoms of gastric retention with objective evidence of delayed gastric emptying

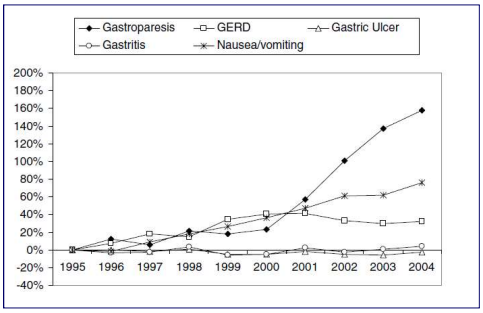
Etiologies
Idiopathic (65%) Diabetes mellitus (31%) Post-surgical (mainly postfundoplication)(3%) Autoimmune, amyloid, paraneoplastic, neuromuscular (1%)

Factor	Epidemiology
Prevalence	9.6/100,000 for men, 37.8 for women Community: 5% type 1 vs. 1% type 2 diabetes Tertiary: 30-40% type 1 vs. 10-30% type 2 diabetes
Incidence	2.4/100,000 years for men, 9.8 for women 5.2% over 11 years for type 1 vs. 1.0% for type 2 diabetes

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

Gastroparesis Impact on Health Resource Utilization

- Hospitalizations increased 158% over 10 years
- Type 1 diabetics hospitalized more than type 2 (5.1 vs. 3.2/year)
- Gastroparesis had longer lengths of stay than other 4 diagnoses
- Causes of admission:
  - Poor glycemic control (36%)
  - Infections (e.g. UTI)(19%)
  - Medication noncompliance (6%)
  - Medication side effects (5%)



Wang et al., Am J Gastroenterol 2008
Koch et al., Neurogastroenterol Motil 2016
Nusrat and Bielefeldt, Neurogastroenterol Motil 2013
Uppalapati et al., Dig Dis Sci 2009

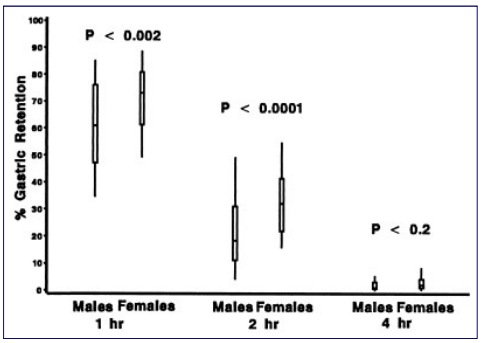
Symptoms in Gastroparesis

- Nausea and vomiting:
  - Nausea in 96% (severe in 40%)
  - Nausea relates to meals in 71%, esp. fats, dairy foods
  - Vomiting 81% in diabetics, 59% in idiopathics
- Early satiety/postprandial fullness:
  - 60% report severe early satiety/fullness
  - Relates to decreased BMI, impairs QOL
- Abdominal pain:
  - Two thirds report severe pain (more common in idiopathics)
  - Impairs QOL and 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

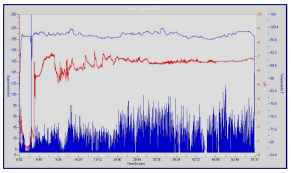
- 123 volunteers given ^{99}Tc EggBeaters, toast, jam, water (2% fat, 255 kcal). Assess emptying at 1, 2, and 4 hours
- Delayed: Retention >60% at 2 hr, >10% at 4 hours for diagnosis of gastroparesis
- Recommended by US motility and nuclear medicine societies in 2008
- Inconsistently adopted

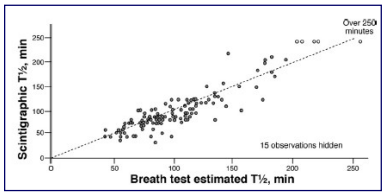


Tougas et al., Am J Gastroenterol 2000
Abell et al., Am J Gastroenterol 2008
Abell et al., J Nucl Med Tech 2008

Other Methods to Measure Gastric Emptying

- Wireless Motility Capsule:
  - Measures pH (transit) and contractions
  - 3 published prospective studies validating as a measure of 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 and digested to liberate $^{13}CO_2$ exhaled 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

Diet in Gastroparesis

- Accepted diet recommendations based on physiology:
  - Frequent small meals (soft to liquid consistency)
  - Low fat
  - Low fiber
  - Low residue
- Actual patient compliance:
  - 1.4±1.0 meals/d; 37% small portions
  - 10% on low fat diet
  - 67% on low fiber diet
  - Residue not assessed
  - 2% following a "gastroparesis diet"

Parkman et al., Gastroenterology 2011

Food Tolerance in Gastroparesis

- Methods: 45 patients completed Food Toleration and Aversion survey on -3 (greatly worsening) to +3 (greatly improving) scale.
- Results:
  - Symptoms provoked by fatty, acidic, spicy, high roughage foods
  - Tolerated bland, salty, sweet, and starchy

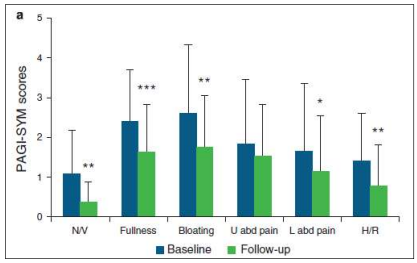
Worsened	Improved	Tolerated
Orange juice Fried chicken Cabbage Sausage Pizza Peppers Onions Tomato juice Lettuce Coffee Bacon Roast beef	Saltine crackers Graham crackers Jello	Ginger ale Gluten-free Tea Potatoes Pretzels Fish Clear soup White rice Popsicles Applesauce

Wytiaz et al., Dig Dis Sci 2015

RCT of Small Particle Diet in Gastroparesis

- Methods: 56 diabetics with gastroparesis given a "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

Glycemia in Diabetic Gastroparesis

- Higher A1c values over 27 years associated with worse gastric emptying delays in 78 patients from DCCT cohort
- Acute hyperglycemia >275 mg/dL delays gastric emptying
- On continuous glucose monitoring, delays in gastric emptying lead to:
  - Lower early postprandial blood glucose levels
  - Prolonged high blood sugar levels many hours after eating

Bharucha et al., Gastroenterology 2015
Phillips et al., Nat Rev Endocrinol 2015
MacGregor et al., Gastroenterology 1976
Homko et al., J Diab Comp 2016
Ramzan et al., Dig Dis Sci 2011
Olausson et al., J Diab Sci Tech 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 after screening and run-in
- 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) and decreased time in hypo-, hyperglycemia on CGM

Measure		Study Visit			P Value	
		Baseline	12 Weeks	24 Weeks	Baseline vs. 12 Weeks	Baseline vs. 24 Weeks
Symptoms	Total symptom score (0-45)	29.3±7.1	-7.2±8.2	-6.6±8.8	<0.0001	<0.0001
	Nausea/vomiting subscore (0-15)	8.1±4.2	-2.9±4.0	-2.8±4.1	<0.0001	<0.0001
	Fullness/early satiety subscore (0-20)	14.1±3.6	-3.1±4.5	-2.4±4.5	<0.0001	0.002
	Bloating/distention subscore (0-10)	7.1±2.3	-1.3±2.9	-1.5±2.5	0.0009	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

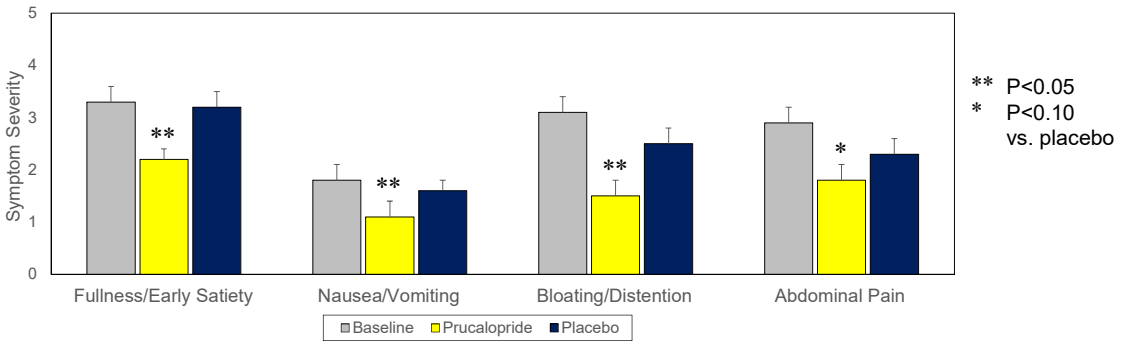
Prokinetic Safety in Gastroparesis

- Metoclopramide:
  - FDA warning (2009) for tardive dyskinesia reduced prescription from 70% to 24%
  - Tardive dyskinesia 1 per 2000-2800 treatment years (2nd most common after haloperidol); risk groups—age >70 yrs, dose >30 mg, treatment >20 months
- Domperidone:
  - Netherlands (1304 pts): 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): Risk increased age >60 years 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
  - Health Canada (2012) and European Medicines Agency (2014) recommended limitations
  - Cardiac arrhythmias also with erythromycin, TCAs, 5-HT_3 antagonists, other antiemetics

Lee and Kuo, Exp Rev Endo Metab 2010
Ehrenpreis et al., AJG 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-octanoate 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% response rates)
NK_1 antagonists	Aprepitant, rolapitant	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 and nausea 25 mm on 100 mm VAS given 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 GCSI 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

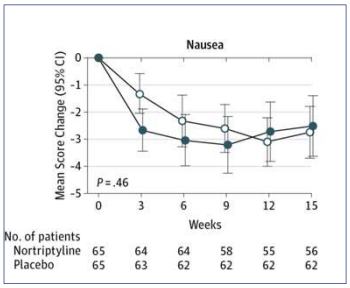
Jehangir and Parkman, Am J Gastroenterol 2019

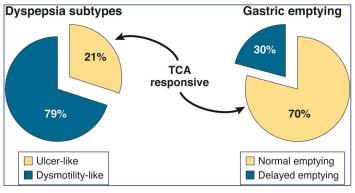
Neuromodulators With Theoretical Benefit in Gastroparesis

Drug(s)	Mechanisms of Action	Reported Clinical Utility
Tricyclics (amitriptyline, nortriptyline, desipramine)	Norepinephrine reuptake inhibition with variable serotonin (and dopamine) reuptake inhibition	Functional dyspepsia Cyclic vomiting syndrome Functional vomiting Nausea and vomiting with diabetes
Mirtazapine	"Indirect" CNS 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 Nausea of pregnancy 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

RCT of Tricyclic Agent in Gastroparesis

- Methods:
  - Nortriptyline escalating to 75 mg qhs vs. placebo x 15 wk in 130 idiopathic gastroparetics
  - Primary outcome ≥50% decrease from baseline on 2 serial 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

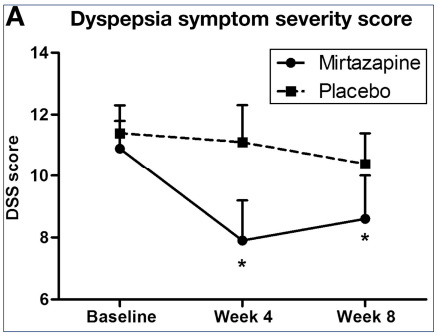




Parkman et al., JAMA 2013
Talley et al., Gastroenterology 2015
Hasler, Koch, Gastroenterology 2015

RCT of Mirtazapine in Functional Dyspepsia

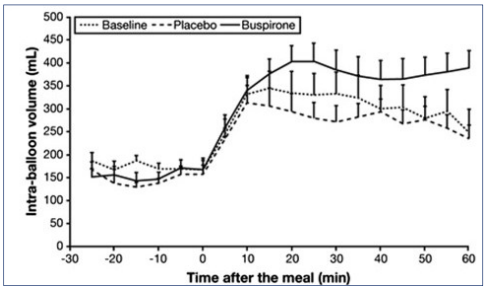
- 34 functional dyspeptics with >10% weight loss treated with mirtazapine 15 mg/d vs. placebo x 8 weeks
- Mirtazapine reduced dyspepsia scores at 4 wk (P=0.003) and 8 wk (P=0.02)
- Mirtazapine produced ~4 kg wt gain over 8 wk; placebo produced no change
- Only case reports in gastroparesis



Tack et al., Clin Gastroenterol Hepatol 2016

RCT of Buspirone—a Stomach Relaxant to Improve Meal Tolerance

- 5-HT_{1A} agonist (buspirone) relaxes the gastric fundus and improves meal tolerance
- In RCT in functional dyspepsia, buspirone 10 mg tid reduced overall symptoms and pain
- No trials in gastroparesis



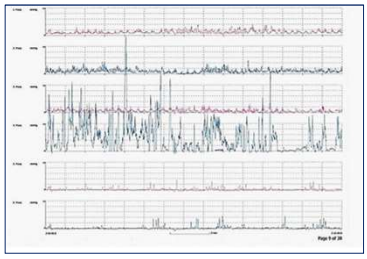
Tack et al., Clin Gastroenterol Hepatol 2012

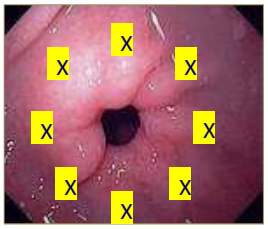
Non-Medication Treatment of Gastroparesis

- Pyloric therapies:
  - Botulinum toxin
  - Pyloroplasty—uncontrolled studies show ~80% responses to accelerate gastric emptying
- Other surgeries:
  - Gastric electrical stimulation
  - Gastric resection—~60-70% improved with gastric bypass or subtotal gastrectomy for diabetic/idiopathic gastroparesis
  - Pancreas transplant (diabetic gastroparesis)—no convincing 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



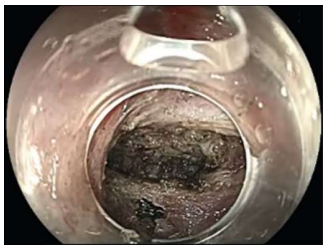


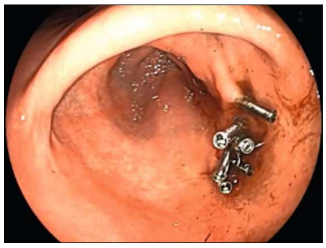
- >20 articles report reduced symptoms or improved stomach emptying
- Largest study (179 patients) showed higher doses (200 units) work better than lower doses (100 units)
- 2 inadequately powered trials compared Botox to placebo—no symptom benefits or consistent acceleration of gastric emptying

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 the pylorus and 2-3 cm proximally.
  - Close tunnel with endoclips.





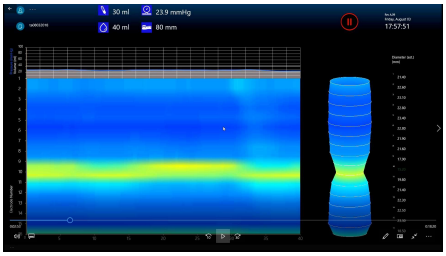
Benefits of G-POEM in Gastroparesis

- Largest single center study of 177 patients:
  - Intraprocedure 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% 4 hour retention to 18%
- Systematic review of 14 studies of 276 patients:
  - 61% normalized gastric emptying
  - Symptom improvements n 90% at 1 month and 57% at 18 months
  - Complications in 3.2%

Strong et al., J Gastrointest Surg 2019
Zhang et al., Gastroenterol Hepatol 2019

Use of EndoFLIP to Measure Pyloric Compliance/Distensibility

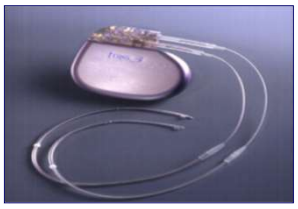
- Measured pyloric pressure and compliance in 27 gastroparesis patients vs. 21 controls:
  - Compliance lower in gastroparesis vs. control (17±2 vs. 25±2 mm^2/mmHg)(P<0.05)
  - Pyloric dilation increased distensibility in 10 patients from 7±1 to 20±5 mm^2/mmHg (P<0.01)

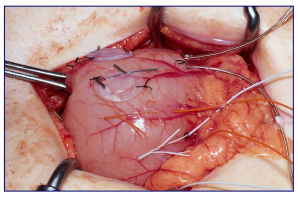


- In another study, 19/35 (54%) had decreased distensibility:
  - Symptoms reduced in patients with reduced distensibility (13.5 to 10.5, P<0.01) but did not change with normal distensibility

Gourcerol et al., Aliment Pharmaco Ther 2015
Desprez et al., Gastrointest Endosc 2019

Gastric Electric Stimulator for Gastroparesis

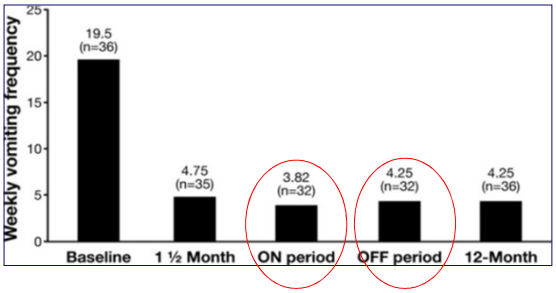




- Misconceptions:
  - Not a true pacemaker
  - Does not improve gastric emptying
- Benefits in 50-90% of patients in 25 articles (1 to 221 patients):
  - Reduced symptoms
  - Lower A1c
  - Improved nutrition
  - Less health care usage
  - Less effective for idiopathic patients, for pain, for opiate dependence
- FDA approved as a humanitarian device:
  - Restricted to sites managed by research board oversight
  - Never definitively proved to be effective

Concerns Raised About Gastric Stimulator

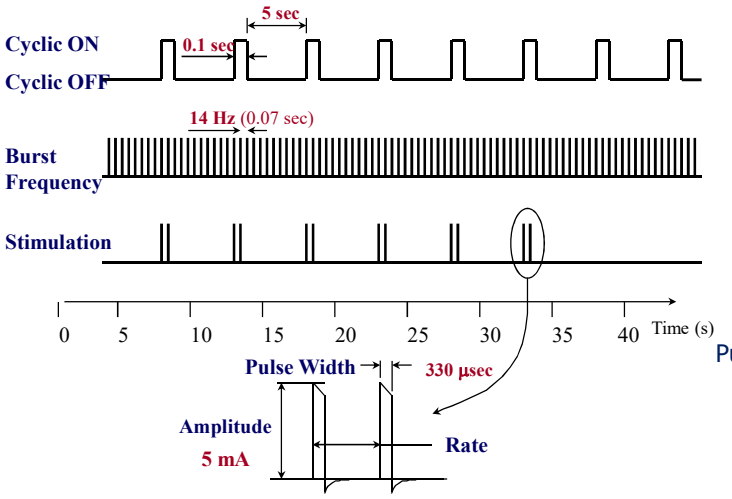
- In 3 trials, no differences in symptoms when device turned ON or OFF



- Many centers discontinued performance or never started because of lesser responses/skepticism about data

Abell et al., Gastroenterology 2003
McCallum et al., Clin Gastroenterol Hepatol 2010
McCallum et al., Neurogastroenterol Motil 2013

Gastric Electrical Stimulation Parameters



Parameters of My Last 12 Patients

ON time: 0.8±0.2 sec (8 X factory setting)

Frequency: 23±9 Hz (1.6 X factory setting)

Pulse width: 357±34 µsec (1.1 X factory setting)

Current: 7.5±2.9 mA (1.5 X factory setting)

Bottom line: Controlled trials did not study effective current settings

The Problem of Patient Access to Gastroparesis Therapy

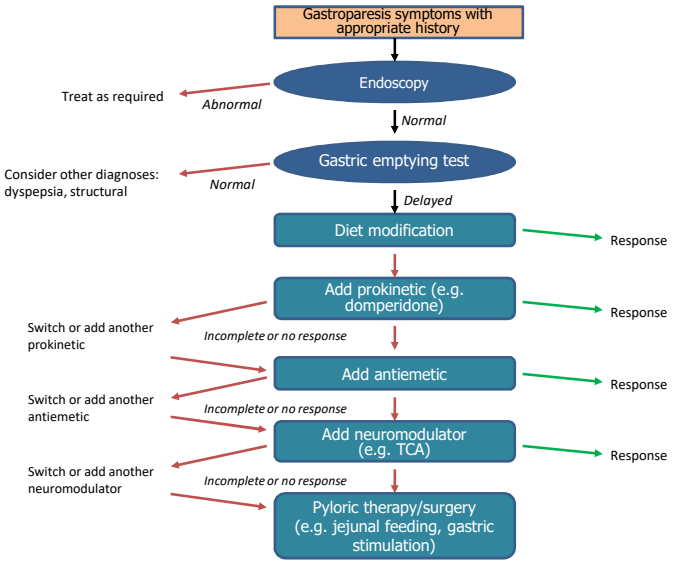
NOT SO BAD

Therapy	Monthly Cost
Metoclopramide	$6
Erythromycin	$7
Prochlorperazine	$30
Promethazine	$15
Ondansetron	$35

CHALLENGING

Therapy	Cost	Coverage by Payers
Prucalopride	$200 monthly	Online pharmacies (Canada); not covered
Dronabinol	$500 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	$40-75,000	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

Final Thoughts

- Gastroparesis is not a stagnant field
- New methods of testing may influence outcomes; pyloric testing may help patient selection
- New medications and endoscopic therapies expand the available treatment options
- Future studies will determine if these new options improve the clinical course of gastroparesis

Audience Participation

Poll Everywhere

1. Take out your cell phone, tablet or computer to participate
2. Text jamikinnucan615 to **37607**
3. You will get a welcome message!
4. You are then all set to participate

Health Maintenance in IBD: What every gastroenterologist should know

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Assistant Program Director, GI Fellowship Training
Michigan Medicine, Division of Gastroenterology

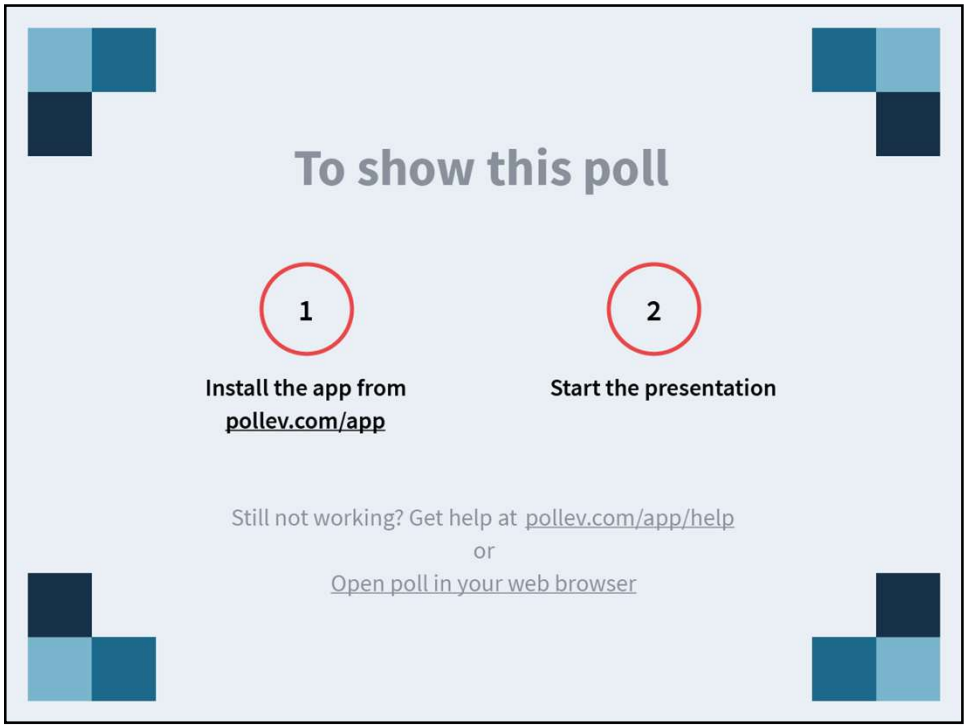
MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

Disclosures

- Advisory board member
  - Abbvie
  - Janssen
  - Pfizer
  - Genetech
- Crohn's and Colitis Foundation
  - National Scientific Advisory Committee Chair, Patient Education Committee

Outline

1. Review of quality measures and guidelines for preventative care in IBD
2. Outpatient: Case-based approach to health maintenance
3. Inpatient: Case-based approach to preventative care



AGA IBD Quality Measures

aga American Gastroenterological Association

Measure # 1: Inflammatory bowel disease (IBD): type, anatomic location and activity all assessed

Measure # 2: IBD preventive care: corticosteroid sparing therapy

Measure # 3: IBD preventive care: corticosteroid related iatrogenic injury – bone loss assessment

Measure # 4: IBD preventive care: influenza immunization

Measure # 5: IBD preventive care: pneumococcal immunization

Measure # 6: Testing for latent TB before initiating anti-TNF therapy

Measure # 7: Assessment of hepatitis B virus before initiating anti-TNF therapy

Measure # 8: Testing for *Clostridium difficile* – inpatient measure

Measure # 9: Prophylaxis for venous thromboembolism — inpatient measure

Measure # 10: IBD preventive care: tobacco user – screening and cessation intervention

AGA IBD performance measures set 2011.

Crohn's and Colitis Foundation: "Top Ten" Measures (2013)

Processes	Outcome
Steroid sparing therapy (if steroids >4m)	Steroid-free clinical remission
Pre-treatment: Testing for TB	Days lost from work/school
Pre-treatment: TPMT before thiopurine	Days hospitalized
Education for vaccinations	ED visits
Smoking cessation in Crohn's disease	Malnutrition
LGD: Colectomy OR close surveillance	Anemia
Testing for *C. difficile* in active flare	Narcotic use
Flex sig for CMV evaluation in steroid refractory hospitalized patients	Fecal incontinence
	Normal health-related QOL
	Nocturnal symptoms

LGD= low grade dysplasia

Melmed G *IBD* 2013

ACG Preventative Health Clinical Guideline (2017)

Farraye FA et al. *Am J Gastro* 2017.
C= conditional S= STRONG

	Recommendation	Guideline
1a	Annual influenza vaccination (C)	AGA, CCF, PQRS
2	Pneumonia vaccination in patients on immunosuppression (C)	AGA, CCF, PQRS
3	Adults (>50) should be vaccinated against Herpes Zoster (S)	
4	Adults should be assessed for prior exposure to varicella (C)	
5	Travel to endemic areas of yellow fever should consult travel spec (C)	
6	Adolescents should receive meningococcal vaccination (C)	
7	Household members of immunosuppressed patients can receive LIVE vaccination (C)	
8	Adults should receive age-appropriate vaccinations	CCF
9	Vaccination to Tdap, HAV, HBV, HPV per ACIP guidelines (C)	CCF
10	IBD women on immunosuppression should undergo annual pap (C)	
11	Screening for anxiety and depression is recommended in all patients (C)	
12	a- IBD patients should undergo screening for melanoma, independent of biologic therapy (S) b- Immunomodulator use should have annual screening for NMSC (S)	
13	Patients with risk factors should undergo BMD evaluation at diagnosis (C)	AGA, PQRS
14	Crohn's disease patients should have counselling to quit smoking (S)	AGA, CCF, PQRS

AGA Performance Measures (2018)

Bone Loss Assessment
Iatrogenic steroid related injury Steroids >600 mg exposure (10 mg/d x 60d)

Pre-anti-TNF Treatment
Annual assessment of Hepatitis B and TB

Post-operative assessment
Evaluation within 6-12 months of surgery in patients with Crohn's disease

Outpatient Quality Measures Health Maintenance Cases

Case: Disease evaluation

50 year old female with ulcerative pancolitis on mesalamine monotherapy with complaints of urgent, gas, bloating and intermittent diarrhea x 1 month

What does this typical visit look like?

Disease documentation

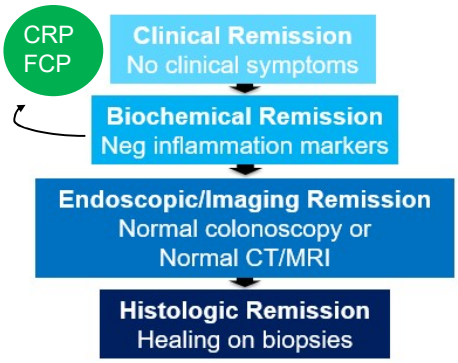
- All IBD patients should have disease documentation assessed during outpatient clinic visit

- In practice what does this look like?
  - ☑ Disease type Ulcerative colitis
  - ☑ Disease location Pancolitis
  - ☑ Disease activity Clinical and biochemical activity
  - ☑ Steroid sparing therapy Mesalamine

AGA Quality Measures: #1, #2
PQRS Measure #270

My typical IBD Clinic Visit

- ✔ How are you feeling today?
- ✔ Review of recent labs and if they are up to date (last 3-12m)
- ✔ Review of last objective assessment (last 12m)?
- ✔ Review of health maintenance
- ✔ If active symptoms, why?
- ✔ Education



CRP- C-reactive protein
FCP- fecal calprotectin

Case: Disease evaluation

50 year old female with ulcerative pancolitis on mesalamine monotherapy with complaints of urgent, gas, bloating and intermittent diarrhea x 1 month

- ✔ Clinically active symptoms (but atypical for her colitis)
- ✔ Last labs 1 year ago, normal
- ✔ Last colon 1 year ago histologic healing, FCP (1 month ago) was normal (<15.6)
- ✔ So why is she having symptoms?

Active
Symptoms ≠ Disease ≠ Symptoms

Clinical Remission
Endoscopic Remission

Clinical Remission
Biochemical Inflammation

Subclinical Inflammation

Optimize Treatment

Clinical Symptoms
Endoscopic Remission

Non-inflammatory causes to symptoms

Case: Disease evaluation

50 year old female with ulcerative pancolitis on mesalamine monotherapy with complaints of urgent, gas, bloating and intermittent diarrhea x 1 month

CBC Iron studies
CMP Vitamin D
CRP UA

Infection eval
Repeat FCP

Surveillance endoscopy

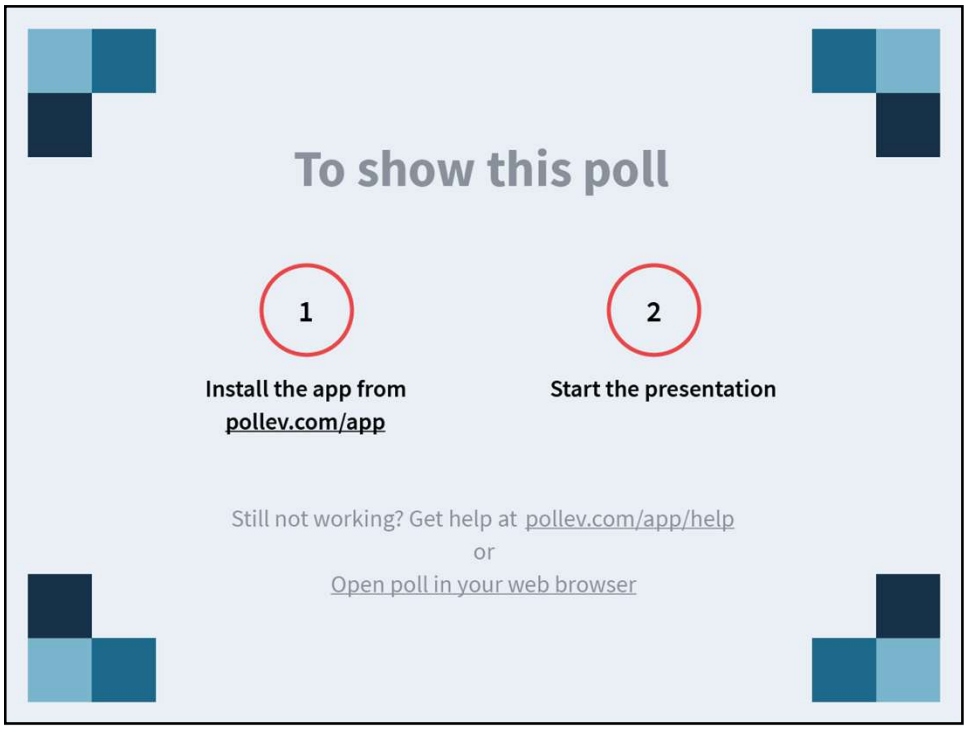
Treatment based lab evaluation

Mesalamine
Annual kidney function
(BMP, +/-UA)

Thiopurines/Methotrexate
CBC + CMP q3-4m

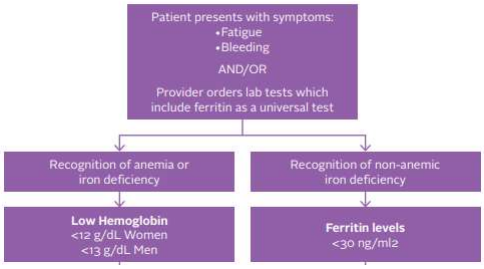
Biologic Therapy
Screen: TB, Hepatitis B
CBC + LFT, CRP at least q6m

Tofacitinib
Screen: TB, Hepatitis B,
CBC + LFT, lipids
Lipids 4-8w after starting



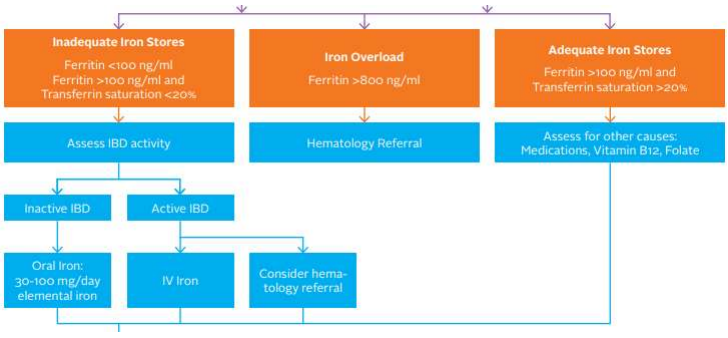
Iron Deficiency Screening/Management

- Screening for iron deficiency
  Inactive/mild q6-12m Active disease q3-6m



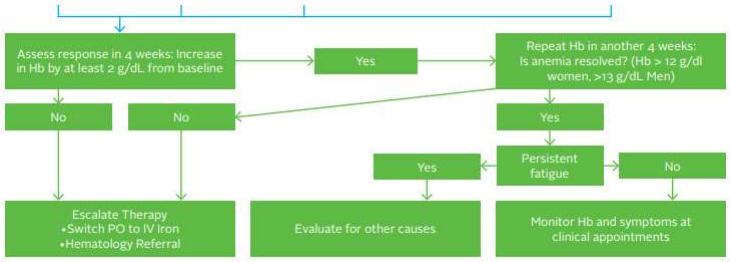
Crohns and Colitis Foundation. Anemia Care Pathway.

Iron Deficiency Screening/Management

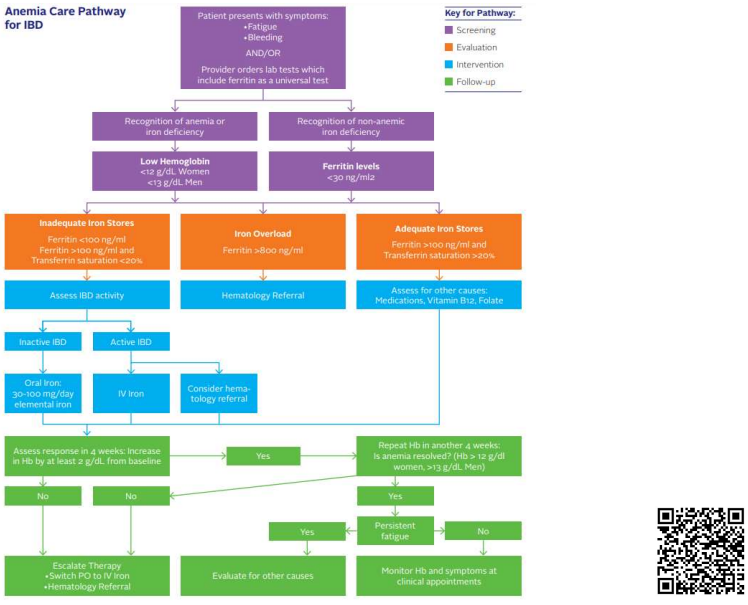


Crohns and Colitis Foundation. Anemia Care Pathway.

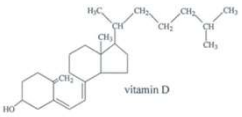
Iron Deficiency Screening/Management



Crohns and Colitis Foundation. Anemia Care Pathway ECCO guidelines 2015.



Preventative Health: Vitamin D



- Vitamin D is a fat-soluble vitamin that plans a role in bone, Ca and phosphorus metabolism and immune function
- Vitamin D **might** play a role in disease pathogenesis
  - Higher Vitamin D levels reduce risk for incident Crohn's disease
  - Vitamin D supplementation might decrease risk of relapse at 12m and reduced risk for surgery in CD
  - Low Vitamin D levels (≤ 35 ng/nl) ↑ risk of relapse by 25%
  - Studies show impact of supplement on disease activity, QOL
- Prospective studies are needed to evaluate further relationship

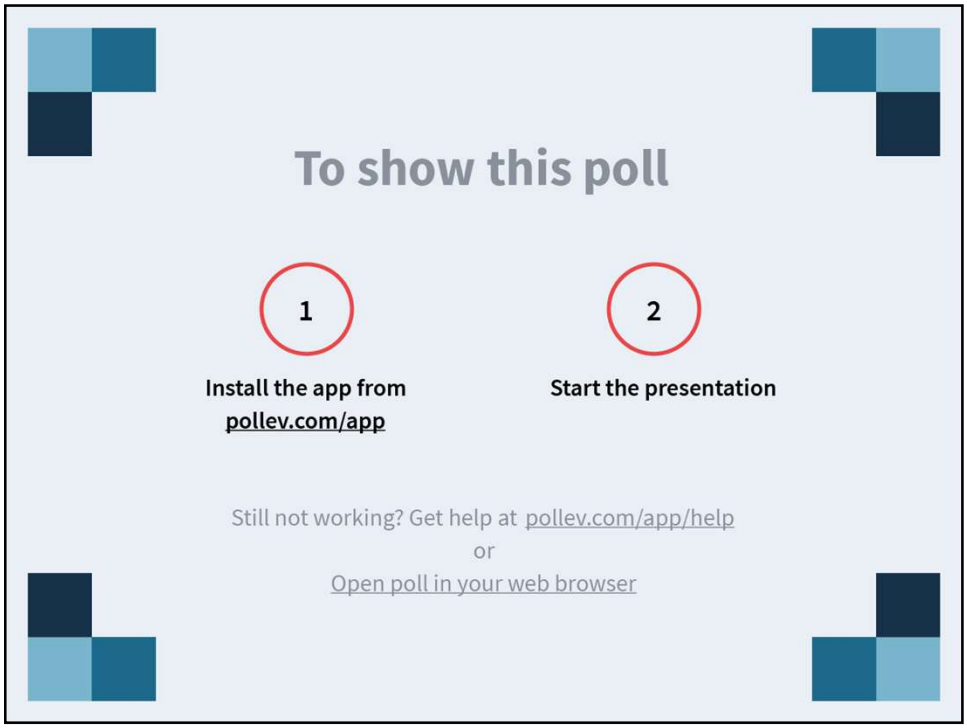
*Assessment of 25-OH Vitamin D levels in all IBD patients
*Replacement with goal Vitamin D ≥ 30 ng/ml[1]

1. Ananthakrishnan AN *IBD* 2013. 2. Ananthakrishnan AN *Gastro* 2012.
3. Gubatan J *Clin Gastro Hepatol* 2016. 4. Ulitsky A et al. *J Parenter Enteral Nutr* 2011.

Case: Pre-treatment evaluation

50 year old female with ulcerative pancolitis who is failing outpatient management with mesalamine therapy and currently prednisone dependent x 2 months with ongoing active symptoms and elevated fecal calprotectin. Recommend escalation of therapy to anti-TNF therapy in combination with azathioprine. **Based on quality measures what pre-treatment labs we should we check?**

A. Nothing, she can start therapy now
B. Hepatitis B screening
C. TB screening
D. Hepatitis C screening
E. Hepatitis B + TB screening
F. Hepatitis B + Hepatitis C + TB screening



Prevention of infection: Pre-immunosuppression assessment

- Prior to starting medical therapy *(any immunosuppression)*
  - **Hepatitis B** (also check Hep A)
    - Hepatitis B surface antigen (Hep Bs Ag)
    - Hepatitis B surface antibody (Hep Bs Ab)
    - Hepatitis B core antibody (Hep Bc Ab)
  - **TB assessment**
    - PPD skin testing
    - QuantiFERON-TB Gold
  - **TPMT** (if considering azathioprine or 6MP)

AGA Quality Measures: #6, #7
CCF, PQRS Measurements #274, #275

Prevention of infection: Assessment and Vaccination

ACG Guideline #8
AGA 2018

- If non-immune to Hepatitis B

Standard Vaccination
Hepatitis B vaccination* Dose 1: Day 0 Dose 2: 1 months Dose 3: 6 months Hep Bs Ab: 1-3m later

Accelerated Vaccination**
Hepatitis B vaccination Dose 1: Day 0 Dose 2: Day 7 Dose 3: Day 21 or 30 Booster: 12 months Hep Bs Ab: 1-3m later

*Assessment of Hepatitis B and TB is important before starting any immunosuppression therapy
*It is important to vaccinate those patient who are non-immune
*Assess immunity 1-3 months after vaccination

*can substitute Engerix-B, Recombivax HB (Hep B) with Twinrix (HepA+B)
**used rarely, high risk patients or high risk travel

Adult recommended vaccination Schedule. *CDC*. 2017 ACIP Guidelines

Case: Pre-treatment evaluation

50 year old female with ulcerative colitis who is steroid dependent who underwent pre-treatment evaluation:

QuantiFERON-TB Gold: negative
Hepatitis Bs Ab: non-reactive
TPMT: normal

Patient received initial dose of Hepatitis B standard vaccination schedule. Follow-up with primary care for completion of series. Assessment of immunity in 4-6 weeks.

Initiated anti-TNF therapy and azathioprine 1 week after initial labs

***DON'T** delay adequate therapy for IBD for vaccination series

Pre-treatment evaluation

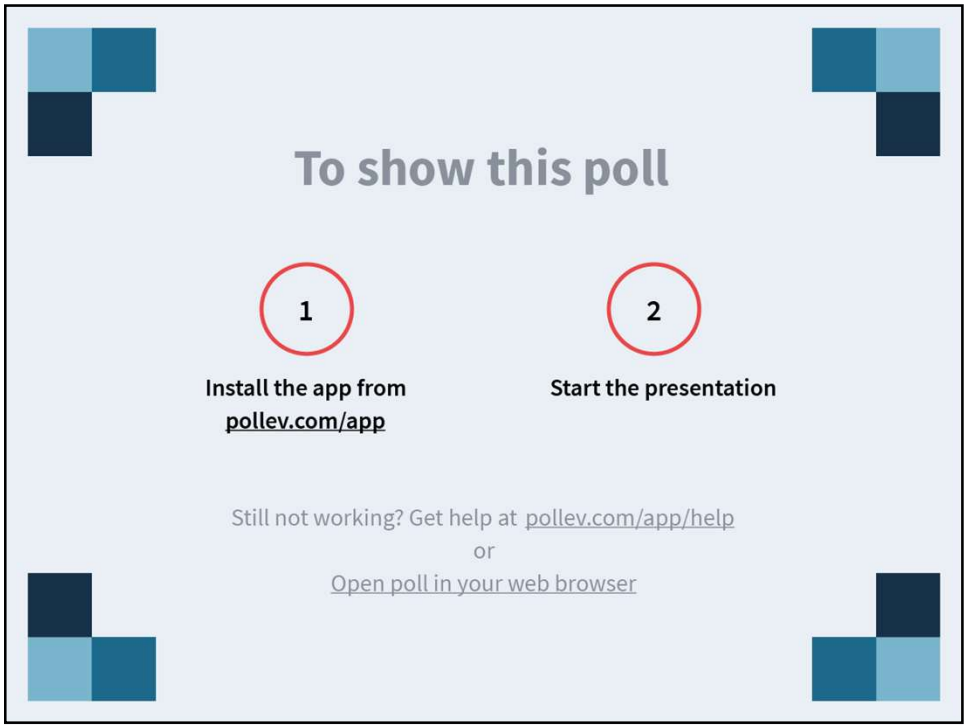
Other lab considerations on initial visit/evaluation:

Measles, Mumps, Rubella- Ruebella IgG
EBV- EBV IgG
Varicella- Varicella IgG

Case: Vaccination

Same 50 year old patient presents now for her 3 month follow-up after initiation of anti-TNF therapy with azathioprine. She inquires about what vaccinations she needs. **What vaccinations are indicated in this patient?**

A. No additional vaccinations
B. Influenza
C. Pneumonia vaccination
D. Influenza + pneumonia
E. Herpes Zoster (Zostavax)
F. All of the above



Prevention of infection: Influenza and pneumonia vaccinations

AGA Quality Measures: #3, #4

- Annual influenza vaccination in recommended in **ALL** patients with IBD
  - LIVE vaccination contraindicated in patients on IS*

- Pneumonia vaccination is indicated in patients ≥ 65 years old or **patients on immunosuppression therapy**

Vaccine naive	PCV13 → PPSV23 2m-12m later *ideal is 2m (8 weeks)
PPSV23 prior	PCV13 at least 1 year after PPSV23
PCV13 + PPSV23	Up to date, PPSV23 should be given 5 years from the last PPSV23

PCV13- Prevnar
PPSV23- Pneumovax

Okay to give Influenza + Prevnar together

*LIVE vaccination was less effective, no longer available

ACIP *MMWR* 2013.

Avoid LIVE vaccines in immunosuppressed patients

- Avoid LIVE vaccinations in those patients who are on **"high-level"** immunosuppression based therapy
- CDC has clear recommendations about timing for how long to wait as well as recent ACG guidelines

High level
Anti-TNF therapy Vedolizumab (*benefits>risks) Ustekinumab

Low level (within 3 months)
Prednisone 20 mg/d >14d MTX <0.4 mg/kg/week AZA <3 mg/kg/day or 6MP <1.5 mg/kg/day

Live Vaccines
MMR (measles, mumps, rubella) Shingles (Zostavax) Chicken pox (varicella) Rotavirus (oral) Yellow fever BCG vaccination Polio vaccination (oral) Smallpox vaccination Adenovirus vaccine Typhoid (live)

Adult recommended vaccination Schedule. *CDC.* 2017.

Prevention of infection: Shingles

- **Zostavax** is a LIVE vaccination
  - Single dose vaccination
  - Recommended in all adults age 60 and older
  - Okay on patients on "low level" immunosuppression
  - Patients starting biologic therapy need to wait 4w
  - Low effectiveness

Low level
Prednisone 20 mg/d >14d MTX <0.4 mg/kg/week AZA <3 mg/kg/day 6MP <1.5 mg/kg/day

- **Shingrix** is NON-LIVE, recombinant subunit vaccination
  - Approved by FDA 10/2017
  - 2-dose vaccination series (0 → 2-6m)
  - Recommended in all adults age 50 and older
    - Even if they have previously received Zostavax
  - Not studied specifically in immunocompromised patients
  - FYI: Not typically covered by insurance in patients <50

Current national shortage of vaccine

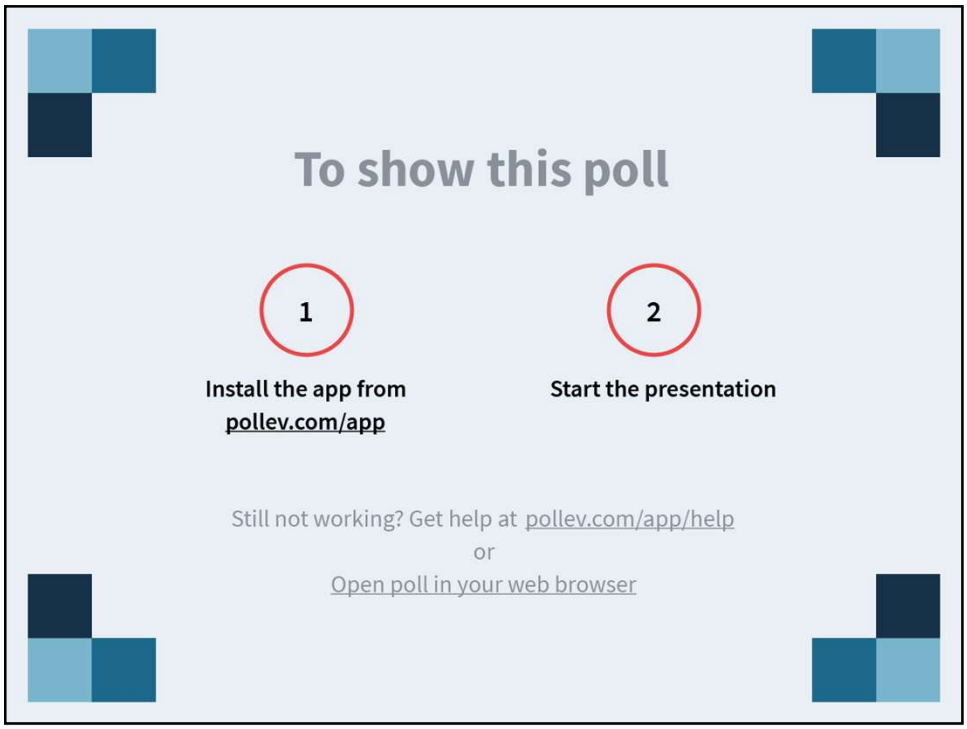
ACG Recommendation #3

Adult recommended vaccination Schedule. *CDC.* 2017.

Case: Bone Health Assessment

50 year old female with ulcerative pancolitis who is failing outpatient management with mesalamine therapy and currently prednisone dependent x 2 months (cumulative lifetime exposure >6m steroids). **Given her steroid exposure what is indicated for evaluation?**

A. Nothing currently
B. Vitamin D level and supplementation
C. Dual-energy x-ray (DEXA)
D. Both B + C



Preventative Health: Bone Health

- IBD patients are higher risk for developing bone disease[1-3]
  - Crohn's disease > ulcerative colitis
  - Higher risk with cumulative exposure to steroids
  - Risk for lower **Vitamin D** levels which is linked to bone disease

Prednisone 600 mg=
Pred 7.5 mg/d (3m)
Pred 10 mg/d (2m)
Pred 20 mg/d (1m)
Pred 40 mg/d (2w)

- Indications of dual-energy x-ray (DEXA)
  - Prednisone >7.5 mg/day x 3 months
  - >60 years old
  - Post-menopausal women
  - History of fracture

*DEXA when indicated (as above)
*Referral to endocrinology when indicated

AGA Quality Measures: #3
PQRS Measure #271

1. Shirazi KM et al. *Saudi J Gastro* 2012. 2. Farraye FA et al. *Am J Gastro* 2017 (guidelines)
3. Driscoll RH et al. *Gastroenterology* 1982. 4. Ananthakrishnan AN *IBD* 2013.

Case: Tobacco Assessment

30 year old female smoker with ileal Crohn's disease with history of ileocecal resection on 6-MP since surgery with evidence of clinical and biochemical (normal fecal calprotectin) remission (healing) presents for follow-up. She is currently smoking ½ PPD. **How should we be counseling patients on tobacco use?**

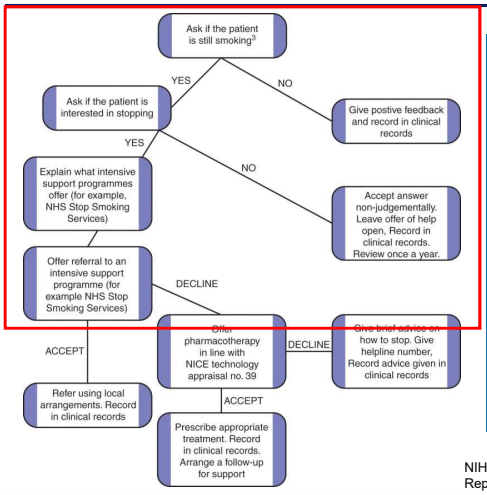
Tobacco Use Assessment

- All patients: assessment and documentation of tobacco use
- Crohn's disease: documentation of tobacco use **and** counseling of smoking cessation (each visit)
- Active tobacco use is associated with worse disease outcomes[1-3]
  - Higher risk for development of Crohn's disease
  - Increased risk for disease relapse
  - Increased risk for post-surgical recurrence and resection

AGA Quality Measures: #10

1. Calkins BM et al. Meta-analysis. *Dig Dis Sci* 1989.
2. Duffy LC et al. *Am Rev Prev Med* 1990.
3. Sutherland LR et al. *Gastroenterology* 1990.

Tobacco Cessation Counseling



Our role as their GI provider:

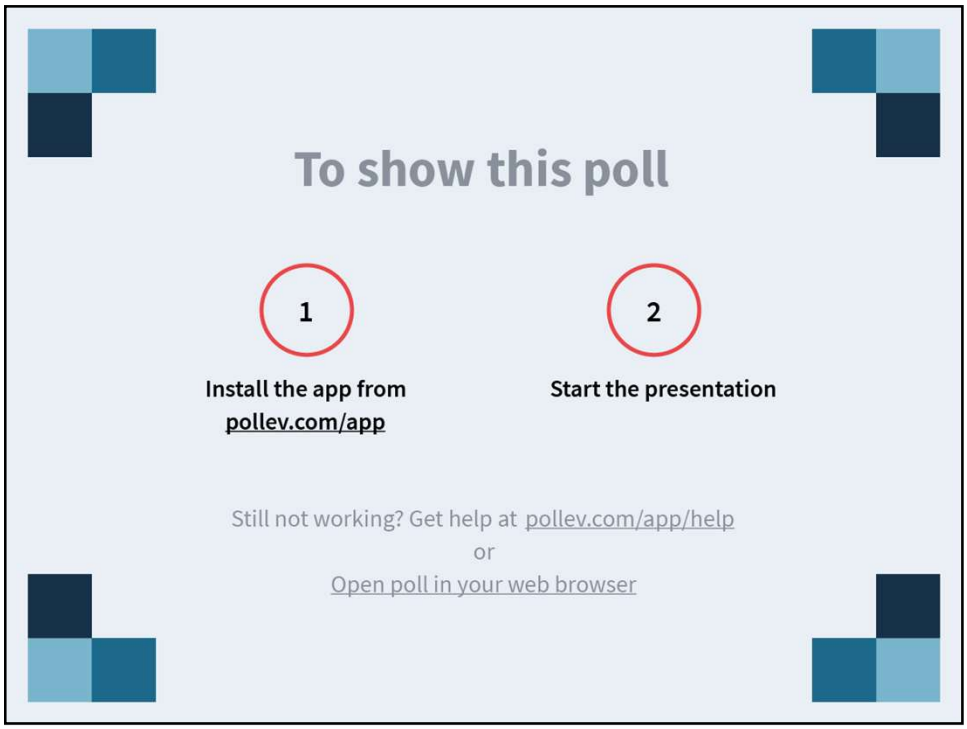
- Ask if patient still smoking
- **Educate** about the importance of smoking cessation for Crohn's disease
- **Inquire** about interest in smoking cessation
- **Refer** to program or primary care physician
- **Communicate** with primary care physician regarding assistance needed

NIH and Clinical Excellence guidelines for brief interventions for smokers. Reproduced from the National Institute for Health and Clinical Excellence. 2006.

Case: Cancer Screening

40 year old female with Crohn's disease on infliximab with azathioprine (5 years) currently in clinical remission presents for routine follow-up exam. Recent MRI shows no signs of active disease. Focus this visit is on preventative health for this patient. **What are important preventative health measures are recommended on thiopurines?**

A. Nothing- she is in remission
B. Cervical cancer screening- annual
C. Skin cancer education and screening- annual
D. Both B+C



Preventative Health: Cervical Cancer Screening

- IBD patients have an increased risk of cervical dysplasia and neoplasia
  - Women with IBD are increased risk for abnormal pap smear
  - IBD patients have lower compliance in screening programs

- Highest risk associated with thiopurine therapy
  - Data also show that corticosteroid and 5-ASA use are also associated with increased risk for abnormal pap

*HPV vaccination is available and safe in IBD patients (9-26yo)
***Annual** pap smear for those on thiopurines, general population screening guidelines for other female patients

ACG Guideline #8,10

1. Kane S et al. *Am J Gastro* 2008. 2. Allegretti JR et al. *IBD* 2015

Preventative Health: Skin Cancer Screening

- IBD patients (independent of therapy) are at an increased risk for skin cancer[1-4]
  - **Melanoma**: Meta-analysis suggests increased risk over general pop in all patients, several studies show anti-TNF therapy possibly 2x risk
  - **NMSC**: increased risk in patients on thiopurine therapy, not clear if goes to baseline risk after discontinuation

*Educate **ALL** IBD patients about risk and sun avoidance and use of sunscreen and protective clothing, SPF ≥ 30
*NMSC: Patients on thiopurines require **annual** evaluation
*Melanoma: **ALL** IBD patients should have initial screening evaluation

ACG Guideline #12

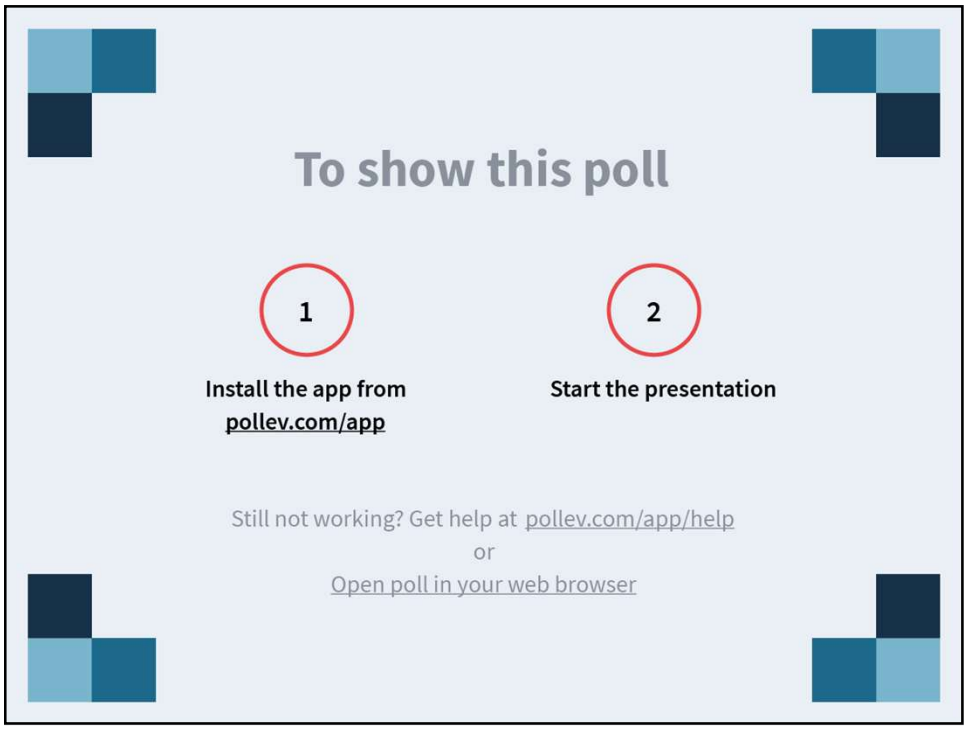
NMSC= non-melanomatous skin cancer

1. Singh S et al. Meta-analysis. *CGH* 2014. 2. Long M et al. *CGH* 2011. 3.. Farraye FA et al. *Am J Gastro* 2017
4. Kimmel et al. *J Skin Cancer* 2016. 5. Van *Assche G et al.* ECCO Guidelines. *J Crohns Colitis* 2013 5. Torres et al. *IBD* 2013.

Case: Colon Cancer Screening

30 year old male with ulcerative pancolitis since age 22 currently in remission on mesalamine therapy. Last colonoscopy was 3 years ago showing deep remission. He would like to know when he should undergo colon cancer screening? **What do you recommend?**

A. General population risk, age 50
B. Now, after 8 years of disease
C. In the next few years



ASGE Guidelines: Dysplasia and Colon Cancer Screening in IBD

Indication	Screening	Surveillance	Recommendations	Comments
UC: left-sided or extensive **CD**: >1/3 colon involvement	Starting at duration 8y*	Every 1-3y based on risk factors**	Techniques: -4-quadrant biopsies every 10 cm limited to greatest extent of prior involvement (minimum 33 biopsies) -Chromoendoscopy with pancolonic dye spray and **targeted** biopsies	*PSC starting at diagnosis and then **annually**

**Risk factors: Active inflammation, anatomic abnormality (stricture, multiple pseudopolyps), history of dysplasia, family history of CRC (FDR), primary sclerosing cholangitis (PSC)

*Starting 8 years after disease in at risk patients, they should begin colon cancer screening program.

CCF Recommendation
ASGE Guideline Based

ASGE Guidelines. *GIE* 2015.

Preventative Health: Mental Health Screening

- Up to 25% of patients with IBD have underlying anxiety and/or depression
- **Screening** is the most important thing that we as providers can do to ensure they get appropriate referral and treatment
  - Studies have shown that untreated depression can increase clinical relapse and decreased medication compliance
- ROS screening (do you have anxiety or depression) is not adequate for screening
  - Brief screening tool (see next slide)
  - Anxiety- GAD-7
  - Depression- PHQ-9
  - SIBDQ- quality of life has anxiety/depression questions

Mikocka-Walus A et al. *IBD* 2016 Mikocka-Walus A et al. *J Psychosom Res* 2012
Ediger JP et al. *Am J Gastro* 2007.

Preventative Health: Mental Health Screening

Depression: PHQ-9
Anxiety: GAD-7

Living with inflammatory bowel disease can be challenging

- ❑ Have you been experiencing any difficulties with stress, worry or anxiety?
- ❑ Have you been feeling nervous, jitter, or tense much of the time?
- ❑ Have you felt down or depressed most of the day or experienced decreased interest or enjoyment in most things?

Further assessment

- ❑ How long have you been experiencing these difficulties?
- ❑ Have they interfered with your daily functioning?
- ❑ Have these difficulties (ie. stress, anxiety or depression) affected your management of your IBD?

*Assessment of underlying anxiety and depression
*Management by primary care or referral

ACG Guideline #11

Slide adapted from Dr. Megan Riehl, University of Michigan.
Keefer L, Kane S. *Gastro & Hepatol* 2017. Walker JR. *Lancet* 2017.

Inpatient Quality Measures

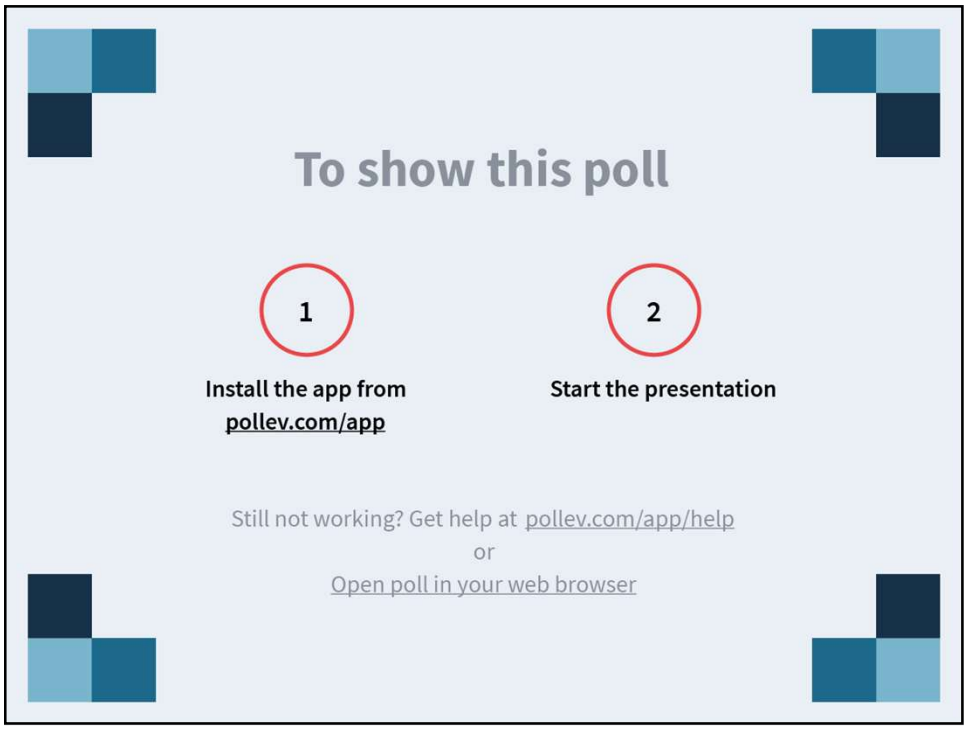
Inpatient Quality Measures: Case

25 year old patient with ulcerative colitis presents with low grade fever, abdominal pain, watery diarrhea (12+ bm/day) and rectal bleeding. HgB 8 (baseline 10).

True or False? It is important to assess for infection including *C. difficile* in this patient and any patient hospitalized with IBD and diarrhea.

A. True

B. False



Inpatient Quality Measure: *Clostridium difficile* evaluation

- IBD patients are up to **8x** more likely to have *C. diff* than non-IBD patients[1]
  - Prevalence is increasing 2.4% → 3.9%[2]
  - Risk higher in ulcerative colitis > Crohn's disease
  - Study in Rhode Island showed providers only assessed *C. diff* in 50% of hospitalized IBD pts


Clostridium difficile

*Patients with increasing symptoms (clinical relapse) of IBD should be tested for *C. diff*

AGA Quality Measure: #8

1. Nguyen GC. *Am J Gastroenterol.* 2008 3. Khanna *CGH* 2017.
2. Ananthakrishnan AN. *Gut* 2008..

Inpatient Quality Measure: *Clostridium difficile* treatment + steroids

- Treatment
  - Initial treatment Vanocmyin or fidaxomicin
  - No role for Flagyl in the treatment of *C diff*
- Should you delay steroids?
  - Small study showing possible increase mortality related to escalated of immunosuppression + *Cdiff*
  - Other larger studies showing no change in outcomes with escalation of immunosuppression with active disease

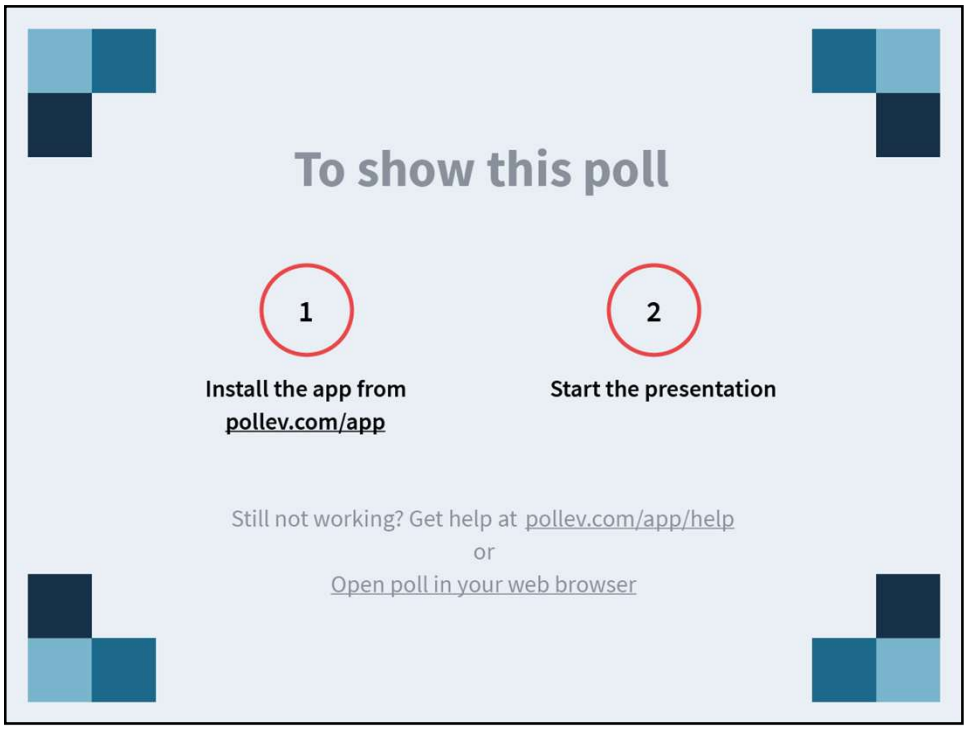
1. Nguyen GC. *Am J Gastroenterol.* 2008 3. Khanna *CGH* 2017.
2. Ananthakrishnan AN. *Gut* 2008..

Inpatient Quality Measures: Case

25 year old patient with ulcerative colitis presents with low grade fever, abdominal pain, watery diarrhea (12+ bm/day) and rectal bleeding. HgB 8 (baseline 10). Hemodynamically the patient is stable.

True or False? Given the patients anemia and ongoing bleeding it is contraindicated to start this patient on DVT prophylaxis.

A. True
B. False



Inpatient Quality Measure: Venous Thromboembolism Prevention

- Hospitalized IBD patient are **2-3x** more likely to have VTE than general population
  - Study in Boston only 7% received adequate prevention despite no contraindications
  - Blood clots are PREVENTABLE
  - Rectal bleeding is not an absolute contraindication to VTE prophylaxis

*Clinical guidelines recommend that **all** hospitalized IBD patients receive pharmacologic prophylaxis (unless a clear contraindication)

AGA Quality Measure: #9

1. Yuhara *Aliment Pharmacol Ther* 2013.
2. Pleet *Aliment Pharmacol Ther* 2014

Inpatient Quality Measures: Case

60 year old male with history of penetrating Crohn's disease refractory to anti-TNF therapy who underwent ileocecal resection with primary anastomosis, currently POD #3. Inpatient consult for recommendations for transition of care?

What are recommendations in post-operative Crohn's disease management?

Inpatient Quality Measures: Case

✔ Decide if this patient requires post-operative treatment

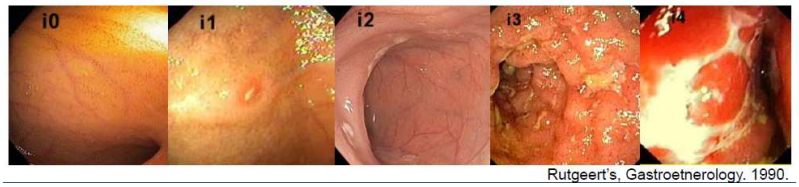
✔ How will you monitor patient post-operatively?

3 month FCP

↓

6m post-operative colonoscopy

Rutgeert's scoring



Rutgeert's, Gastroetnerology. 1990.

My annual visit check list

Annual assessment of need:

- ✓ Disease activity assessment
- ✓ Routine lab monitoring
- ✓ Vitamin assessment
- ✓ Pre-treatment labs needed
- ✓ Vaccinations
- ✓ Bone health assessment
- ✓ Colon cancer screening
- ✓ Skin cancer screening
- ✓ Cervical cancer screening
- ✓ Tobacco screening
- ✓ Anxiety screening
- ✓ Depression screening

Labs
Blood counts (CBC)
Electrolytes (BMP)
Liver testing (LFT)
Inflammation (CRP/ESR)
Iron studies
Vitamin D level
B12 level
Hepatitis A, B, C screening
TB testing

Vaccinations
Pneumonia vaccinations (2)
Influenza vaccination
Hepatitis B vaccinations (3)
Shingles vaccination (non-live)

Quality IBD Care: Crohn's and Colitis Foundation Checklist!

Health Maintenance Checklist for Adult IBD Patients

CROHN'S & COLITIS FOUNDATION

Vaccine-Preventable Illnesses	Which Patients	Check Titer	How Often
Influenza (non-live)	All	No	Annually
PCV13 (Prevnar) and PPSV23 (Pneumovax)	All ≥ 65 years All on/planning immunosuppression[1]	No	• If ≥ 65 years: PCV13 then PPSV23, separated by ≥ 1 year • If ≥ 19 years AND immunosuppressed: PCV13 then PPSV23 at least 8 weeks later; 2nd dose of PPSV23 after 5 years
Tdap	All	No	• 1st dose ≥ 19 years if not previously given • Tetanus and diphtheria toxoid (Td) booster every 10 years
HPV	All ≤ 26 years	No	3-dose series at 0, 1–2, and 6 months
Group B Meningococcal meningitis	Ages 16–23 at high risk	No	• MenB-4C, 2 doses, ≥ 1 month apart • MenB-FHbp, 2 doses, ≥ 6 months apart
Hepatitis A	All	Yes (HAV IgG)	• 2-dose series: Havrix at 0 and 6 months or Vaqta at 0 and 6–18 months apart • 3-dose series: Twinrix (HepA-HepB) 0, 1 and 6 months
Hepatitis B	All	Yes (HBsAg, HBsAb, HBc IgG)	• 2-dose series: Heplisav-B at least 4 weeks apart • 3-dose series: Engerix-B, Recombivax HB or Twinrix (HepA-HepB) given at 0, 1 and 6 months
MMR (live vaccine)*	If non-immune	Yes (IgG titers)	2-dose series, at least 4 weeks apart (≥ 4 weeks before immunosuppression[1])
Varicella/Chicken Pox (live vaccine)*	If non-immune	Yes (IgG titers)	• 2-dose series, 4–8 weeks apart (≥ 4 weeks before immunosuppression[1])
Zoster (recombinant vaccine preferred)	All patients > 50 Any starting tofacitinib	No	• 2-dose series, 2–6 months apart (minimum 4 weeks apart)

Cancer Prevention	Which Patients	How Often
Cervical PAP Smear	All women on systemic immunosuppression[1]	Annual
Full Skin Screen	All on systemic immunosuppression[1]	Annual
Colonoscopy	All with extensive disease for > 8 years	Every 1–3 years

Other Screenings	Which Patients	How Often
DEXA Scan	Women ≥ 65, and all at high risk[2]	Once identified, and no sooner than 2 years later based on DEXA findings
PPD or IGRA	Prior to anti-TNF or anti-IL-12/23	Once (annual repeat if potential TB exposure or in a high-risk region)
Smoking status	All	Annual
Depression check	All	Annual

Thank you

Current Landscape in the Treatment of Crohn's Disease

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Inflammatory Bowel Disease Program
Division of Gastroenterology and Hepatology
University of Michigan

October 18, 2019

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Relationship Disclosures

Supported Research and Outside Relationships

I have received industry grant support from the following:

- Siemens Imaging, USA
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- Pfizer, Inc
- UCB, Inc
- Abbvie, Inc

I have served as a consultant for the following:

- Abbvie
- Janssen
- Merck
- Takeda

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Outline

- Modern Disease Activity Monitoring
- Current Treatment Landscape
- Biosimilars in IBD
- Biologic Drug Monitoring and Assessing Loss of Response
- Emerging Treatments

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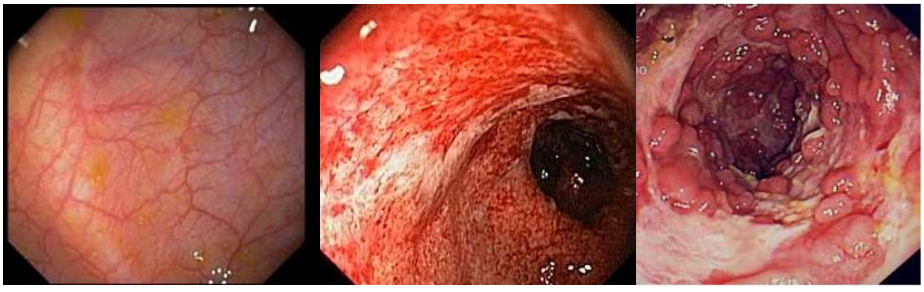
Inflammatory Bowel Diseases

- Major forms are Crohn's disease and ulcerative colitis
- Common symptoms: diarrhea, abdominal pain, bloody stool
- Affects all ages but primarily late teens to early 20s



Normal | Ulcerative colitis | Crohn's disease

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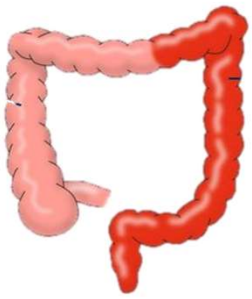
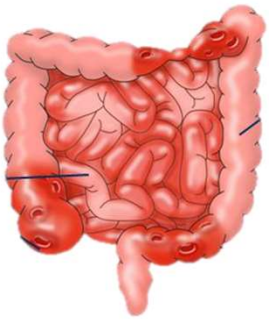
Difference in Disease Distribution

UC	CD
	
Continuous Begins in Rectum, Moves Proximally	Patchy (can be continuous) Can Involve Any Location Can Involve Any Length Typically Involves Terminal Ileum

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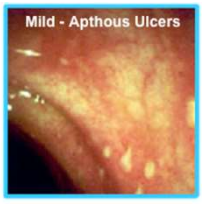
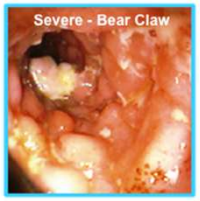
Potential for deeper intestinal wall damage





<u>Clinically more variable presentation</u>

- Symptoms can be identical to (UC)
- May present with pain only
- Obstructive bowel symptoms (bloating, abdominal distension)
- Fistula or perianal abscess
- Anemia without symptoms !

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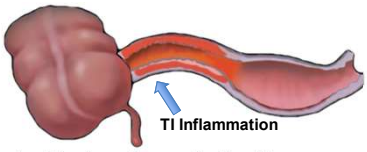
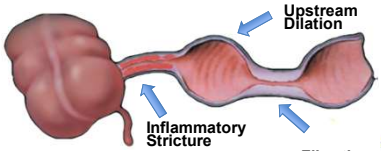
CD: Complications – Intestinal Strictures

Inflammatory Disease



- Diarrhea (frequently bloody)
- Abdominal pain (RLQ)
- Weight loss, fever, anorexia

Obstructive Disease



- Bloating, Nausea, Vomiting
- Abdominal distension
- Right lower quadrant pain

Over Time….

Inflammation

Accumulation of Fibrosis

Stricturing
(combination of inflammatory and chronic fibrotic damage in section of intestine)

Obstruction & Penetration

***control intestinal inflammation**, to avoid progression to **medically irreversible** stricturing disease*

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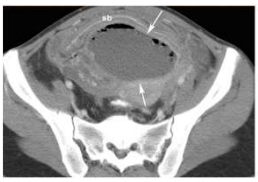
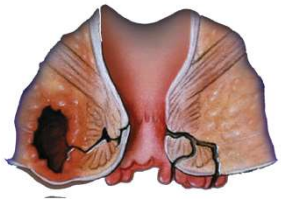
Crohn's disease – Penetrating Complications

The potential for ***Transmural PENETRATING COMPLICATIONS***
Key difference between CD & UC



- Severe inflammation leads to breach in wall integrity
- If penetrating disease infected fluid accumulates in abdomen
  Abscess



- Penetration can tunnel from damaged intestine to skin or other organs (bowel, bladder, vagina)
  Fistula (here perianal fistula)

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Goals of Care in IBD

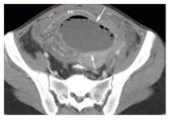
Ulcerative Colitis (UC)

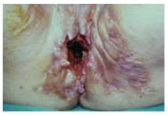
1. Manage Symptoms
2. Prevent Flares
3. Prevent Surgery
4. Avoid Colorectal Cancer

Crohn's Disease (CD)

1. Manage Symptoms
2. Avoid Asymptomatic Progression

- *Stricture Development*





- *Abscess/Fistula Development*

3. Minimize Surgery – Non Curative

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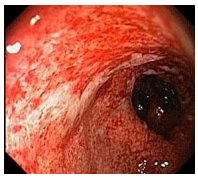
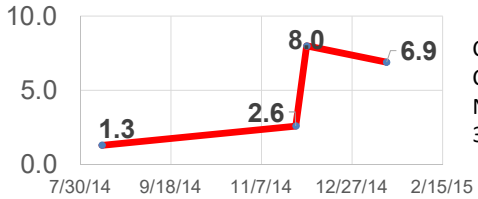
Monitoring IBD Mucosal Inflammation

Ileocolonoscopy



Most Sensitive and Specific Test for Mucosal Inflammation
Difficult to perform frequently
Invasive, Expensive

C-Reactive Protein



Convenient blood test, inexpensive
Can trend inflammation over time
Non-specific inflammation biomarker
30% of population does not produce

Fecal Calprotectin (FCP)

Stool test for gut inflammation
Quantitative
Very sensitive (>95%)
Non-IBD gut inflammation can make positive

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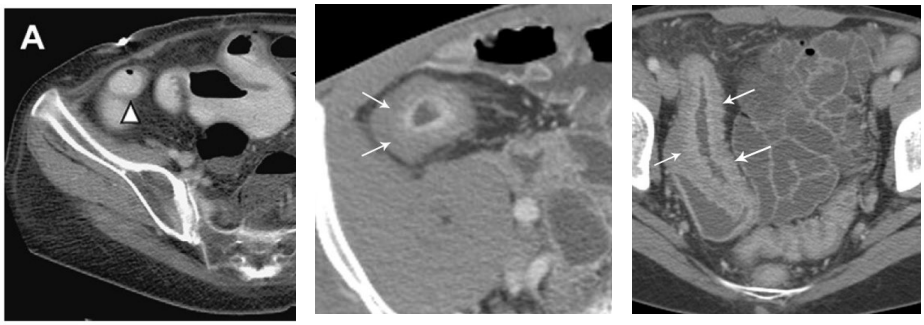
Imaging for Crohn's Disease: CT and MR-Enterography

- Enterography protocol is superior to standard CT/MR
- Provides structural damage information in CD
- Essential for initial CD workup, every few years for those with known fistulas/strictures
- MR and CT not helpful in UC



Standard CT CT-Enterography

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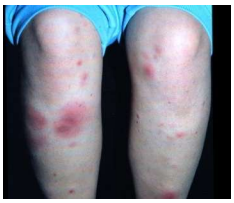
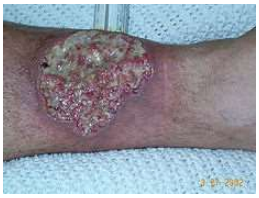
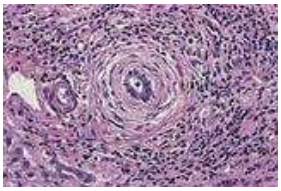
Extraintestinal Manifestations of IBD



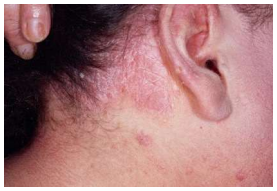
Erythema Nodosa



Pyoderma gangrenosum



PSC



Psoraisis

Synovitis/Arthritis
- Enteropathic Arthritis (15-25%)
- Ankylosing Spondylitis

Skin Disease
- Erythema Nodosa (5-15%)
- Psoriasis (5-10%)
- Pyoderma Gangrenosum (<3%)

Hepatobiliary
- PSC (most patients have IBD)

Occular
- Uveitis (5-8%)
- Episcleritis

Other
- Nephrolithasis
- **Venous Thromboembolic disease**

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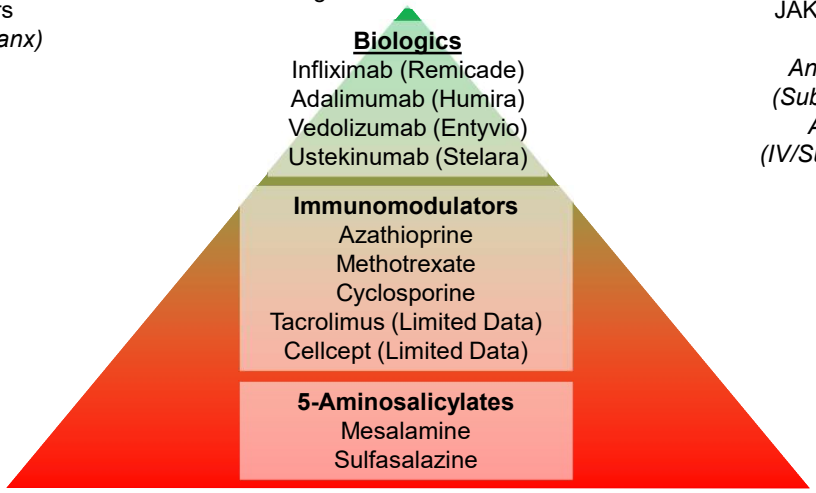
IBD Therapeutics: Traditional Pyramid

Recent Additions
JAK-Inhibitors
Tofacitinib (Xeljanx)

Combination Therapy
Biologic+Immunomodulator



Near Term
JAK-1 Inhibitors
(oral)
Anti-Integrins
(SubCutaneous)
Anti IL-23
(IV/Subcutaneous)

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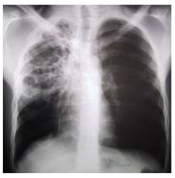
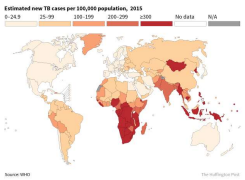
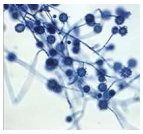
Anti-TNF: Safety Profile

Tuberculosis
HBV Reactivation

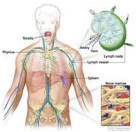


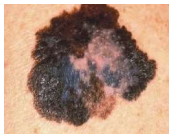


Opportunistic Infections:
Fungus & Histoplasmosis



Specific Malignancies:
Lymphoma & Melanoma





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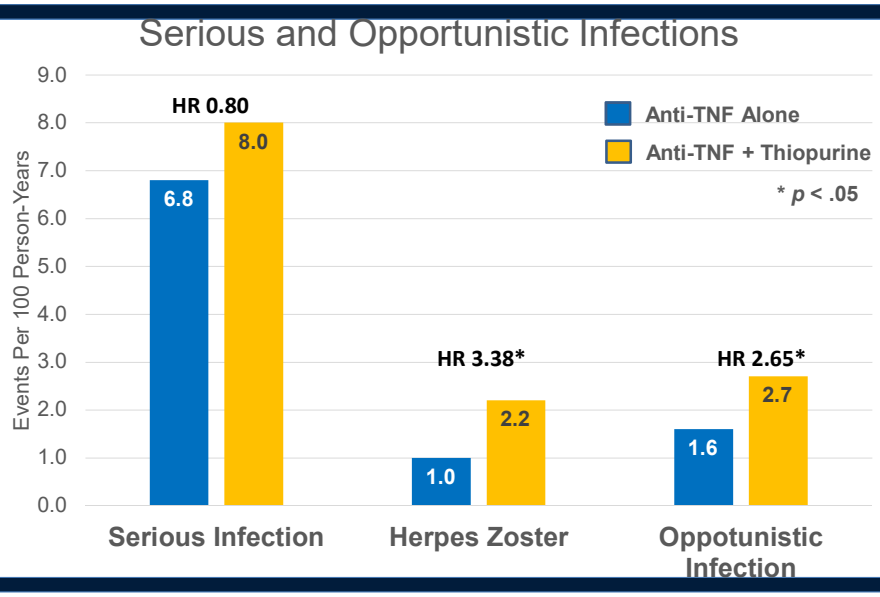
Risks of anti-TNF Combination Therapy



Osterman et. al CGH 2015

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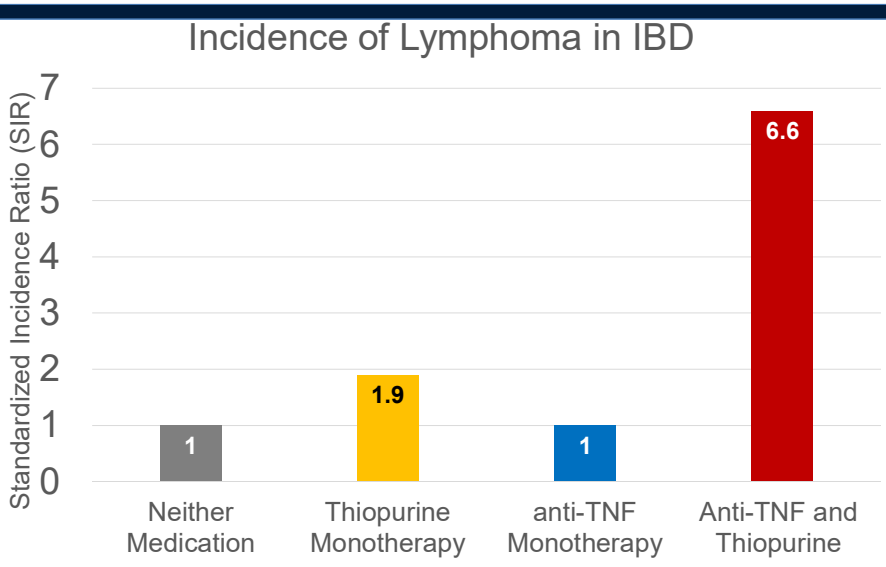
Risks of anti-TNF Combination Therapy



Herrinton et al. AJG 2011

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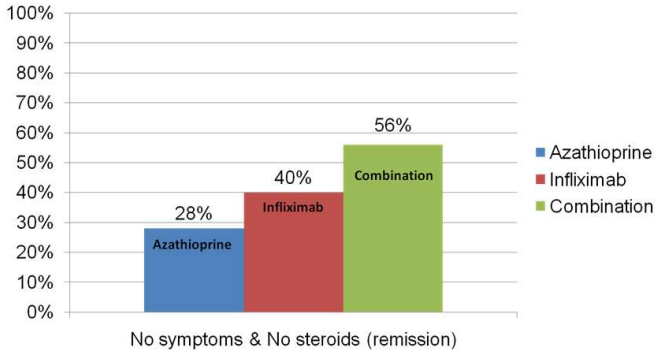
Combination Therapy More Effective - **SONIC Trial**

In a research study comparing azathioprine *versus* infliximab *versus* a combination of both drugs, this is what happened:



Sandborn W, et al. Gastroenterology 2009;136:A-116.

Slide Courtesy of Jami Kinnucan, MD

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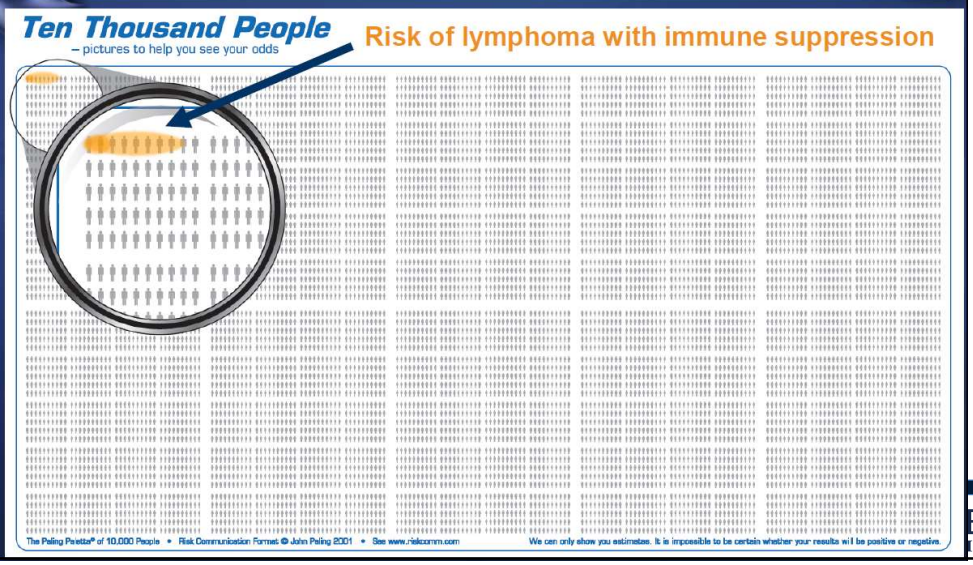
Risk of Developing non-Hodgkin's Lymphoma

Patient receiving Immunomodulator +/- anti-TNF Therapy for 1 year



Biosimilars Have Arrived

PRODUCT NAME	PROPRIETARY NAME	DATE OF LICENSURE
adalimumab	**Humira**	**12/31/02**
adalimumab-adbm	Cyltezo	8/25/17
adalimumab-atto	Amjevita	9/23/16
infliximab	**Remicade**	**8/24/98**
infliximab-abda	Renflexis	4/21/17
infliximab-dyyb	Inflectra	4/5/16
infliximab-qbtx	Ixifi	12/13/17

https://www.fda.gov

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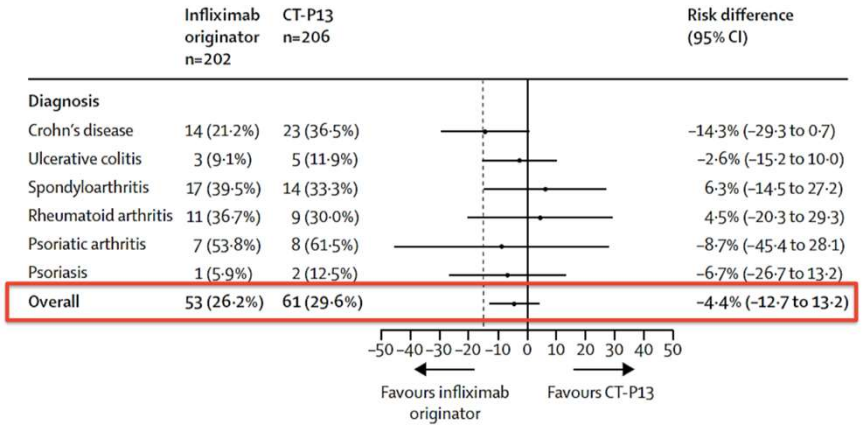
Biosimilar Interchangeability

Data Supports Good Outcomes

NOR-SWITCH: 52 Week Study of IFX Biosimilar Non-Inferiority



Jorgensen et al. Lancet 2017

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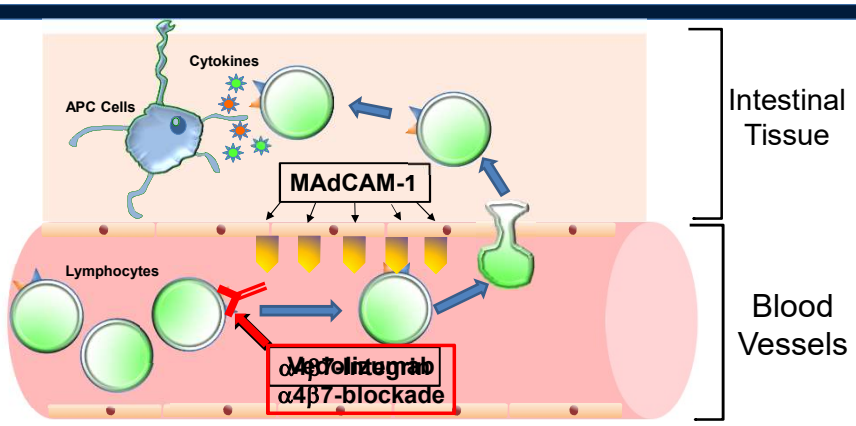
Vedolizumab (Entyvio): Approved for CD and UC



- **Monoclonal Antibody (IgG_4)**
- **Specific to Gastrointestinal Tissue (anti-α4β7)**
- **IV Infusion Every 8 Weeks (30-60min)**

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Vedolizumab: *Excellent Safety*

ORIGINAL ARTICLE

The safety of vedolizumab for ulcerative colitis and Crohn's disease

Jean-Frédéric Colombel,[1] Bruce E Sands,[1] Paul Rutgeerts,[2] William Sandborn,[3] Silvio Danese,[4] Geert D'Haens,[5] Remo Panaccione,[6] Edward V Loftus Jr,[7] Serap Sankoh,[8] Irving Fox,[8] Asit Parikh,[8] Catherine Milch,[8] Brihad Abhyankar,[9] Brian G Feagan[10]

***n*=2830 patients, 4811 person years (2009-2013)**

1. No increased risk of any infection vs. placebo
2. No Progressive multifocal leukoencephalopathy (PML)
3. Malignancy occurred at background rate

Colombel et al. Gut 2016

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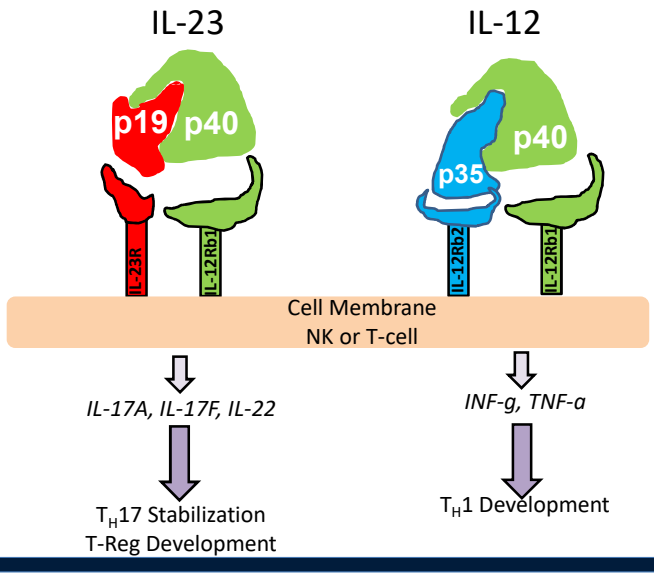
Ustekinumab (Stelara): Approved for CD



- **Monoclonal antibody, IL-12/23 Blockade via p40**
- **Approved for CD but clinical trials underway in UC**
- **Systemic effects**
- **Other Approvals include psoriatic arthritis & plaque psoriasis**

Teng MWL et al Nature Med. 2015

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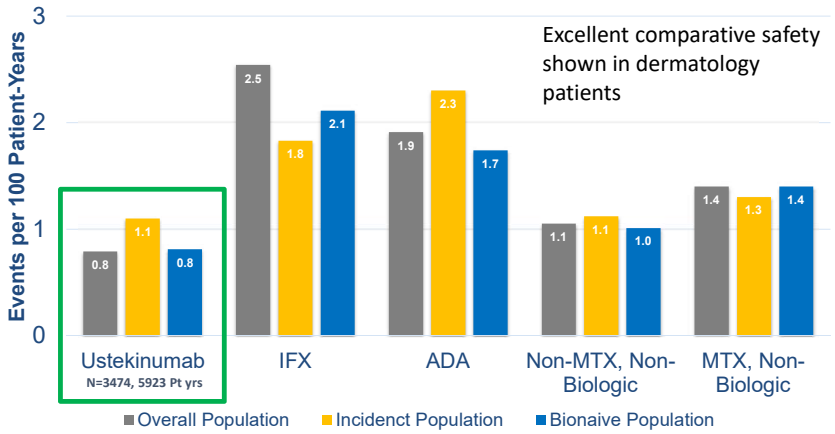
Ustekinumab - PSOLAR: Psoriasis Dermatology Safety Registry

Cumulative Incidence of Serious Infections Per 100 Patient Years



N=11,466 Patients
Follow Up: 23,311 Patient Years (up to 8 years)

Post-Hoc analysis of all RCT clinical trials in PsA, PS, CD
6280 pts (5884 treated)
Incidence Per Patient Year at 1yr

	UST	PBO
Infection:	125.4 vs	129.4
Cardio:	0.5 vs.	0.3
Malignancy:	0.4 vs.	0.2
Death	0.1 vs.	0.0

Ghosh et al. Drug Safety 2019

Kalb et al. JAMA Derm 2015

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JAK Inhibitors : Tofacitinib (Xeljanz)

Small molecule oral inhibitor of Janus Kinase 1, 2, 3

Approved for UC Treatment in 2018

Oral dosing

**Induction 10mg Twice Daily (4-8 weeks)
Maintenance 5mg Twice Daily

Relatively Fast onset (Days for Some Patients)

Risks

Herpes Zoster (Shingles)
Concern for other chronic infection reactivation
Increased Cholestrol
Potential Bone Marrow Suppression
Non-melanoma skin cancer

Venous thromboembolism at 10mg dose
FDA Boxed Warning for VTE Risk in 2019

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Rethinking IBD Treatment Sequence

<u>Biologics</u>
Vedolizumab (safe, slow)
Anti - Il-12/23 (effective, safe)
Anti-TNF (IFX fastest)

Maximize Biologic Dose & Frequency

<u>Combination Therapy</u>
Methotrexate + Biologic
Thiopurine + Biologic

Excellent Safety Margin

NOTE: This is my opinion and does not represent formal Society guidelines (but its close)

Severity Justifies Treatment Risks

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Approach to Lost of Response and Interpreting Drug Levels

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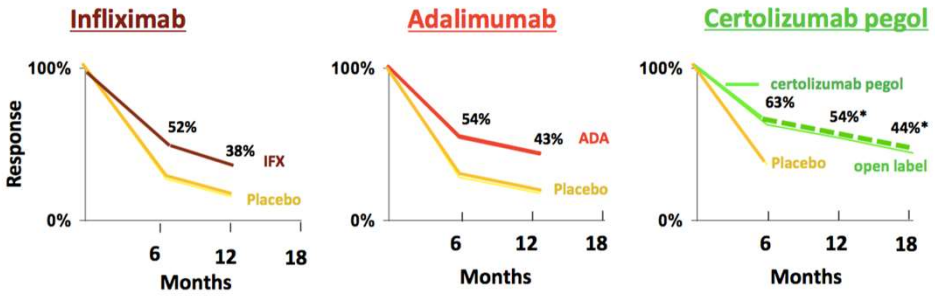
Anti-TNF Therapies Often Fail



1. Primary Failure (*Wrong Mechanism)*
2. Insufficient Dosing
3. Anti-Drug Antibodies

1. Hanauer, Lancet 2002, 2. Colombel Gastro 2007,
3. Schreiber Gut 2006, 4. Lichtenstein Gastro 2007.

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Approach to Loss of Response

- ❑ Rule out Infection
- ❑ Objective Inflammation assessment (UC and CD)
- ❑ Rule out strictures if obstructive symptoms or atypical abdominal pain (CD)
- ❑ Confirm medication 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-ADA Level : **55** ng/mL
(normal <25ng/mL)

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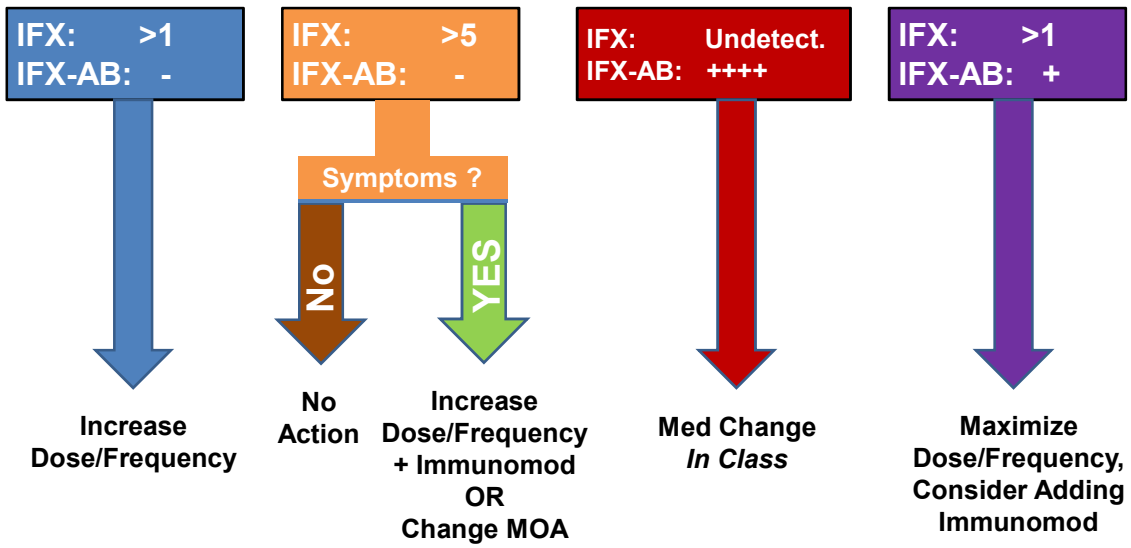
Anti-TNF Drug Level Interpretation



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Therapeutic Drug Monitoring (TDM)

Drug	Trough Level
Infliximab	≥ 5 mcg/ml (luminal) 10-15 mcg/ml (perianal)
Adalimumab	≥ 7.5 mcg/ml
Certolizumab	≥ 20 mcg/ml
Golimumab	>2.5 mcg/ml (induction) >1.2 mcg/ml (maintenance)
Vedolizumab	≥ 14 mcg/ml
Ustekinumab	≥ 4.5 mcg/ml

These are baseline guides for monitoring, we typically run patients higher this pending clinical response

AGA Guideline on Therapeutic Drug Monitoringin Inflammatory Bowel Disease. Feuerstein et al; Gastroenterology. 2017

Slide Courtesy of Jami Kinnucan, MD

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Emerging Therapies

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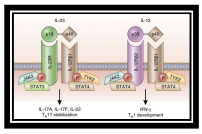
Updated Medications in Late Phase Development

Anti-IL-23s

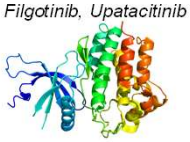
Etrolozumab, Risakizumab



Anti-IL-23 only
Currently Approved for Plaque Psoraisis
Phase III – early data suggests more effective than IL-12/23

JAK-1 Inhibitors

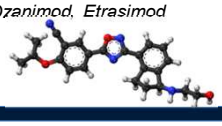
Filgotinib, Upatacitinib



JAK-1 Specific Agents
No JAK 2,3 effect, less side effects
Study ongoing, no VTE signal at this time.
Phase III - Will seek approval for UC and CD

SP-1 Receptor Agonist

Ozanimod, Etrasimod



Agonist of sphingosine SP-1 Receptors
Reduced lymphocyte count and trafficking to tissues
Oral therapy

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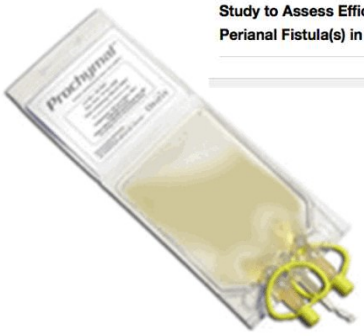
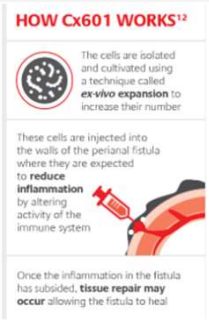
Stem Cell Therapy for Crohn's Fistulas

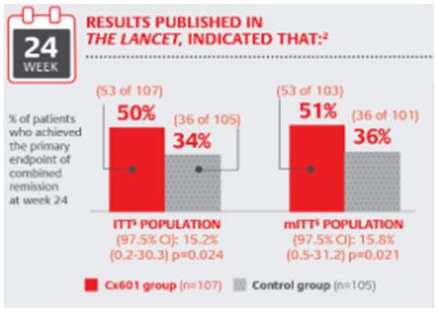
ADIPOSE DERIVED MESENCHYMAL STEM CELLS INVESTIGATED FOR INDUCTION OF REMISSION IN PERIANAL FISTULIZING CROHN'S DISEASE (ADMIRE-CD)

Study to Assess Efficacy and Safety of Cx601, Adult Allogeneic Expanded Adipose-derived Stem Cells (eASC) for the Treatment of Complex Perianal Fistula(s) in Participants With Crohn's Disease (CD) (ADMIRE-CD-II)



ClinicalTrials.gov Identifier: NCT03279081





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Crohn's Treatment Update 2019

- Objective Resolution of Inflammation is the Primary Treatment Target
- New Mechanisms Have Unique Efficacy and Safety Profiles
- Minimizing the Use of Thiopurines (Azathioprine and 6-Mercaptopurine)
- Biosimilars Effectiveness Indistinguishable from Originator.
- Drug Monitoring Aids in Decision Making in Anti-TNF Users
- Treatment Pipeline Outlook is Optimistic

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Role of Diet in IBD

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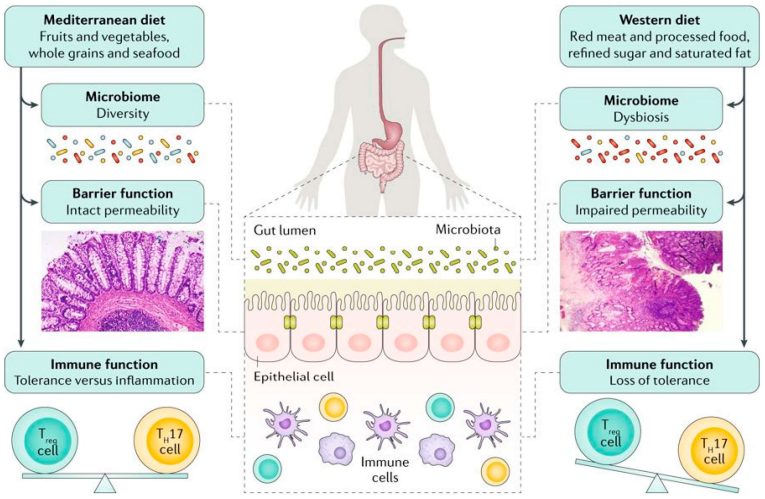
Gastroenterology Update: A Case-Based Approach to Common GI Problems

Emily Haller, MS, RDN
@ea_haller

Proposed Mechanisms of Diet's Role in IBD Development



Keshteli.Nutrients 2019, 11, 1498

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Diet and Risk of IBD

- 19 studies: Evaluated diet patterns prior to IBD diagnosis
- 2,609 IBD patients

Increased IBD risk:		Decreased IBD risk:	
• Total fat	2-3X	• Fiber	< 1/2 X
• PUFA	2-6X	• Fruits	< 1/2 X
• Omega 6	2-3X		
• Meats	3-4X		

Hou et. al. AJG 2011;106

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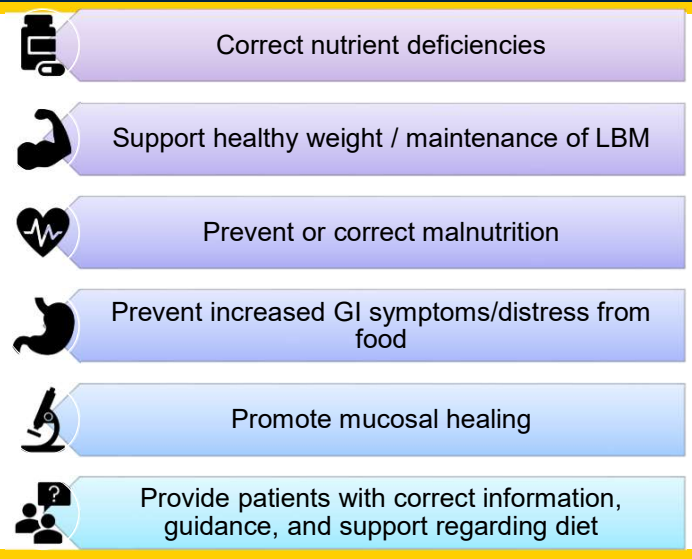
IBD: Goals of Nutrition Therapy



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Malnutrition

Major complication of IBD

~65-75% CD

~18-62% UC

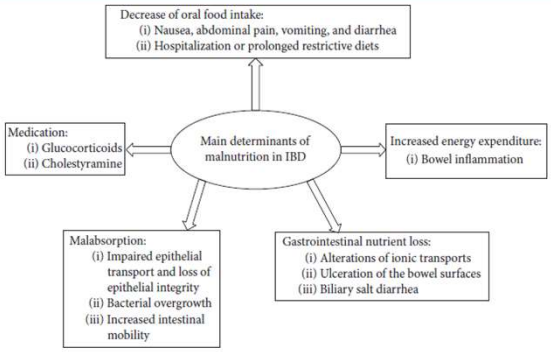

FIGURE 1: Main determinants of malnutrition in IBD.

Micronutrient deficiencies:

- Vitamin: B12, folate, Vit A,D, and K
- Mineral: iron, calcium, selenium, zinc, and magnesium

Scaldaferri F, et al. Nutrition and IBD: Malnutrition and/or Sarcopenia? A Practical Guide. *Gastroenterol Res Pract*. 2017

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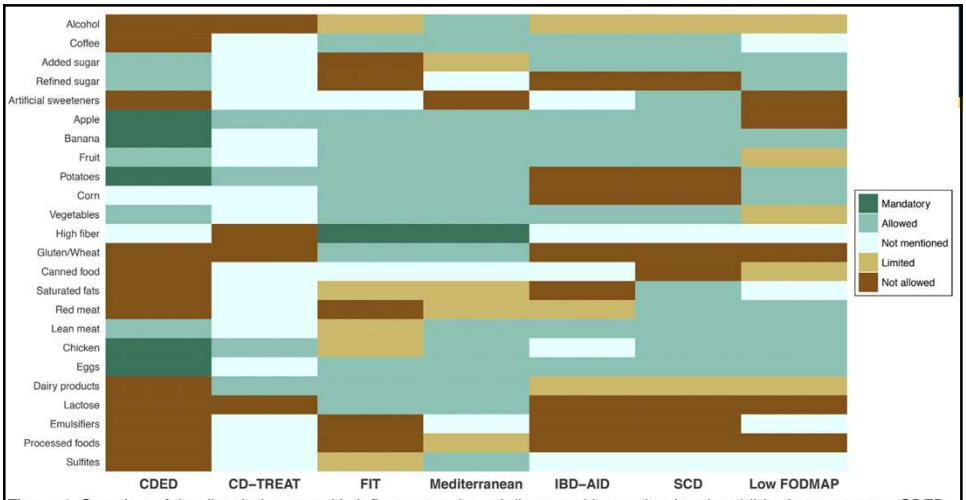

Figure 1. Overview of the diets being tested in inflammatory bowel disease with permitted and prohibited components. CDED, Crohn's disease exclusion diet; CD-TREAT, Crohn disease treatment-with-eating diet; FIT, food influence on the Intestinal microbioTa diet; SCD, specific carbohydrate diet; IBD-AID, anti-inflammatory diet; low FODMAP, low-fermentable oligosaccharide, disaccharide, monosaccharide, and polyols diet.

Savino *Gastroenterology* 2019;157(2):295-297

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Case #1: What can I eat with IBD?

- 28 y/o Male with UC
- Dx 1 year ago
- Est. care at MM due to move to AA
- Hasn't eaten vegetables other than mushed carrots and over cooked green beans in 1 year
- Minimal fruit
- Told to eat low fiber diet – pt under the assumption this is indefinitely

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Nutrition Assessment

- Diet Recall: pop tarts, soda, white bread, white rice, banana, fruit cups, pasta with butter, cooked carrots, green beans, ice cream, milk, yogurt, chicken, red meat, lunchables
  Skips meals on occasion
- Symptoms: feels relatively fine, some issues with dairy products

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- Adequate calorie, protein intake
- Reduce fat intake, reduce fiber (*only as needed*) intake
- Small, frequent meals and snacks
  - Use or oral supplements, smoothies, shakes
  - Simple, high-quality foods: bananas, yogurt, kefir, cooked fruits & veggies
- Protein at meals/snacks: eggs, firm tofu, creamy peanut or almond butter, Greek yogurt, lean poultry, fish
- Avoid trigger foods (fatty & spicy foods, lactose, FODMAPs)

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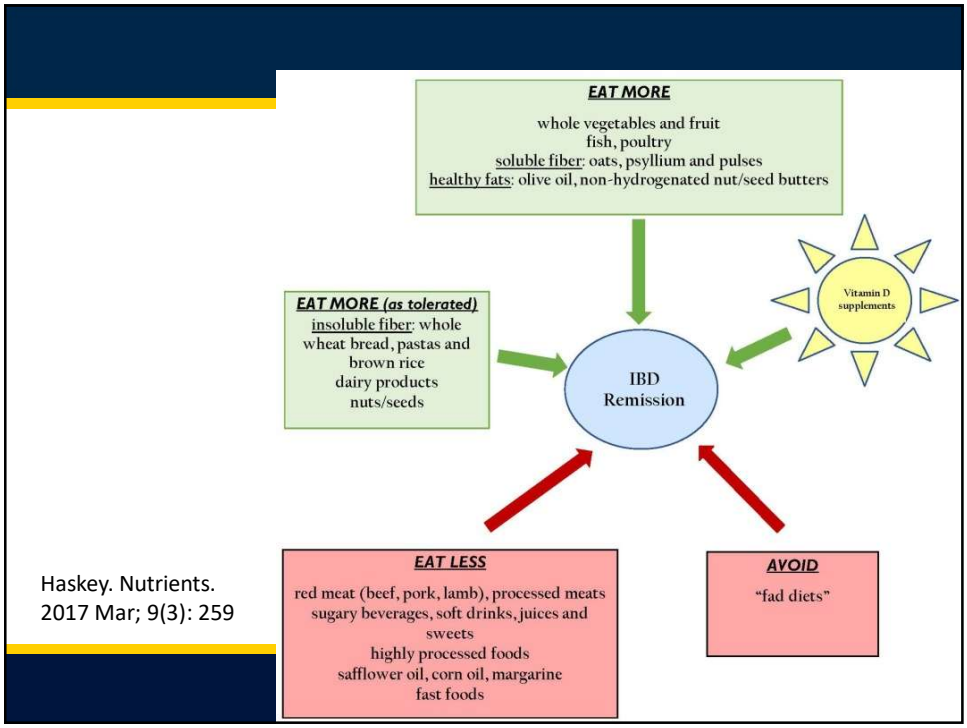

Haskey. Nutrients. 2017 Mar; 9(3): 259

Provide Meal and Snack Ideas

Mediterranean Sample Menu

Breakfast

½ cup oatmeal, ½-1 cup fresh berries, walnuts, made with skim/2% or plant-based milk of choice

Greek yogurt layered with crunchy cereal, chia seeds, and blueberries for a breakfast parfait

2 eggs (or 1 egg + 2 egg whites) or tofu scramble, 1 slice whole grain toast
½-1 cup cantaloupe

2 egg omelet (or egg whites) with sautéed veggies: tomatoes, spinach, mushroom etc., 1-ounce low fat cheese
Roasted potatoes

Hard-boiled egg slices with sliced vegetables (cucumber, tomatoes, bell peppers) in a whole-wheat pita

Toasted whole-wheat bread topped with sliced avocado, cumin, black pepper, with 1/2 cup pineapple

Whole-grain bagel or 2 slices of toast with nut butter, 100% fruit preservatives, hummus, or tahini

Breakfast burrito-beans, veggies, salsa and avocado

1 cup low fat cottage cheese, sliced peach or other fruit, 1 tbsp nuts/seeds

Lunch/Dinner

Sandwich on whole-wheat bread, lean turkey, hard cheese, lettuce, tomato, mustard, with 1 cup (15-17) grapes and serving of baked chips

Chicken and rice or vegetable soup (low sodium), whole-grain crackers, ½ cup mandarin oranges

Tacos or burrito filled with beans, lettuce, tomato, salsa, guacamole, brown rice, and lean protein (chicken, lean ground turkey, tofu, or tempeh)

Large tossed salad with lean protein (chicken, tuna, or chickpeas), cucumber, tomato, shredded carrots, feta, and olive oil/balsamic vinegar or vinaigrette dressing, sunflower or pumpkin seeds, apple or orange

Veggie burger with lettuce, tomato, mustard on a whole-grain bun, sweet potato fries

Stir-fry: firm tofu or lean chicken sautéed with bok choy, carrots, red bell pepper, broccoli bits, onion, with ½ cup brown rice and low sodium soy sauce

Grilled chicken, medium baked potato, Earth Balance butter, 1 tbsp sour cream, roasted carrots

Baked pork chop, ½ cup sweet potato
Spinach salad with olive oil/balsamic vinegar or vinaigrette dressing

1-2 slices veggie pizza with low fat cheese (try making at home), side salad

Grilled scallops, quinoa with sautéed vegetables (peppers, broccoli bits, carrots, corn, garlic, onion, etc.), 1 cup raspberries with whipped cream

Grilled kabobs with chicken, green bell pepper, tomato, mushroom, onion, zucchini, brown rice or quinoa

Whole-wheat pasta with tomato sauce plus vegetables (mushrooms, tomatoes, eggplant, peppers, spinach), parmesan cheese

Grilled salmon or white fish with lemon, herbs
Baked potato or brown rice, 1 cup steamed broccoli, spinach or other veggie of choice.

Sushi – California roll, salmon avocado, spring roll, etc. low sodium soy sauce, side of edamame

Snacks:

- 5-7 whole-grain crackers or pita with 1- ounce low fat cheese or ¼ cup hummus
- Piece of fruit and a handful of nuts or 1-2 tbsp of natural nut butter
- Edamame
- Sliced bell peppers, carrots, cucumbers and ¼ cup hummus
- 3 cups air-popped popcorn tossed with 1 teaspoon coconut oil or Earth Balance butter
- Greek yogurt topped with 2 tablespoons natural granola and/or strawberries
- Half of a sandwich made with whole-grain bread
- Baked apples with cinnamon

NE

Eating with a Stricture

Avoid foods that might get "stuck"

- Fibrous, fatty meats
- Raw veggies
- Popcorn / Corn
- Nuts (large amounts)
- Fruits with skins
- (Insoluble fiber)

Forbes et al. *Clin Nutr* 2017

Customary recommendations, per ESPEN:

•Asymptomatic stenosis: Low *insoluble* fiber diet

•Symptomatic stenosis: Low *insoluble* fiber plus soft texture or liquid diet

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- Help patients achieve adequate nutrient intake
- Least restrictive diet as possible
- For a soft-texture diet
  - Peel fruits and vegetables that can be peeled
  - Cook fruits, vegetables until fork-mashable or puree
  - Meats and poultry ground, pulled or fork tender
  - Use of slow cooker
  - Chew thoroughly
  - Can utilize soups/smoothies

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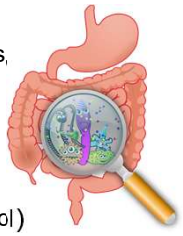
FODMAP Diet & IBD

Fermentable
Oligosaccharides – few simple sugars linked together (fructans, galactans)
Disaccharides – double sugar (lactose)
Monosaccharides – single sugar (fructose)
And
Polyols – sugar alcohols (sorbitol, mannitol, isomalt, xylitol, glycerol)



- Short chain carbohydrates
- Poorly absorbed in the small intestine & delivered to the colon
- **Rapidly fermentable** by gut bacteria resulting in gas and SCFA
- Small, **osmotically active** molecules increasing water load to the intestine

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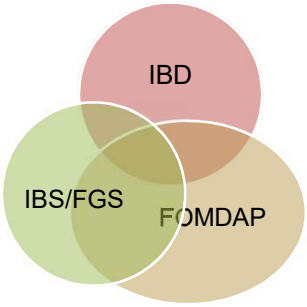
FODMAPs and IBD

- ~35-40% of patients with quiescent IBD meet criteria for IBS
- Impacts health-related QoL
- Low FODMAP diet can be used to manage concurrent functional gut symptoms in those with IBD
  - *Reduced flatulence, pain, bloating, fecal urgency, and improved stool consistency*



Barbalho S.*J Med Food.* 2018 Jan 12 doi: 10.1089/jmf.2017.0120

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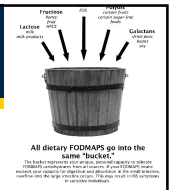
FODMAP Counseling Approach



Elimination Phase (2-6 weeks) → Challenge Phase (6-8 weeks) → Personalization Phase (Long-term maintainence)

Improvement in GI symptoms → Identify trigger foods → Increase variety as much as possible

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Case Study #2 Low FODMAP Diet

- 49 y/o F
- **IBD Phenotype/Geography**: Crohn's distal/TI and mid SB diagnosed 2012
- **IBD Surgeries**:
  - 2011 resection for cecal volulus (ileocecectomy)
  - 2012 spontaneous anastomotic colon perforation
- **Current IBD Medications**: Entyvio (2/2015), AZA 75mg daily (5/2014, decr from 150 for LFTs, 3/2018 decr from 75 for de-escalation, incr to 75 due to fistula formation), Miralax-prn
- **Prior IBD Medications**: prednisone (2012 x6 mos), Entocort (2012-2013), Humira (2012 x2 mos no benefit), Cimzia 400q2wks (3/2013), gluten free (x6mos),
- **3/18/18:** In deep remission since adding Entyvio to AZA in 2015 with 2017 FCALP, MRE & colonoscopy all with normal results

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Case Study #2 Low FODMAP Diet

- **9/2019** GI Symptoms increase: Bowel movements vary between formed, loose, mushy to watery. Bloating, Abdominal pain and cramping
  - Labs and FCP checked - returned normal, GI nutrition services referral was placed
- **11/15/2018** Patient seen by a GI Registered Dietitian (RD)

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Nutrition Assessment

11/15/2018

Diet recall:

- Breakfast: Zipfizz, couple eggs + egg white, English muffin, tea (chai or sweet n spicy or black tea) more often than coffee
- Lunch: noon - leftovers from the night before - chicken, beef, pork, fish, veggie, garlic, onion
- Snack: cereal bar or almonds or protein shake - protein powder (plant-based)
- Dinner: chicken, beef, pork, or fish + veggies- broccoli, brussels, salad, rice or potatoes, pasta; sometimes black beans or hummus
- Snack: glass of red wine or honey wheat pretzels
- Beverages: water, wine, tea with coconut milk
- Vitamin/Mineral/Supplement intake: B-complex, vitamin D 2,000, calcium with vitamin D, fish oil, biotin, probiotic (notes she has been taking the probiotic for years - unsure if this is helpful at this time)

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Reassessment // Implement Challenge Phase

12/12/2018 On Low FODMAP diet ~ 4 weeks. Tracking her Bowel movements, medications, food in Cara app. Using Pinerest for low FODMAP recipes. Some issues with cramping when she stopped taking her the probiotic so she restarted it. Having regular bowel movements. The patient endorsed an overall 80% improvement in GI symptoms with the elimination phase.

Diet recall:

- B: couple of eggs, sourdough bread; zipfizz
- L: leftovers from dinner the night before
- D: chicken + veggies (carrots, spinach, green beans) + potato or rice OR short ribs, or shepherds pie OR GF pasta + Prego sensitive sauce
- Snacks: LF yogurt + kind granola + almond milk or grapes, clementine, FODY bars or trail mix, string cheese, banana
- Beverages: water, tea -green, early grey, sweet n spicy OR red wine or beer.

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Personalization Phase

2/4/2019

- Triggers: Greek yogurt (lactose) -cramps and diarrhea; celery (mannitol) - belching, increased gas, bloating; onions (fructan) - gas, bloating, diarrhea
- Tolerated: Avocado (sorbitol), honey (fructose), garlic (fructan), wheat bread (fructan), black beans (GOS)- a little bit boating

- GOAL: consume a modified low FODMAP diet - bringing back in foods that did not bother her. Limit/avoid high FODMAP foods that trigger symptoms
- Review importance of portion sizes and re-challenging FODMAP trigger foods in the future as desired

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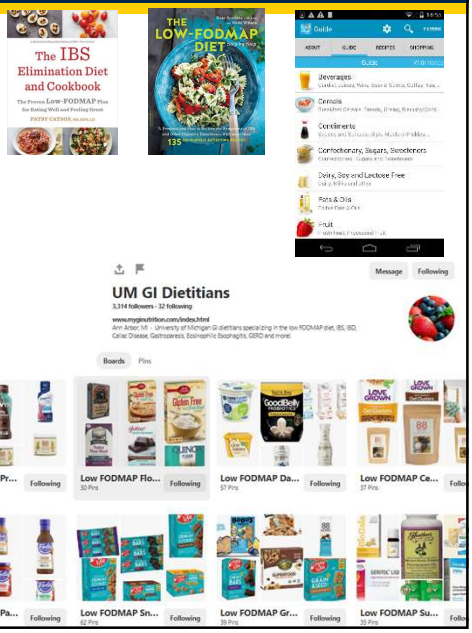
FODMAP Resources

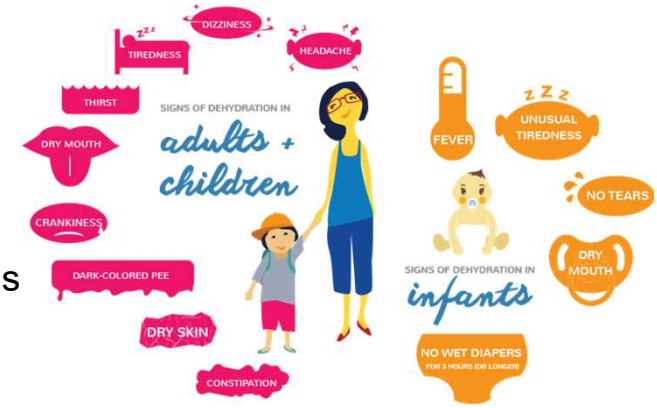
Websites / Books

1) UM GI Dietitians Pinterest Page
2) MyGINutrition.com
3) Kate Scarlata website: www.katescarlata.com
4) Patsy Catsos's website: www.ibsfree.net/
5) Monash University: http://fodmapmonash.blogspot.com
6) FODMAP Everyday www.fodmapeveryday.com



Risk factors/causes:

- High ostomy output
- Diarrhea
- Inadequate intake of fluids
- Short gut syndrome



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Case #3: Short Gut Syndrome

56 y.o. female with stricturing Crohn's disease s/p multiple resections currently on ustekinumab. Diagnosed 1984. Underwent multiple bowel resections (1984, 1993, 2003, 2015) including but not limited to jejunectomy, ileocolectomy, R hemicolectomy, and appendectomy. Precise length of remaining bowel is unknown.(?) Experiencing symptoms of short gut syndrome since at least 2008.

Symptoms: 8-13 bowel movements per day. Has nothing but watery stools.

Notes she can't expel gas, will cause pain as well as loud gurgling. Bloating with distension daily - worse after eating. Vomiting 3 times per week when she tries to make herself eat.

Height: 163.8cm Weight: 106 lbs (4/2019) BMI: 17.9 UBW: 175-185 lbs (2/2018)

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Diet recall

4/2019

Breakfast: skips

Lunch: skips

Dinner: 5-7pm, chicken breast, hamburgers or steak and potatoes OR fish sticks, french fries, Oreos OR pasta or pizza, applesauce

Beverages: Mountain Dew -regular, 2-4 cans/day, water, Gatorade, LF milk

Vitamin/Mineral/Supplement intake: probiotic - takes 4 times per day, 1 billion CFU, chewable

Pt meets criteria for severe Malnutrition

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Nutrition Interventions

- Increase caloric/protein intake: Recommend smaller more frequent meals/snacks (~5-6 per day)
- High quality protein at each meal and snack
- Generous complex carbohydrate intake (pasta, rice, potatoes, breads, quinoa, etc.)
- Avoid high sugar/concentrated sweets/HFCS
- Adequate fluid intake, minimize fluid intake at meals to ~ 4 ounces, consume most of liquids in between meals
- NO oral supplements (Boost, Ensure)
- Trial of ORS
- Recommend daily Multivitamin - chewable or liquid

Parrish, CR. A Patient's Guide to Managing a Short Bowel, 4th Ed. June 2016:1-66. Available at no cost to patients & clinicians @ www.shortbowelsyndrome.com/sign-up

Oral Rehydration Solutions

- Better than a sports drink
- Optimal balance of electrolytes
- Sodium and glucose increase fluid absorption
- Can buy OTC or can make at home

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Do-It-Yourself Options:

United Ostomy Association of America has recipes available for replacing electrolytes & fluids:

Homemade Drink:

- 1 teaspoon salt
- 1 teaspoon baking soda
- 1 teaspoon white Karo syrup
- 1, 6-ounce can frozen orange juice
- Add water to make one quart, mix well

Quick Fix

- 1 teaspoon salt
- Orange juice – 4 ounces
- Water – 4 ounces
- Pinch of salt

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Follow Up 2 Months Later

Symptoms: Decreased bowel movements, nausea, and vomiting

B: eggs and grits or steak and eggs or veggie omelet w/ onions, peppers, cheese, tomatoes

L: soup- chicken noodle or tomatoes, cucumbers and ranch dressing

D: steak or fish, vegetables-string bean, lima beans, carrots, tomatoes, with potato or rice, baked beans

Beverages: juice - diluted, soda-diluted, no koolaid - feels this has been helpful - less urgency, less diarrhea

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Continued Follow Up

- 6/2019: Wt up to 117 lbs
- 3 bowel movements per day
- "Changing her diet has really helped her symptoms in the setting of short gut"
- Pt reports she is able to leave the house

- 9/2019: wt up to 132 lbs. BMI 22.3
- Maintaining balanced diet

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Exclusive Enteral Nutrition (EEN)

- EEN very popular in pediatrics, in Japan
- Truly exclusive enteral=
  - No food antigens, bacteria, fungi
- Does not have to be elemental
  - Multiple RCTs of elemental vs. non-elemental – no difference
- About 1/3 as effective as steroids in inducing remission
  - EEN addresses nutrition deficits, few/no adverse side effects
- Concern hard to maintain in adult population
  - Non-compliance with EEN treatment in early studies adversely affected the efficacy of EEN compared with CS therapy

Cochrane Database Syst Rev. 2007 Jan 24;(1):CD000542.
Aliment Pharmacol Ther. 2017 Oct;46(7):645-656

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IBD patients care about nutrition. RDs are best suited to assess and implement nutrition therapy

No single diet suitable for all IBD patients; unique dietary recommendations must be developed for each patient

Collaborate: Partnership between patient, gastroenterologist, and dietitian

Role for diet to reduce symptoms and lessen effects of IBD complications

Role for diet to assist with inducing remission, reducing relapse

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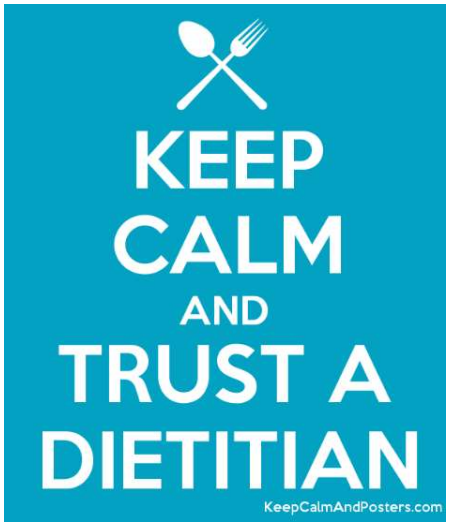

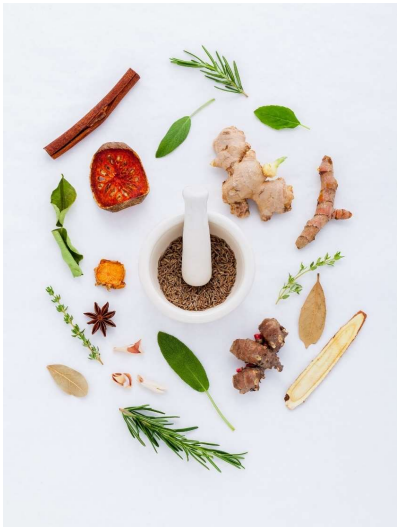

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Suspected Small Bowel Bleeding

Gastroenterology Update 2019

18 October 2019

Michael D. Rice, MD

Outline

- Definition of Obscure/Small bowel GIB
- History of endoscopic eval of small bowel
- Algorithm for evaluation for obscure GIB
- Cases
  - Evidence based approach

The reach of traditional endoscopy

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Challenge of Obscure GI Bleeding

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

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Obscure GI Bleeding (OGIB) Definition

- 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

"Small Bowel Bleeding"

- Small intestinal bleeding 5-10% of all GIB pts
- Advances in small bowel imaging
  - VCE, DAE, radiographic imaging modalities
  - Bleeding can be detected in majority of patients
- Favor reclassifying to "**Small Bowel Bleeding**"

Lau WY , Fan ST , Wong SH et al. Preoperative and intraoperative localization of gastrointestinal bleeding of obscure origin . Gut 1987 ; 28 : 869 – 77 .
Longstreth GF . Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage
Thompson JN, Hemingway AP, McPherson GA, et al. Obscure gastrointestinal hemorrhage of small-bowel origin. Br Med J (Clin Res Ed) 1984;288:1663-5.

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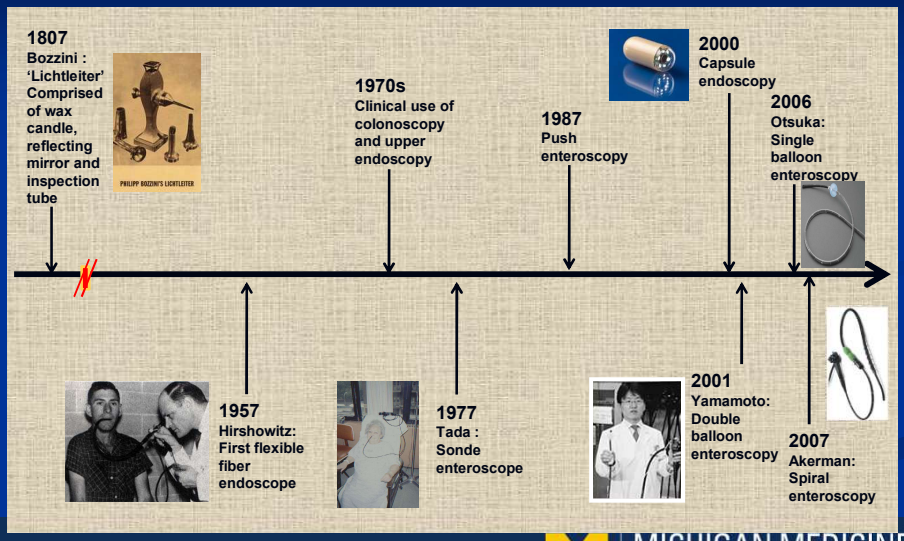
Obscure GI Bleeding

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

Lau WY , Fan ST , Wong SH et al. Preoperative and intraoperative localization of gastrointestinal bleeding of obscure origin . Gut 1987 ; 28 : 869 – 77 .
Longstreth GF . Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage
Thompson JN, Hemingway AP, McPherson GA, et al. Obscure gastrointestinal hemorrhage of small-bowel origin. Br Med J (Clin Res Ed) 1984;288:1663-5.

Endoscopy Timeline

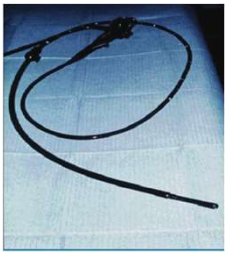


Historic Enteroscopy methods

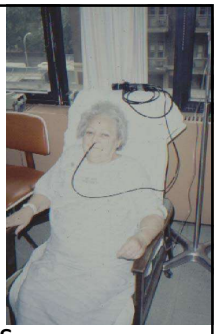
- Length and tortuosity of SB limited exam to the most proximal and distal portions
- Passage of endoscope beyond L.O.T.
  - Push enteroscopy
  - Sonde enteroscopy
  - Intraoperative enteroscopy
- Differ in ability to reach distal SB, therapeutic interventions

Push Enteroscopy (PE)

- Limited to proximal 150cm of SBowel
  - 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%



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

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

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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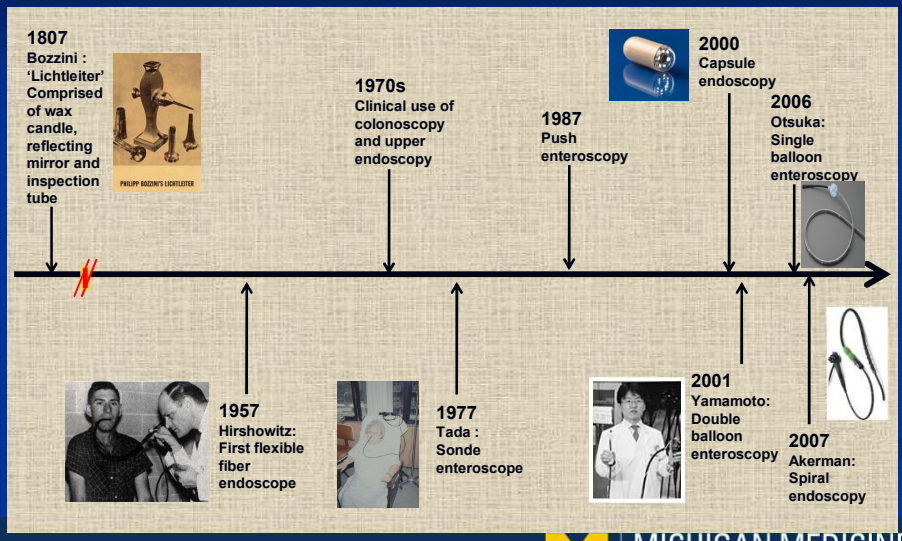
Endoscopy Timeline



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Video Capsule Endoscopy

- Design specifications (SB3)
  - 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

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Performance

1. Bowel prep
2. Sensors placed
3. Patient wears a belt
   - battery pack and data recorder.
4. Ingest capsule around 0800
5. May have clears 2 hours after ingestion
6. Light lunch 4 hours after swallowing capsule
7. Avoid other patients who ingested a capsule.
8. Patient returns 7-8 hours later

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Retrieving Data

- Images transmitted by radiofrequency to sensor array attached to patient (SensorBelt)
- Data downloaded from beltpack recorder to workstation
- Available for reading

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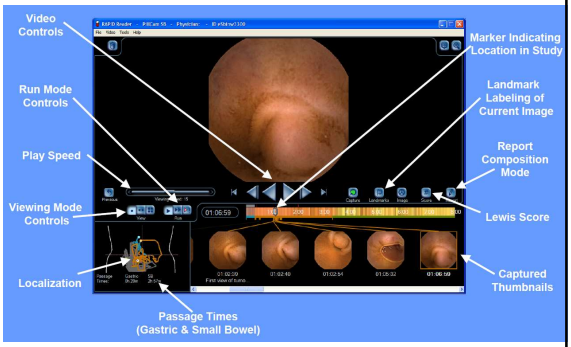
Rapid Reader

- Reading times vary
  - 20 mins to 2 hrs
- Can read up to 25 frames/sec.
- Tools -↓reading time
  - Red finding software
  - Double frame imaging
  - Quad view



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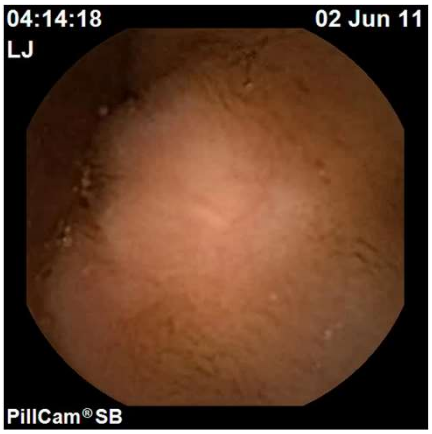
"Physiologic Endoscopy"

- 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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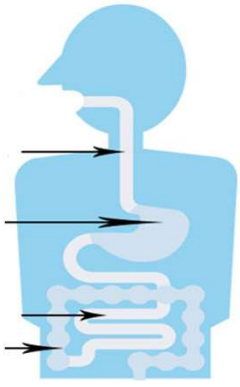
Average Transit Times

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



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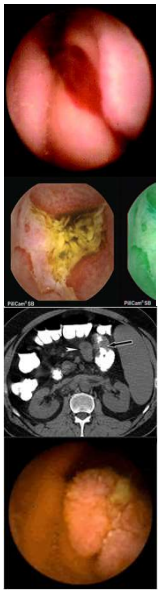
Indications for VCE

- 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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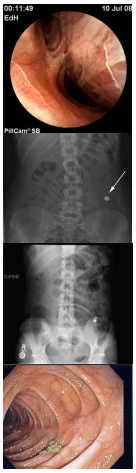
Informed Consent

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



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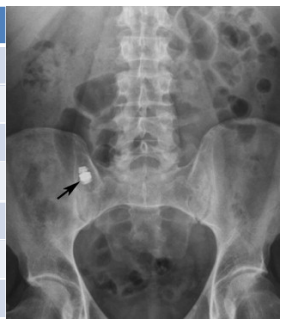
Capsule Retention Rates

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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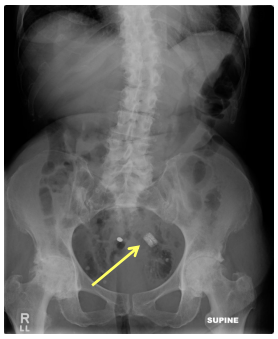
Patency Capsule

- Intended to verify adequate patency
  - known or suspected strictures
- Crohn's
- Chronic NSAID use
- SB tumors
- Radiation enteritis
- Adhesive disease
- Anastomotic stenosis



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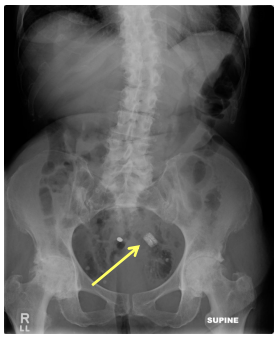
Patency Capsule

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



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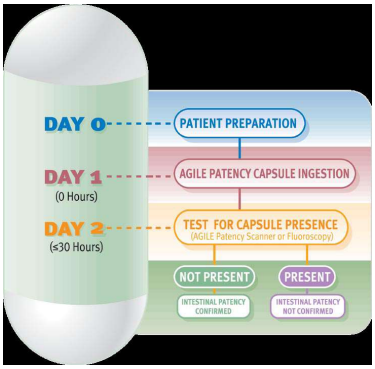
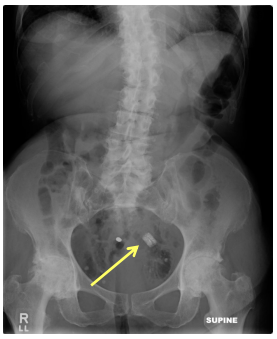
Patency Capsule





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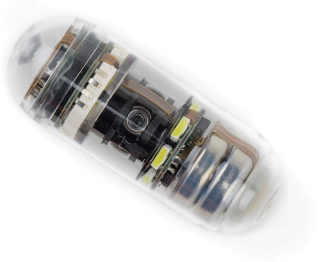
CapsoCam Plus: Retrievable VCE



- 360° visualization
- Requires capsule retrieval
- Eliminates theoretical risk of RF interference for cardiac devices

Larger vertical field of view displays the full 360° image

CapsoCam Plus image of the small bowel mucosa viewed at 1152 x 212 pixels

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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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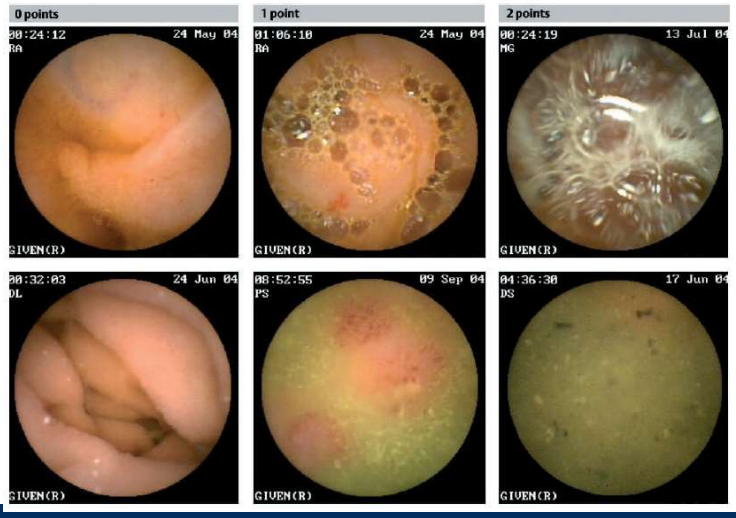
VCE Bowel Prep



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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: $\chi^2 = 45.137$, $P < .001$.

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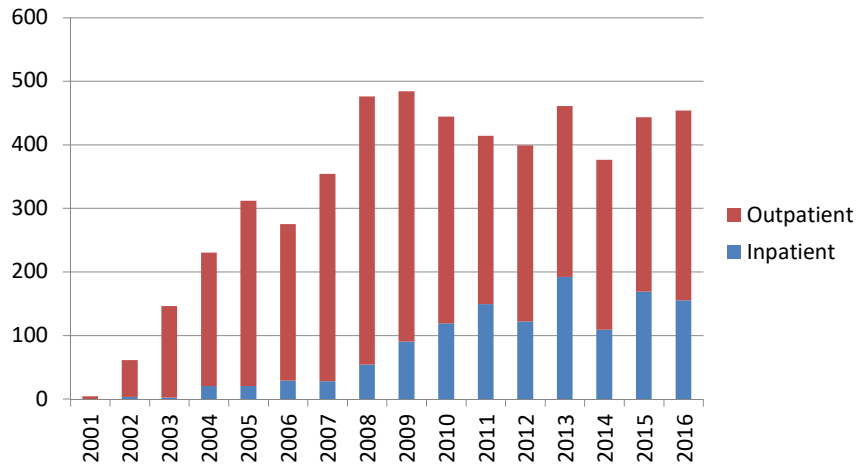
UMHS VCE Volume



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Challenges In Achieving Deep Enteroscopy

- Length of small intestine (400-600 cm)
- Loop formation
  - Gastric
  - Small bowel / mesentery
  - Colonic (sigmoid, transverse)
- Diminish transmission of force to tip of scope
- Technical and safety restrictions on all enteroscopy devices (eg, diameter, rigidity)

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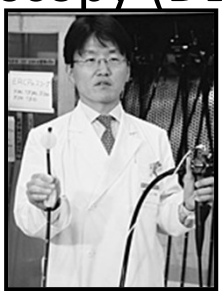
Double Balloon Enteroscopy (DBE)



- 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

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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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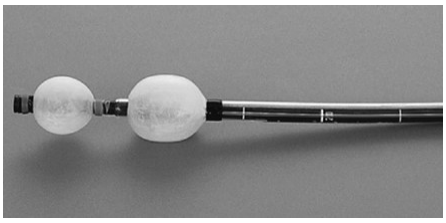
DOUBLE BALLOON ENTEROSCOPY

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



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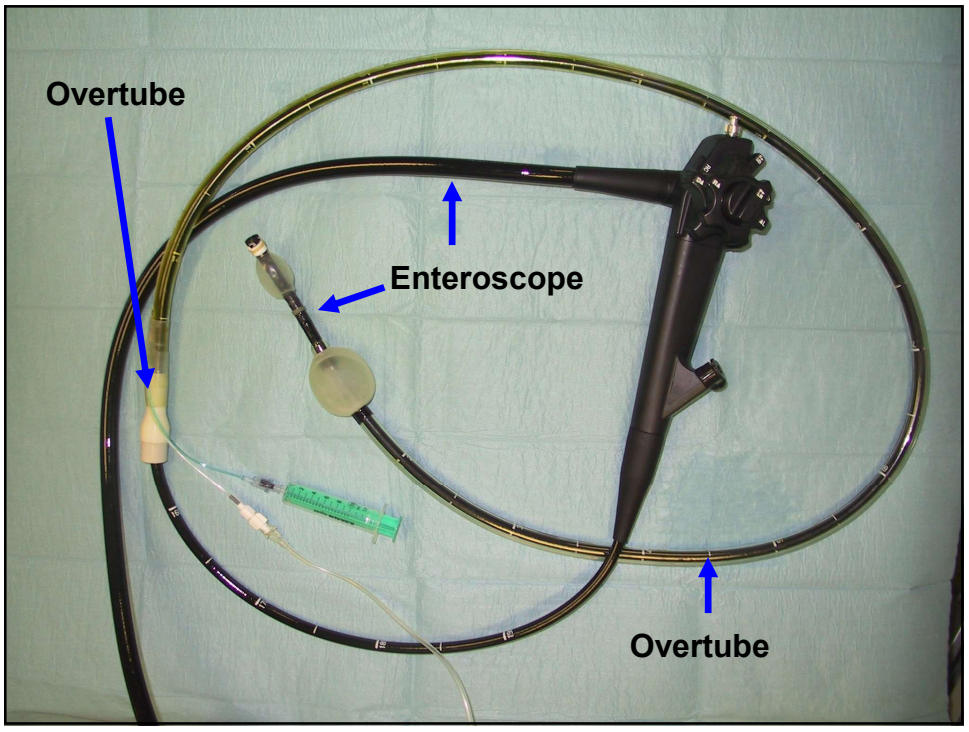

DOUBLE BALLOON ENTEROSCOPY

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

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Potential Uses For DBE

- Obscure GI 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

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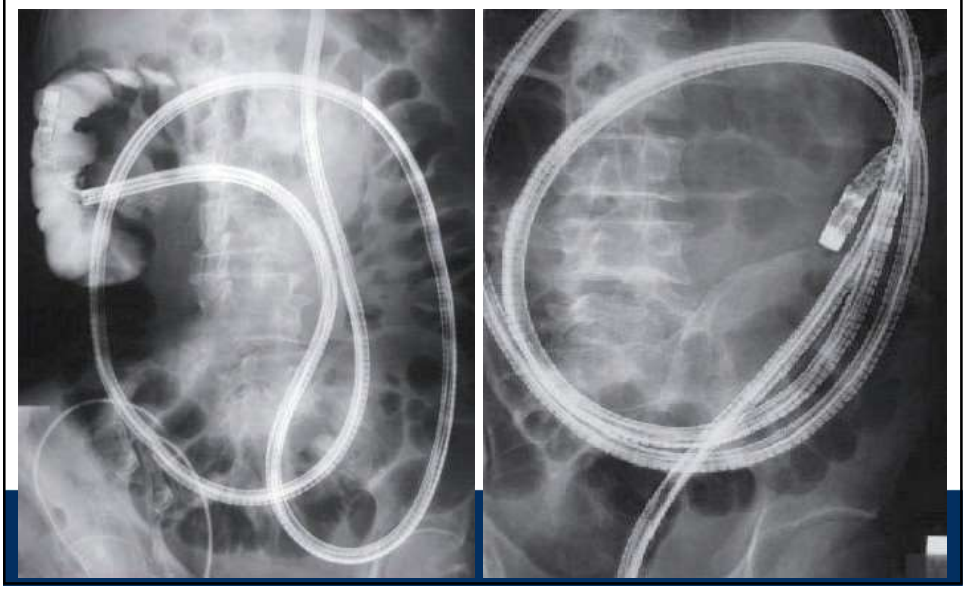
DBE

- 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

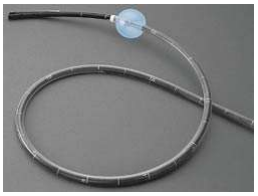


Safety of DBE

- DBE Register in Germany 2003-2006
- N=3894 DBE 64 centers (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

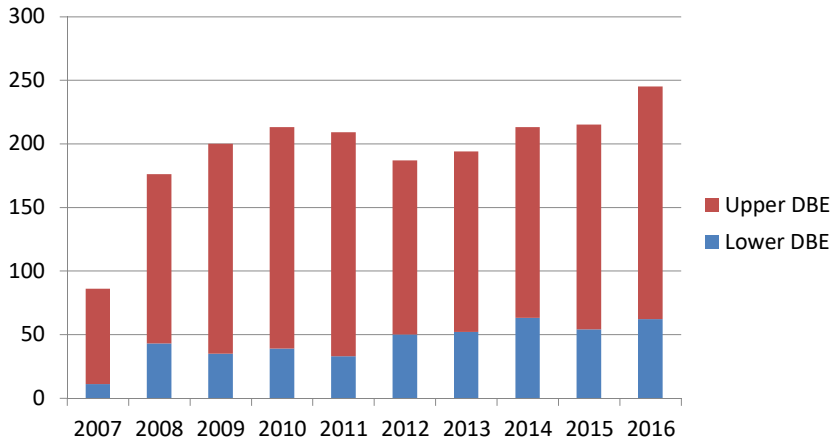
Other Device Assisted Enteroscopy

- Single Balloon Enteroscopy



- Spiral Enteroscopy

UM DBE Volume



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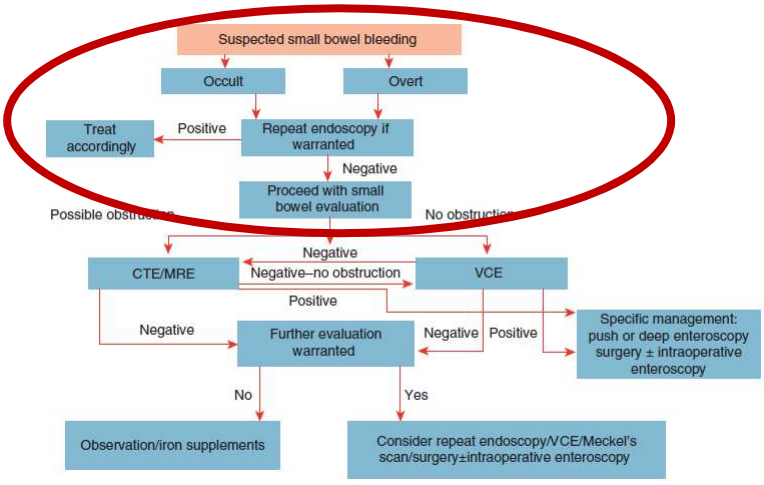
Algorithm for suspected small bowel bleeding



ACG Guidelines 2015 for Diagnosis and Management of Small Bowel Bleeding

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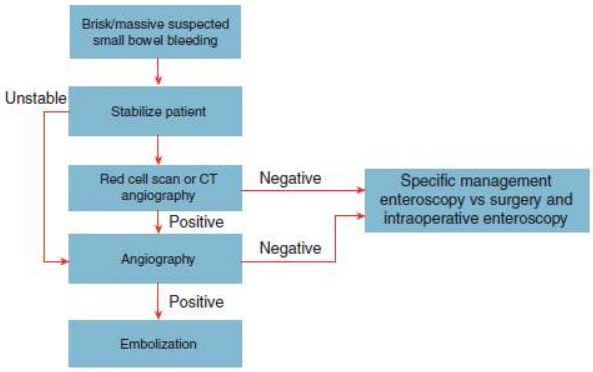
Algorithm for brisk or massive suspected small bowel bleeding



ACG Guidelines 2015 for Diagnosis and Management of Small Bowel Bleeding

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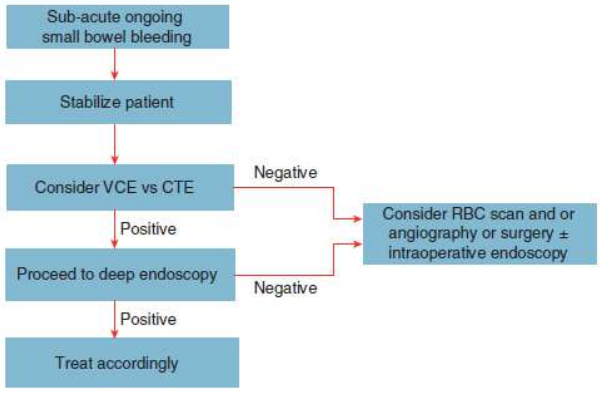
Algorithm for sub-acute ongoing suspected small bowel bleeding



ACG Guidelines 2015 for Diagnosis and Management of Small Bowel Bleeding

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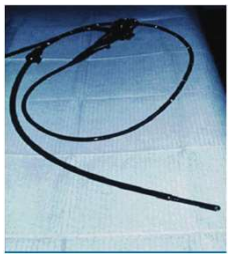
Push Enteroscopy

- 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



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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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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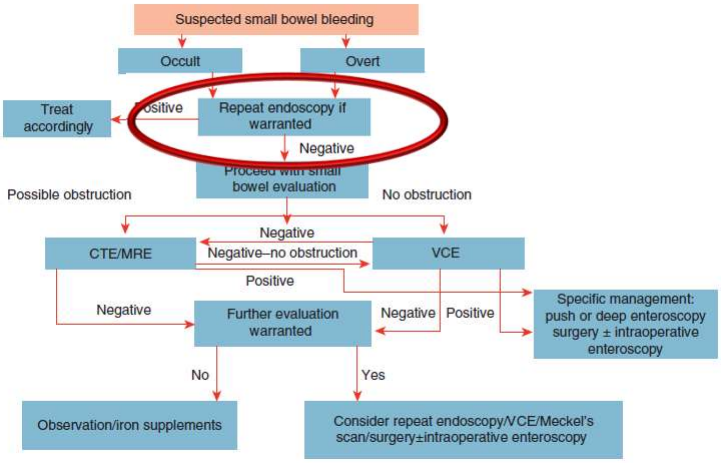
Role of Relook Endoscopy



Role of Relook Endoscopy

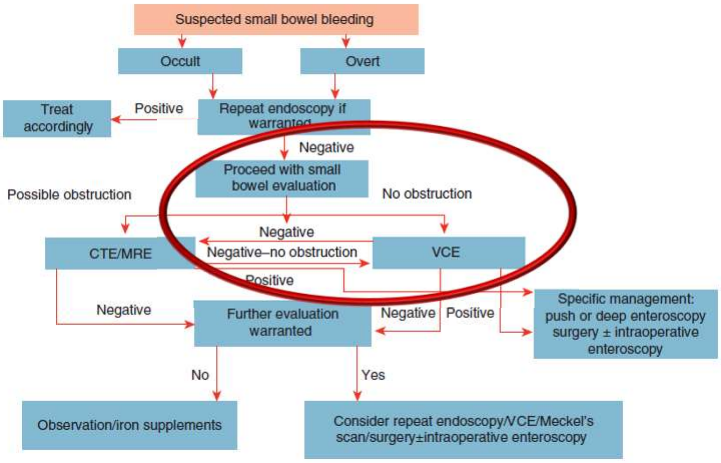
- Def: OGIB have undergone EGD and colonoscopy
- Many have undergone several evaluations
- VCE shows bleeding lesions within reach
  - 3-17% in upper GI tract
  - 2-4% in lower GI tract

Relook endoscopy

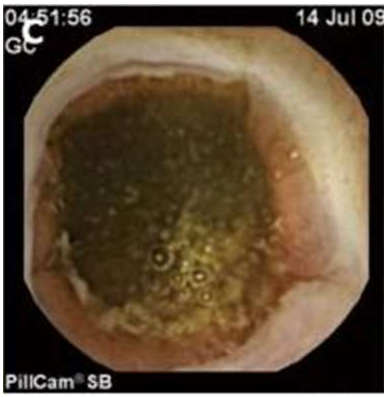
- Attempt to identify patients referred for VCE likely to harbor lesions within reach
  - Significant difference in rate of lesion outside the SB
    - patients referred from centers who do not perform VCE
    - EGD, colonoscopy at VCE at same center
  - (6.3% vs. 1.15% respectively, p = 0.026.)

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. doi: 10.1007/s10620-011-1592-3

Algorithm for suspected small bowel bleeding



VCE



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Capsule Retention Rates

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Healthy Volunteers	0%
Suspected Crohn's	1.4%
Known Crohn's	5%
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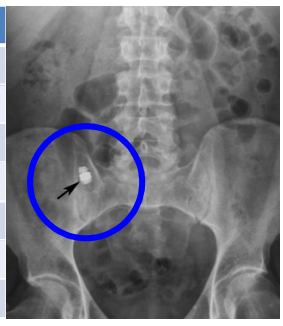

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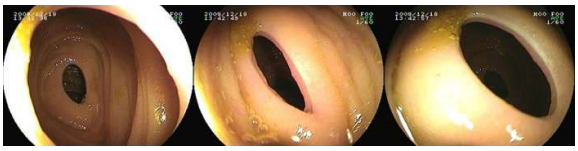

- NSAIDs are one of the most commonly used medications world wide
- Most aware of NSAID complications in the UGI
  - pill esophagitis and gastroduodenal ulceration and hemorrhage
- Significant potential for NSAID injury of the small intestine.

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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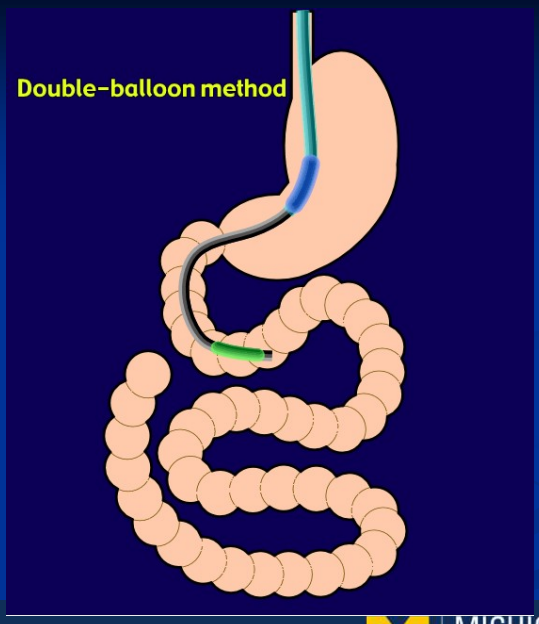

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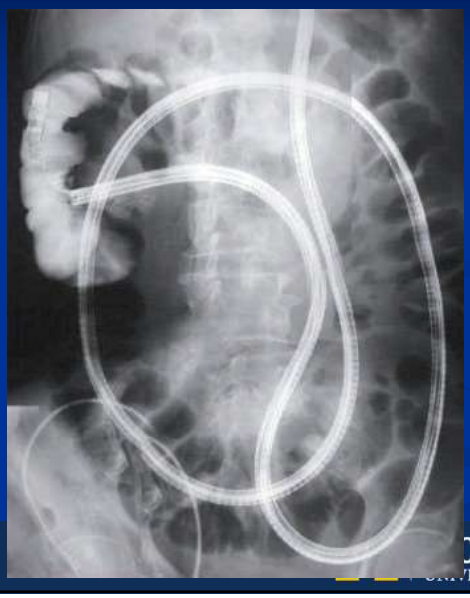
DOUBLE BALLOON ENDOSCOPY

Antegrade (oral) DBE



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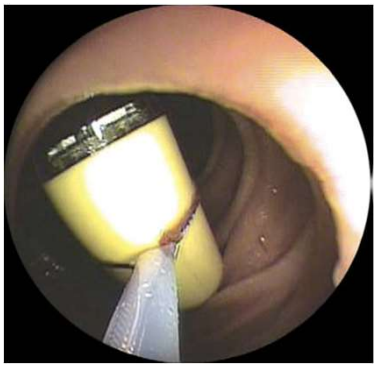
Retained Capsule



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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.

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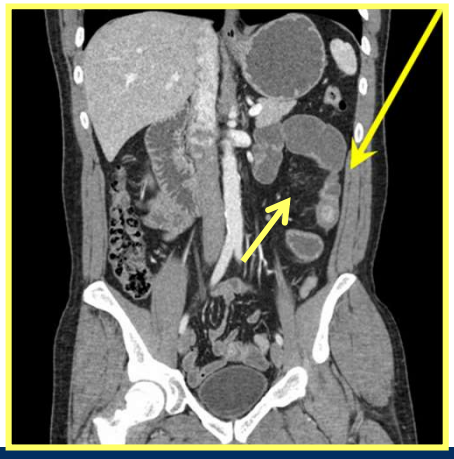
Inflammatory stricture with proximal bowel dilation



Loftus, 2006.

HEALTH SYSTEM
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Crohn's Disease
VCE vs. BAE

- When IC is negative→VCE helpful
  - Relatively noninvasive
  - Higher rate of success for achieving total enteroscopy
- BAE is useful for tissue diagnosis

DBE in Crohn's disease

- Two recent International Consensus statements
- Insufficient data to recommend DBE unless:
  - Conventional studies (C+I and rad imaging) inconclusive
  - Histologic dx would alter management

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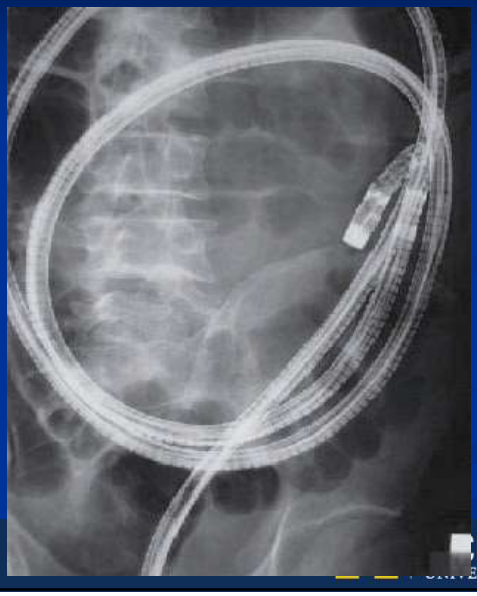
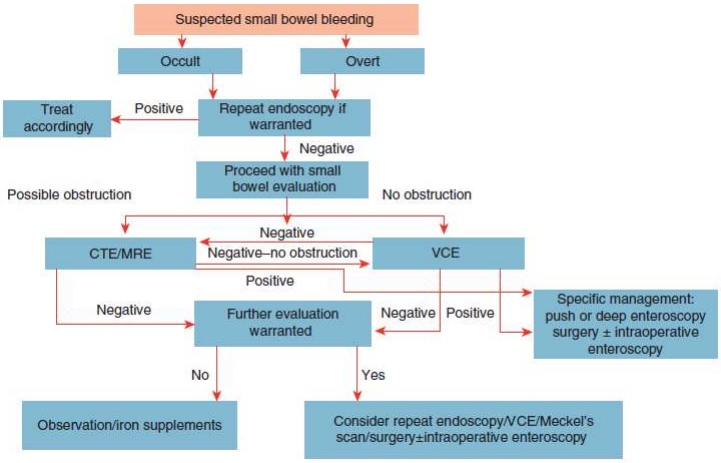
Retrograde (anal) DBE



Summary

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

Algorithm for suspected small bowel bleeding



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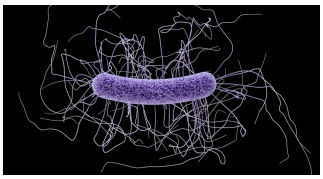
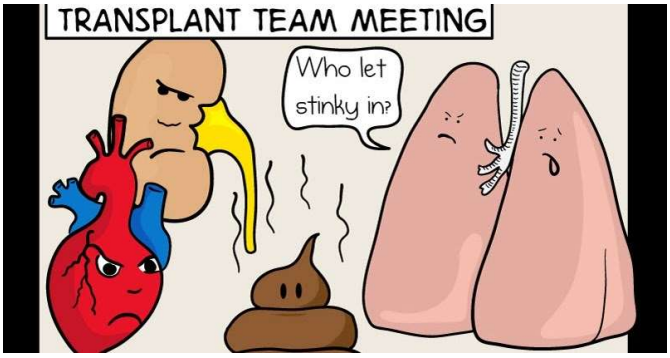
FMT: Present & Future

Michelle Muza-Moons, MD, PhD
IBD Faculty
University of Michigan



Disclosures

none



PoorMD.com (J. Chang)

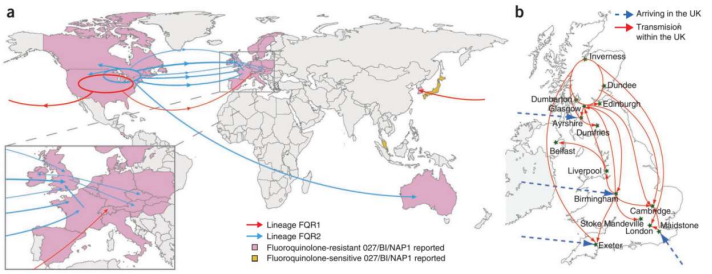
MICHIGAN MEDICINE
GI update 2019 ● FMT: Present & Future

Case #1

- 28y M patient present with 12 days of diarrhea
  - 6-8 small, loose stools daily
  - Slight greenish color with mucous
  - No abdominal pain
  - No weight loss
  - Recent dental work including root canal
  - Completed 7 days clindamycin prior to endodontic procedure

Scope of the C. difficile Problem

- ↑Diagnosis: 2-fold
- ↑ Mortality: 10-fold
- ~500,000 cases per year[1]
- ~50,000 deaths annually[1]
- Annual cost >$1 billion[2]
- Now a global epidemic[3]



[1]Lessa et al. 2015
[2]Zimlichman et al. 2013
[3]He et al. 2013

C. Diff testing: Who?

- Diarrhea
  - >3 loose BMs/24 hours
  - No alternate explanation
- Ileus + leukocytosis
- Colitis on imaging
- Acute abdomen with bowel wall thickening
- Toxic megacolon
- Pseudomembranes on endoscopy

Who should NOT be tested?

- Asymptomatic Patients
- Colonization
  - 60-70% of infants
  - 3% of healthy adults
  - 20-50% of adults in LTACs
- While on therapy
- Immediately following therapy
  - Prolonged shedding in 50% @ 6 weeks
- Post infectious IBS

Use of Rectal swabs & PCR

- Indications
  - Ileus
  - Endoscopy unsafe
  - Performs well[1]
    - PPV 95.7%
    - NPV 99.1%

[1]Kundrapu et al. 2012

Summary of Available Tests for *Clostridium difficile* Infection, in Decreasing Order of Sensitivity

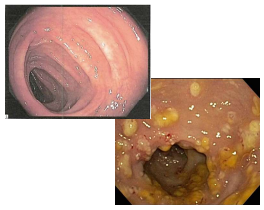
Must be combined with a toxin test.

Test	Sensitivity	Specificity	Substance Detected
Toxigenic cultur			*Clostridium* getative cells
Nucleic acid amplification tes			nucleic acid es)
Glutamate dehydrogenase			common
Cell culture cyto neutralization as			s
Toxin A and B e immunoassays			s

IDSA guidelines: (any of these)
GDH + toxin
GDH + toxin +/- NAAT
NAAT + toxin

Clinical Infectious Diseases, Volume 66, Issue 7, 19 March 2018, Pages e1–e48,

C diff treatment based on severity



- Mild/Moderate CDI
  - None of the severity criteria
- Choices:
  - Metronidazole 500 mg PO TID x 10-14 days
  - Vancomycin 125 mg PO QID x 14 days (recurrence)
  - Fidaxomicin 200 mg PO BID x 10 days (more on this later)

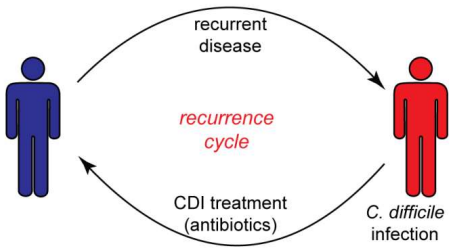
- Severe CDI
  - Age >65
  - WBC >15,000
  - Albumin <2.5
  - Fever
  - Colonic thickening / Severe Abd pain
  - AKI (Cr >1.5 x premorbid level)
  - Pseudomembranous colitis
- Severe
  - Vancomycin 125 mg PO QID x 14 days
  - Fidaxomicin 200 mg PO BID x 10 days
- Severe complicated
  - Vancomycin 500 mg PO QID PLUS
  - Vancomycin 500 mg PR QID PLUS
  - Metronidazole 500 mg IV q8h
    - Only situation where IV metronidazole is used/useful

Case #2 – recurrent C. diff

- 54y woman
  - h/o SLE/RA overlap and hypogammaglobulinemia
- C. difficile infection, treated with flagyl
- 3 weeks later, recurrence of diarrhea, tested positive for C. diff
- Treated with vancomycin prolonged taper
  - Patient responded with normal stools for about one month then acute onset diarrhea
  - Started on vancomycin again, 250mg QID

Recurrent Disease

- Definition: initial resolution of symptoms followed by clinical re-emergence with positive testing >2 weeks but <8 weeks from the index episode
- Happens in up to 25%!
- 2nd Recurrence: 30-45% of 1st
- 3rd Recurrence: 45-60% of 2nd
- ≤5% of all patients → chronic, recurrent pattern
- No universal treatment algorithm
- Patients with recurrent CDI have a microbiota characterized by lower-than-normal community diversity



Infect Dis Clin North Am. 2015 Mar; 29(1): 109–122.
Gough et al. 2011

Case #3 - 1958, Denver

- Elderly gentleman, admitted to the ICU with fulminant, life-threatening pseudomembranous colitis.
- Physicians wanted to “re-establish the balance of nature” after recent antibiotic treatment
- Administered donor feces by enema to their patient.
- Resulted in “immediate and dramatic” responses and concluded that “this simple yet rational therapeutic method should be given more extensive clinical evaluation.”

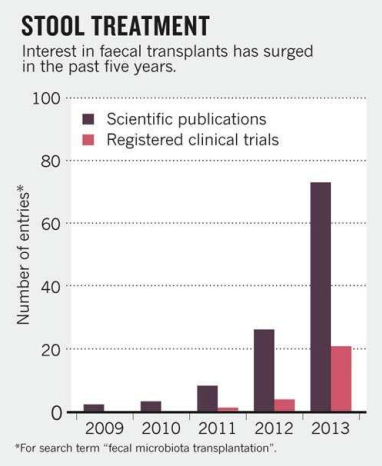
B. Eiseman, W. Silen, G.S. Bascom, A.J.Kauvar **Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis.** Surgery, 44 (1958), pp. 854-859

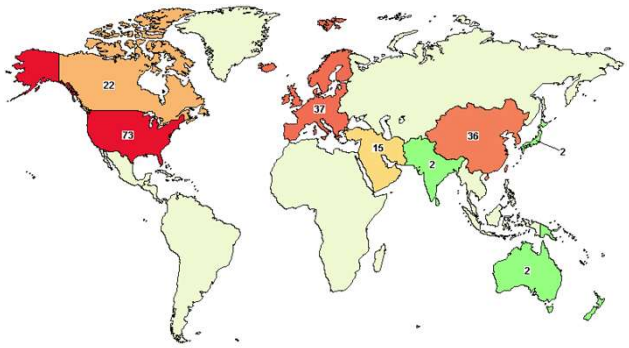
B. Eiseman MD

- “In the early days of oral antibiotics we were plagued by frequent diarrhea in our patients due presumably to killing off intestinal bacteria. I was Chief of Surgery at the VA and simplistically considered merely reintroducing normal organisms to counter such absence. Those were days when if one had an idea, we simply tried it. It seemed to work and I wrote it up. It made a small splash…Best wishes. Ben Eiseman Emeritus Professor of Surgery ” (2012).
  - (A. Khortus, Human Microbiome Science 2013)

Growth in fecal transplants worldwide; clinical trials

2016
# of clinical trials on Clinical Trials.gov
193
2018
# of clinical trials on Clinical Trials.gov
197





M. Smith *et al Nature* 2014

FMT is Effective

- 92% of patients had resolution, 89% after 1 treatment and 5% after retreatment
- 4% had a relapse; 87.5% had resolution with retreatment.
- No serious adverse events

REVIEW ARTICLE

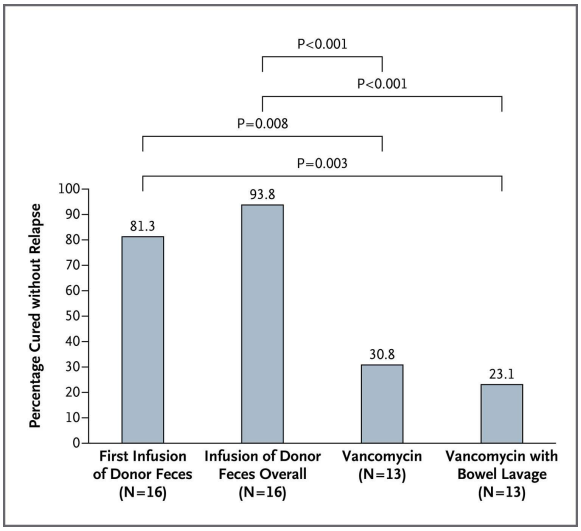
Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent *Clostridium difficile* Infection

Ethan Gough,[1] Henna Shaikh,[2] and Amee R. Manges[1,3]
Departments of [1]Epidemiology Biostatistics and Occupational Health, and [2]Biology, McGill University, and [3]Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

- In 317 patients treated across 27 case series and reports, IMT was highly effective, showing disease resolution in 92% of cases.

Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

The primary outcome was cure defined as absence of diarrhea or persistent diarrhea from another cause, with 3 consecutive stool tests negative for *C difficile* toxin.



Early termination of study
94% in FMT group achieved cure
Vs 31% in vanco alone
Vs 23% in vanco + bowel lavage

The study was stopped early
Off-protocol FMT offered to patients in other treatment arms (n=18):
83% cure rate

van Nood E et al. N Engl J Med 2013;368:407-415.

Effectiveness is not route specific.

Upper GI tract

Endoscopic

NG tube

Capsules

-less appealing to patients

-requires radiology assistance to confirm tube placement

-risk of vomiting and aspiration

Van Nood E, Vrieze A, Nieuwdorp M, et al. N Engl J Med. 2013;368:407–15.

Youngster I, Russell GH, Pindar C, et al. Jama. 2014;312:1772–8.

Proximal Colon

Colonoscopy

-well tolerated

-examination of colonic mucosa, and exclusion of pathology which may be contributing to the patient's symptoms

-procedural risk

-increased health care utilization and costs*

Khoruts A, Dicksved J, Jansson JK, et al. J Clin Gastroenterol. 2010;44:354–60.

Persky SE, Brandt LJ. . Am J Gastroenterol. 2000;95:3283–5.

*Varier RU, Biltaji E, Smith KJ, et al. Clin Microbiol Infect. 2014;20:1343–51.

Distal colon

Enema

Flex sig

- inexpensive

-little procedural risk

-may be difficult for some patients to retain the donor material

-may require multiple treatments.

Kassam Z, Hundal R, Marshall JK, et al. Arch Intern Med. 2012;172:191–3.

Silverman MS, Davis I, Pillai DR. Clin Gastroenterol Hepatol. 2010;8:471–3.

Case #4 - FMT

- 54y woman
  - h/o SLE/RA overlap and hypogammaglobulinemia
- C. difficile infection, treated with flagyl
- 3 weeks later, recurrence of diarrhea, tested positive for C. diff
- Treated with vancomycin prolonged taper
  - Patient responded with normal stools for about one month then acute onset diarrhea
  - Started on vancomycin again, 250mg QID and referred for FMT
- 250cc of commercially available donor stool delivered via colonoscopy (terminal ileum)
- At 6 week follow up, her diarrhea had resolved without any further episodes of abd pain, loose stools, fevers/chills, nausea or weight loss.

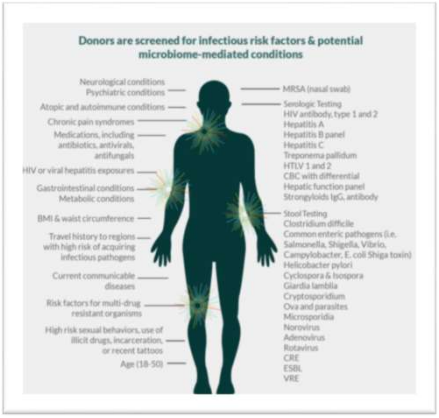
"Only the best stool will work for me"

- Currently, most common is commercial stool bank samples
- Growing participation obtaining stool from a bank, such as Openbiome
  - Single donor, frozen, filtered stool
- Work ongoing to optimize best strategy
  - Pooled stool
  - Most diverse donor samples

Openbiome.org

Commercially available stool

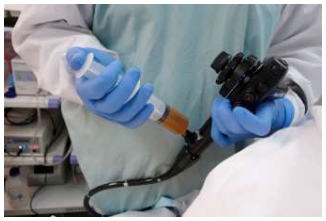
- OpenBiome – non-profit stool bank
  - provide hospitals with screened, frozen material ready for clinical use
  - < 3% perspective donors pass clinical and stool screening
  - perform **high-throughput 16S rRNA sequence characterization on stool** from each of their donors
  - Stool is filtered for particulate, homogenized in glycerol buffer and frozen at -80C and shipped on dry ice.
  - At this time, insurance companies are not covering the stool product as a medication, therefore in our program patients pay the out-of-pocket expense for stool of $1595 (colonoscopy delivery)

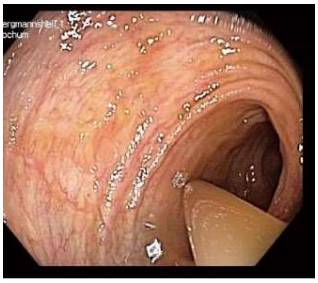


www.openbiome.org

Technical aspects of delivery

- Routine colonoscopy prep
- loperamide prior to procedure
- Colonoscopy to terminal ileum
- Delivery via instrument channel, using 60cc slip-tip syringes
- Recover on R-side in reverse trendelenberg for 1h
- Administer loperamide in recovery to promote retention





Short Term Complications

Minor (common)[3]

- abdominal discomfort
- Bloating
- Flatulence
- Diarrhea
- Constipation
- Borborygmi
- Vomiting
- transient fever

Serious (rare)

- Complication of endoscopy (perforation, bleeding, complication of sedation)
- Rare transfer of infection (reported cases of norovirus) but not seen with increased screening
- fever and E. coli bacteremia [1]
- 17% of IBD patients experience flare
- Multi-center restrospect of immunosuppressed recipients.[2]
  - two deaths
    - aspiration event related to procedure
    - secondary to progressive pneumonia

1 Quera R, Espinoza R, Estay C, et al. J Crohns Colitis. 2014;8:252–3.
2 Am J Gastroenterol. 2014;109:1065–71.
3 Gastroenterology. 2015 Jul; 149(1):223-237.

Long Term Complications

Infectious disease

- possible transmission of infectious agents via FMT
- unrecognized infectious agents
  - Historical lesson of HepC and HIV

Chronic diseases

- development of diseases/conditions related to changes in the gut microbiota
  - report the development of new conditions, including autoimmune disease, ovarian cancer, myocardial infarction, and stroke
- Conditions linked to microbiota (partial list)
  - Obesity
  - Diabetes
  - Atherosclerosis
  - IBD
  - colon cancer
  - non-alcoholic fatty liver disease
  - irritable bowel syndrome
  - Asthma
  - autism

Gastroenterology. 2015 Jul; 149(1):223-237.

Recent FDA warning and safety concern

- One death and one severe ICU illness due to ESBL-producing *E. coli* infection.
  - Two immunocompromised adults received experimental/investigational FMT from same donor
  - Donor stool tested positive for identical strain of bacteria
  - FDA has recommended increased informed consent, mandatory testing of all donated stool for MDROs (ESBL, VRE, CRE) and screening of all donors for higher risk of colonization, recommended quarantine of all previous stool that does not meet this standard
  - The largest commercial stool bank, Openbiome, tests for these organisms and excludes donors who are colonized.

FMT and Regulation

- Regulation Guidelines
  - None in Australia, China or Europe
  - Canada classifies as “new biologic drug” and requires Clinical Trials Application
  - United States Food and Drug Administration (FDA) has determined that administered stool constitutes a biological product and a drug in that it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or is intended to affect the structure or function of the body FDA classifies stool as drug, requires IND [1]
  - The FDA will not enforce its own requirement that FMT be done under IND, as long as providers obtain informed consent, detail risks around the procedure, and explain that FMT is considered an investigational therapy. The enforcement discretion policy does not extend to other uses of FMT such as IBD. Furthermore, clinical trials of FMT for *C. difficile* do not fall under enforcement discretion and require an IND. [2]

1 U.S. Food and Drug Adminstration. FDA Drug Definition. FDA Glossary of Terms. Accessed May 1 2015:
2 U.S. Food and Drug Adminstration. Guidance for Industry: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies. 2013 Jul; Accessed May 1 2015

Primary indications for FMT

- Recurrent or relapsing CDI:
  - Three or more episodes of mild-to-moderate CDI and failure of a 6–8 week taper with vancomycin with or without an alternative antibiotic (e.g., rifaximin, nitazoxanide or fidaxomicin).
- At least two episodes of CDI resulting in hospitalization and associated with significant morbidity.
- Moderate CDI not responding to standard therapy (vancomycin or fidaxomicin) for at least a week.
- Severe (even fulminant CDI) with no response to standard therapy after 48 hours.

Bakken JS, Borody T, Brandt LJ, et al. Clin Gastroenterol Hepatol. 2011;9:1044–9
Surawicz CM, Brandt LJ, Binion DG, et al. Am J Gastroenterol. 2013;108:478–98.
Trubiano JA, Gardiner B, Kwong JC, et al. Eur J Gastroenterol Hepatol. 2013;25:255–7

FMT for C. diff in special populations

- **IBD patients with recurrent C. diff**
  - Decreased effectiveness (75-82%) with some patients requiring multiple transplants
  - If you include multiple transplants for recurrent C. diff, efficacy approaches 90%
  - However, ~14% of patients may experience a worsening of IBD or acute flare after FMT
- **Immunosuppressed (BMT, solid organ transplant) patients with recurrent C. diff**
  - FMT appears effective and safe without increased risk of infection ***
- **Pediatrics**
  - Limited to case reports and small studies (recurrent C. diff and IBD)
  - Reports of treating C. diff with NG tube instillation, colonoscopy and capsules
    - 92% cure rate with no serious adverse events reported
  - Data is mixed for children with recurrent C. diff and IBD, also mixed results in children with IBD alone
  - Shared concern for long term consequences of microbiome manipulation in children as this is unknown.

Expanded applications for FMT

- Dysbiosis (variations in the microbiome) has been associated with a variety of diseases
- FMT is being explored as a potential therapeutic approach
  - promotion of colonization resistance against drug-resistant bacteria
  - inflammatory bowel disease
  - irritable bowel syndrome
  - liver disease – hepatic encephalopathy
  - metabolic syndrome
  - Checkpoint inhibitor colitis
- **316 Studies found for fecal transplant on clinical trials.gov**

Colonization resistance against drug resistant bacteria

- Similar mechanism to recurrent C. difficile treatment
- Bilinski and colleagues successfully decolonized 60% of subjects 1 month following FMT and 93% of subjects at 6 months
- Mahieu and colleagues also showed the ability of FMT to decolonize the gut of vancomycin-resistant *Enterococci* (VRE) and carbapenemase-producing *Enterobacteriaceae* (CPE).

Bilinski J,et al. Clin Infect Dis. 2017.
Mahieu R, et al. J Inf Secur. 2017;75(1):75–7.

FMT and inflammatory bowel disease

- Systematic review suggests efficacy
  - Ulcerative colitis 36% clinical remission
  - Crohns disease 50.5% clinical remission
  - Pouchitis 21.5%
- Ulcerative colitis – 3 RCTs
  - Improvement noted in one study, two others were halted due to futility
  - Moayyedi et. al, N=75 active UC weekly FMT or water enema for 6 weeks. Remission (full Mayo score <3 and complete mucosal healing) was achieved in 24% of patients after FMT and 5% with placebo
  - 50 patients with mild to moderately active UC, donor feces or autologous fecal transplant via naso-duodenal tube. FMT was administered at the start of the study and again 3 weeks later with no significant difference in outcomes
- Crohns disease
  - Small open-label trial, improvement in 58% of enrolled patients

Gastroenterology. 2015 Jul; 149(1):223-237.

FMT and checkpoint inhibitor colitis

- Immune checkpoint inhibitors (PD1, CTLA-1, PD-L1) are associated with colitis that can range from mild to severe and debilitating.
- Checkpoint inhibitor colitis therapy
  - Currently treated similar to IBD with corticosteroids, anti-TNFs
  - Case series looking at FMT for refractory ICI-colitis were successful at resolving colitis
- Recent data indicate microbial dysbiosis may alter efficacy of ICI therapy. "**Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors"** Science. 2018 Jan 5;359(6371):91-97

Mature Medicine 2018, 24, 1804.

FMT and IBS

- Single center study – 69% experienced improvement, but only 46% achieved long term patient-specific treatment goals
- Slow transit constipation (STC) in 36.7% of subjects 12 weeks following FMT, in comparison to 13.3% in the control group
- In combination with dietary fiber and probiotics, FMT resulted in clinical remission in 12/23 (52.5%) of STC
- Treatment of chronic intestinal pseudo-obstruction (CIPO) with FMT resulted in 44.4% of subjects regaining the ability to eat normally 8 weeks after treatment

Curr Infect Dis Rep. 2017 Sep;19(9):31.

FMT and Liver Disease

- NASH (non-alcoholic steatohepatitis) is associated with microbial dysbiosis
  - Improvement in animal model after 8 week FMT therapy
- Severe alcoholic hepatitis (steroid ineligible)
  - resolution of ascites and hepatic encephalopathy following FMT alongside an improved 1-year survival rate compared to controls (87.5% compared to 33.3%)
- Hepatic encephalopathy
  - Hepatology, 2017; two studies (England and US, Virginia) looking at FMT vs SOC for HE and dysbiosis. Promising with decreased hospitalizations and improved cognition.
  - Hepatology April 2019, phase 1 trial with FMT capsules, appears safe, improved dysbiosis markers (LBP, AMP and EncephalApp scores)

Hepatology. 2019 Apr 30. Hepatology. 2017 Dec;66(6):1727-1738 Curr Infect Dis Rep. 2017 Sep;19(9):31.

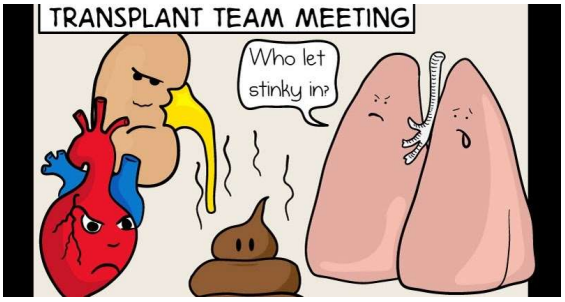
Obesity

- Global epidemic
- Lean and obese individuals have dramatically different microbiomes
- Transfer of gut microbiota from lean and obese individuals can recapitulate the metabolic phenotype in ex-germ free mice.
- double blind RCT transferred stool from lean individuals to obese
  - improved insulin sensitivity
  - increased gut microbial diversity
  - increased butyrate-producers following transplant.
- Highlights promising possibilities for obesity, metabolic syndrome and diabetes treatment

Progression past stool…..

- Super-donor phenomenon
- Designer transplants
  - Refined and defined microbial communities
  - microbial ecosystem therapeutics “MET”
  - Encapsulated spores – Ser109

Public Perception



- My Experience
  - Patients are calling for this therapy
  - Many find it significantly more appealing than antibiotics
  - IBD patients accept this easier than immunosuppression
- The social media experience
  - Multiple patient groups and websites advocating for FMT
  - Some concerning discussions of home based FMT enemas
  - “DIY” fecal transplants and risks

Thank you!

MICHIGAN MEDICINE
GI update 2019 ● FMT: Present & Future

Functional Defecation Disorder

Stacy B. Menees, MD MS
Assistant Professor
Division of Gastroenterology

Conflicts of interest

- ACG Clinical Research Award

Agenda

- Constipation Overview
- Definition
- Criteria
- Case-based Learning

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Constipation

- Common!
- Affects approximately 25% of North American Adult population
- Women> Men (2:1)
- > 2.5 million office visits/year
- > $500 million spent on laxatives/year
- Leads to ↓ productivity and ↑ absenteeism

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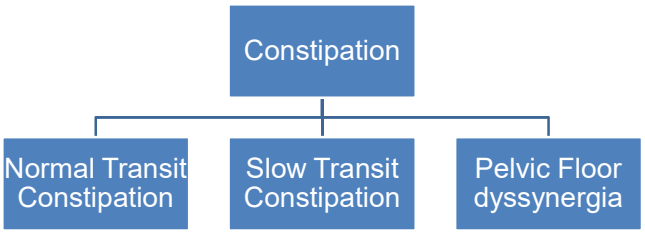
Constipation Overview



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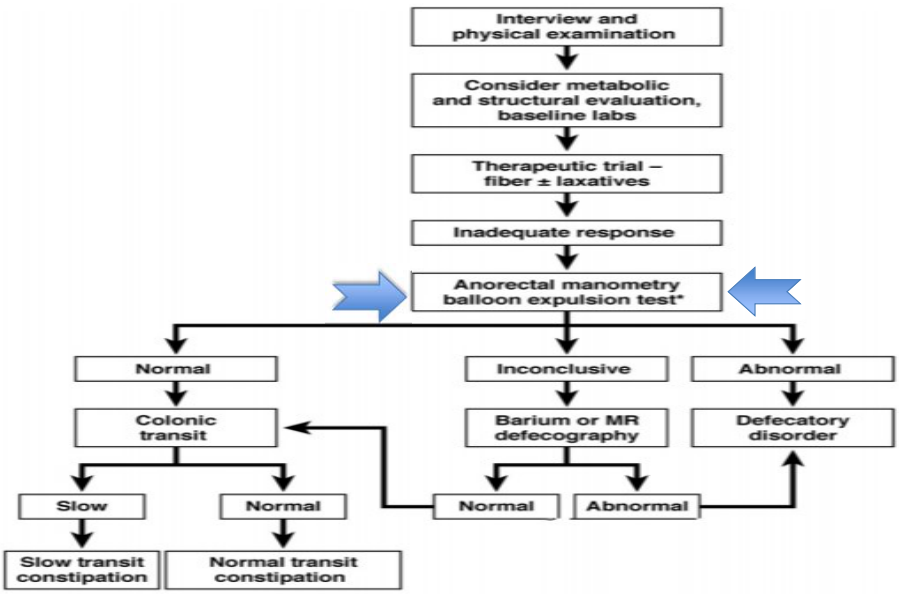
AGA Constipation Algorithm



Gastroenterol 2013 Vol 144 no.1

What's in a name?

- Functional Defecation Disorder
  - Anismus
  - Paradoxical puborectalis contraction
  - Pelvic outlet obstruction
  - Spastic pelvic floor syndrome
  - Obstructive defecation
  - Pelvic floor dyssynergia- Rome II
  - Dyssynergic defecation-Rome III
  - Functional defecation disorders- Rome IV

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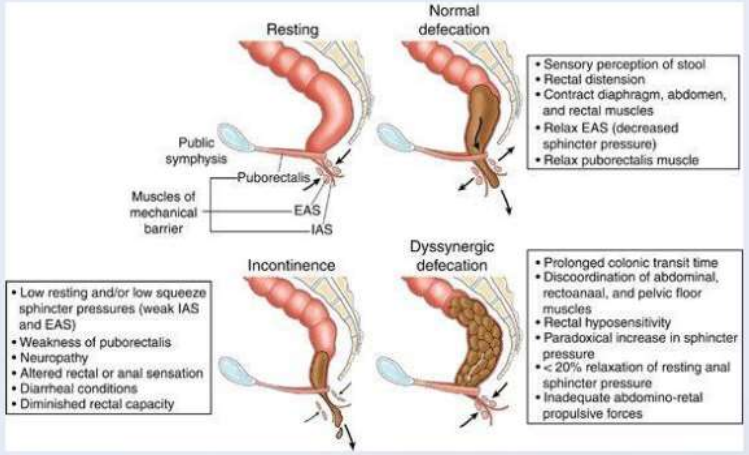
Anatomy and Physiology of Normal Pelvic Floor and disorders



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Functional Defecation Disorder

- Prevalence: 20-81%
  - Tertiary care centers, may be false positives
  - Women 3x more likely than men
- Etiology? Unclear
  - Began in childhood-31%
  - Particular event: pregnancy, trauma or back injury-29%
  - Unidentifiable-40%
  - 60% report intermittent passage of hard stool
  - Does excessive straining to expel hard stools ➡ predispose?
  - Sexual abuse 22% and physical abuse in 32%

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Functional Defecation Disorder

- Quality of life significantly decreased*
  - 74% significantly interfered with social life
  - 56% affected sexual life
  - 33% affected work life
- DD worse than CC for SF-36**
  - Vitality
  - General health
  - Role-physical
  - Role-emotional

* Rao J Clin Gastroenterol 38; 8 page 380. **Rao J Psychosom Res 2007 Oct;63 (4) 441-9

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Functional Defecation Disorders

- Symptoms:
  - prolonged or excessive straining
  - a feeling of incomplete evacuation,
  - use of perineal or vaginal pressure during defecation to allow the passage of stool
  - digital evacuation of stool

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Clinical Case

- 30 yo female with constipation since birth of child (>5 yrs ago)
  - Has BM every 10 days
  - Hard, pellet like
  - Uses enema to evacuate
  - Notes excessive straining, incomplete evacuation
  - Sometimes requires digital disimpaction
  - Tried OTC laxative: MOM, Colace and miralax without relief

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Clinical Case History

- PMH: Seasonal allergies
- PSH: No back/pelvic injuries/surgeries
- Obstetric history-G1P1-6 lb baby, vaginal delivery
- Medications: Allegra D

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Clinical Case Physical Exam

- No fissures, +internal and external hemorrhoids
- Hard stool in vault
- Normal resting EAS pressure
- On push, paradoxical movement of EAS (contraction instead of relaxation)

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How Good is Digital Rectal Exam?

- 4 studies N=781
- Heterogeneity (I^2=91%)

Comparator	Sensitivity	Specificity	PPV	NPV
HRM	93	59	91	61
ARM +BET	73	85	97	31
ARM + CTT	83	95	98	65
DEF +EMG	58	88	62	87

- Pooled Sensitivity: 80%; 95% CI 64-90%
- Pooled Specificity: 84%; 95% CI 64-94%

Caetano AC, Can J Gastroenterol Hepatol. 2016; Article ID 8654314, 8 pages

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Rome IV Criteria: Functional Defecation Disorder

- Must satisfy diagnostic criteria for functional constipation and/or IBS-C
- Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

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Rome IV Functional Constipation

- **Functional constipation:** experienced at least two of the following symptoms over the preceding three months:
  - Fewer than three spontaneous bowel movements per week
  - Straining for more than 25% of defecation attempts
  - Lumpy or hard stools for at least 25% of defecation attempts
  - Sensation of anorectal obstruction or blockage for at least 25% of defecation attempts
  - Sensation of incomplete defecation for at least 25% of defecation attempts
  - Manual maneuvering required to defecate for at least 25% of defecation attempts

Rome IV Diagnostic Criteria for IBS

- **IBS:** recurrent abdominal pain on average at least 1 day per week during the previous 3 months that is associated with two or more of the following:
  - Related to defecation (may be increased or unchanged by defecation)
  - Associated with a change in stool frequency
  - Associated with a change in stool form or appearance

Rome IV Diagnostic Criteria

AND

- During repeated attempts to defecate, there must be features of impaired evacuation, as demonstrated by 2 of the following 3 tests:
  - a. Abnormal balloon expulsion test
  - b. Abnormal anorectal evacuation pattern with manometry or anal surface EMG
  - c. Impaired rectal evacuation by imaging

Rome IV FDD subcategories

- Diagnostic Criteria for Inadequate Defecatory Propulsion
  - Inadequate propulsive forces as measured with manometry with or without inappropriate contraction of the anal sphincter and/or pelvic floor muscles
- Diagnostic Criteria for Dyssynergic Defecation
  - Inappropriate contraction of the pelvic floor as measured with anal surface EMG or manometry with adequate propulsive forces during attempted defecation

Anorectal Manometry

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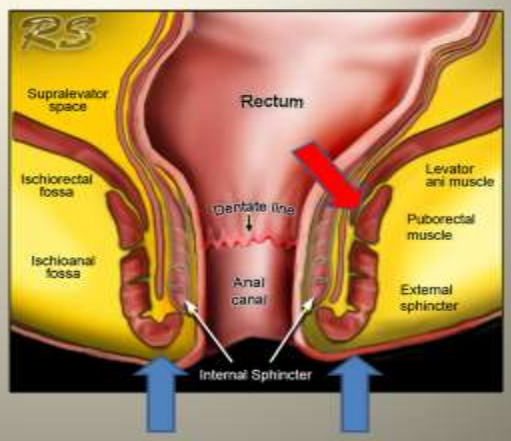
Anorectal Manometry

ANORECTAL MANOMETRY: COMPONENTS

- **Internal Anal Sphincter:**
  - Autonomic Control (Resting Tone)
  - Responds to Stimulation
- **External Anal Sphincter:**
  - Voluntary Control: Pressures Increases and Decreases in response to Defecatory Maneuver
  - Responds to Abdominal Muscle Contraction
- **Puborectalis Muscle:**
  - Responsible for maintaining continence
  - Becomes obtuse during defecation



Tonnis, S. & Swithuis, R. (2009). Radiology Assistant. Adapted from http://www.radiologyassistant.nl/en/p492a88d748185/rectum-perianal-fistulas.html

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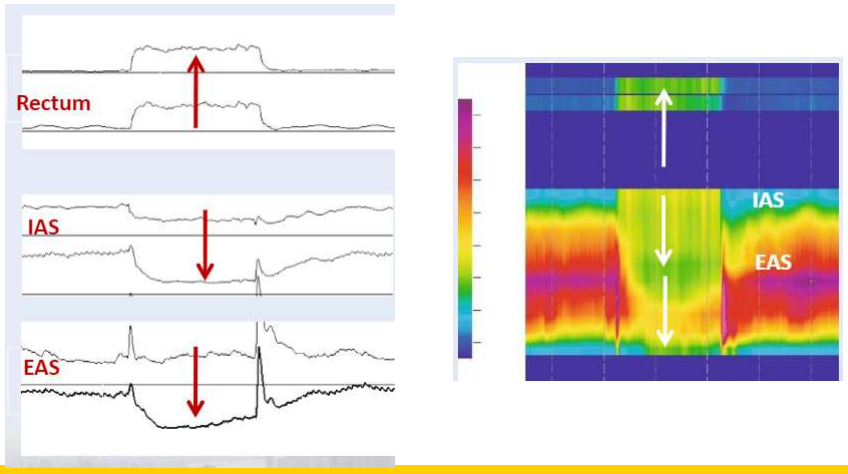
Normal Defecation on ARM



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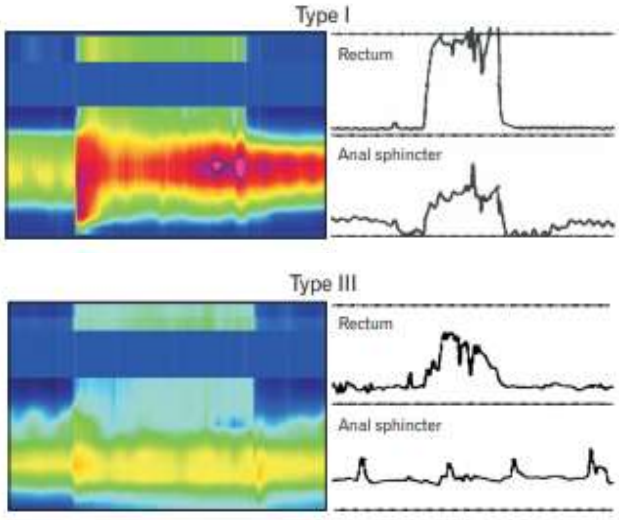
Dyssynergic Defecation on ARM



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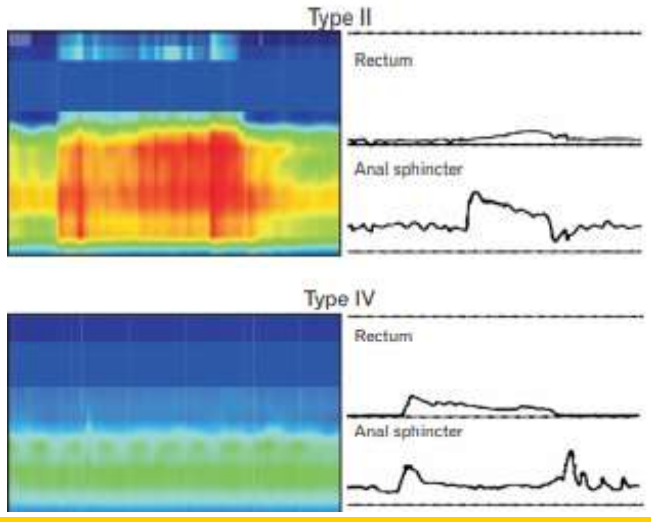
Inadequate Defecatory Propulsion on ARM



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Balloon Expulsion Testing (BET)

- Procedure: Catheter with a 4cm rectal balloon is inserted and inflated with 50 ml of water in the rectum
  - Patients given privacy
  - Instructed to expel the balloon
  - Length to expel is timed
- How good is BET?
  - 14 studies (1760 subjects with CC)
  - AUC 0.80 (0.61-0.91)
  - Sensitivity 70% (52-83%) Specificity 81% (70-82%)
  - Positive LR 3.0 (2.1-4.3) Negative LR 0.39 (0.23-0.67)

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Defecography

Ruma, J.; Al-Hawary, M.et al..,. ARRS 2009 University of Michigan, Ann Arbor, MI
Address correspondence to M. Al-Hawary (alhawary@umich.edu)

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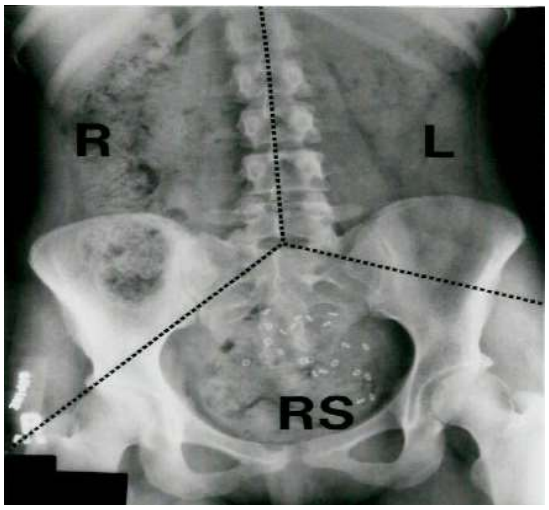
AXR



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Nonpharmachologic Treatment

- Toilet training
  - Instruct patients to:
  - Attempt BM at least bid, 30 minutes after a meal
  - Not ignore urge to defecate
  - Diaphragmatic breathing while defecating
  - Avoid straining when passing stool
  - Not stay on the toilet for more than 5–10 minutes

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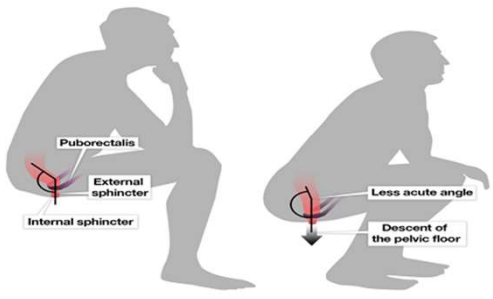
Nonpharmachologic Treatment

- Use correct posture, ie, “brace-pump” technique: sit on the toilet and lean forward, with knees higher than hips and with feet supported on a step to straighten the anorectal angle



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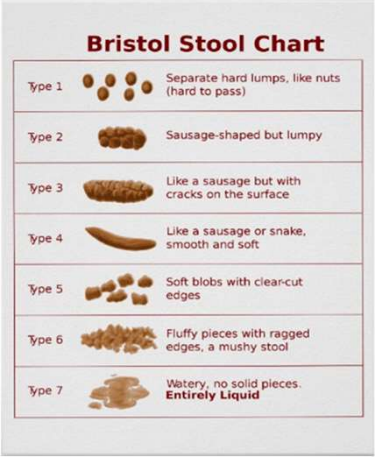
Treatment

- Standard treatment for constipation as adjunct
  - Fiber
  - Osmotics
  - Stimulants
  - Intestinal secretagogues
  - Enemas/suppositories
- Goal of a soft BM type 5-7



Treatment

- Biofeedback
- Mainstay of treatment:
  - Technique of conditioning and retraining the mind to regulate defecation

Treatment

- Biofeedback Goals
  - Teach diaphragmatic breathing exercises
  - Teach anal sphincter and pelvic floor relaxation
  - Improve rectal sensation
  - Eliminate sensory delay
  - Improve recto-anal coordination

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Gastroenterology
Volume 130, Issue 3, March 2006, Pages 657-664

Clinical–alimentary tract

Biofeedback Is Superior to Laxatives for Normal Transit Constipation Due to Pelvic Floor Dyssynergia

Giuseppe Chiarioni *, William E. Whitehead ‡, Vincenzo Pezza §, Antonio Morelli ||, Gabrio Bassotti ||

- Pelvic Floor Physical Therapy with Biofeedback
  - 79.6% “Major” subjective improvement
  - 81.5% normalization of balloon expulsion
- Laxatives/Bowel Retraining
  - 21.8% “Major” subjective improvement
  - 3.6% normalization of balloon expulsion

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Treatment

Diseases of the Colon & Rectum
April 2007, Volume 50, Issue 4, pp 428–441 | Cite as

Randomized, Controlled Trial Shows Biofeedback to be Superior to Alternative Treatments for Patients with Pelvic Floor Dyssynergia-Type Constipation

Authors | Authors and affiliations

Steve Heymen, Yolanda Scarlett, Kenneth Jones, Yehuda Ringel, Douglas Drossman, William E. Whitehead

- Pelvic Floor Physical Therapy with Biofeedback
  - 70% Adequate symptom relief
  - More than 50% decrease in EMG during simulated defecation
- Diazepam
  - 23% Adequate symptom relief
  - EMG with simulated defecation worsened
- Placebo
  - 38% Adequate symptom relief

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Treatment

- Biofeedback Efficacy
- 70–80% in randomized controlled trials (RCTs) and it is more effective than sham therapy, polyethylene glycol or diazepam
- Long term studies have shown that the efficacy is maintained for more than 2 years after treatment
- The success of biofeedback therapy depends on both the patient's motivation and the skill of the biofeedback therapist.

- Mainstay of treatment:
  - Technique of conditioning and retraining the

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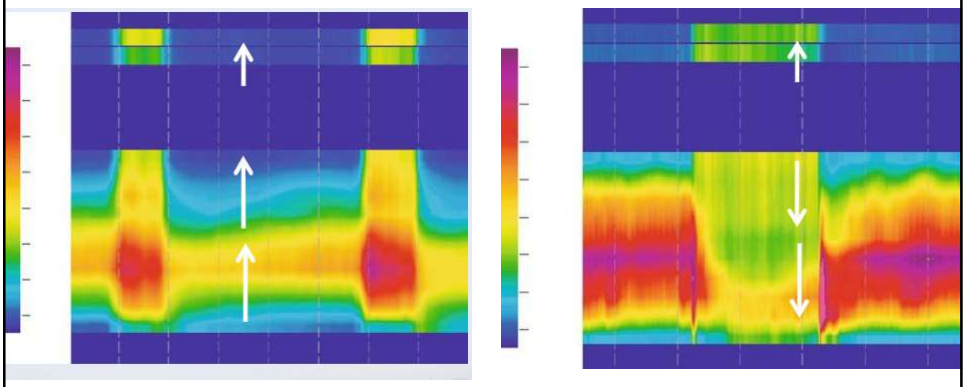
Biofeedback Treatment at 3 months



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Treatment-options for failed response

- Botulinum toxin
  - Non invasive
  - Readily available for clinical use
- Surgical division of the puborectalis
  - Invasive
  - Potential high rate of FI
  - Complications
- Sacral neuromodulation
  - Investigational
  - Mixed results

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Botulinum toxin

- Emile et al. systematic review of literature for Botox for anismus
- Included all studies with sample size of at least 15 and followed patients for at least 6 months
  - 7 studies
  - 5 Observational cohorts
  - 2 comparative studies
    - Botox vs. Division of PR
    - Botox vs. Division of PR vs. pelvic floor physical therapy with biofeedback
- Too few for meta-analysis

Study Characteristics

Table 3 Characteristics of the studies included

Ref.	Country	Type	*n*	Male	Mean age (yr)	Duration of complaint (mo)	Follow up (mo)	Dose of BTX-A (IU)	Site of injection
Shafik *et al*[17]	Egypt	Prospective	15	2	41.2	105.6	14.6	25	Lateral (3, 9 o'clock)
Ron *et al*[18]	Israel	Prospective	24	9	23.7	Not reported	61.0	10-20	Lateral and posterior
Maria *et al*[19]	Italy	Prospective	24	10	56.0	28.0	39.0	60	Lateral (3, 9 o'clock)
Farid *et al*[12]	Egypt	Prospective RCT	15	15	34.7	71.1	14.7	100	Lateral (5, 7 o'clock)
Farid *et al*[20]	Egypt	Prospective RCT	24	7	34.7	Not reported	12.0	100	Lateral (5, 7 o'clock)
Hompes *et al*[21]	United Kingdom	Retrospective	56	20	47.5	Not reported	19.2	100	Lateral (3, 9 o'clock)
Zhang *et al*[22]	China	Retrospective	31	18	50.1	67.2	8.4	100	Lateral and posterior (3, 6, 9 o'clock)

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Summary Results

- 189 patients
  - 57% Women
  - 43% Men
- All had outlet obstruction symptoms
  - Median duration 69.1 months (28-105.6)
- Median age 41.2 years (23.7-56)
- Median follow-up 14.6 months (6-19.2)

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Efficacy

- Clinical Efficacy-Measured variably
  - 77.4% Initial improvement
  - 46% at 4 months post injection
  - Maria et al. used repeated injections at 2 and 4 months
    - Reports 100% improvement long term
    - No increase in complications

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Complications

- 7.4% complication rate
- Median was 0 (range 0-22.6)
- Fecal Incontinence
  - Transient
  - 5.8% (11 patients)
- Anal fissure – 2 patients
- Rectal prolapse – 1 patient

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Botulinum Injection-Implementation Barrier

- Insurance coverage
  - Constipation is NOT listed as indications on Botox website
  - Several insurers specifically qualify use for pelvic floor muscle dysfunction as "investigational"

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Botox vs. Division of Puborectalis

- 30 men with anismus
- Randomized
  - Botox 100 units
  - Bilateral partial division of the Puborectalis
- Success defined as return to normal bowel habits
- Also had post procedure ARM, defo, balloon, and EMG
- Follow up at 1 month, then second follow up between 6 and 24 months

Results

- Both groups showed improved constipation scores
  - Botox success 86.7% → 40%
  - Surgery success 100% → 66.6%

Table 2 Comparison between preoperative–injection and postoperative–injection constipation scores in our patients

	Preop–inj.	Early postop–inj.	Late op–inj.	Student *t* test	
				Preop–inj. vs. early postop–inj.	Preop–inj. vs. late postop–inj.
Group I	11.20±0.94	5.00±2.10	8.20±2.57	0.0001	0.0001
Group II	11.40±0.74	2.27±1.62	6.13±1.69	0.0001	0.0001

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Complications

- Botox – None
- Surgical division of the puborectalis
  - Wound infection/disruption 66.7%
  - Flatal incontinence 13%
  - Rectal intussusception 26.7%

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Take Home Points

- Get a good history
- Perform a complete rectal exam
- Send patient for further testing for dyssynergic defecation if criteria is met
- Laxative therapy as adjunct

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Take Home Points

- Biofeedback
  - Established treatment for pelvic floor dyssynergia
  - Success rate 75-85% of patients
  - Randomized Control Trials: Both short and long term efficacy of biofeedback in dyssynergic defecation
- Botox for dyssynergic defecation should be considered for patients who do not have success with biofeedback
  - Short term success approaches 80%
  - Low complication rates
  - Likely need repeated injections for efficacy

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Thank you for your attention

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Exocrine Pancreatic Insufficiency

5th Annual GASTROENTEROLOGY UPDATE
A Case-Based Approach to Common GI Problems

October 19, 2019

Matthew J. DiMagno, MD, AGAF

Associate Professor of Medicine
Director, Comprehensive Pancreas Program
Gastroenterology Director, Adult CF Program
Division of Gastroenterology and Hepatology

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Disclosures – All Academic / Educational
(Last 24 months)

Funding
- 2016-2018 NIH R21 – acute pancreatitis

Honoraria *(all for academic /educational activities)*
- 2008-2018 British Medical Journal: chapter & updates on chronic pancreatitis, published in BMJ Point of Care
- 2013-2018 Oakstone Publishing, LLC: podcasts for *Practical Reviews, Gastroenterology*

Consultant / Speakers Bureau *(all for academic /educational activities)*
- 2016-2017 Consultant, Cystic Fibrosis Foundation Therapeutics (CFFT), Inc. (Bethesda, MD, USA).

Editorial Board Membership: Pancreatology, Pancreas

Advisory Board Membership *(all for academic /educational activities)*
- 2012- Faculty of 1000 Research (www.f1000research.com)
- 2016-2018 AGA Institute Council Pancreatic Disorders (PAN) Section Committee
- 2017-2019 The National Pancreas Foundation (NPF) State Chapter of Michigan

No conflicts of interest related to this program

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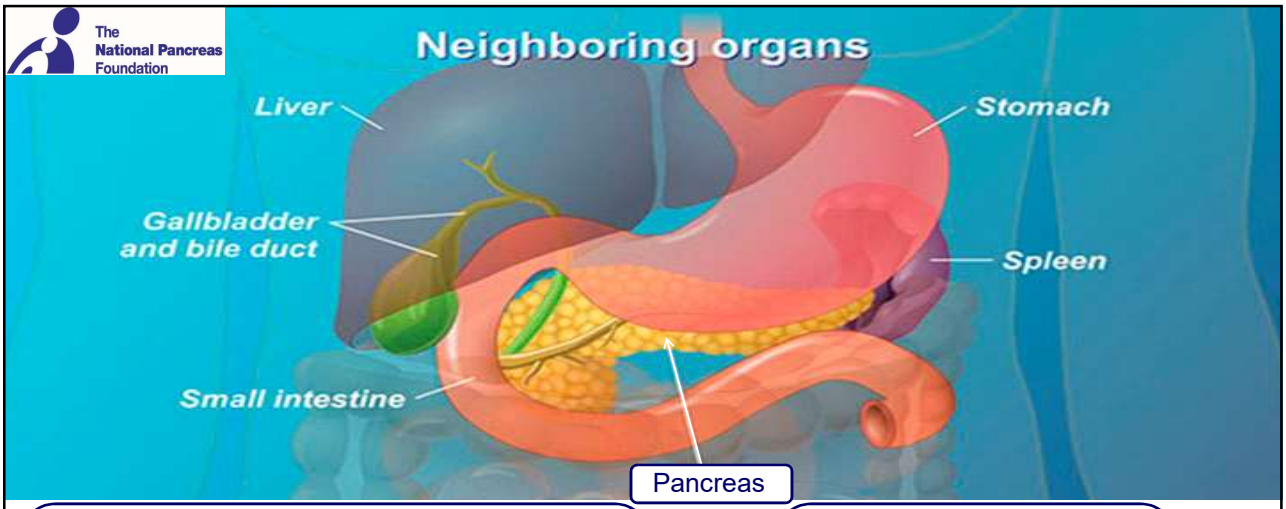

Exocrine Pancreas Juice
- Secretion: smell, gastric distension, food
- 1.5 L/d enzyme rich juice: digest all food groups
  - proteinases (80%)
  - lipase (1%)
  - α-Amylase (5%)
  - others
- Bicarbonate & water flush and buffer

Endocrine Pancreas
- 1,000,000 islets
- 4 hormones (60-80% insulin)
- Insulin released into blood
  - Glucose & metabolism
  - Exocrine function

Terminology: Maldigestion vs Malabsorption

Maldigestion
- Defective hydrolysis of nutrients within intestine
- Examples: enzyme deficiency (pancreatic, lactase, etc)

Malabsorption
- Defective mucosal absorption
- Causes: maldigestion, defective absorption/transport (e.g. celiac)

Use of terms
- When distinction not clinically important, malabsorption used

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Exocrine Pancreatic Insufficiency (EPI)

Diminished luminal pancreatic enzymes

- Primary EPI: decreased (acinar) secretory capacity
- Secondary EPI: preserved secretory capacity

Malabsorption *From* Luminal Pancreatic Enzyme Deficiency

Primary EPI - *reduced secretory capacity*

- Pancreatitis – primarily chronic but also acute pancreatitis (up to 1/3)
- Pancreatic resection
- Cystic fibrosis
- Schwachman-Diamond Syndrome
- Adult pancreatic lipomatosis or atrophy
- Johanson-Blizzard Syndrome
- Isolated lipase deficiency
- Congenital pancreatic hypoplasia
- Agenesis of the pancreas

Mandalia A, DiMagno MJ. *Exocrine pancreatic insufficiency and nutritional complications. In Cystic Fibrosis. 2020.*

Malabsorption *From* Luminal Pancreatic Enzyme Deficiency

Secondary EPI - *preserved secretory capacity*

Obstruction:	pancreatic / ampullary neoplasm
Decreased CCK release:	small bowel diseases (e.g. Celiac, Crohn's)
Intraluminal lipase inactivation:	gastrinoma, lipase inhibitor
Postcibal asynchrony:	gastrointestinal surgery, dysmotility (*poor mixing, ↓ CCK release, ↓ contact time*)
Enterokinase deficiency:	↓ luminal activation pancreatic proteases
Reduced synthesis:	protein calorie malnutrition (marasmus, Kwashiorkor) reversible with repletion of essential amino acids

Mandalia A, DiMagno MJ. *Exocrine pancreatic insufficiency and nutritional complications. In Cystic Fibrosis. 2020.*

CCK, cholecystokinin; EPI, exocrine pancreatic insufficiency

Symptoms of Exocrine Pancreatic Insufficiency (EPI)

In Mild-Moderate EPI

- Asymptomatic
- Mild abdominal discomfort / bloating

In Severe EPI (enzyme output falls below 10% lowest normal)

- Oily, bulky, foul smelling stools
- Excess flatulence
- Postprandial crampy abdominal pain and/or bloating
- Appetite may increase (ravenous) or decrease
- Weight loss

NOTE: Symptoms not specific to EPI

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Select Complications of Severe Exocrine Pancreatic Insufficiency

• **Weight loss**	
• **Muscle wasting**	protein malnutrition
• **Edema**	protein malnutrition
• **Non-traumatic bone fractures**	vitamins D & K, copper
• **Night-blindness**	vitamin A
• **Bleeding tendencies**	vitamin K
• **Neuropathy**	vitamin E, copper
• **Dermatitis & alopecia**	zinc

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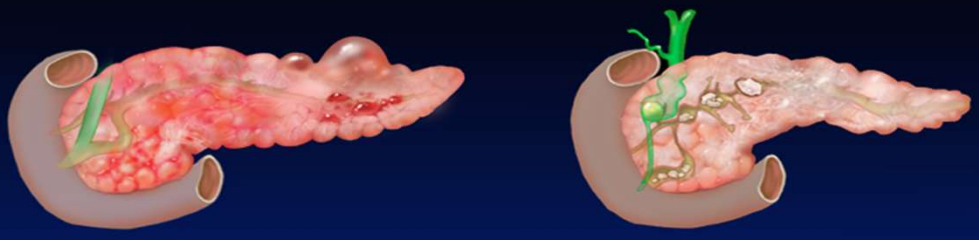
Clinical Manifestation of Fat Soluble Vitamin and Select Mineral Deficiencies

Vitamin A	Xerophthalmia Night blindness Bitot's spots Follicular hyperkeratosis Immune dysfunction
Vitamin D	Rickets Bowed legs Osteomalacia
Vitamin K	Elevated prothrombin time Coagulopathy ↓ bone health
Vitamin E	Peripheral neuropathy Spinocerebellar ataxia Skeletal muscle atrophy Retinopathy Anemia
Copper	Neutropenia Impaired bone calcification Myelopathy Neuropathy Anemia
Zinc	Dermatitis Alopecia Diarrhea Weight loss Infection Hypogonadism

Mandalia A, DiMagno MJ. *Exocrine pancreatic insufficiency and nutritional complications. In Cystic Fibrosis. 2020.*

Primary EPI: PANCREATITIS



Acute

- Acute inflammation
- Acute abdominal pain
- Elevated pancreatic enzymes in serum
- Self-limiting

Chronic

- Chronic inflammation
- Recurrent or chronic abd pain
- Progressive loss of pancreatic
  - endocrine function and
  - exocrine function

AGA Institute teaching slides

Classification of Chronic Pancreatitis by *TIGARO System Plus Celiac Disease*

Toxic metabolic
- **Alcohol**
- Tobacco
- Hypercalcemia (↑ PTH)
- ↑ Triglycerides (familial)
- Chronic kidney disease

Idiopathic (early vs late onset)

Genetic

Autosomal dominant
- PRSS1 (hereditary pancreatitis)

Autosomal recessive/modifier genes
- CFTR (cystic fibrosis)
- SPINK 1 (tropical pancreatitis)
- Others

Historically 60-90% of CP worldwide due to alcohol. Now perhaps less frequent

Autoimmune
- Type 1
- Type 2

Recurrent & severe pancreatitis
- Necrosis

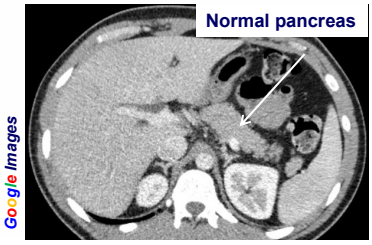
Obstruction
- Neoplasm
- Post-traumatic

Celiac disease

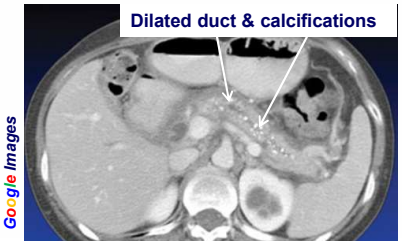
Etemad et al. *Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology. 2011; 120:682-707*
Sadr-Azodi et al. *CGH 2012;10:1136-1142;* ***Ludvigsson et al.*** *CGH 2007;5:1347-1353;* ***Patel et al.*** *GIE. 1999;50:823-827.*
Worning H. *Clin Gastroenterol. 1984;13:871-894;* ***Yadav et al.*** *Arch Intern Med. 2009;169:1035-1045*

Case #1 *(Illustrates Pancreatitis Terminology)*

A 38 year-old man had 3 hospitalizations for pancreatitis in 2009, described as severe epigastric abdominal pain radiating to the back along with marked increases in serum lipase. He is asymptomatic between attacks. Between 2010-15 he has relapsing but less severe attacks at varying intervals. Pancreatitis risk factors include alcohol (8 beers / day x 15 yrs) & 1 pack of cigarettes daily. He now has diabetes, steatorrhea and CT findings of pancreatic calcifications and dilation of the main pancreatic duct.



2009: Chronic Relapsing Pancreatitis



2015: Established Chronic Pancreatitis

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Mayo Clinical Diagnostic Criteria
For Definite CP Requires ≥ 4 Points

Diagnostic Criteria	Points
• **Symptoms** *(pain, relapsing pancreatitis, weight loss)*	2
• **Pancreatic calcifications**	4
• **Histology** *(inflammation, scar, calcification)*	4
• **Abnormal imaging** *(ductal, parenchymal)*	3
• **Decreased exocrine function** *(steatorrhea)*	2
• **Diabetes**	1

2009: Chronic relapsing pancreatitis = CP Suspected (Score =2)
2015: Established CP = CP Definite (Score =12)

***Layer et al**. Gastroenterology. 1994;107:1481–1487.*
***Raimondo et al.** Clinical Gastroenterology and Hepatology. 2003; 1:397–403*
***Reddy et al.** Pancreas. 2016; 45:1276–1281.*

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Early Diagnosis of Chronic Pancreatitis (CP)
Remains a Clinical Challenge

Diagnostic criteria may be delayed years after onset of symptoms

Delay in diagnosis varies by etiology

- Shorter (3-5 yrs) – alcohol & hereditary CP
- Longer (8-15 yrs) – idiopathic (early onset)

Diagnosis of CP requires

- Application of diagnostic criteria, involving
- Laboratory and imaging tests
- Understanding influence of etiology
- Prospective follow-up

Future Biomarkers (e.g. Pancreatic juice prostaglandin E2)

DiMagno EP & DiMagno MJ. *Chronic Pancreatitis. Landmark Papers, Management Decisions, and Future. Pancreas. 2016; 45(5):641-650*
Ammann et al*. Gastroenterology. 1984; 86:820–828;* ***Ammann et al****. Gastroenterology. 1999;116:1132-40;*
Layer et al*. Gastroenterology. 1994;107:1481–1487.* ***Abu Dayyeh et al****. Clin Transl Gastroenterol. 2015;29;6:e72.*

Predicting Progression to Chronic Pancreatitis (CP)
After 1st Attack Pancreatitis

Pancreatitis due to alcohol *(Meta-Analysis of 8 studies)*

- **Progression to CP over 2-15 yrs: pooled prevalence 65%** ***95% CI 48%-80%***

Pancreatitis due to any etiology *(Dutch series of 15 hospitals)*

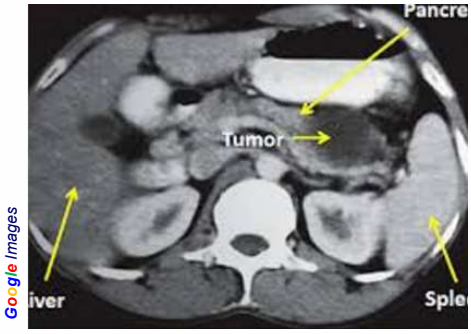
- **4 variables independently predicted progression to CP**
  - **Current smoking**
  - **Idiopathic etiology**
  - **Alcohol etiology**
  - **Necrotizing pancreatitis**

Illustrated by first clinical case

Future Goal: Identify biomarker to strengthen predictive model

Sankaran et al*. Frequency of progression from acute to chronic pancreatitis and risk factors : A meta analysis. Gastroenterology. 2015; 149:1490-1500*
Ahmed et al. *Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. CGH. 2016;14:738-746*

Secondary EPI: Pancreatic Cancer



Google Images

3 cm hypoattenuating mass in the tail of the pancreas

Definite Risk Factors (RFs)

- Age
- Smoking
- Hereditary pancreatitis
- Other familial syndromes (10%)
- Diabetes *(particularly recent dx)*
- Obesity
- Non-O blood group
- Pancreatic cysts (e.g. IPMN)
- Chronic pancreatitis (inflammation)

Possible RFs

- Diet: Fat, Dairy, Red meat
- Alcohol
- Chemicals: Benzidine, beta-naphthylamine

Yadav and Lowenfels. *The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology, 2013;144(6):1252-61*

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Age >40 + Unexplained Pancreatitis Warrants Imaging to Exclude Neoplasia

VA National Medical Care Data Set (1998-2007)

- **495,504 patients** **5720** 1st attack acute pancreatitis (AP)
  710 pancreatic cancer (PCa)

Pancreatic cancer (PCa)

- **11% (76 of 710) had AP in prior 2 yrs**
- **Incidence greatest within 1st yr after AP (~1.5%)**
- **Incidence correlates with age**

→ *Note: Esoph Ca Incidence in Barretts <1%*

	≤40 y	41-50 y	51-60 y	61-70 y	≥70 y
Incidence *per 1000 patient yrs*	0	8	14	21	29

MESSAGE: Consider & screen for PCa as potential etiology of unexplained AP in patients >40 years old

[1] Munigala 2014 CGH; [2] Minato 2013 J Hepatobiliary Pancreat Sci; [3] Talamini 2000 JOP:

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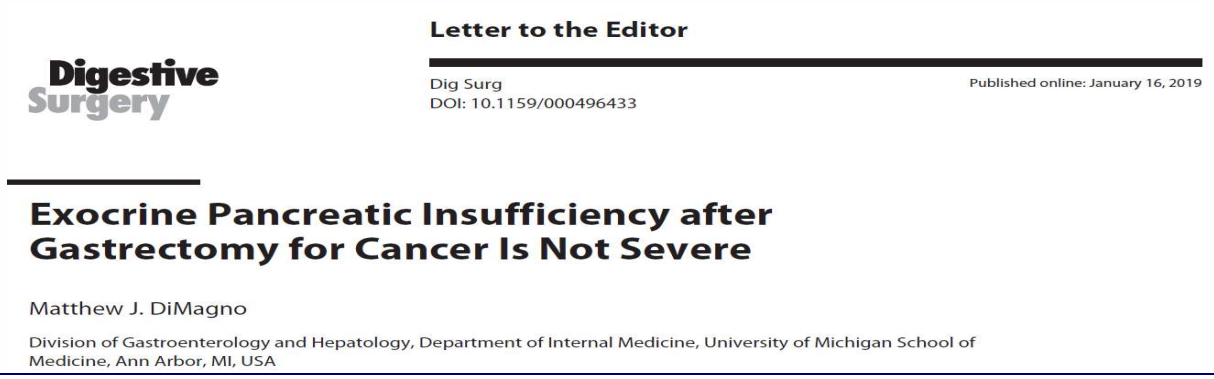
Secondary EPI: Post-Gastrectomy Surgery



Digestive Surgery

Letter to the Editor

Dig Surg
DOI: 10.1159/000496433

Published online: January 16, 2019

Exocrine Pancreatic Insufficiency after Gastrectomy for Cancer Is Not Severe

Matthew J. DiMagno

Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Michigan School of Medicine, Ann Arbor, MI, USA

3 studies of patients with post-surgical duodenal continuity (not Roux-En-Y anatomy) EPI mild-moderate, not severe enough to cause steatorrhea - related to denervation

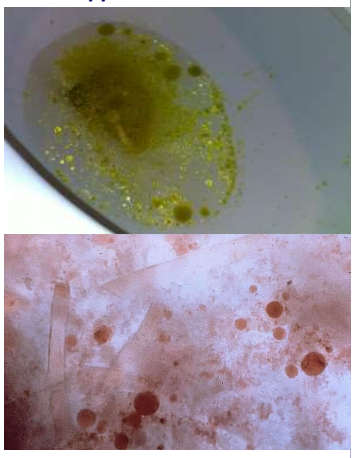
Roux-En-Y gastrectomy: steatorrhea from mixing disorder, bacterial overgrowth, etc.

Secondary EPI: Celiac Disease

Exocrine Pancreatic Insufficiency (EPI) Non-Invasive Diagnostic Tests

- Clinical suspicion: oily stools (right), weight loss
- Definition of severe EPI - pancreatic steatorrhea
  - quantitative fecal fat >7 gm/24 hrs
- Qualitative fecal fat (lower right)
- Severe EPI & fecal elastase
  - <100 ug/g stool suggestive
  - >100 ug/g stool 99% NPV
  - *unreliable with watery stool*

Gross appearance of steatorrhea



Sudan Red Stain for lipids

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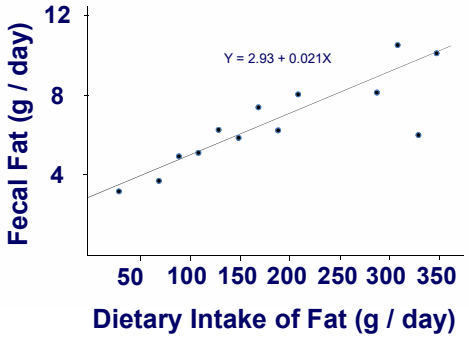
Important Concepts for Normal and Abnormal Digestion of Fat

Implications for treating exocrine pancreatic insufficiency

Exocrine Pancreatic Insufficiency

Coefficient of Fat Absorption (CFA)

- **Linear correlation between ingested and excreted fat**
- **Expressed as % absorbed (or CFA)**

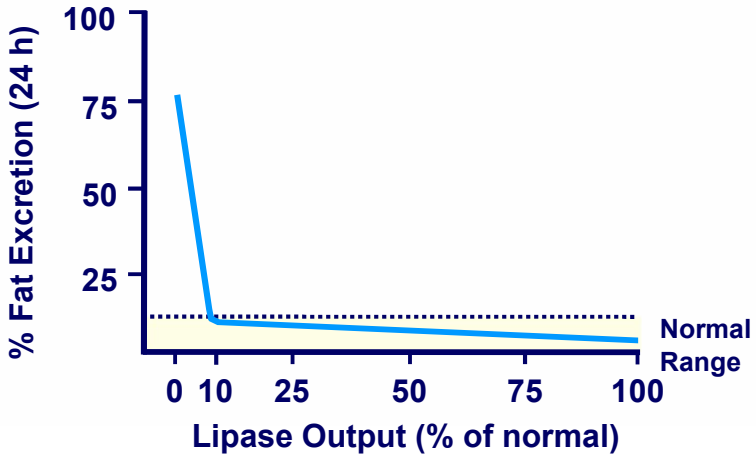


$$\text{CFA} = \frac{\text{g / day fecal fat}}{\text{g / day dietary fat}} \times 100$$

Wollaeger et al. *Total solids, fat and nitrogen in the feces: III. A study of normal persons taking a test diet containing a moderate amount of fat; comparison with results obtained with normal persons taking a test diet containing a large amount of fat. Gastroenterology. 1947;9:272-283.*

Pancreatic Physiologic Reserve

Onset Steatorrhea at <10% Lipase Output

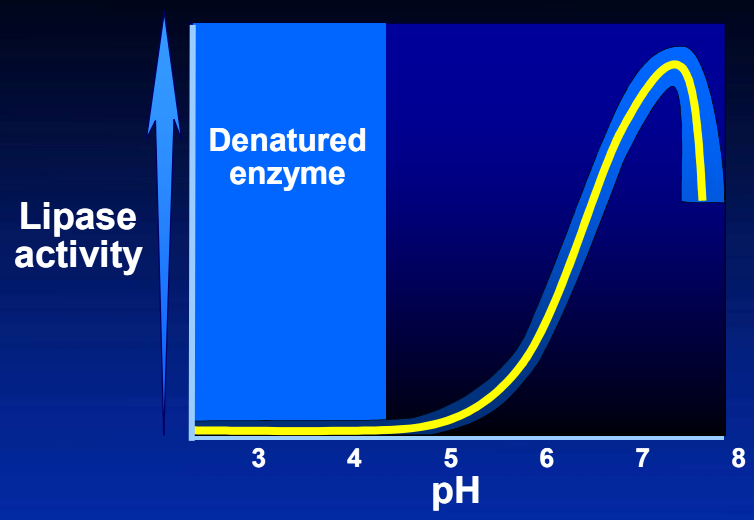


Impact of Steatorrhea
- Weight loss
- Nutritional deficiencies
- Bone disease
- Cardiovascular disease
- Risk of infection

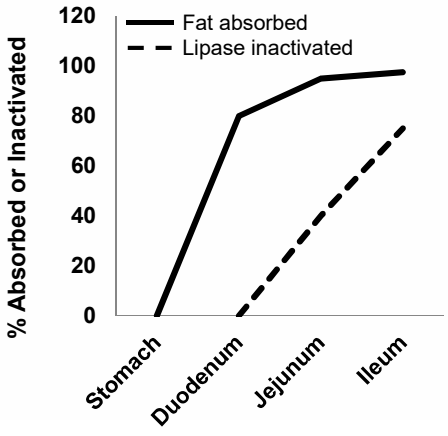
Treat = 10% lipase output
- 22,500 units/hr x 4hr
- 90,000 USP units/meal

DiMagno EP et al. *Relations between pancreatic enzyme ouputs and malabsorption in severe pancreatic insufficiency. NEJM 1973;288(16):813-815*
DiMagno EP & DiMagno MJ. *Chronic Pancreatitis. Landmark Papers, Management Decisions, and Future. Pancreas. 2016; 45(5):641-650*

Raising Luminal pH Above 4.6
Prevents Acid Denaturation of Lipase



To Normalize Fat Digestion Deliver Lipase to Duodenum



- 80% fat absorbed during duodenal transit
- 40% lipase inactivated during transit to jejunum (& 70% to ileum)
- Optimal fat digestion requires maximal lipase activity in the duodenum

Holtmann et al. *Survival of human pancreatic enzymes during small bowel transit: effect of nutrients, bile acids, & enzymes. Am J Physiol, 1997;273: G553-8*
DiMagno EP & DiMagno MJ. *Chronic Pancreatitis. Landmark Papers, Management Decisions, and Future. Pancreas. 2016; 45(5):641-650*

Severe Exocrine Pancreatic Insufficiency
Principals of Therapy

- **Need ≥10% of lowest normal pancreatic lipolytic activity / meal**
  - Dose: 90,000 USP units of lipase per meal
  - May have some residual pancreatic secretion and compensatory increase in gastric lipase
- **Timing: Use enzymes during a meal**

  (¼ first couple bites, ½ middle of meal, ¼ last couple bites)
- **Suppress gastric acid** for non enteric-coated enzymes
- **Avoid low fat diet in EPI**, particularly due to cystic fibrosis

Pancreatic Enzyme Replacement Therapy (PERT)

Product	Formulation	Manufacturer	Lipase content/capsule or pill
Zenpep®	Enteric-coated porcine	Allergan	3000, 5000, 10000, 15000, 20000, 25000, 40000
Creon®	Enteric-coated porcine	AbbVie	3000, 6000, 12000, 24000, 36000
Pancreaze®	Enteric-coated porcine	Janssen	4200, 10500, 16800, 21000
Viokace®	Non-enteric coated porcine	Allergan	10440, 20880
Pertzye®	Enteric-coated porcine with bicarbonate	Digestive Care	4000, 8000, 16000

Often under-dosed

Mandalia A & DiMagno MJ. *Exocrine pancreatic insufficiency and nutritional complications. In Cystic Fibrosis, 1st Edition, SD Davis, M Rosenfeld, J Chmiel editors. Springer International Publishing AG, Cham, Switzerland, (in Press)*

Severe EPI in Chronic Pancreatitis (CP) Efficacy of PERT

2017 systematic review of PERT for EPI (due to CP)

- **Primary outcome – (mean) coefficient of fat absorption (CFA)**

Primary outcome	*Placebo*	*PERT*	*P*
CFA (normal ≥93%)	67% ±7	83% ±5	0.0001

- **MESSAGE: *PERT only partially corrects CFA****

***(PERT also improved nitrogen absorption & nutrition, fecal weight, abdominal pain, QOL)**

de la Iglesia-García et al. *Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review & meta-analysis. Gut 2017;66(8):1354-1355*
Sikkens et al. *Patients with exocrine insufficiency due to chronic pancreatitis are undertreated: a Dutch national survey. Pancreatology. 2012;12:71–3*
Waljee et al. *Aliment Pharmacol Ther 2009;29:235–46;* ***Taylor et al.*** *Aliment Pharmacol Ther 2010;31:57–72;* ***Shafiq et al.*** *Cochrane Database Syst Rev 2009*

Persistent Steatorrhea Despite PERT for Severe EPI

PERT	- Inadequate dose, non-adherence, limited efficacy
Mixing disorder	- Timing of PERT, gastroparesis, intestinal surgery
Acid	- (pH <4.5) degrades uncoated PERT - Delays release of coated PERT (jejunum) - Precipitates/inactivates bile acids
Bile acid deficiency	- Bacterial overgrowth (deconjugation) - Biliary obstruction & ileal disease
Duodenal disease	- Celiac disease plus others; Infection (e.g. giardia)
Alternative dx	- Pancreatic cancer

Don't forget bone health, Vitamin D, calcium, other micronutrients

DiMagno EP et al. *NEJM 1973;288(16):813-815;* ***Regan et al. NEJM****. 1977;297:854-858;* ***Dominguez-Muñoz et al.*** *Gut 2006;55:1056–7;*
Capurso et al. *United European Gastroenterol J, 2016;4(5):697-705;* ***Tabaqchali et al.*** *Lancet 1966;2:12–15;* ***DiMagno EP et al****. Gastroenterology 1972;*
63(1):25-32; ***Ludvigsson et al****. Clin Gastroenterol Hepatol 2007; 5(11):1347-53;* ***Domínguez-Muñoz JE et al.*** *Aliment Pharmacol Ther 2005;21:993–1000*

Costs Can Affect Access to PERT

- **Out of pocket expenses** -> may lead to under-dosing or no therapy
- **Patient assistance programs**
  - https://www.creon.com/creon-support-programs
  - https://www.abbvie.com/patients/patient-assistance.html
  - https://www.allergan.com/responsibility/patient-resources/patient-assistance-programs/zenpep - Zenpep: Allergan USA INC. 1800 Waters Ridge Drive, Lewisville, Tx 75057 (800)377-7790
- **Caution: OTC formulations unregulated**

PERT Side Effects

Symptoms

- Constipation – treatment may unmask underlying constipation
- Nausea
- Abdominal cramps
- Diarrhea

Other

- Hyperuricosuria
- DKA

PANCREAS

40.8%

Small Intestinal Bacterial Overgrowth Is Common in Chronic Pancreatitis and Associates With Diabetes, Chronic Pancreatitis Severity, Low Zinc Levels, and Opiate Use

Allen A. Lee, MD[1], Jason R. Baker, PhD[1], Erik J. Wamsteker, MD[1], Richard Saad, MD[1] and Matthew J. DiMagno, MD[1]

Am J Gastroenterol 2019;114:1163–1171. https://doi.org/10.14309/ajg.0000000000000200

MESSAGE: Consider SIBO for persistent steatorrhea despite PERT

Summary of Exocrine Pancreatic Insufficiency

Etiology

- Chronic pancreatitis (CP)
  - Definite CP defined by Mayo Score of >4 of 16 points
  - Diagnostic features of CP often delayed (varies by etiology)
  - EUS useful for ruling in or out CP (large diagnostic gray area)
- Acute pancreatitis
  - Up to 1/3 have EPI following attack of pancreatitis
  - Progression to CP in ~10% after 1st attack pancreatitis
- Cystic fibrosis

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Summary of Exocrine Pancreatic Insufficiency

Evaluation

- Pancreatic function testing under-utilized
- Definition of severe exocrine pancreatic insufficiency (EPI)
  - 72 hour quantitative fecal fat >7 gm/24 hrs
- Fecal elastase: <100 ug/g stool suggests severe EPI
  >100 ug/g stool has 99% NPF for severe EPI
  unreliable with watery stool

Summary of Exocrine Pancreatic Insufficiency

Management - Pancreatic enzyme replacement therapy (PERT)

- Incomplete treatment common
- Often under-dosed: 90,000 USP units lipase/meal (1/2 with snacks)
- Timing: ¼ first couple bites, ½ middle of meal, ¼ last couple bites
- Have familiarity with causes of PERT failure
  - Small intestinal bacterial overgrowth

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Summary of Exocrine Pancreatic Insufficiency

Nutritional Screening

- Weight and body mass index (BMI)
- Micronutrient deficiencies
- Bone health (non-traumatic fractures)

Case #1

Vignette: A 52 year old man has had 3 previous admissions for acute alcoholic pancreatitis. He returns complaining of a 20-pound weight loss. He stopped drinking but continues to smoke 1 ppd. Appetite is normal. He reports mild constant epigastric pain. Physical examination is notable for evidence of loss of muscle mass. Laboratory tests include a prealbumin of 16, albumin 3.1, normal liver chemistries, and an amylase of 22. A CT scan reveals an atrophic pancreas with a pancreatic duct of 6 mm, with some calcification in the side branches of the pancreatic duct. No mass is noted.

What is the most appropriate additional treatment for steatorrhea?

A: Fecal elastase
B: Serum CA 19-0
C: Endoscopic ultrasonography (EUS)
D: Endoscopic retrograde cholangiopancreatography (ERCP)
E. Surgical Consultation

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Case #2

Vignette: A 60 year-old has a 4-year history of bulky, semisolid, foul-smelling bowel movements, a ravenous appetite, weight loss and episodic epigastric pain. Pancreatitis risk factors include former heavy alcohol & smoking. He has cachexia, temporal wasting, poor dentition, anicteric sclera, mild epigastric tenderness & boryborygmi. Liver panel is abnormal for low albumin. Celiac testing is negative. CT shows pancreatic calcifications but no mass. 72 hour quantitative fecal fat testing reveals a stool fat of 40 g/d, falling to 32 g/d (still abnormal) on pancreatic enzymes (30,000 units lipase / meal).

What is the most appropriate additional treatment for steatorrhea?

A: Bile acid sequestrant
B: Increase pancreatic enzymes to 90,000 units / meal
C: Gluten free diet
D: 10 grams soluble fiber daily

Case #2

Vignette continued: The 60 year-old man with definite chronic pancreatitis and steatorrhea increases pancreatic enzyme dosing to 90,000 units of lipase per meal, ingested throughout the meal, and starts a proton pump inhibitor. Weight loss slows but persists. 72 hour stool fat falls from 32 to 20 g/d (still abnormal) and multiple blood micronutrient levels are low.

What is the best next management step?

A: Stool C diff toxin
B: Testing for small intestinal bacterial overgrowth
C: Exclude colitis
D: TSH

Case #3

Vignette: A 48 year old woman with idiopathic chronic pancreatitis who recently moved to your area is seen in clinic. She has previously undergone CT, which revealed an atrophic pancreas with a 6 mm pancreatic duct. She notes little pain but does complain of weight loss of 10 pounds over the last year. She had also noted greasy stools. She has been treated 6 months with enteric-coated enzymes, 40,000 USP units of lipase with each meal. She also takes calcium and vitamin D. She still notes some oil in her stools. In addition to increasing the dose of enzymes….

What is the most appropriate additional treatment for steatorrhea?

A: Add a PPI daily
B: DEXA scan
C: Endoscopic ultrasonography (EUS)
D: Endoscopic retrograde cholangiopancreatography (ERCP)
E: Refer to surgery for pancreaticojejunostomy

Michigan Medicine Division of Gastroenterology

https://medicine.umich.edu/dept/intmed/divisions/gastroenterology-hepatology/programs/comprehensive-pancreas-program

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Gastroenterology Update: A Case-Based Approach to Common GI Problems

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Erik-Jan Wamsteker, MD
Associate Professor
Michigan Medicine
IM- Gastroenterology

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Gallbladder diseases

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Erik-Jan Wamsteker, MD
Conflicts of Interest
None

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Gallbladder diseases

- Goals of my talk
  - In a case based format, I will review a selection of 3 cases from my practice involving patients with gallbladder disease that may be similar to patients in your practice and review updated management approaches (evidence based when available) in these patients

Gallbladder diseases

- In broad terms
  - Gallstones (Case #1)
  - Cholecystitis (Case #2)
  - Wall thickening, polyps and tumors (Case #3, #3.5)

Gallbladder diseases

- Greatest burden to patients and health care system is gallstone disease
  - 10-20% of the population (20-25 million adults have gallstones)
  - Expectant management in asymptomatic (2-3% annual rate of symptom development; peaks at 10% at 5 years and 80% never develop complications)
  - Costs of care approximately $6.2 billion dollars annually
  - most common elective abdominal surgical procedure performed in the US today (~750,000 cholecystectomies annually)

Gallbladder diseases

- Symptomatic gallstones
  - Biliary colic:
  - dull, intense pain localized to the right upper quadrant, epigastrium or substernal region with constant pain
  - commonly associated with nausea, vomiting and diaphoresis
  - Generally 30 minutes, plateauing at 60 minutes and then beginning to subside with the entire attack resolving within 6 hours
  - Frequency of attacks are variable from hours (unusual) to years between attacks
  - Symptomatic patients are likely to have recurrent symptoms and are at an increased risk of complications. 70% of patients will develop recurrent symptoms within 2 years of the initial attack.

Gallbladder diseases

– Gallstone disease

- Risk factors

Not modifiable	Modifiable
Family history	Obesity/metabolic syndrome/diabetes mellitus/dyslipidemia
Genetic predilection	Drugs – ceftriaxone, octreotide, thiazide diuretics, female sex hormones
Ethnic background	Reduced physical activity
Female sex	Rapid weight loss
Age	TPN
	Diet
	Underlying disease: cirrhosis, Crohn's disease

TPN, total parental nutrition.

Stinton et. al. 2012

Gallbladder diseases

– Gallstone disease

- Risk factors- geography and ethnicity (in females as determined by ultrasound)

Stinton et. al. 2012

Gallbladder diseases

Complications of gallstone disease

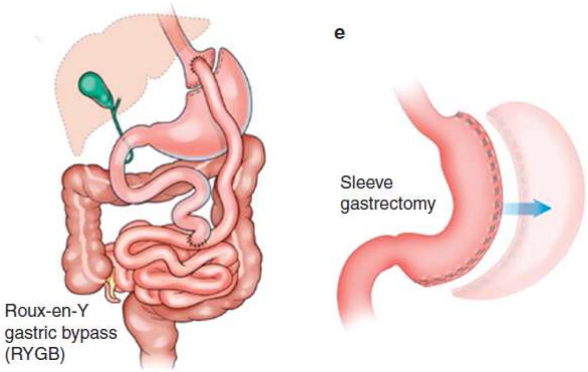
- Cholecystitis
- Choledocholithiasis
- Gallstone pancreatitis
- Rare complications:
  - gallbladder cancer
  - Mirizzi's syndrome (impaction of a gallstone in the cystic duct causing compression of the common hepatic duct)
  - gallstone ileus (now very rare since the advent of laparoscopic cholecystectomy; generally occurs as a result of a cholecystoenteric fistula leading to passage of a large gallstone into the small intestine causing a small bowel obstruction usually when the stone passes into the ileum)

Gallbladder diseases

- Gallstone disease
- Patient #1
- 50-year-old female s/p RYGB 3 years prior presents with a history of:
  - recurrent epigastric pain, fever, chills, nausea and vomiting as well as jaundice.
  - over the last 2 years, worsening over past 2 months she has had episodes of upper abdominal pain with associated generalized weakness, night sweats, and chills/fever. Subsequent MRCP revealed a 2 cm obstructing bile duct stone.

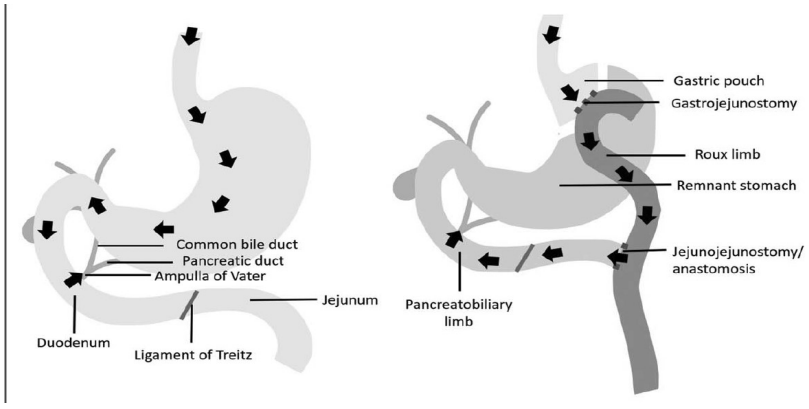
Gallbladder diseases

- Patient #1



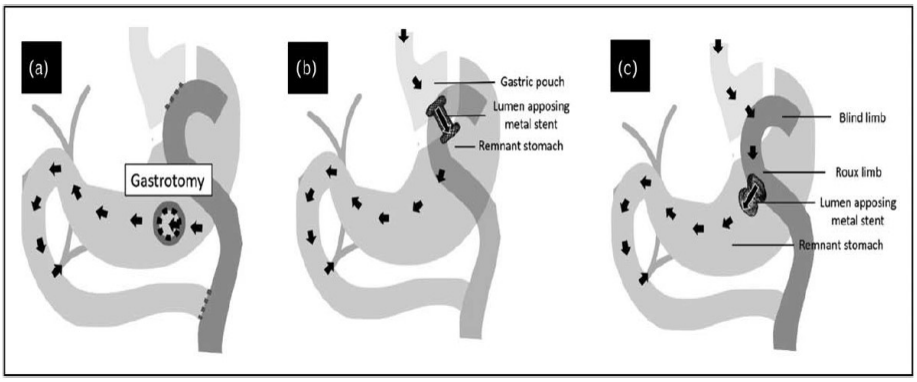
Gallbladder diseases

- Patient #1

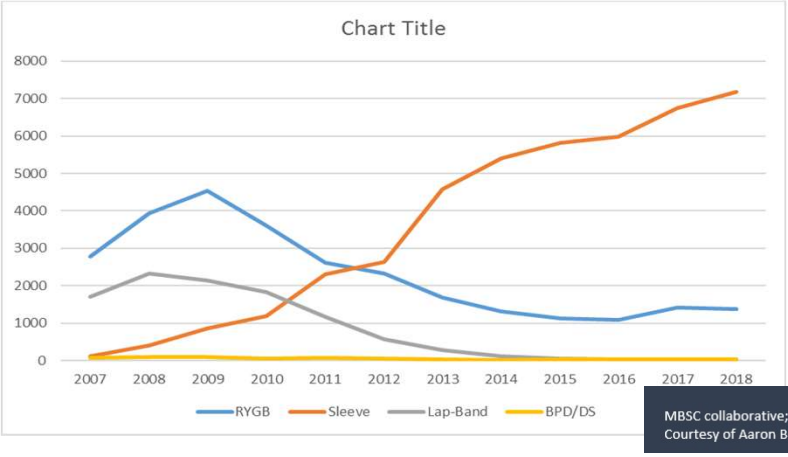


Gallbladder diseases

- Patient #1



Gallbladder diseases
Bariatric surgery trends



MBSC collaborative; Courtesy of Aaron Bonham

Gallbladder diseases

- Gallstone disease
  - Obesity and rapid weight loss are risk factors
    - Risk is high in the acute phase of weight loss (16-42% will develop gallstones in this phase)
    - 25% of those that form gallstones will develop complications
    - Major cause of post bariatric morbidity and significant economic burden

Gallbladder diseases

- Gallstone disease
  - Prevention of GS complications
    - Gallstones form in 16-42 % over 10 years of follow-up with the highest likelihood in patients with greater weight loss (SG/GB)
    - Despite the burden of gallstones in the bariatric population, there is no consensus on prevention of gallstone complications after bariatric surgery.
    - Safety of cholecystectomy concomitant with bariatric surgery is not yet answered

Melmer et al. 2015

Gallbladder diseases

– Gallstone disease

- Prevention of GS complications
  - A large meta-analysis of 1355 patients undergoing bariatric surgery (8 well designed studies)
  - underwent a variety of bariatric operations including VBG, SG and GB
  - Outcomes including gallstone formation and cholecystectomy were examined
  - Urso administration OR 0.20 (reduction in gallstone formation)
  - Urso dose of 500-600 mg daily for 6 months was the recommended dosage
  - In patients treated with urso OR 0.18 (reduction in cholecystectomy)

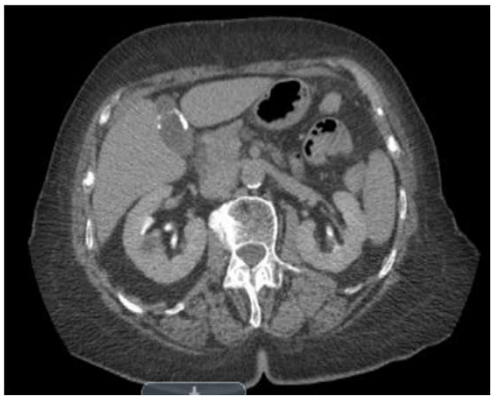
Gallbladder diseases

- Patient #1
  - PEG placement into the gastric remnant; tract healed over 4 weeks
  - ERCP performed through the gastrostomy
  - Stone extraction performed over 2 procedures using mechanical lithotripsy and electrohydraulic lithotripsy
  - PEG removed once stone extraction was successful

Patient #2

- 90 year old female with remote history of breast cancer, htn, hypothyroidism presented with gross hematuria.
- CT urogram was obtained revealed a normal urinary tract but an incidental finding:

Patient #2



- gallbladder wall calcifications consistent with porcelain gallbladder
- mild biliary dilation

Patient #2

Gallbladder cancer

- Risk factors:

(1) Demographic factors:

(a) advanced age,
(b) female gender,
(c) obesity,
(d) geography: South American, Indian, Pakistani, Japanese, and Korean,
(e) ethnicity: Caucasians, Southwestern Native American, Mexican, and American,
(f) genetic predisposition.

(2) Gallbladder pathologies/abnormalities:

(a) cholelithiasis,
(b) porcelain gallbladder,
(c) gallbladder polyps,
(d) congenital biliary cysts,
(e) pancreaticobiliary maljunction anomalies.

(3) Exposures:

(a) heavy metals,
(b) medications: methyldopa, OCP, isoniazid, and estrogen,
(c) smoking.

(4) Infections:

(a) *Salmonella*,
(b) *Helicobacter*.

Kanthan et al

Patient #2
Gallbladder cancer

- Gallbladder cancer is rare in the US
- Accounts for 0.5% of all GI malignancies in the US annually (less than 5000 cases annually); 1.5/100000
- Risk factors for gallbladder cancer
  - Wide geographic variation even in the US where the highest incidence is in Native American women in New Mexico (11/100000) with highest incidence in Northern Indian women 22/100000

Patient #2

- Gallbladder cancer
  Presents late due to vague symptoms and anatomically lacks a serosa
  - Mean survival rate after diagnosis is 6 months (5 yr survival is 5%)
  - Combination of many of the risk factors leads to malignancy (genetic predisposition with chronic inflammation directly resulting from gallstones or chronic infection)

Patient #2
Porcelain gallbladder

- pathogenesis is controversial
- associated with cholelithiasis in more than 95 percent of patients
  1) chronic inflammation due to gallstones results in scarring, hyalinization (tissue degeneration), and calcification
  2) Cystic duct obstruction leading to bile stasis and eventual precipitation of calcium carbonate salts in the wall of the GB which is also replaced by fibrosis

Patient #2
Porcelain gallbladder

- Evidence for porcelain gallbladder was previously biased
  - Literature dating to 1950's to early 1980's suggested gallbladder cancer risk range from 13-62%
  - Biased based on referral bias, selection bias (looked at a group of pts with gallbladder cancer)
  - Publications came from patients referred to academic institutions only
  - When eliminating biased studies, incidence of gallbladder cancer 10/431 (~2%)
  - Additional prospective studies show very low risk over a 3.5 to 5 year follow-up for disease progression to cancer (single center and Kaiser database); high rate of post op complications (10-16%)
  - Authors refute the surgical dogma for cholecystectomy suggesting that treatment be taken on a case by case basis

Chen et al.
Desjardins et al.

Patient #2
Porcelain gallbladder

- My 90 year old patient after weighing the pros and cons of cholecystectomy, elected not to undergo surgery

Chen et al.
Desjrdins et al.

Patient #3

- 49 year old male with type 2 diabetes (on metformin) presents with acute onset epigastric pain and lipase >3 time ULN consistent with acute pancreatitis.
  - Normal LFT's
  - RUQ ultrasound shows gallbladder polyps (non shadowing) with the largest being 5 mm in size
  - Given his age, CT pancreas was performed which was normal (performed a few weeks after resolution of abdominal pain)
  - Chronic diarrhea was investigated with upper endoscopy (normal including small bowel biopsies) and colonoscopy with normal terminal ileum (also normal including biopsies)

Patient #3
Gallbladder polyps (GP)

- GPs are protrusions of the mucosa into the lumen of the gallbladder
- Low malignant potential
- Present in up to 9.5% of ultrasounds of the gallbladder with 5% of those having malignant potential
- In most cases, these are incidental (ie. RUQ ultrasound obtained to assess for fatty liver)
- Clinical concern overall is malignant potential in asymptomatic patients
- In general, patients with biliary colic would undergo cholecystectomy

Patient #3
Gallbladder polyps (GP)

Histology of gallbladder polyps

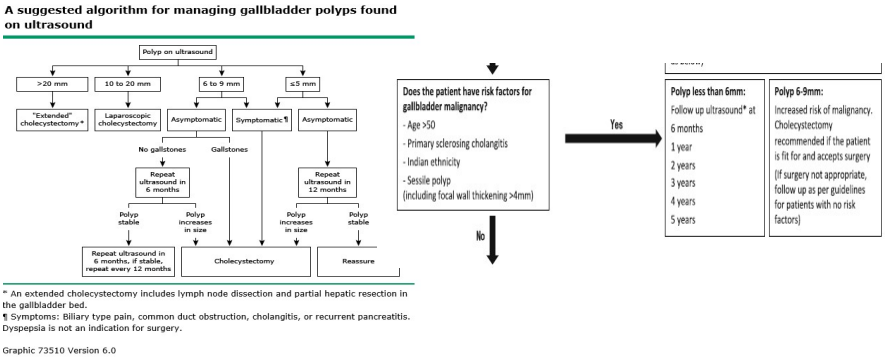
Tumor Polyps	Nontumor Polyps
Benign tumors	
Adenoma (5%)	Cholesterol polyps (70%, <5 mm)
Mesenchymal: leiomyoma, lipoma	Adenomyomatosis (15%, predominantly fundal)
Granular cell tumor	Xanthogranulomatous polyps
Malignant tumor	
Primary gallbladder cancer (7%) Metastases	Inflammatory polyps (10%, associated with chronic cholecystitis)

Data from Mellnick VM, Menias CO, Sandrasegaran K, et al. Polypoid lesions of the gallbladder: disease spectrum with pathologic correlation. Radiographics 2015;35(2):387–99; and Anderson MA, Appalaneni V, Ben-Menachem T, et al. The role of endoscopy in the evaluation and treatment of patients with biliary neoplasia. Gastrointest Endosc 2013;77(2):167–74.

Patient #3
Gallbladder polyps (GP)

- GB Adenomyomatosis:
  - An acquired, benign condition of the GB; generally asymptomatic condition, caused by hypertrophy of the mucosal and muscular layers of the gallbladder with invagination of the mucosal layer through the interstices of the muscularis forming sinuses
    - most common between 50-60 years
    - Male:female=1
    - Ultrasound is generally the definitive test although still lacks sensitivity (in experienced hands ~65%)
    - Cholangio-MRI is then the test of choice
    - If diagnostic uncertainty remains, then proceed to cholecystectomy

Patient #2
Gallbladder polyps (GP)



Patient #2
Gallbladder polyps (GP)

- Risk factors for gallbladder cancer
  - Primary sclerosing cholangitis is associated with gallbladder masses in up to 14% of patients (56% harbor dysplasia or cancer; smallest in case series was 6 mm)
  - General consensus is for cholecystectomy in patients with any mass lesion of the GB

Patient #3.5

- 46 year old female with a history of Crohn's disease (quiescent, on no therapy) presents with a low grade fevers, new onset RUQ pain and elevated liver blood tests (alk phos 648, ast 147, alt 157, total bilirubin 1.6).

  - Ultrasound demonstrated thickened gallbladder folds
  - CT showed changes gallbladder contour deformity and nodular thickening; additional findings showed bile duct wall thickening and enhancement

- What would you do at this point?
  - Liver biopsy
  - Treat for ascending cholangitis with antibiotics and biliary drainage
  - Obtain MRI
  - Consult general surgery

Patient #2.5

TABLE 1: Causes of Gallbladder Wall Thickening

Diffuse Wall Thickening	Focal Wall Thickening
Cholecystitis	Polyps
Acute calculous	Adenomatous
Gangrenous	Cholesterol
Emphysematous	Malignancy
Acalculous	Primary gallbladder carcinoma
Chronic	Metastases
Xanthogranulomatous	Focal adenomyomatosis
Liver disease	Focal xanthogranulomatous cholecystitis
Hepatitis	
Cirrhosis	
Portal hypertension	
Extracholecystic inflammation	
Pancreatitis	
Colitis	
Peritonitis	
Pyelonephritis	
Systemic diseases	
Congestive heart failure	
Renal failure	
Sepsis	
Hypoalbuminemia	
Malignancy	
Primary gallbladder carcinoma	
Lymphoma	
Adenomyomatosis	
Pseudothickening (contracted state)	
Atypical infection	
Tuberculous	
Dengue hemorrhagic fever	

MOC Part II post test questions

- T or F
  - Due to the high incidence of post bariatric surgery gallstone development, prophylactic cholecystectomy should be performed in these patients.

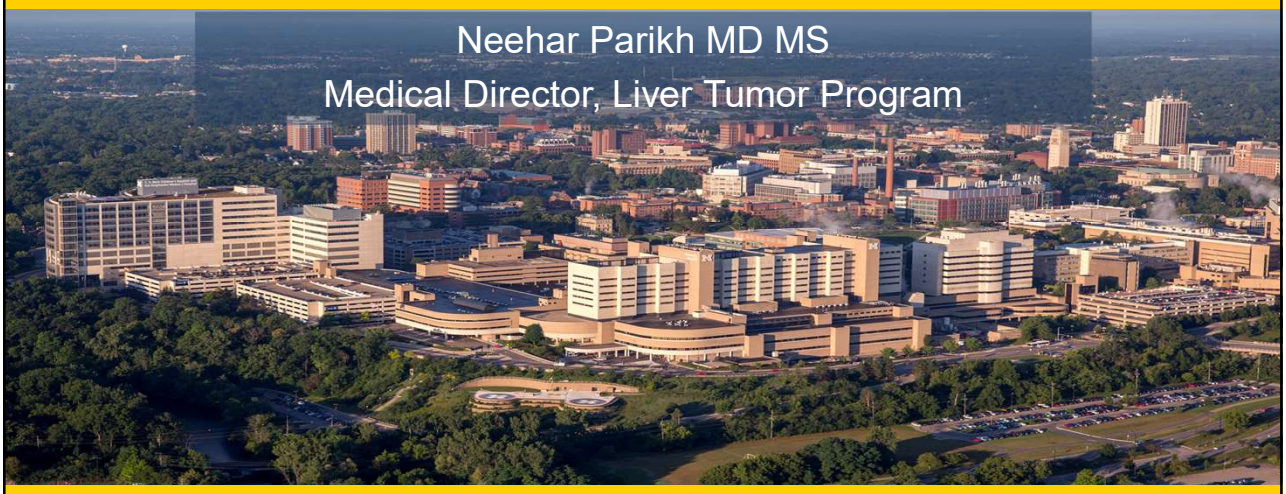
MOC Part II post test questions

- Circle all that apply:
  - Porcelain gallbladder is:

A. An indication for cholecystectomy in a 50 year old healthy female
B. An indication for cholecystectomy in a 90 year old
C. A prohibitive risk for gallbladder cancer
D. Associated with a high risk of post-op complications
E. A model used by Frank Netter to draw the gallbladder for the Netter atlas

Surveillance for Hepatocellular Carcinoma

Neehar Parikh MD MS
Medical Director, Liver Tumor Program



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Disclosures

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- Research Funding: Bayer, Target Pharmasolutions, Exact Sciences, Glycotest

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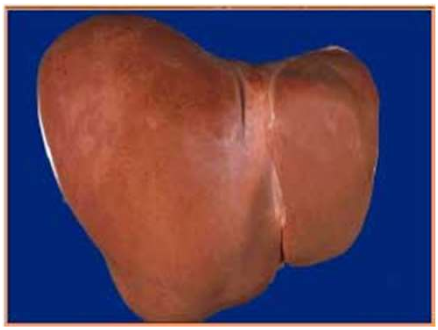
Case:

- 56 yo M with a history of diabetes, obesity, hypertension and hyperlipidemia presents with a new diagnosis of cirrhosis.
- What is his risk of development of hepatocellular carcinoma (HCC)?
- What are best practices in order to reduce his risk of death from HCC?

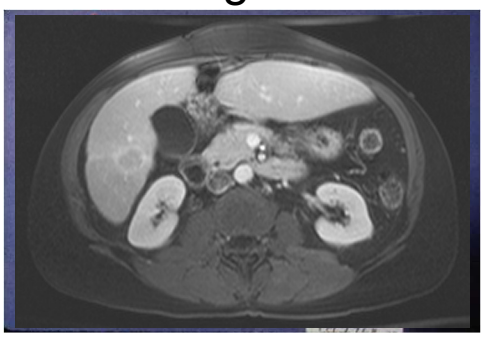
Hepatocellular Carcinoma

- Most common primary hepatic malignancy
- 80-90% cases in US arise in the setting of cirrhosis



Chronic Hepatitis

Chronic inflammation + fibrosis



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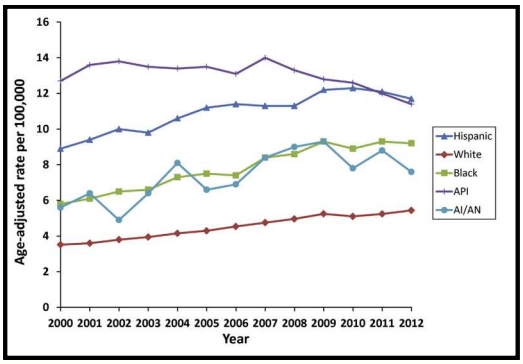
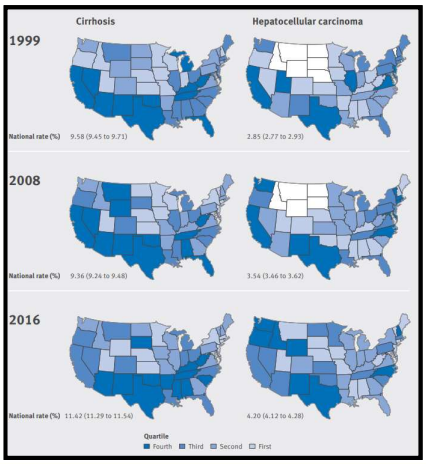
Incidence and Mortality

- Incidence increasing in the US – 4.4/100,000 population in 2000 to 6.7/100,000 population in 2012





White DL, *et al. Gastroenterology.* 2017.
Tapper EB, Parikh ND. *BMJ.* 2018.

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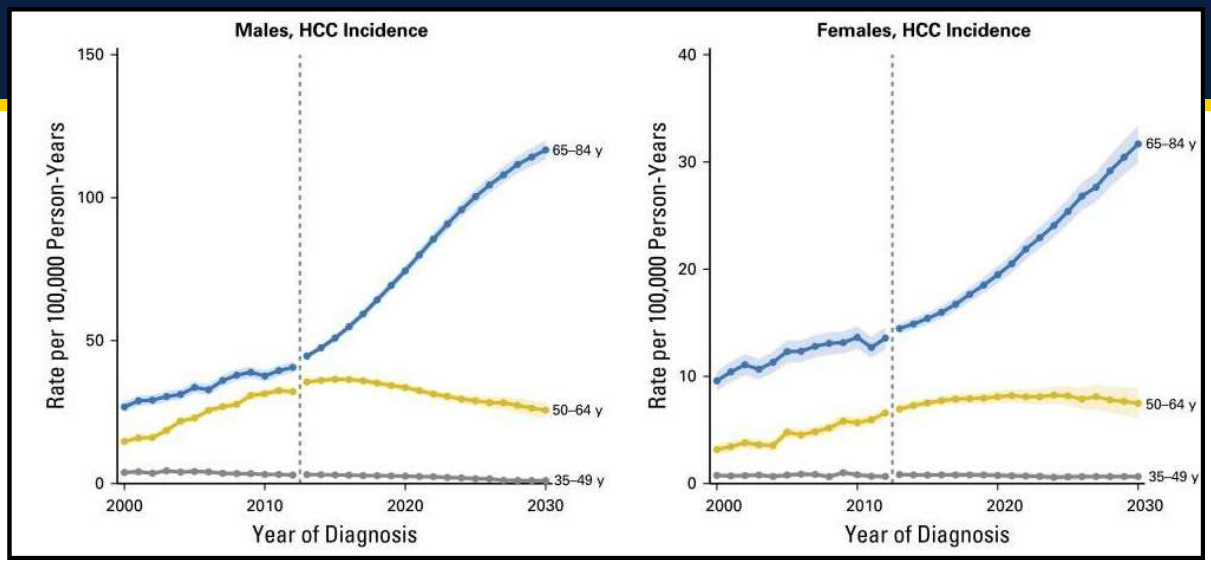

Petrick JL. *J Clin Oncol* 2016.

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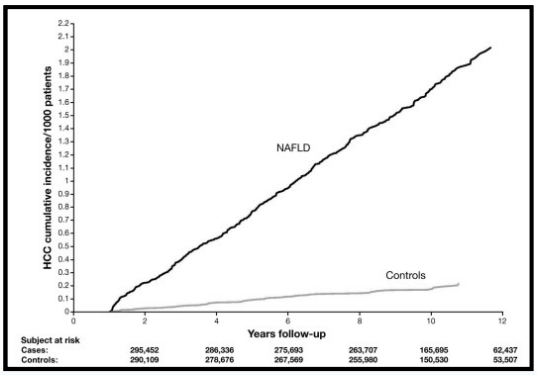
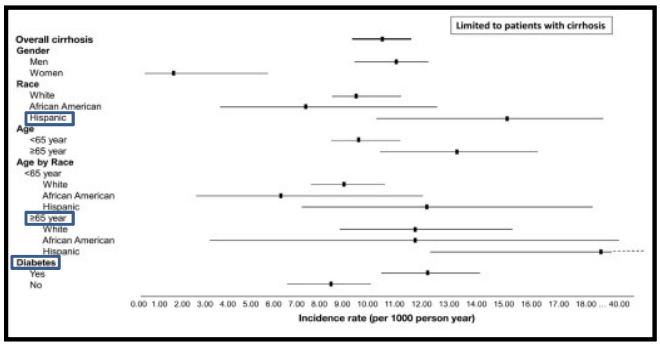
HCC Risk Stratification

- Risk of HCC varies by etiology of cirrhosis:
  - Viral Hepatitis: 2-6% per year
  - NAFLD – 1-2% per year (risk is much lower in non-cirrhotic NAFLD)





Kanwal et al. *Gastroenterology*. 2018

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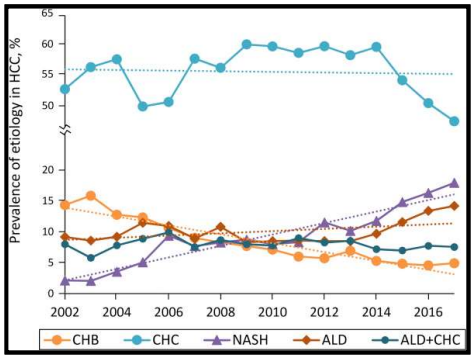
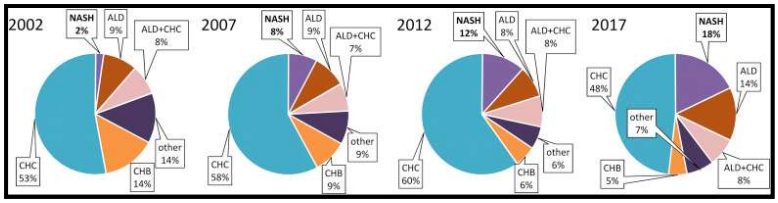
NASH HCC Risk

- Among liver transplant candidates, NASH is a rapidly growing cause of HCC





Younossi et al. *Clini Gastro Hep*. 2019

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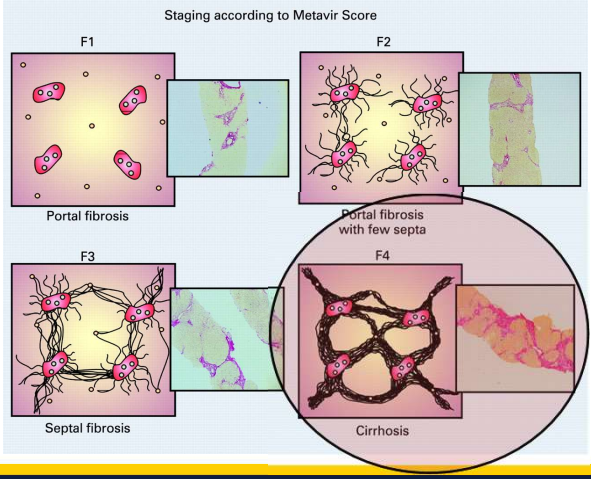
Who do you survey?



Asselah T *et al. Gut.* 2009.

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What about Hepatitis B?

- Hepatitis B can lead to HCC in the absence of cirrhosis
- Recommendation to survey patients with HBV at highest risk:
  - Asian born men>40 yo
  - Asian born female>50 yo
  - African patients >20 yo
  - Family history of HBV induced HCC

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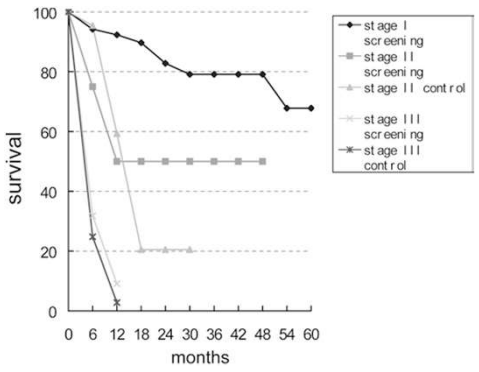
Does etiology matter?

Table 3. Groups for whom HCC surveillance in recommended or in whom the risk of HCC is increased, but in whom efficacy of surveillance has not been demonstrated

Population group	Threshold incidence for efficacy of surveillance (> .25 LYG)(%/year)	Incidence of HCC
Surveillance recommended		
Asian male hepatitis B carriers over age 40	0.2	0.4-0.6%/year
Asian female hepatitis B carriers over age 50	0.2	0.3-0.6%/year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American Blacks with hepatitis B	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2-1.5	3-8%/yr
Hepatitis C cirrhosis	1.5	3-5%/yr
Stage 4 primary biliary cirrhosis	1.5	3-5%/yr
Genetic hemachromatosis and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Alpha 1-antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	< 0.2%/yr
Hepatitis C and stage 3 fibrosis	1.5	< 1.5%/yr
Non-cirrhotic NAFLD	1.5	< 1.5%/yr

Bruix and Sherman, *Hepatology*. 2010.

Randomized trial in HBV patients



Variable	Screen Group (n=9373)	Control Group (n=9443)
HCC cases	86	67
% Stage I	60.5%	0%
% Curative treatment	46.5%	7.5%
# HCC death	32	54
Mortality (per 100,000)	83.2	131.5
Rate Ratio	0.63 (0.4-0.9)	

Zhang et al, J Cancer Res Oncol 2004

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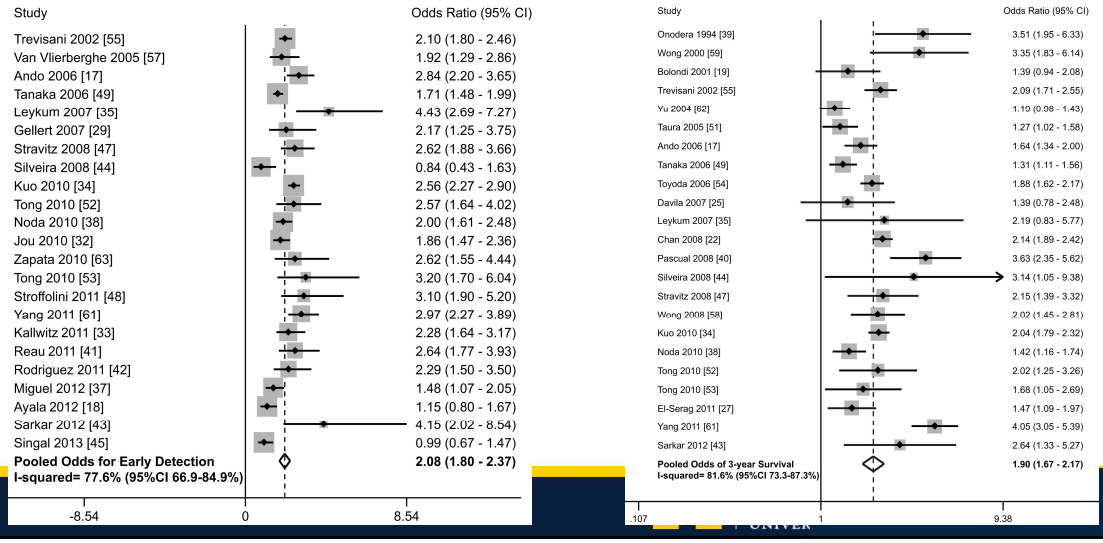
OPEN ACCESS Freely available online

PLOS | MEDICINE

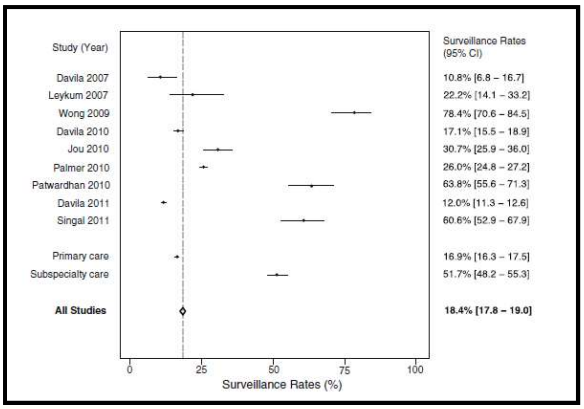
Early Detection, Curative Treatment, and Survival Rates for Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis: A Meta-analysis

Amit G. Singal[1,2,3]*, Anjana Pillai[4], Jasmin Tiro[2,3]



The Problem:

- HCC surveillance is underutilized



- Current surveillance guidelines are intensive with many points of failure:
  - Provider recognition of at risk patient
  - Provider ordering ultrasound
  - Patient obtaining ultrasound
  - Documentation US completed
  - Provider interpretation of results

Every 6 months

Singal *et al. JGIM.* 2012.

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Provider barriers to surveillance

Provider-reported barriers	Safety-net health system (n=77)	Tertiary care system (n=100)
Lack of knowledge about guidelines	68.2%	79.1%
Competing interests in clinic	51.6%	37.4%
Lack of time in clinic	40.5%	52.8%
Difficulty recognizing at-risk patients	35.4%	30.0%
Ultrasound capacity	23.0%	10.1%
Responsibility of subspecialists > PCP	5.3%	29.4%

Dalton Fitzgerald et al. Clin Gastro Hep 2015
Simmons et al Clin Gastro Hep 2018

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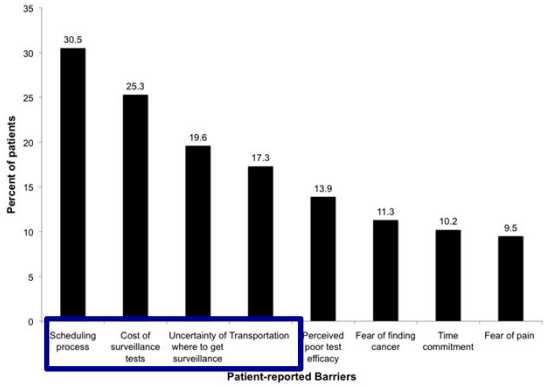
Patient reported barriers to surveillance



Receipt of HCC surveillance was significantly lower in patients reporting barriers to surveillance (54% vs. 71%; OR 0.42, 95%CI 0.25 – 0.70)

Farvardin et al. Hepatology 2017

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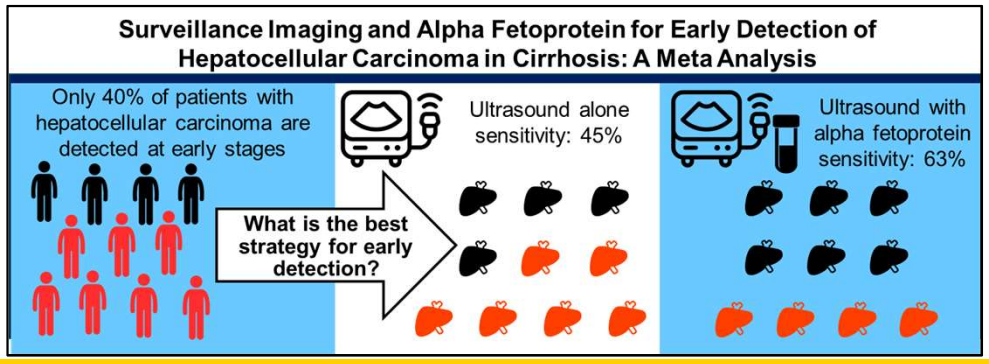
How do we survey for HCC?

- AASLD guidelines recommends: Ultrasound every 6 months
- No specific recommendation for use of AFP, but recent meta analysis showed improvement in early detection with addition of AFP



Tzartzeva *et al.*, *Gastroenterology.* 2018.

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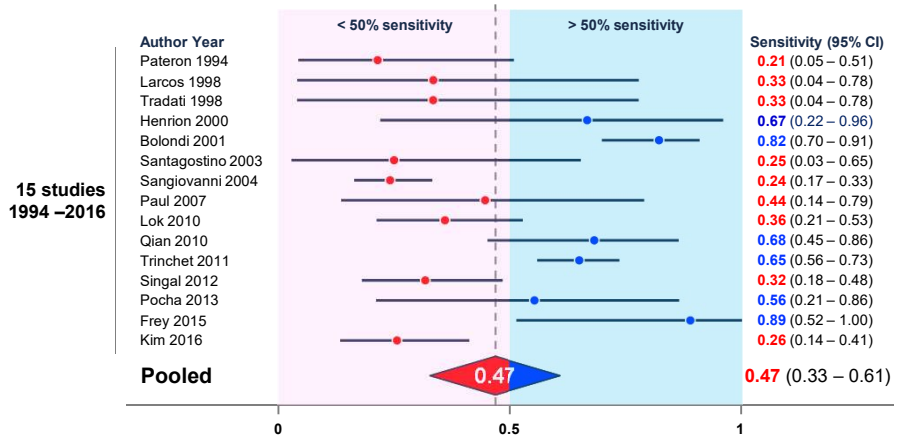
US sensitivity varies significantly



Tzartzeva *et al.*, *Gastroenterology.* 2018.

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Is US for everyone?

- What are predictors of inadequate US?

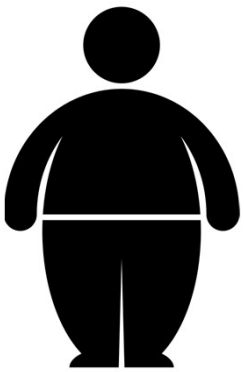
Table 2 | Factors associated with inadequate ultrasound quality (*N* = 941)

	Univariate analysis		Multivariable analysis	
Characteristic	OR	95% CI	OR	95% CI
Male gender	1.42	1.01–2.01	1.68	1.14–2.48
Child Pugh B or C cirrhosis	2.17	1.56–3.00	1.93	1.32–2.81
BMI category				
Normal (BMI <25)	Ref	Ref	Ref	Ref
Overweight (BMI 25–29.99)	2.12	1.28–3.54	2.29	1.35–3.88
Obesity class II (BMI 30–34.99)	2.88	1.70–4.89	2.95	1.67–5.20
Obesity class II (BMI 35–39.99)	5.35	2.96–9.66	6.37	3.35–12.12
Morbid obesity (BMI ≥40)	6.29	3.45–11.47	8.22	4.30–15.73
Aetiology of liver disease				
Hepatitis C	Ref	Ref	Ref	Ref
Hepatitis B	1.09	0.49–2.42	1.87	0.79–4.39
Alcohol-related	2.73	1.80–4.16	2.11	1.33–3.37
Non-alcoholic steatohepatitis	3.16	1.97–5.07	2.87	1.71–4.80
Other	0.66	0.23–1.93	0.67	0.22–2.04
ALT >40 U/L	0.70	0.50–0.97	0.93	0.64–1.34
In-patient status	1.55	1.08–2.23	1.55	1.01–2.37

Simmons *et al.*, *Alimen Pharm and Thera.* 2017.

Surveillance – What are my Options?

- Ultrasound, Ultrasound and AFP, CT, or MRI?
- US based surveillance is most cost-effective, but consider the population
  - Obesity
  - Cirrhosis
  - Ascites
- More data needed, but cross-sectional imaging may be right for certain patients – discuss with your radiologist
- We need better screening and risk stratification tools – is blood based surveillance the answer?



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GALAD Score

- Recently developed and validated composite score of AFP, AFP-L3, DCP and age, sex
- Derivation cohort of 670 patients (331 with HCC) from the UK
  - AUCs >0.95

		Sensitivity			
			Maximum sensitivity	Maximum specificity	Maximum both
Staging system/ treatment type	Criteria for early or late disease	Number of patients	Cutoff = −1.36	Cutoff = 0.88	Cutoff = −0.63
BCLC					
Early	0 and A	42	93	55	86
Late	B, C, and D	327	96	83	94
TNM 6					
Early	1 and 2	154	93	70	89
Late	3 and 4	143	99	90	97
Tumor size					
Early	≤5 cm	169	92	67	88
Late	>5 cm	166	99	92	98
Treatment intent					
Early	Curative	61	85	56	75
Late	Palliative	252	98	86	98

Johnson et al. *Cancer Epidemiol Biomarkers Prev.* 2014

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GALAD Score

- Validation in a retrospective multinational cohort of 6,834 patients (2,430 with HCC)
- Model performed well in all cohorts with AUC>0.90
- Sensitivity 80.2%-81.2% in early stage (within Milan) HCC
- Ongoing Phase III biomarker study being conducted

Berhane et al. *Clin Gastroenterol Hepatol.* 2016.

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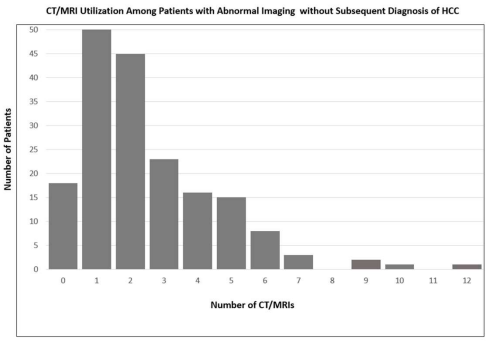
Case

- Your patient comes to clinic after receiving an US
- You get a call from your radiologist prior to going in:
  - Patient has a new 1.3 hyperechoic mass in the R lobe of his liver
- Labs:
  - Bili 0.9, Platelets: 113, INR: 1.0; AFP: 14
- What do you do next?

Nodule on Surveillance – Now What?

- Patient is undergoing surveillance for HCC and a hyperechoic nodule is found on ultrasound.
- Nodules on US surveillance are very common
  - In two cohort studies up to 25% of patients had a nodule on surveillance US that necessitated dynamic cross-sectional imaging
  - However nearly three-quarters of these patients did not end up developing HCC
- For nodule work-up imaging with multiphasic CT or MRI is the next step



Atiq et al. *Hepatology* 2017
Konerman et al. *Liver Transplant* 2019

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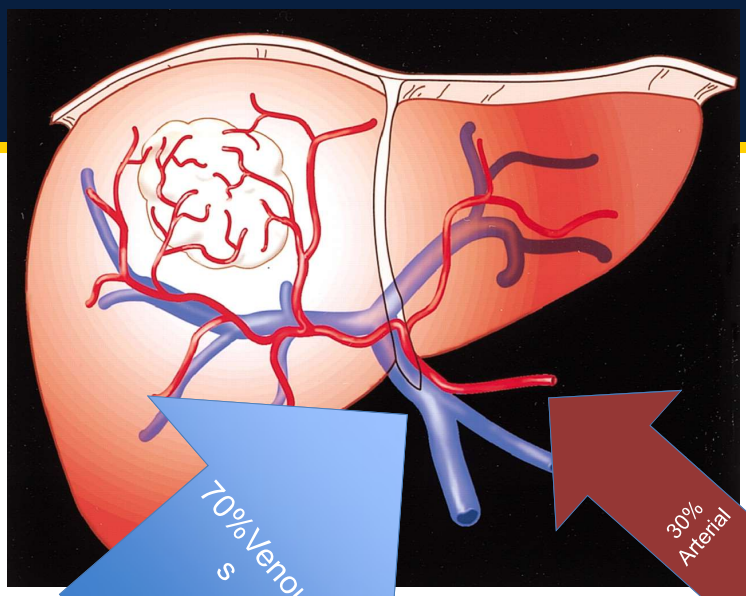
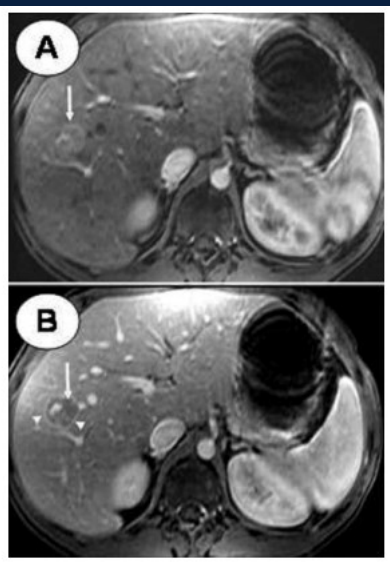


Triple phase imaging

Liver imaging requires an:
1. Arterial phase
2. Venous phase
3. Delayed phase



Lesions that have arterial enhancement with washout have a sensitivity and specificity of >90% for being HCC

Marrero JA, et al. *Liver Transpl.* 2004.

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Imaging modality: CT vs MRI

TABLE 4. Accuracy of Contrast-Enhanced CT Versus MRI for Diagnosis of HCC

Modality	Studies (n)	Sensitivity (95% CI) I^2 (%)	P	Specificity (95% CI) I^2 (%)	P	+ Likelihood Ratio (95% CI)	P	− Likelihood Ratio (95% CI)	P	Diagnostic Odds Ratio (95% CI)	P
All studies irrespective of cohort year											
Contrast-enhanced CT	19	0.66 (0.60-0.72) I^2 = 72.53	0.0003	0.92 (0.84-0.96) I^2 = 86.74	0.83	8.1 (4.1-16.2)	0.86	0.37 (0.30-0.44)	0.001	22 (10-50)	0.24
MRI with and without contrast	19	0.82 (0.75-0.87) I^2 = 72.90		0.91 (0.82-0.95) I^2 = 89.81		8.8 (4.6-16.9)		0.20 (0.15-0.28)		43 (20-92)	
All cohorts started in the year 2000 or later											
Contrast-enhanced CT	17	0.69 (0.63-0.76) I^2 = 73.9	0.002	0.94 (0.87-0.98) I^2 = 88.93	0.82	11.9 (5.1-27.7)	0.96	0.32 (0.26-0.40)	0.01	37 (15-90)	0.3
MRI	17	0.84 (0.77-0.90) I^2 = 86.18		0.93 (0.84-0.97)		12.3 (5.1-29.5)		0.17 (0.11-0.25)		73 (29-181)	

Roberts *et al*. *Hepatology*. 2018

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CT/MRI LI-RADS® v2018 CORE

Untreated observation without pathologic proof in patient at high risk for HCC

- If cannot be categorized due to image degradation or omission → LR-NC
- If definite tumor in vein (TIV) → LR-TIV
- If definitely benign → LR-1
- If probably benign → LR-2
- If probably or definitely malignant but not HCC specific (e.g., if targetoid) → LR-M

Otherwise, use CT/MRI diagnostic table below

- If intermediate probability of malignancy → LR-3
- If probably HCC → LR-4
- If definitely HCC → LR-5

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LIRADS Criteria

CT/MRI Diagnostic Table

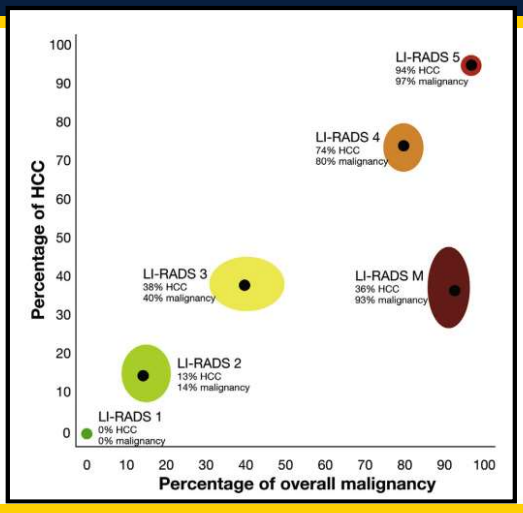
Arterial phase hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count additional major features: • Enhancing "capsule" • Nonperipheral "washout" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4 / LR-5

Observations in this cell are categorized based on one additional major feature:
- LR-4 – if enhancing "capsule"
- LR-5 – if nonperipheral "washout" **OR** threshold growth

LR3 and LR4 – What do we do?

- There is ongoing uncertainty on the work-up and management of indeterminate nodules
- Uncertainty of when to biopsy these masses and how long to follow them
- Routine discussion of individualized management in a tumor board setting is at this time best practice



van der Pol et al. *Gastroenterology* 2018

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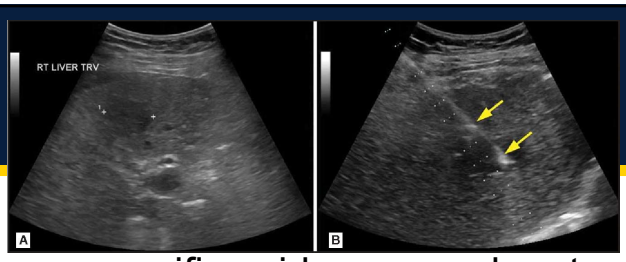
When to Biopsy?



- AASLD HCC guidelines give no specific guidance on when to biopsy
- < 1 cm mass should be followed
- 1-2 cm mass could be considered for biopsy if they have LR4 or LRM features
  - 11-30% of these can be false negatives!
- >2 cm masses that are not clearly benign should routinely be biopsied
- Biopsy can be avoided in LR5 masses (for now)

Caturelli et al. *Gut* 2004

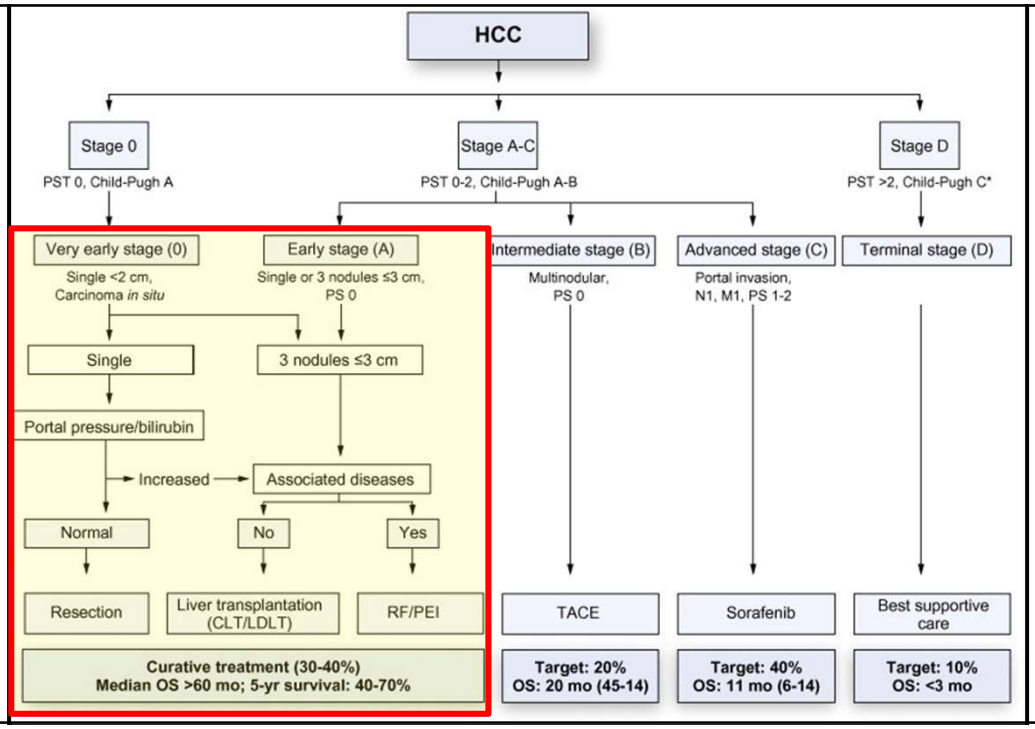
Atypical HCC

- Approximately 15% of lesions >2 cm will not have typical radiologic features of HCC
- Atypical lesions greater the 2 cm should be biopsied in cirrhotic patient, as they have a high likelihood of being HCC
  - –Risk of tumor seeding <0.5%

Bolondi L, et al. *Hepatology.* 2005.

Case

- Our 56 yo patient undergoes an MRI
- 1.6 cm segment 5 lesion near the dome – LR5
- CT chest (staging) negative for mets
- Undergoes a lap wedge resection – negative margins, no vascular invasion
- Follow-up imaging 6 weeks later shows no evidence of cancer
- Management now?



Post-HCC surveillance

- Patient after curative HCC therapy need lifelong surveillance
  - Every 3 months X 2 years
  - After 2 years every 6 months
- Risk of recurrence is highest in first 2 years post, 30-70% after 5 years
- Important to adjust risk modifiers
  - Treat viral hepatitis
  - Alcohol cessation
  - Smoking cessation
  - Weight loss, diabetic control

Case

- Your patients father was just diagnosed with cirrhosis with decompensation.
- He is 84 years old with coronary disease, atrial fibrillation, history of a stroke, decreased mobility, using a walker
- He has developed abdominal ascites and HE
- Labs: Na: 133, Alb: 2.1; INR: 2.4; Cr: 2.1; Bili: 2.3
- Should you offer him surveillance?

Who do you not survey?

- No stringent guidelines here, but Child Pugh C patients who aren't transplant candidates probably shouldn't be offered surveillance
- Patients with declining or severely impaired functional status
- Patients with significant comorbid conditions
  - Surveillance recommendations should be individualized

Conclusions

- In patients with cirrhosis and select patients with hepatitis B, surveillance is recommended and associated with improved early detection and improved survival
- Current surveillance recommendations are US or US+AFP every 6 months
- Once something is seen on US then multiphasic imaging is indicated
  - HCC can be routinely diagnosed non-invasively
  - Indeterminate lesions should be followed with serial imaging or biopsied

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Hepatitis B

Gastroenterology Update: A Case-Based Approach

October 19, 2019

Andrew W. Tai, MD, PhD
Associate Professor of Internal Medicine
Associate Professor of Microbiology & Immunology

Industry Relationship Disclosures
Industry Supported Research and Outside Relationships

- None

Learning Objectives

- Define the phases of chronic HBV infection
- Understand indications for antiviral therapy
- Recognize patients who are candidates for antiviral treatment discontinuation
- Recognize risk factors for HBV reactivation

Case 1

23 yo female graduate student referred to you for +HBsAg

- Tried to donate blood for first time
- Feels well, physically active
- ROS negative

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Case 1

Meds: none

PMH: none

SHx:

Born in China, here in US on student visa. 3-4 drinks weekly, no history of IDU, sexually active in a monogamous relationship

FHx: no known family history of HBV or HCC

Case 1

PE: normal. Liver span normal. No splenomegaly.
No stigmata of advanced liver disease.

Labs:

ALT 23 AST 19 ALP 83 Tbili 0.9 Alb 4.6

Plt 413K

INR 1.0

$HBsAg^+$ $HBsAb^-$

$HBeAg^+$ $HBeAb^-$

HBV DNA 6.11×10^8 IU/mL

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Case 1

Questions:

Additional workup?

Is antiviral treatment indicated?

Chronic HBV – natural history

This patient is from an HBV-endemic region

Five clinical phases of infection based on

-Serology (HBeAg, HBsAg status)

-HBV DNA level

-Hepatic inflammation (ALT) and fibrosis

1. Immune tolerant	HBeAg+ chronic infection
2. Immune active	HBeAg+ chronic hepatitis
3. Inactive carrier	HBeAg- chronic infection
4. HBeAg- negative chronic hepatitis B	HBeAg- chronic hepatitis
	Functional cure

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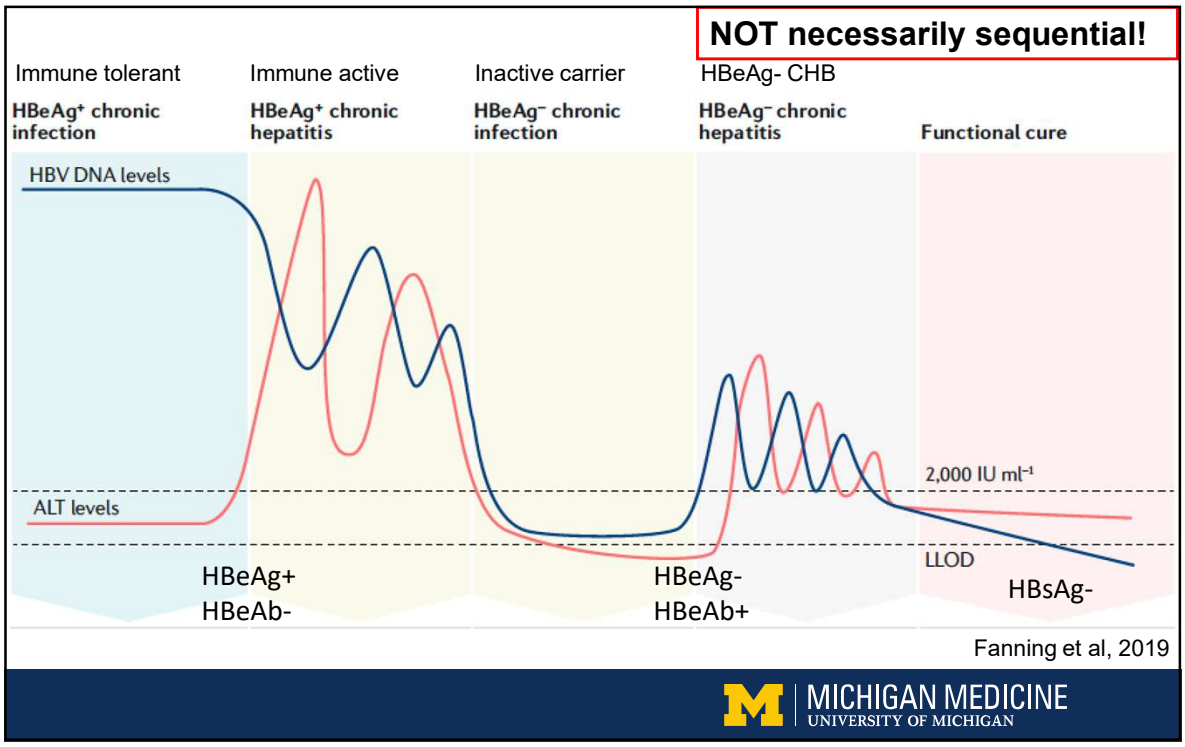

Fanning et al, 2019

Our patient

ALT 23 AST 19 ALP 93 Tbili 0.9 Alb 4.2
WBC 9.6 Hgb 13.2 MCV 89 plt 413K
INR 1.0
HBsAg^{+} HBsAb^{-}
HBeAg^{+} HBeAb^{-}

HBV DNA 6.11 x 10^{8} IU/mL

Young patient with CHB, HBeAg+, high HBV DNA but normal ALT = likely **immune tolerant** aka **HBeAg+ chronic infection**

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Entecavir and Peginterferon Alfa-2a in Adults With Hepatitis B e Antigen–Positive Immune-Tolerant Chronic Hepatitis B Virus Infection

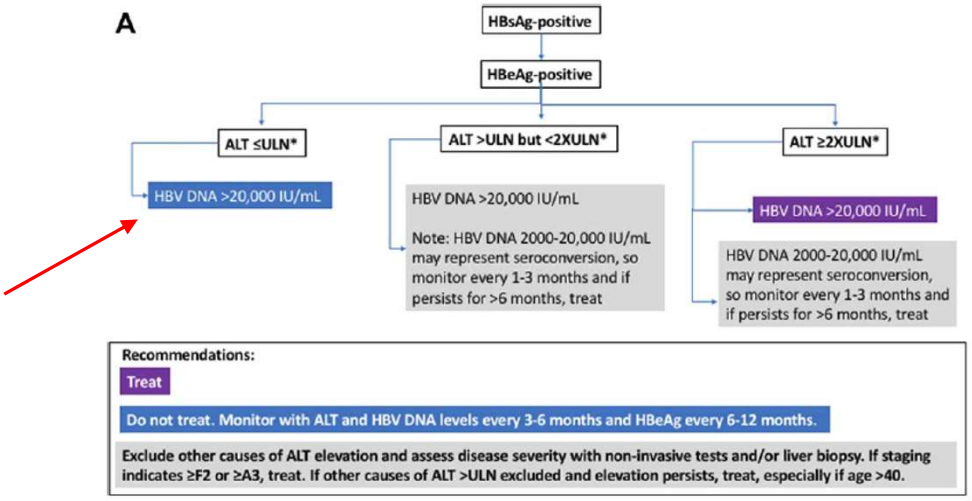
Jordan J. Feld,[1] Norah A. Terrault,[2] Hsing-Hua S. Lin,[3] Steven H. Belle,[3] Raymond T. Chung,[4] Naoky Tsai,[5] Mandana Khalili,[2] Robert Perrillo,[6] Stewart L. Cooper,[7] Marc G. Ghany,[8] Harry L.A. Janssen,[1] and Anna S. Lok[9], for the Hepatitis B Research Network

Hepatology 2019;69:2338

Multicenter single-arm trial of entecavir for 8 wk ➡ entecavir/PEG-IFN for additional 40 wk, n=28. Patients had ALT ≤ 1.5x ULN, median age 37

Only 1/28 achieved HBeAg seroconversion, and this pt transitioned to immune-active HBV after discontinuation of therapy
None achieved off-therapy virologic control

HBeAg+



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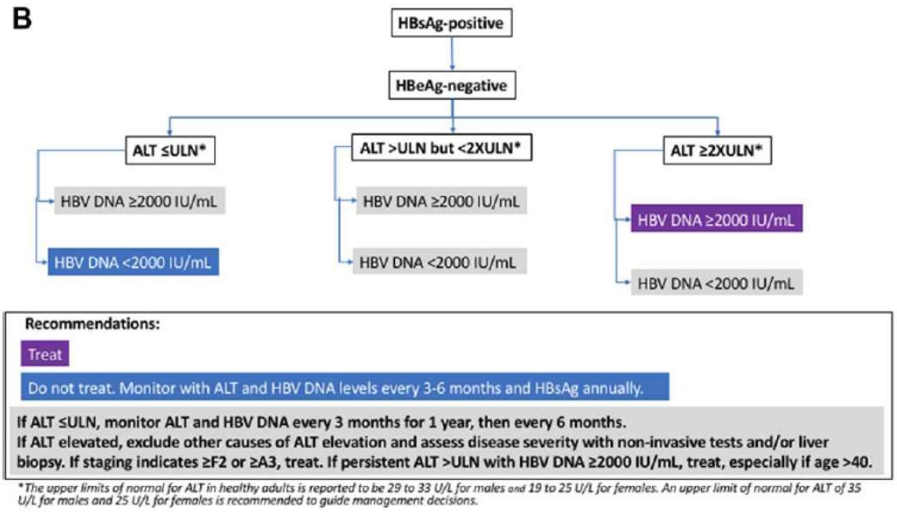
HBeAg-



Case 1

Questions:

Additional workup?

Is antiviral treatment indicated?

Assessment and recommendations:

- Patient is immune-tolerant (HBeAg positive chronic infection)

-Antiviral therapy not indicated

-Monitor HBV DNA, ALT, HBeAg q6mo

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Case 2

44 yo man with a history of chronic HBV on entecavir

- Diagnosed with **eAg-positive chronic hepatitis B** ("immune-active") 10 years ago: ALT 129, HBV DNA 670,000 IU/mL, HBeAg+
- Started on ETV
- Most recent labs: ALT 21, HBV DNA undetectable, HBeAg–, HBeAb+, HBsAg+, HBsAb–

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Case 2

He hates taking medications (though he has been compliant with ETV) and asks whether he can stop treatment.

Question: can he stop therapy?

Update on preferred regimens

Entecavir
-0.5 mg daily (1 mg daily if lamivudine-experienced or decompensated cirrhosis)

Tenofovir dipovoxil fumarate (TDF)
-300 mg daily
-Small risk of renal adverse events (GFR decline) or BMD loss

Tenofovir alafenamide (TAF)
-25 mg daily, approved 2016
-Lower risk of renal or bone adverse events vs TDF but magnitude of benefit and cost-effectiveness unclear/controversial

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Endpoints of HBV therapy

HBV DNA suppression (undetectable DNA)
ALT normalization

HBeAg loss (if eAg+ ➡ eAg–)
HBeAg seroconversion (eAg+/eAb- to eAg-/eAb+)

HBsAg loss (sAg–) = “functional cure”

Endpoints of HBV therapy

After 3 years of continuous therapy:

	Entecavir	Tenofovir (TDF)
HBV DNA suppression (%)	61	76
ALT normalization	68-81	68
HBeAg loss (%)	22-25	
HBeAg seroconversion (%)	21-22	21
HBsAg loss (%)	4-5	8

Terrault et al, Hepatology 2018

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Treatment discontinuation

Consider treatment discontinuation in the following patients:

1. HBeAg+ CHB *without cirrhosis* who seroconvert to HBeAg- and HBeAb+ (after a period of consolidation)
   - suggest ≥12 months of undetectable HBV DNA and normal ALT
   - monitor HBV DNA, ALT, HBeAg/HBeAb q3mo for at least 1 year

2. HBsAg loss (currently insufficient evidence but reasonable if persistent loss)
   - monitor as above

Treatment discontinuation

Guidelines currently recommend **indefinite** therapy for:

1.Chronic hepatitis B with cirrhosis (regardless of HBV DNA or ALT)

2.HBeAg negative chronic hepatitis B

Case 2

44 yo man with a history of chronic HBV on entecavir

- Had **eAg-positive chronic hepatitis B** ("immune-active")
- Most recent labs: ALT 21, HBV DNA undetectable, HBeAg–, HBeAb+, HBsAg+, HBsAb–

He has eAg seroconverted; if noncirrhotic and remains eAb+/eAg- for >1 yr, can consider stopping tx

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Case 3

47 yo male with new diagnosis of diffuse large B-cell lymphoma and “positive HBV serology”

Plan is for chemotherapy with R-CHOP (with rituximab) beginning this week

Case 3

Labs:

Normal liver tests

HBsAg–
HBsAb–
HBcAb+

HBV DNA undetectable

Case 3

Questions:

Does he need HBV monitoring or antiviral therapy for his planned chemotherapy?

What if he were HBsAb+ HBcAb+?

HBV reactivation

When initiating immunosuppressive or cytotoxic therapy, consider:

1. HBV status

2. Type of immunosuppression

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HBV reactivation

Refer to:

Gastroenterology 2015;148:215–219

AGA SECTION

American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy

K. Rajender Reddy,[1] Kimberly L. Beavers,[2] Sarah P. Hammond,[3] Joseph K. Lim,[4] and Yngve T. Falck-Ytter[5]

HBV reactivation

1. HBV status

- Use HBsAg+ and HBcAb+ status to identify patients at risk for HBV reactivation (HBVr)
  - HBsAg+ = higher risk, check HBV DNA and ALT
  - HBsAg- HBcAb+ = lower risk (but at risk)

- Disregard HBsAb positivity if HBcAb+: confers only *partial* protection from reactivation

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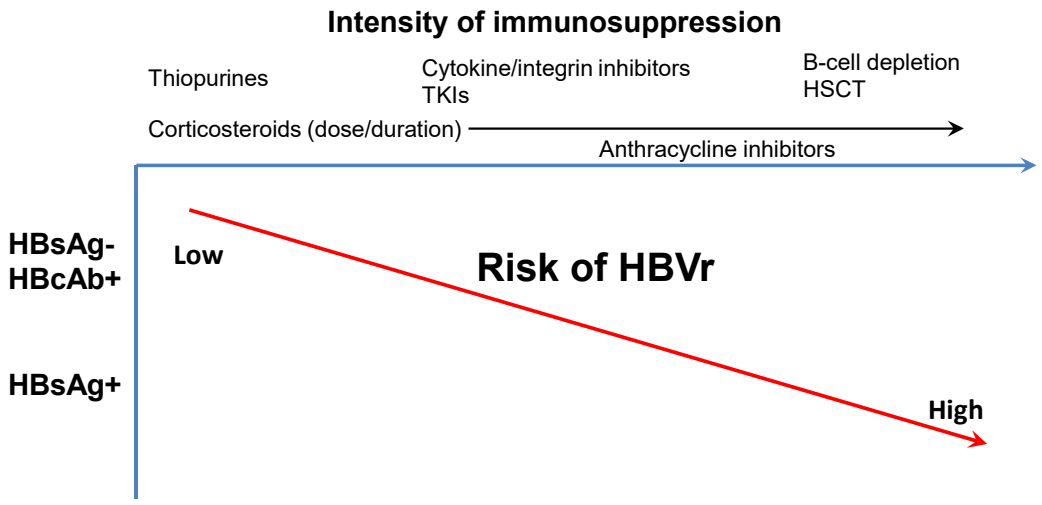
HBV reactivation



HBV reactivation

High risk of HBVr (>10% risk):

- HBsAg+ or HBsAg-/HBcAb+ with B-cell depleting tx or HSCT
- HBsAg+ with anthracycline derivatives (including TACE)
- HBsAg+ on long-term (≥4 wk) steroid therapy at ≥10 mg/d prednisone equivalent
- HBsAg+ with potent TNFα inhibitors

Antiviral prophylaxis recommended over monitoring

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Monitoring for HBVr

Moderate risk of HBVr

-Monitoring versus prophylaxis

-Monitor by HBsAg (if HBsAg- HBcAb+), HBV DNA, ALT q3mo

Low risk of HBVr

- Monitor

Our patient

HBsAg- HBcAb+ receiving B-cell depleting therapy

High risk of HBVr

HBsAb status irrelevant in this case

Recommend **antiviral prophylaxis** (entecavir or tenofovir)

Continue for 1-2 years after completion of therapy (B-cell depletion; in other cases ≥ 6 mo)

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Thank you!

Questions?

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Functional Diarrhea

Richard J. Saad, MD, MS, FACG
Clinical Associate Professor of Medicine

Clinical Case

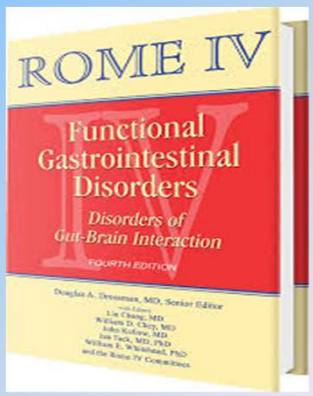
- 30 year old woman
  - 3 years of progressively worsening diarrhea
    - Alternates with formed stool
    - Eating worsens diarrhea
  - Associated lower abdominal pain & urgency
  - Only taking periodic Imodium

Is this a functional diarrhea?

What else needs to be considered?

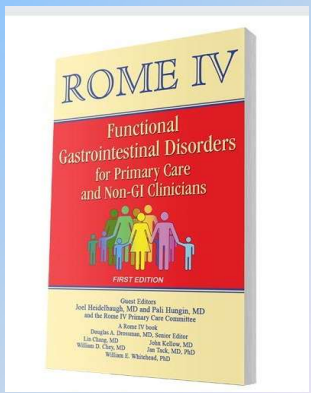
What is functional diarrhea?

- Chronic or recurrent diarrhea not explained by structural or biochemical abnormalities
  - May include symptoms of bloating, abdominal pain, cramping, urgency, fecal incontinence



Functional diarrheal Syndromes

- Rome 4
  - Irritable bowel syndrome with diarrhea (IBS-D)
  - Functional diarrhea (FDr)

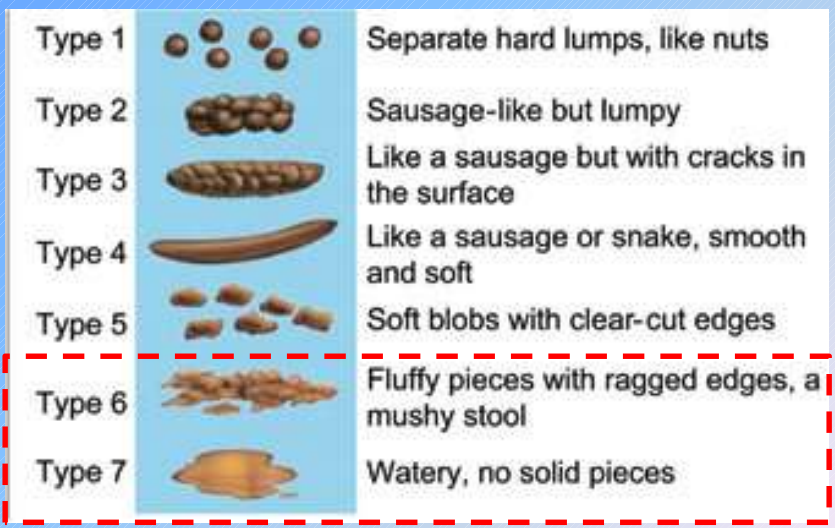


IBS-D (Rome 4)

- Recurrent abdominal pain
  - Average of 1 day/week or more in the last 3 months
  - Associated with two or more of:
    - Related to defecation
    - Associated with a change in frequency of stool
    - Associated with a change in form (appearance) of stool
- Predominance of loose or watery stool
  - >25% of BMs are BSS 6 or 7, < 25% are BSS 1 or 2

Lacy BE, et al. Bowel Disorders. Gastroenterology. 2016;150:1393-1407

IBS-D: the Bristol Stool Scale



FDr (Rome 4)

- Loose or watery stools
  - without predominant abdominal pain or bothersome bloating
  - occurring in >25% of BMs
  - Symptoms for at least 3 months
- Symptoms do not fulfill criteria for IBS-D

Lacy BE, et al. Bowel Disorders. Gastroenterology. 2016;150:1393-1407

FDr (Rome 4): Potential Causes

- Post cholecystectomy
- Dietary
  - FODMAP intolerance
  - Carbohydrate malabsorption
  - Lactose or fructose malabsorption
  - Artificial sweeteners
  - Caffeine
- Overflow diarrhea

Organic Causes of Chronic Diarrhea to Consider

- Infection
  - C diff, Giardia, other parasitic infections
- Celiac disease
- Inflammatory bowel disease
- Microscopic colitis
- Small intestinal bacterial overgrowth
- Pancreatic insufficiency

The History in Chronic Diarrhea

- The History is critical in the evaluation
  - More detailed history of bowel movements
    - Blood in the stool
    - Difficulty with evacuation or other constipation symptoms
    - Presence of fecal incontinence
  - Dietary history
    - Ingestion of caffeine, sugar free products, alcohol
    - Triggers foods? Trials of elimination diets
  - Medications
    - In particular, is there a temporal relation
  - Family history
  - Travel history
  - Other alarm signs/symptoms

Diagnostic Approach to Chronic Diarrhea

- Fecal calprotectin (or fecal lactoferrin)
  - 50 mcg/g or less (4 to 7.25 mcg/g)
- Fecal antigen or PCR for Giardia
- IgA-tTG and serum IgA
  - IgG-tTG or IgG deaminated gliadin peptide if serum IgA low
- ESR and CRP not recommended
- CBC?
- Testing for bile acid malabsorption if available

Smalley et al. AGA Practice Guideline on the laboratory evaluation of FDr and IBS-D in adults. Gastroenterology. 2019;157:851-854

Additional Diagnostic Testing: Chronic Diarrhea

- Other testing as clinically indicated
  - Colonoscopy
    - blood in stool, family history, age, anemia, elevated fecal calprotectin/fecal lactoferrin, immunosuppression
  - EGD with biopsy for positive celiac antibody screening
  - Abdominal xray
    - Constipation history with concern for fecal loading
  - Stool for C diff or O/P
    - Travel history/ recent immigration from endemic area
  - Stool for fecal elastase
    - Concern for pancreatic insufficiency
  - Breath testing
    - Glucose, lactulose, fructose, lactose

Case 1: Continued

- Chronic diarrhea with associated abdominal pain and bloating, no blood in stool
- No constipation, no fecal incontinence
- Some relief with prn Imodium
- No FHx of IBD or colon cancer
- No travel abroad
- Hgb 13, IgA-tTG negative, Serum IgA normal, fecal calprotectin > 50
- What is your diagnosis?
  - IBS-D

Now that you have a Diagnosis

- Give the patient the diagnosis
- Briefly explain pathophysiology
- Outline treatment
  - General dietary/lifestyle measures
  - Low FODMAP diet*
  - Probiotics*
  - Pharmacologic therapy*
  - Behavioral therapy*

***Evidence for FDr largely extrapolated from IBS studies**

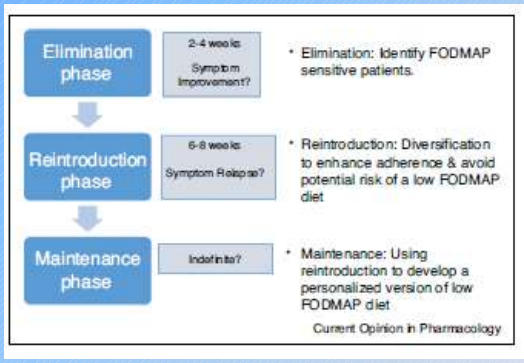
General Dietary/Lifestyle Considerations

- Elimination of alcohol, caffeine, coffee
- Limit artificial sweeteners
- Avoidance of specific trigger foods
- Reduce fried, processed and fatty foods
- Increased dietary fiber (insoluble vs. soluble)
- Regular, unhurried meals

FODMAPs: Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyos

- Fructose   
- Lactose 
- Fructans 
- Galactans 
- Sugar alcohols  
  - xylitol, sorbitol, maltitol and mannitol

Low FODMAP Diet (LFD): A three phase treatment



Eswaran et al. Current Opinion in Pharmacology 2017, 37:151–157

LFD: Clinical Pearls

- Use of registered dietician with expertise in the low FODMAP diet strongly recommended
- If not a dietician, patient will need adequate instruction
  - Books, apps, other internet-based tools
- Minimum of 2 weeks on FODMAP elimination
  - May take up to 4 weeks
  - Re-introduction phase is very important

Probiotics in IBS-D & FDr

- Few products studied clinically
  - Results strain-specific & contradictory
  - AEs are not consistently reported
- Quality & consistency of preparations questionable
  - Shelf-life limitations
  - Lack of government-sanctioned quality-control standards
- Must weigh benefits and cost to patient

Probiotics in IBS: The Latest Evidence

- Systemic review with meta-analysis
  - 53 RCTs (up to July 2018)
  - 5545 total participants
  - Beneficial effects on global IBS symptoms and abdominal pain shown with particular strains, species and combinations
- Conclusions:

  "Which particular combination, species or strains of probiotics are effective for IBS remains, for the most part, unclear"

Ford AC et al. Aliment Pharmacol Ther. 2018 Nov;48(10):1044-1060

Pharmacotherapy

FDA Approved for IBS-D

- Alosetron (Lotronex®)
- Eluxadoline (Viberzi®)
- Rifaximin (Xifaxan®)

Other Agents

- Loperamide (Imodium®)
- Diphenoxylate/Atropine (Lomotil®)
- Peppermint
- Bile acid resins
- Hyoscyamine (Levsin®)

Antidiarrheals for IBS-D

- Loperamide
  - Dose: begin at 2 mg & titrate to effect to max 12mg/day (4mg tid)
    - More effective than placebo on diarrhea[1] Grade 2C
    - Conditional recommend for use over no therapy based on very low quality evidence (AGA)
- Diphenoxylate with atropine
  - Max of 5 mg and .05 mg up to qid
  - CNS side effects may limit use
  - No evidence-based recommendation from ACG or AGA

[1]ACG Task Force, Am J Gastroenterol, 2009; 104(S1)S1-35
Chang et al, Gastroenterology, 2014; 147 (5) 1149-1172

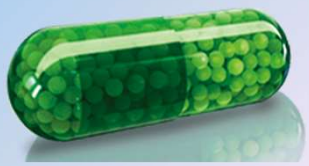
Loperamide and FDr

- Decreased stool and reduced FI[1]
  - R,PC,DB trial of 11 patients
  - Loperamide 4 mg bid vs. Placebo
    - Reduced colon transit time
    - Increased internal anal sphincter tone
- Decreased Bowel movement frequency[2]
  - O,R,CO trial of 19 patients
  - Loperamide vs. Ispagula + calcium
  - Loperamide 4mg + 2 mg after BM to max of 16 mg/d x 1 week
    - Both reduced daily BM by 50%,

[1]Sun WM et al. Scand J Gastroenterol. 1997 Jan;32(1):34-8
[2]Qtivzau S et al. Scand J Gastroenterol. 1988 Dec;23(10):1237-40

Peppermint for IBS-D

- Purified peppermint oil (IBgard®)
  - Medical food product
    - Not a drug or nutritional supplement
    - As such, not FDA approved or monitored
  - Utilizing targeted delivery technology

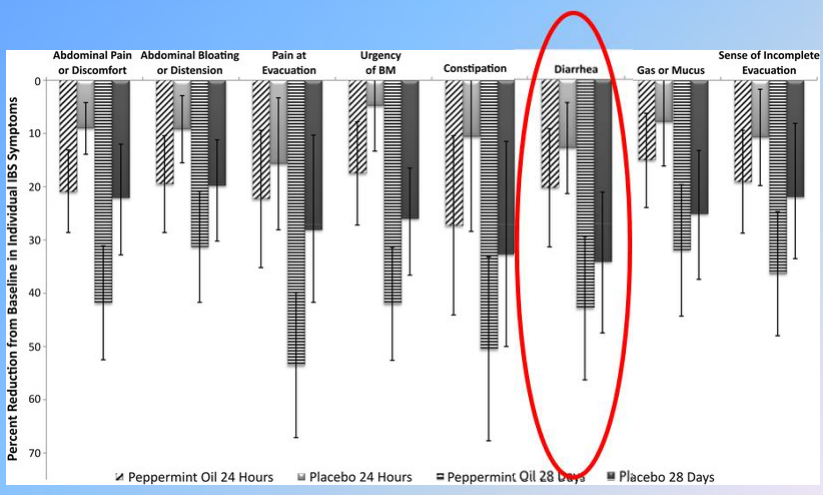


IBgard: Published data

- 4 wk, DB, PC trial
  - 72 patients(40.7 years, 75 % F, 38 IBS-D)
  - 2 capsules 3 times daily vs. placebo
  - Primary endpoint:
    - Change from baseline in the Total IBS Symptom Score (TISS)

Cash BD et al. Dig Dis Sci. 2016 Feb;61(2):560-7

Effect of IBgard on Diarrhea



Cash BD et al. Dig Dis Sci. 2016 Feb;61(2):560-7

Ibgard Clinical Pearls

- Minimal effect on diarrhea (primarily for pain)
- Appears safe
  - Fewer AEs than placebo
- Dosing suggestions
  - 1-2 capsules prn up to 3 times daily
  - Not exceed 8 capsules/24 hours
  - Can open and mix the contents in applesauce
- Expensive ~ $1 per capsule

Alosetron (Lotronex®)

- Selective 5-HT_3 receptor antagonist
  - Improved global symptoms, abdominal pain, rectal urgency, stool frequency, stool consistency in women [1]
- Initially approved in 2000 for IBS-D
  - Voluntarily withdrawn 9 months later
    - Ischemic colitis & complications of constipation
- Reintroduced in 2002 (risk mgmt program)
  - Requested by IBS pts and advocacy groups
- Pregnancy category B

Camilleri et al. Arch Intern Med. 2001 Jul 23;161(14):1733-40
Lembo et al. Am J Gastroenterol. 2001 Sep;96(9):2662-70
Lembo et al. Clin Gastroenterol Hepatol. 2004 Aug;2(8):675-82

Alosetron: FDA Indication

- Women with severe* IBS-D
  - chronic symptoms (≥ 6 months)
  - Excluded anatomic & biochemical abnormalities of the GI tract
  - Failure to respond to conventional therapy

Severe = one of more of the following:
1. **frequent and severe abdominal pain/discomfort**
2. **frequent bowel urgency or fecal incontinence**
3. **disability or restriction of daily activities due to IBS**

Prescribing Program for LOTRONEX™ (PPL)

- Essential part of risk evaluation and mitigation strategy (REMS)
  - Reduce the risk of ischemic colitis and other complications of serious constipation
- Prescriber must enroll in the PPL
  - www.lotronexppl.com

Alosetron: Contraindications

- Constipation
- History of obstruction, stricture, perforation or toxic megacolon
- Adhesions
- Ischemic colitis
- impaired intestinal circulation
- Thrombophlebitis
- Hypercoagulable state
- IBD
- History of diverticulitis
- Severe hepatic impairment
- Use of fluvoxamine

Alosetron Dosing

- Initial dose of 0.5mg PO BID
- Observe for initial 4 weeks of therapy
  - If effective, continue therapy indefinitely
  - If tolerate and not effective, increase dose to 1mg PO BID
  - If not tolerated, stop
- Stop therapy if not effective after 4 weeks at 1 mg PO BID

Alosetron Side Effects

- Serious
  - Ischemic colitis (0.2% in 3 mos, 0.3% in 6 mos)
  - Complications of constipation (0.1%)
    - Obstruction, ileus, impaction, toxic megacolon
- Other
  - Constipation (29%)
  - Abdominal pain (7%)
  - Nausea (6%)
  - Heartburn, regurgitation, reflux (2%)
  - Hemorrhoids (2%)

Eluxadoline

- Orally mixed mu-opioid receptor agonist and delta-opioid antagonist
- FDA approved for the treatment of IBS-D
- No pregnancy category assigned
  - No studies in humans
  - No teratogenicity in rat (51x) or rabbit (115x) human dose

Eluxadoline: MOA

- Activation of mu-opioid receptors
  - Decreased GI motility and transit
  - Promotes visceral analgesia
- Inactivation of delta-opioid receptors
  - Potentiates the effects of mu receptor activation on GI motility and visceral analgesia

Eluxadoline Risks & AEs

- Acute pancreatitis
  - 5 cases in1666 pts (0.3%)
- Abd pain with ↑LFTs in 8 of1666 pts (0.5%)
- All cases had biliary disorders or Etoh use
- Other AEs
  - Constipation (8%)
  - Abdominal pain (7%)
  - Nausea (8%)
  - Vomiting (4%)

Lembo et al. N Engl J Med. 2016 Jan 21;374(3):242-53

Eluxadoline Dosing

- 100 mg PO BID with food
- 75 mg PO BID with food
  - Intolerance to 100 mg
  - Use of OATP1 BI inhibitors (cyclosporine, gemfibrozil, antiretrovirals, rifampin, eltrombopag)
  - Hepatic impairment
- Do not double next dose, if one missed
- Discontinue if constipated > 4 days

Eluxadoline Contraindications

- **No gallbladder!!!!**
- Known/suspected bile duct obstruction
- Known/suspected sphincter of Oddi dysfunction
- Alcoholism/alcohol abuse
  - 3 or more alcoholic beverages/day
- Hx of pancreatitis or pancreatic structural disease
- Severe hepatic impairment (Child's Class C)
- Severe constipation
- Known or suspected mechanical GI obstruction

Rifaximin

- Semisynthetic derivative of rifamycin
  - Non-absorbable (<1%)
- FDA Indication for adults with IBS-D
  - 550 mg PO TID x 14 days
  - For symptom recurrence may retreat up to 2 more times at same dose
  - Can be taken with or without food
- No pregnancy category assigned
  - No studies in humans
  - Teratogenicity in rat (0.9-5x) & rabbit (0.7-33x) human dose

Lembo A et al. Gastroenterology. 2016 Dec;151(6):1113-1121

Rifaximin & IBS: MOA

- Exact MOA unclear
- Three leading theories that alteration in gut flora (small bowel?) results in:
  - Reduction of bacterial products that negatively affect gut function
  - Reduction in interaction of bacteria with gut mucosa
  - Direct alteration of both the bacterial and gut response to one another

TARGET 1 & 2

- 2 identical Phase 3 R,DB,PC trials (179 centers in US & Canada)
  - 1260 pts IBS without constipation (Rome II)
  - TARGET 1: 623 pts, TARGET 2: 637 pts
- Rifaximin 550 mg TID x 14d vs. placebo
- Followed for 10 weeks following therapy
- Primary Endpoint:
  - Global relief of IBS symptoms for 2 of 4 weeks following therapy

Pimentel et al. N Engl J Med. 2011 Jan 6;364(1):22-32

TARGET 1 & 2: Diarrhea Response

First 4 weeks following therapy

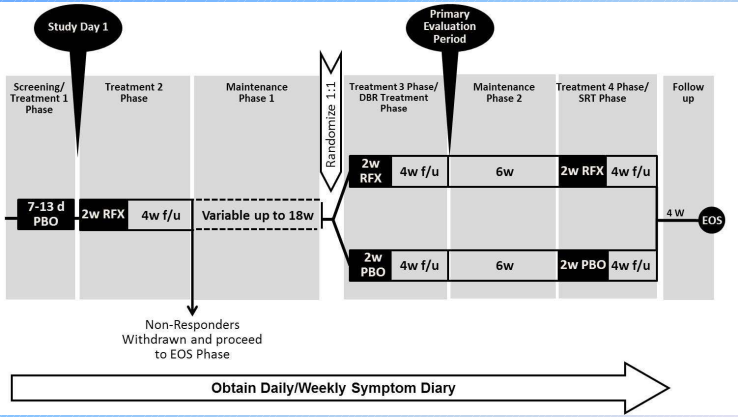
	Rifaximin	Placebo	P value
Adequate relief of abdominal pain & loose, water stool			
TARGET 1	46.6 (n=309)	38.5 (n=314)	0.04
TARGET 2	46.7 (n=315)	36.3 (n=320)	0.0008
Combined	46.6 (n=624)	37.4 (n=634)	< 0.001

Odds Ratio of response at 3 months in favor of rifaximin over the 3 months of the study:

TARGET 1	**1.36 (1.01-1.83), p = 0.04**
TARGET 2	**1.44 (1.08-1.92), p = 0.01**
Combined	**1.40 (1.14-1.72), p = 0.001**

Pimentel et al. N Engl J Med. 2011 Jan 6;364(1):22-32

TARGET 3



Enrollees: IBS-D (Rome III) with severity scores of ≥ 3 for IBS-related abdominal pain (scale 0-10) and bloating (scale 0-6), and experienced ≥ 2 stools with Bristol Stool Scale Type 6 or 7 (watery) during screening

Lembo A et al. Gastroenterology. 2016 Dec;151(6):1113-1121

TARGET 3: Results

- 1074 of 2579 (44%) responders to OL tx
  - 36% remained responders (over 18 weeks)
  - 636 of 692 relapsing entered R,DB,PC trial

Response rates following first retreatment:

	Rifaximin	Placebo	p value
Overall response	38.1%	31.5%	0.03
Abdominal pain	50.6%	42.2%	0.018
Diarrhea	51.8%	50%	NS

Response rates following second retreatment were NS

Lembo A et al. Gastroenterology. 2016 Dec;151(6):1113-1121

Rifaximin: Safety In Clinical Trials

- AEs similar to placebo
- No cases of c difficile or ischemic colitis
- 3 courses of therapy (vs 1 course) of therapy did not affect:
  - Bacterial sensitivity to other antibiotic classes
  - Promote pathogenic bacterial growth
  - Alter the overall microbiota
  - increase the occurrence of opportunistic infections

Lembo A et al. Gastroenterology. 2016 Dec;151(6):1113-1121

Bile Acid Resins in FDr & IBS

- Bile acid malabsorption (BAM) proposed as cause of functional diarrhea
  - Idiopathic
  - Post cholecystectomy
- ^{75}Selenium homocholic acid taurine (SeHCAT) test
  - Not available in US
- Bile acid resins have been used empirically (up to 70% response reported)

Bile Acid Resins: Clinical Caveats

- Evidence is essentially anecdotal
- Cholestyramine is unpleasant (take with applesauce)
  - Alternatives include colestipol and colesevelam
- Will lower cholesterol (may elevated triglycerides)
  - Avoid if triglycerides > 200 mg/dL
- Drug interactions with anion drugs
  - Warfarin, thiazide diuretics, propanolol, phenobarbital, thyroid and thyroxine preparations, estrogens, progestins, and digitalis, should be administered 1 hour before or 4 hours after the resin
  - Not so with colesvelam (theoretically)
- Long term use could affect fat soluble vitamin levels

Hyoscyamine

- Use is based solely on anecdotal evidence
  - Post-prandial cramping, urgency & diarrhea
  - Similar effects to atropine
- Dosed 0.125 -0.25 mg SL 15-30 min prior to meals
- Use with caution in those aged 65 & older
  - Confusion, dry mouth, blurry vision, urine retention
- Avoid with glaucoma & obstructive uropathy

Behavioral Therapy in IBS

- Those with co-existent stress & anxiety
  - Relation of stress to GI symptoms
  - Requires patient buy-in
- Treatment directed by a psychologist
  - Cognitive behavioral therapy[1]
    - Problem solving process
  - Gut-directed hypnosis[2]
    - Similar to FODMAP diet intervention
    - Durable with 74% response @ 6 months

[1]Jang AL et al. Eur J Gastroenterol Hepatol. 2014 Aug;26(8):918-26
[2]Peters SL et al. Aliment Pharmacol Ther. 2016 Sep;44(5):447-59

Summary: Functional Diarrhea

- Rule out secondary causes
- Make a definitive diagnosis
  - IBS-D vs functional diarrhea
- Outline treatment plan
  - Often times a process involving trial & failure
  - Dietary, pharmacologic and behavioral interventions exist
  - Combination therapy may be needed

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Avoidant/Restrictive Food Intake Disorder (ARFID)

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- **Objectives**

Use a case-based approach to:

- Define ARFID and sub-classifications
- Discuss the prevalence of ARFID
- Describe how ARFID presents in GI clinic
- Outline current treatment recommendations for ARFID

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- **Disclosures**
  - No financial disclosures or conflicts of interest

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Disordered Eating in GI

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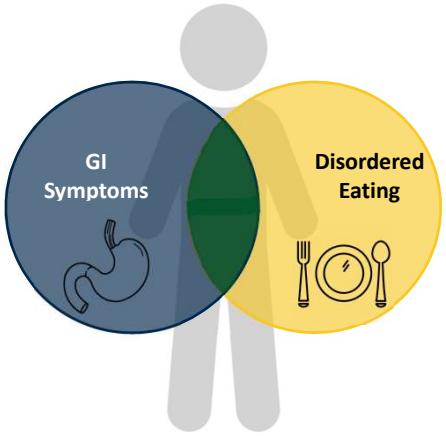
Disordered Eating

- Disordered eating
  - Patterns of eating that differ from cultural norms
  - Keto diet, missing meals, etc.
- Meta-analysis demonstrated ~23% of patients with GI disease displayed disordered eating patterns[1]
- ARFID is a form of disordered eating
  - Not an organic GI disorder, but is important diagnosis in GI



Satherley R, Howard R, Higgs S. Disordered eating practices in gastrointestinal disorders. *Appetite*. 2015;84:240-250

Patient Case

- 43 year old diabetic female, gastroparesis for 10 years
- Last year was particularly challenging- daily abdominal pain, nausea, and vomiting
- Restricted her diet to mainly ice tea, bread, and soup.
- Started on a new medication regimen and she reports her symptoms have been well controlled for the past 6 months
- Despite reported improved nausea and vomiting, she struggles with expanding her diet.
- She frequently complained of bloating, not eating due to the fact "it will cause pain and nausea".
- Currently, drinking only ice tea and primarily eats a few foods she identifies as safe.
  - She states all other liquids and foods cause pain and nausea.
  - Drinking 2 ensures a day and weight is stable

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Patient Case

- A confusing clinical situation
  - Is this uncontrolled gastroparesis?
  - Why is she only able to drink ice tea?
  - Is this something non-gastroparesis related?
  - Am I missing something? Should I do further testing?
  - Should I prescribe the low FODMAP diet for her bloating?

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ARFID Overview

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DSM-5: Avoidant/Restrictive Food Intake Disorder (ARFID)

- The disturbance in eating/feeding is associated with **one or more of the following**:
  - Substantial weight loss (or lack of expected weight gain)
  - Nutritional deficiency
  - Dependence on tube feeds or dietary supplements
  - Significant psychosocial interference
- Disturbance not due to:
  - Unavailability of food
  - Anorexia/bulimia nervosa (no body dysmorphia in ARFID)
  - Another medical condition
    - when experienced concurrently with another condition, the disturbance EXCEEDS what is normally caused by that condition

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Avoidant/Restrictive Food Intake Disorder (ARFID)

- **Proposed subcategories**
  - Sensory-based avoidance based on smell, texture, color, etc.
    - "picky eater" crowd

  - A lack of interest in food
    - "I eat to live", "I forget to eat" crowd

  - Fear of negative consequences
    - Learned behavior, food becomes fear-evoking stimuli
    - "I am afraid to eat, its going to hurt me" crowd
      - "Food PTSD"

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- **Symptoms & Warning Signs**
  - Restricted or reduced food intake
  - Frequent complaints about bodily discomfort with no organic cause
  - Lack of appetite or interest in food
  - Fear of negative effects of eating food (e.g., choking, vomiting)
  - Inability or reluctance to eat in front of others
  - Picky eating that is unresolved by late childhood

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- **Health Consequences of ARFID:**
  - Failure to thrive
  - Anemia
  - Weight loss
  - Gallbladder disease
  - Malnutrition
  - Osteoporosis or osteopenia
  - Dependence on tube feeds or TPN
  - Death
  - Eating disorders have the highest mortality rate of any mental illness.
  - Increased health care costs (particularly when not diagnosed)

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- **Prevalence of ARFID**
  - Children: 3%[1]
  - Adults: no prevalence data or adequate case definitions of ARFID in adult populations available in published studies
  - Pediatric GI patients: 1.5% based on one retrospective study[2]

1.Kurz S, van Dyck Z, Dremmel D, Munsch S, Hilberg A. Early-onsent restrictive eating disturbances in primary school boys and girls. European Child Adolesccent Psychiatry. 2015;24:779–85.
2.Eddy KT, Thomas JJ, Hastings E, Edkins K, Lamont E, Nevins CM, *et al.* Prevalence of DSM-5 avoidant/restrictive food intake disorder in a pediatric gastroenterology healthcare network. *Int J Eat Disord*2015;**48**:464–70. https://doi.org/10.1002/eat.22350.

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- **ARFID vs Anorexia in Adolescents**
- ARFID patients
  - were younger (12.4 vs. 15.1 years, $p < .0001$)
  - were more likely to be male (41% vs. 15%, $p < .0002$)
  - were less likely to be admitted to the hospital (14.2% vs. 27.6%, $p = .02$)
  - were less likely to experience acute weight loss vs. chronic weight loss ($p = .0001$)
  - reported significantly fewer symptoms of depression, anxiety, perfectionism, clinical impairment, concerns about weight and shape (all $p < .0001$).
- No differences were observed by race, anxiety disorder, orthostatic instability, suicidal ideation, and history of eating disorder treatment.

Keery H, LeMay-Russell S, Barnes TL, Eckhardt S, Peterson CB, Lesser J, *et al.* Attributes of children and adolescents with avoidant/restrictive food intake disorder. *J Eat Disord* 2019;**7**:31. https://doi.org/10.1186/s40337-019-0261-3.

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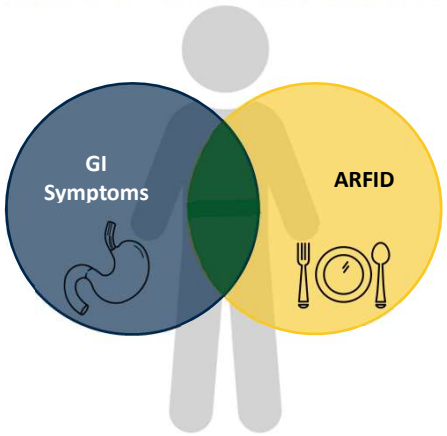
ARFID in GI: Overview



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- **ARFID in Gastroenterology**
  - Paucity of data
  - Dietary changes are common in patients with GI conditions
  - Concern for ARFID raised when dietary habits exceed expected changes
  - Often due to a "fear of negative consequence"

GI Diagnosis	Expected Dietary Change Example	Avoidant/Restrictive Behavior Example (concerning for ARFID)
Gastroparesis	"When my symptoms flare, I consume a liquid diet and then slowly start to add foods back in."	"Ice tea is the only fluid I can drink. All other fluids, even water, cause nausea and vomiting."
Irritable Bowel Syndrome	"I followed a low FODMAP diet and am currently working on slowly reintroducing foods."	"I am on a strict low FODMAP diet, and have found 10 'safe' foods on the list. I do not want to attempt the food reintroduction protocol."

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- **Prevalence of ARFID in adult GI patients**
  - Of 317 outpatient GI patients screened for ARFID: 19% screened positive
  - Of 223 GI Behavioral Health patients: 12.6% met ARFID DSM-5 criteria

2 Harer K, Baker J, Reister N, et al. Avoidant/restrictive food intake disorder in the adult gastroenterology population: an under-recognized diagnosis? *Am J Gastroenterol*. 2018;113(suppl):S247-S248

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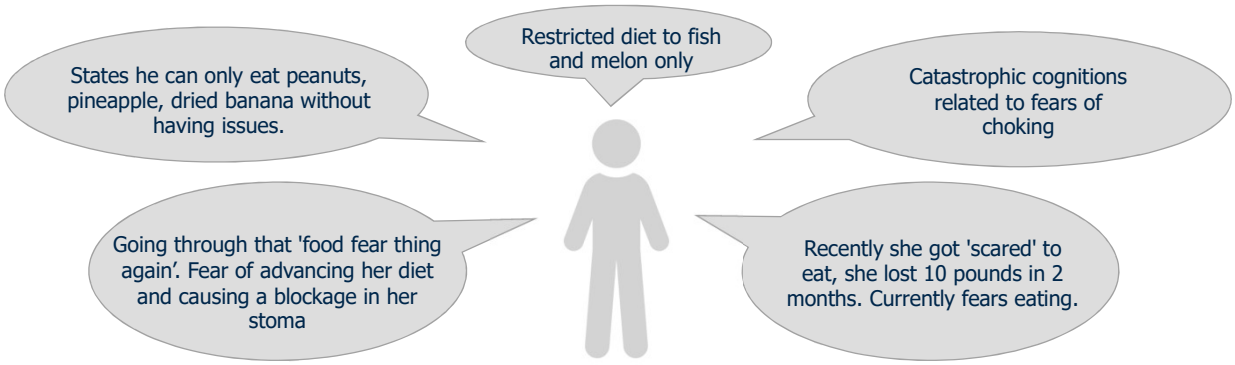
- **What does ARFID in GI patients look like?**
  - Dietary restriction that exceeds expected response to GI symptoms
  - Quotes from ARFID clinic notes:



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ARFID in GI: Research

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Prevalence of Avoidant/Restrictive Food Intake Disorder Among Adult Gastroenterology Outpatients:

- The Nine Item ARFID Screen (NIAS) questionnaire was prospectively administered to 317 adult gastroenterology outpatients
- 62 (19.6%) had a positive ARFID screen

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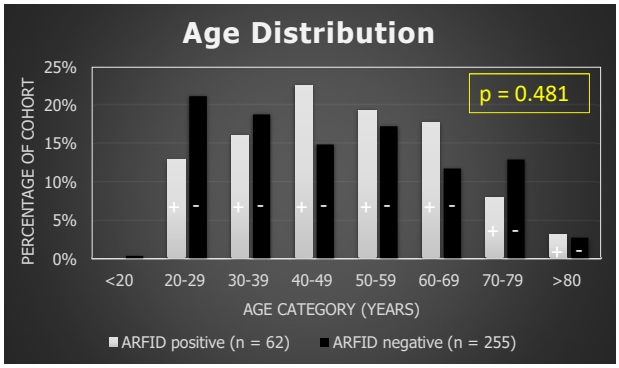
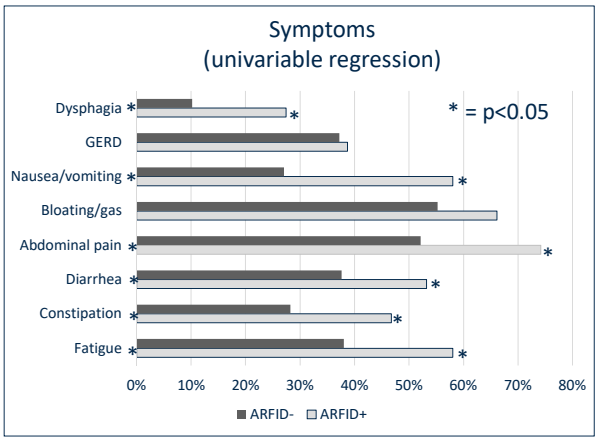
- **Results: Demographics (comparison of ARFID + vs ARFID -)**
  - **No statistically significant differences in demographics between positive and negative screeners**

	Positive ARFID Screen (n=62)	Negative ARFID Screen (n=255)	p value
Gender			0.08
Male	13 (20.97%)	80 (31.37%)	
Female	47 (75.81%)	161 (51.37%)	
Unknown	2 (3.23%)	14 (5.49%)	
Race/Ethnicity			0.54
White/Caucasian	45 (72.58%)	218 (85.49%)	
Black/African American	5 (8.06%)	14 (5.49%)	
Asian	2 (3.23%)	8 (3.14%)	
Hispanic/Latino	2 (3.23%)	4 (1.57%)	
American Indian	0 (0%)	4 (1.57%)	
Hawaiian/Pacific Islander	0 (0%)	1 (0.39%)	
Middle Eastern	2 (3.23%)	3 (1.18%)	
Other	1 (1.61%)	1 (0.39%)	
Declined	5 (8.06%)	2 (0.78%)	
Clinic type			0.87
General GI	44 (70.97%)	172 (67.45%)	
Motility Subspecialty	18 (29.03%)	82 (32.15%)	



- **Results: Symptoms (regression analyses)**

MOU27



Symptom	Crude OR	p value	Multivariable OR	p value
Dysphagia	3.3	<0.01	2.2	0.045
GERD	1.1	0.83	0.7	0.21
Nausea/vomiting	3.7	<0.01	2.7	<0.01
Bloating/gas	1.6	0.12	0.8	0.50
Abdominal pain	2.6	<0.01	1.6	0.25
Diarrhea	1.9	0.03	1.5	0.23
Constipation	2.2	<0.01	1.5	0.22
Fatigue	2.3	<0.01	1.1	0.71

- Nausea/vomiting and dysphagia demonstrated statistically significant associations with a positive ARFID screen in the multivariable analysis

MOU1
MMOU18
MOU29

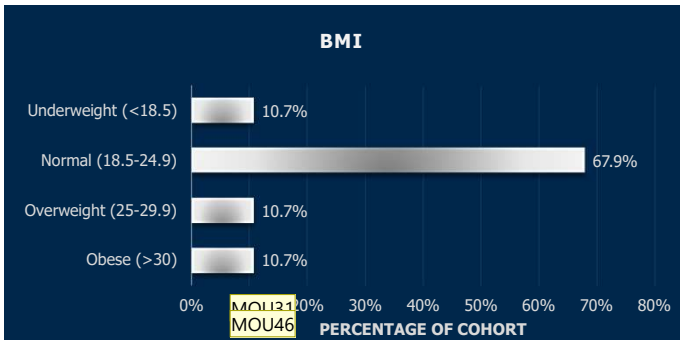
Prevalence and Clinical Characteristics of Avoidant/Restrictive Food Intake Disorder Among Adult Gastroenterology Behavioral Health Outpatients

- 223 adult GI patients seen by GI psychologists at a tertiary care center
- (12.6%) met criteria for ARFID

MOU7

Results: Demographics

	ARFID Patients (N=28)
Age (mean years)	39.5 (range 19-84)
Gender	
Male	5 (17.9%)
Female	23 (82.1%)
Mean BMI at GI presentation	22.9 (range 13.9–37.7)
Weight loss (mean lb)	19.04 (range 6-60)
Time weight loss occurred over (mean)	13.1 months



MOU31
MOU46

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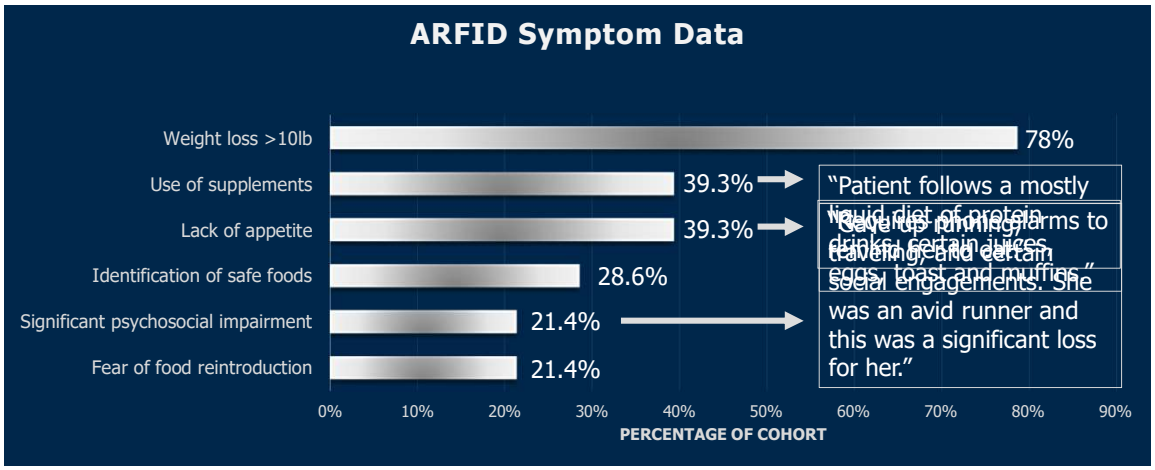
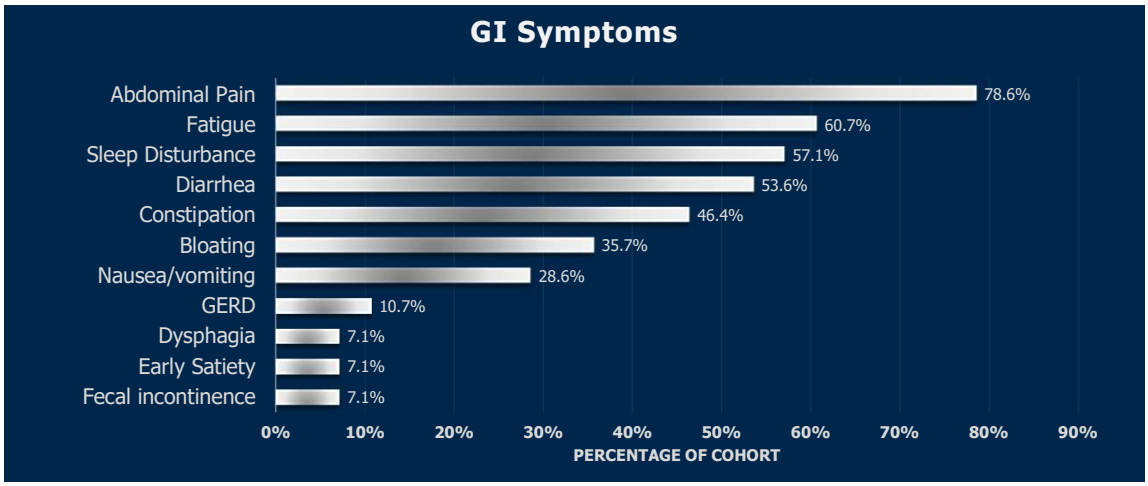
MOU32

• Results: ARFID Symptom Data



MOU28
MOU44

• Results: Symptoms



MOU34
MOU40

Results: Nutrition Consult Information

- 20 (71.4%) were prescribed a low FODMAP diet in the setting of meeting ARFID criteria, having an underweight BMI (BMI <18.5), or actively losing weight
- Concern for ARFID was mentioned in 0% of cases

MOU35

Psychiatric Data

	ARFID Patients (N=28)
Behavioral Health	
GI visits prior to GIBH referral (mean)	2.8 (range 1–8)
GIBH visits (mean)	6.7
Prior Psychiatric History	
History of psychiatry visit	2 (7.1%)
Active psychotropic medication use	4 (14.3%)
History of eating disorder	1
At least 1 psychiatric diagnosis	8 (28.6%)
Anxiety disorder	5 (17.9%)
Depression disorder	5 (17.9%)
PTSD	1 (3.6%)
Other	1 (3.6%)

→ Institutional GIBH ~ 40%

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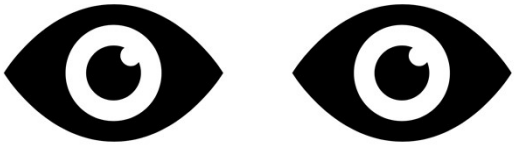
Keep watching…the interest in ARFID is increasing and more published studies are coming



MOU1
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ARFID Diagnosis

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MOU36

- **Diagnosing ARFID**
  - Should be diagnosed by a qualified professional (psychiatrist, eating disorder specialist, etc.)
  - The task for the gastroenterologist is to identify red flag symptoms, not to make a formal diagnosis.
    - If there are red flags, and refer if necessary
  - NIAS screener is currently available, but not validated in GI patients
    - Does not differentiate ARFID restriction from other causes of dietary restriction

MOU1
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MOU29

Importance of Diagnosis ARFID in GI Patients

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MOU36

- **Importance of diagnosing ARFID**
  - Delay in ARFID treatment
  - Mis-assignment of dietary restriction to uncontrolled GI symptoms can result in
    - Increased testing
    - Use of ineffective or even harmful therapies (i.e. prescribing restrictive diets like the low FODMAP diet)

Back to the case….

- 43 year old diabetic female, gastroparesis for 10 years
- Severely restricted diet
- After further questioning, patient identifies fear of introducing new foods
- Looks at food and thinks "it is going to hurt me"
- You are concerned for ARFID
- But now what do you do?

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ARFID Treatment

MOU36

- **Treatment**
  - Paucity of data in adults, and none in adult GI patients
  - Likely multi-disciplinary approach for GI patients
    - Psychology (cognitive behavioral therapy, exposure therapy, etc.)
    - Nutrition (slow food reintroduction)
    - GI (continued GI symptom management)
  - Medications
    - No current evidence in adult population
    - SSRIs ,Remeron, and olanzapine trials in children

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• Food Reintroduction Suggestions

- Practice exposure and response prevention techniques
  - Shaping- rotate preferred foods, repeatedly introduce non-preferred foods in small amounts. It may take 50-100 presentations before a food is no longer considered novel.
  - Chaining- introduce new foods that are relatively close to a preferred food and switch back and forth(e.g. pancakes and waffles, cheese pizza vs pepperoni pizza)
  - Work through the exposures, building confidence as progressively scarier foods are added
- Practice normal social eating (with modifications)- eating with friends, at restaurants, being more flexible
- Introduce more challenging (vegetables), complex and "mixed" foods
- Nutritionist/registered dietitian led

MOU1
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Summary

- **Concluding Remarks**
  - More research is required to better understand the role ARFID plays
    - Risk factors
    - Treatments (CBT, food reintroduction protocol, medications, etc.)
    - Should we screen patients prior to starting restrictive diets?
      - Need validated tool for GI patients

MOU42

- **Concluding Remarks**
  - ARFID complicates the clinical picture of GI patients
    - Clinical presentation is a casserole, not single item dish
    - It is not ARFID or GI diagnosis, it is most often BOTH contributing

MOU42

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- **Concluding Remarks**

Diet not used as therapy

Diet used as first-line therapy

Where does nutrition therapy fit?

Thank you for your time and attention.

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The Role of Trauma in GI Disorders

Christina Jagielski, PhD, MPH
GI Health Psychologist
Michigan Medicine

Please consider the environment before printing this PowerPoint

Disclosure

- None to report

Outline

- Overview on trauma
- Impact of trauma on health
- Mediating factors
- Impact of trauma on the health system
- Assessing for trauma in the medical setting
  - Why it's important
  - Factors that may increase suspicion for abuse
  - Approaching the patient
- Additional resources

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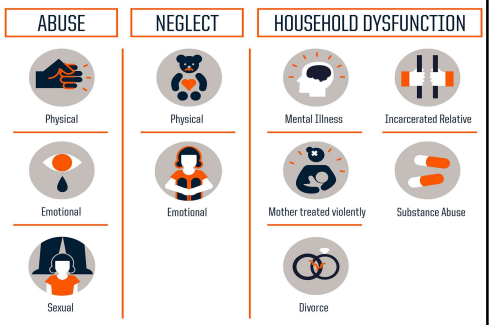
Overview on Trauma – The ACEs Study

Adverse Childhood Experiences Study (ACEs)

- Longitudinal epidemiological study of 17,000 patients
- CDC/Kaiser Permanente
- Recruited1995-1997
- ACE score
- Impact of ACE events on physical/mental health



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Defining Abuse

- Physical Abuse - Use of force resulting in pain, discomfort or injury. (i.e. assault, threats of assault or forcible confinement.)
- Emotional Abuse - Speech and/or behavior that's controlling, punishing, or manipulative. (i.e. gaslighting, withholding love, support, or money as means of control and maintaining power.)
- Sexual Abuse - Unwanted sexual activity, with perpetrators using force, making threats or taking advantage of victims not able to give consent.

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Abuse Statistics

- Physical abuse
  - In 2015 ~683,000 children were victims of physical abuse or neglect (NCA)
  - ~10 million Americans are victims of intimate partner violence each year (NCADV.org)
- Sexual Assault/Abuse
  - Sexual assault occurs every 98 seconds in the US (RAINN)
  - 63,000 children are victims of sexual abuse each year (RAINN)
  - 1 in 5 women, and 1 in 71 men have been a victim of rape in their lifetime (NCADV.org)

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Impact of Trauma on Health

Physical Health

- Pelvic pain and other genito-urinary sx
- Back pain
- Face pain/headaches
- Neurological sx
- Obesity
- Fatigue
- Loss of appetite

Mental Health

- Depression
- Attempted suicide
- Distress
- Nightmares
- Insomnia
- Choking sensations
- Chest pain
- SOB
- Increased psychiatric diagnoses

Quality of Life

- More disability
- Missed work
- Relationship problems

Leserman (1996) Psychosom Med, Drossman (1990) Ann Intern Med

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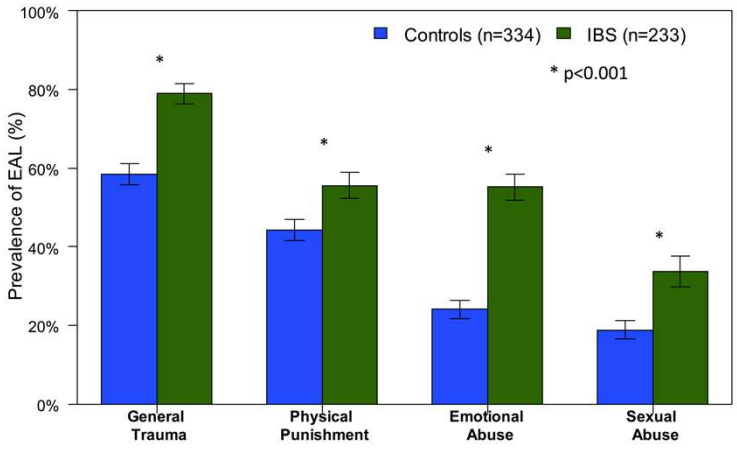
Trauma and IBS (females)

Figure 2B



Bradford, K. et al (2012) Clin Gastroenterol Hepatol

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Trauma and IBS

- ~30–50% of women with IBS report a history of early life adverse events including abuse
- 31% of IBS pts reported a history of sexual abuse
- History of sexual abuse is associated with 305% higher odds of having IBS
- More refractory symptoms and severe GI symptoms

Bradford, K. et al (2012) Clin Gastroenterol Hepatol

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Mediating Factors

- Greater cortisol response to visceral stressor (Videlock, 2009)
- Allostatic load and deleterious effects on HPA axis function (McEwen, 2002)
- Visceral hypersensitivity and altered microbiota (O'Mahony et al., 2009)
- Altered 5-HT responses (O'Mahony et al., 2008)
- Altered central pain modulation (Ringel, 2003)
- Lower levels of Neuropeptide Y (Rasmusson, 2000)
- Likely multiple factors at work

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Impact on the Medical System

- ↑ medical symptoms
- ↑ doctors visits
- ↑ refractory symptoms
- ↑ requests for procedures and tests
- ↑ surgeries
- Challenges with the HCP/Pt relationship

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GE Experience in Discussing Trauma

U.S.A (1990)	• Only 17% of doctors discussed abuse history with pts
Canada (2002)	• 50% of GEs asked about SA history in pts with IBS
Netherlands (2012)	• 70% of female physicians asked about sexual abuse in response to specific GI complaints, compared to 31% of male physicians

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Why is assessing for trauma important?

- Trauma is associated with refractory symptoms
- Can assist patient's with getting appropriate mental health care
- Allow HCPs to provide more informed medical treatment
- Patients are often willing to discuss
- Acknowledging impact of trauma can be the first step towards healing

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Factors that may indicate history of abuse

Psychological Factors

- Trust issues
- External locus of control
- Helplessness and dependency
- Feelings of vulnerability, shame, and guilt

GI/medical concerns

- Chronic pain
- Severe constipation (slow transit and pelvic floor dyssynergia
- Pelvic pain
- Narcotic bowel
- Morbid obesity
- Unexplained vomiting
- Sexual dysfunction
- Multiple somatic complaints

Comorbid Psych Dx

- Depression
- Anxiety disorders
  - PTSD
  - OCD
  - Panic
- Somatoform disorders
- Dissociative disorders
- Eating disorders
- Personality disorders

Drossman (2011) Am J Gastroenterol

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Factors (cont)

Illness-Related Behaviors

- Strong denial that stress impacts sx
- Anxiety, tearfulness, startle rx w/ exam
- Disability
- Frequent and excessive use of HC services
- Multiple procedures, treatments, and surgeries
- Borderline behaviors
- Substance abuse
- Disability seeking

Drossman (2011) Am J Gastroenterol

Approaching the patient

- Some distress is expected
- Can incorporate as part of a psychosocial history (all patients)

  Or
- Follow the patient's lead
  - Mentioning of vague stressors
  - Anxious or fearful reactions during exam/procedures
- "Is there anything else that you would like to discuss that you think is important?"

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Approaching the patient

Frame in the context of other patients:

"Many patients with GI conditions have experienced traumatic events or situations in the past. I'm wondering if you've had any traumatic experiences?

Nonverbal communication

- Importance of rapport/trust
  - Active listening
  - Empathy
- Power dynamics
- The role of silence
- Body language
  - Eye contact
  - Face patient with open posture

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Empathic responding

- Validation
- Respect patient right to share or not disclose
- Do not need to ask about details
- Consider a referral to a mental health provider
- If referring to a mental health provider, remind them you will still provide medical care
- There is hope. Therapy can help!

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Additional Resources

How to find a mental health provider (see handout)

Adverse Childhood Experiences Study (ACES)
https://www.cdc.gov/violenceprevention/childabuseandneglect/acestudy/index.html

National Children's Alliance (NCA)
www.nationalchildrensalliance.org

Rape, Abuse & Incest National Network (RAINN):
www.rainn.org

National Coalition Against Domestic Violence (NCADV):
www.ncadv.org

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Thank you!

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