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FACULTY
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Continuing Medical Education

NASPGHAN CME Mission Statement

The education mission of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition is to:

1) Advance understanding of normal development, physiology and pathophysiology of diseases of the gastrointestinal tract, liver and nutrition in children
2) Improve professional competence, quality of care, and patient outcomes by disseminating knowledge through scientific meetings, professional and public education.

Our activities, education, and interventions will strive to use Adult Learning Methods (ALM) designed to improve competence, practice performance, and patient outcomes in measurable ways. These educational activities will be targeted to board certified or board eligible pediatric gastroenterologists, physicians with an expertise in pediatric gastroenterology, hepatology and nutrition, subspecialty fellows in pediatric gastroenterology, and nurses specializing in pediatric gastroenterology, hepatology and nutrition.

Physicians

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AMA PRA Statement

NASPGHAN designates this educational activity for a maximum of 8.25 *AMA PRA Category 1 Credit(s)*^{TM} Physicians should only claim credit commensurate with the extent of their participation in the activity.

Postgraduate Course
Thursday, November 2
Course Directors: Jennifer Strople MD and Maria Oliva-Hemker MD

Module 1 – Endoscopy
Moderators: Jennifer Strople MD and Maria Perez MD

8:00am – 8:20am Strictures beyond the esophagus

Petar Mamula MD, Children's Hospital of Philadelphia
Learning objectives:
1. Review endoscopic techniques for stricture therapy
2. Review side effects of endoscopic stricture therapy
3. Review literature on endoscopic therapy of IBD-related strictures

8:20am – 8:40am GI bleeding update

Diana Lerner MD, Medical College of Wisconsin
Learning objectives:
1. Review basics of electrocautery
2. Review endoscopic techniques for control of GI bleeding
3. Update on emerging techniques in hemostasis

8:40am – 9:00am Management of pancreatic fluid collections

Matt Giefer MD, Seattle Children's Hospital
Learning objectives:
1. Recognize the various complications of pancreatic fluid collections
2. Create a treatment/monitoring approach for both complicated and uncomplicated pancreatic fluid collections
3. Analyze the risks and benefits of percutaneous, endoscopic and surgical management of complicated pancreatic fluid collections

9:00am Q&A

Module 2 – GI Potpourri
Moderators: Maria Oliva – Hemker MD and Terry Sigman MD

9:15am – 9:35am Celiac disease diagnosis: ESPGHAN vs. NASPGHAN guidelines

Michelle Pietzak MD, University of Southern California Keck School of Medicine and Children's Hospital of Los Angeles
Learning objectives:
1. To review the previous evidence-based ESPGHAN guidelines for the diagnosis of celiac disease
2. To discuss the current NASPGHAN criteria for the diagnosis of celiac disease
3. To understand the new diagnostic algorithms and guidelines proposed by ESPGHAN for this disorder

9:35am – 9:55am Fad diets: The good, the bad and the just plain ugly

Mark Corkins MD, University of Tennessee Health Science Center
Learning objectives:
1. The attendees will know the dietary philosophies that define the common fad diets
2. The learners will be aware of the potential nutritional deficiencies and components that can cause harm with common fad diets utilized by pediatric patients
3. The learners will know methods to work with families and guide them to a nutritionally complete diet regimen

9:55am – 10:15am Update on *H. pylori*

Nicola Jones MD, PhD, Hospital for Sick Children

Learning objectives:

Understand updated guidelines for:

1. Who to test
2. How to test
3. How to treat *H. pylori* infection in children and adolescents

10:15am Q&A

10:30 am Break

Module 3 – Liver/Pancreas

Moderators: Jennifer Strople MD and Henry Lin MD

10:50am – 11:10am Biliary Atresia: Update on diagnostic and prognostic biomarkers and therapeutic interventions

Cara Mack MD, Children's Hospital Colorado

Learning objectives:

1. Educate audience on recent studies pertaining to diagnostic and prognostic biomarkers in biliary atresia
2. Provide summary of recent studies pertaining to maximizing health in chronic liver disease through medical and nutritional interventions

11:10am – 11:30am Diagnosis and management of pediatric NAFLD in 2017

Stavra Xanthakos MD, Cincinnati Children's Hospital Medical Center

Learning objectives:

1. Understand advantages and limitations of available diagnostic tools for NAFLD in children
2. Describe and implement available treatments for NAFLD in children
3. Review status of therapeutic options in development for NAFLD

11:30am – 11:50am SMOFlipid and the pediatric patient

Paul Wales MD, Hospital for Sick Children

Learning objectives:

1. To review role of composite lipid emulsions in intestinal failure associated liver disease
2. To review the evidence for role of alternative lipid emulsions in IFALD

11:50am – 12:10pm Painful chronic pancreatitis: Management/therapeutic interventions

Vikesh K Singh MD, Johns Hopkins University School of Medicine

Learning objectives:

1. To review currently available medical, endoscopic and surgical therapies for painful chronic pancreatitis
2. To review the outcomes and factors which influence the outcomes of current interventions for painful chronic pancreatitis
3. To discuss future directions for the management of painful chronic pancreatitis

12:10pm Q&A

12:25pm **PG Course Learning Lunches**

1. Wheat – To eat or not to eat?
   Moderator: Terry Sigman MD
   Michelle Pietzak MD and Sharon Tam MD
2. Fad diets: Good, bad and ugly
   Moderator: Iona Monteiro MD
   Mark Corkins MD, Ruba Abdelhabi MD and Sharlene Coombs, RD
3. Abdominal Pain: Evaluation and Management
   Moderator: Deborah Neigut MD
   Miguel Saps MD and Rina Sanghavi MD
4. Treatment of GERD: What's new?
   Moderator: Ritu Walia MD
   Rachel Rosen MD and Eric Chiou MD
5. IBD monitoring pre and post-surgery
   Moderator: Jeanne Tung MD
   Miguel Regueiro MD and Jeanne Tung MD
6. The patient with IBD – When nothing seems to work
   Moderator: Dinesh Pashankar MD
   Andrew Grossman MD and Jess Kaplan MD
7. Acute and chronic pancreatitis
   Moderator: Melanie Greifer MD
   Vikesh Singh MD and Jay Freeman MD
8. Evaluation of the cholestatic infant
   Moderator: Nadia Ovchinsky MD
   Cara Mack MD and Saeed Mohammad MD
9. GI bleeding – Difficult cases
   Moderator: Marsha Kay MD
   Diana Lerner MD and Heidi Hagerott MD

Module 4 - Inflammatory Bowel Disease
Moderators: Jennifer Strople MD and Dinesh Pashankar MD

1:50pm – 2:10pm Therapeutic drug monitoring
Andrew Grossman MD, Children's Hospital of Philadelphia
Learning objectives:
1. Review the evidence regarding use of therapeutic drug monitoring to optimize dosing of biologic therapies
2. Describe how to optimize use of therapies via reactive measurement of therapeutic drug levels
3. Discuss role of proactive therapeutic drug monitoring

2:10pm – 2:30pm What if anti-TNF fails
Maria Oliva-Hemker MD, Johns Hopkins University School of Medicine
Learning objectives:
1. Understand the importance of reassessing the IBD patient that is nonresponsive to anti-TNFs
2. Review the evidence in support of biologic and small molecule therapies beyond anti-TNF medications
3. Develop alternate treatment strategies for patients nonresponsive or intolerant to anti-TNFs

2:30pm – 2:50pm Prevention of postoperative Crohn's disease

Miguel Regueiro MD, University of Pittsburgh

Learning objectives:

1. Understand the risk factors associated with postoperative Crohn's disease recurrence
2. Determine the appropriate postoperative treatment
3. Review the AGA postoperative guidelines in the management of postoperative Crohn's disease

2:50pm Q&A

3:05pm Break

Module 5 - Functional/Motility disorders

Moderators: Maria Oliva – Hemker MD and Deborah Neigut MD

3:25pm – 3:45pm The quest for the holy grail: Accurately diagnosing and treating extraesophageal reflux

Rachel Rosen MD, Boston Children's Hospital

Learning objectives:

1. To recognize the broad differential diagnoses for extraesophageal symptoms
2. To understand the benefits and limitations of reflux testing in patients with extraesophageal symptoms
3. To understand the unique difficulties in treating extraesophageal symptoms

3:45pm – 4:05pm POTS and joint hypermobility: What do they have to do with functional disorders?

Miguel Saps MD, Nationwide Children's Hospital

Learning objectives:

1. To define postural orthostatic tachycardia syndrome (POTS), and joint hypermobility (JH) including clinical presentation and diagnostic methods
2. To review the prevalence of POTS and JH in patients with FGIDs
3. To discuss the management of patients with FGIDs and POTS and JH

4:05pm – 4:25pm Do I need to test that C.R.A.P?

Rina Sanghavi MD, Children's Medical Center of Dallas

Learning objectives:

1. Understand indications for testing in chronic abdominal pain
2. Learn what tests can be ordered for chronic abdominal pain
3. Understand interpretation of tests for chronic abdominal pain

4:25pm –4:45pm The child with refractory constipation

Jose Garza MD, Children's Hospital of Atlanta

Learning objectives:

1. Recognize common causes of treatment failure in constipation
2. Establish a diagnostic approach to children with refractory constipation
3. Identity alternative treatments for refractory constipation

4:45pm Q&A

Strictures Beyond Esophagus

Petar Mamula, M.D.
The Children's Hospital of Philadelphia

I have no financial relationships with a commercial entity to disclose.

Objectives

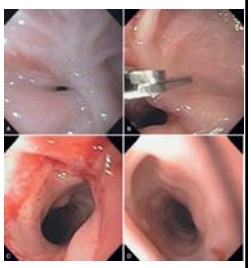
- Review endoscopic techniques for stricture therapy
- Review side effects of endoscopic stricture therapy
- Review pediatric literature on endoscopic therapy of IBD-related strictures

Etiology

- Congenital anomalies
- Caustic ingestion
- Medication (NSAIDs)
- Inflammatory diseases (Crohn disease, chronic granulomatous disease, eosinophilic gastroenteritis)
- Post-surgical (short gut syndrome, IBD)
- Infection, ischemia, trauma, malignancy

Equipment

- Balloon dilators
- Endoscopic scissors
- Needle-knife cautery
- Accessories for therapy of complications (over-the-scope clips, stents, suturing devices)
- Fluoroscopy



Technique questions

- Which instruments to use?
- When to start dilations in relation to onset of injury/illness or operation?
- Which size to start with and how far to go?
- Number and duration?
- How frequently to perform them?
- What other techniques aside from dilations are available?
- How to define refractory or recurrent strictures?

The “difficult” stricture

The refractory or recurrent stricture:

- *Refractory:*
  inability to successfully remediate to ≥14 mm diameter over 5 sessions at 2-week intervals
- *Recurrent:*
  inability to maintain a satisfactory luminal diameter for 4 weeks once the target diameter of 14 mm has been achieved

Complex stricture

- Unable to pass endoscope
- Greater than 4-7 cm in length
- Angulation

“Rule of three”

- Once moderate resistance is felt with a bougie dilator no more than 2 additional dilators with an increase in size of 1 mm should be passed
  - Initial reference thought to be attributed to Worth Boyce and Eddy Palmer
  - Thought to decrease perforation
  - Only applies to rigid dilators

Ignore “rule of three”?

TABLE 4. Identification of variables associated with perforations

	Odds ratio	95% confidence interval	*P* value
Gender	1.9 ⇦	0.6-6.2	.29
Simple vs complex	2.1 ⇦	0.3-16.5	.48
Benign vs malignant	8.3 ⇦	2.2-31.9	.002*
Proximal vs distal strictures	1.0	0.1-9.2	.99
Bougie vs balloon (missing n = 16)	1.0 ⇦	0.3-3.9	.99
According rule of 3 (missing n = 9)	0.8	0.2-3.3	.80
>3 mm dilation (missing n = 12)	0.6	0.2-2.2	.44
Additional intervention (missing n = 6)	2.7	0.7-10.1	.14

*Statistically significant.

Grooteman et al, GIE 2017

Location

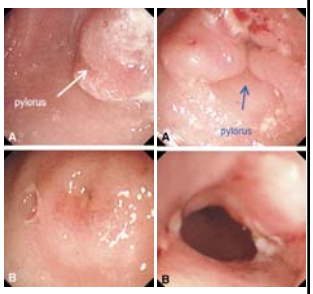
- Stomach
- Duodenum
- Small bowel (jejunum and ileum)
- Colon
- Pouch

Location- stomach

- Stomach:
  1. Pyloric stenosis (congenital or acquired)
  2. Caustic ingestion
  3. Chronic granulomatous disease and Crohn disease

Pyloric stenosis

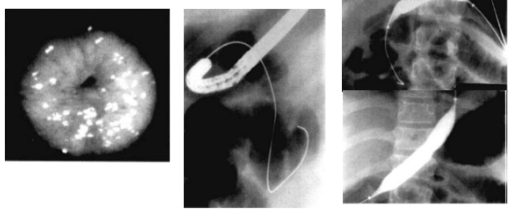
- 10 infants with pyloric stenosis
- 7 procedures with needle-knife and 3 with a sphincterotome



Ibarguen-Secchia, GIE 2005

Caustic ingestion

12-year old boy with accidental caustic ingestion who underwent a series of 3 balloon dilations (8-20 mm)



Treem et al, JPGN, 1987

Video- pyloric balloon dilation

Location- small bowel

Duodenum:

1. Duodenal web or cyst
2. Crohn disease

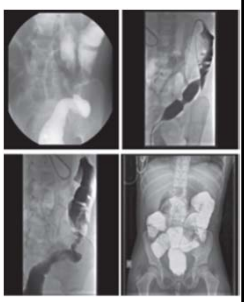
Jejunum/ileum:

1. Crohn disease and eosinophilic enteropathy
2. Short gut syndrome
3. Ischemia, trauma
4. NSAIDs

Video- duodenal web incision

Short gut syndrome

- Postoperative strictures in short gut syndrome
- 98 patients with intestinal failure from 2011-2015
- 5 required 6 dilations (one had a leak)
- 2 small bowel, 4 accessed via rectum
- Directional catheter (IR)



Belza et al, J Ped Surg 2017

Video- GVHD balloon dilation

Video- NSAID stricture incision

Location- colon

1. Crohn disease – inflammatory stricture (not longer than 4-5 cm and not associated with fistula or abscess)

2. Post-operative

– Anastomosis (18-20 mm)
– Pouch (18-20 mm)

Location- colon

- Systematic review of 347 patients with Crohn disease in 13 studies who underwent balloon dilation

- Dilations varied from 18-25 mm
- Successful instrument passage 45-100%
- Short-term improvement 71-100%
- Long-term improvement 50-100%

Hassan et al. Aliment Pharm Ther, 2007.

Pre-operative dilation

- 29 pediatric patients randomized to receive intra-stricture corticosteroid (CS) injection or placebo after endoscopic balloon dilation
- Followed clinically with SB contrast, US and MR imaging at 1, 3, 6, and 12 months; and colonoscopy at 12 months
- 1/15 patients receiving CS required re-dilation vs. 5/14 placebo patients ($p<.04$)
- Surgery needed in 4 of the placebo patients, and none of those receiving CS ($p<.02$)

Di Nardo et al. Gastrointest Endosc. 2010.

Video- Crohn disease stricture incision therapy

- Technique used for stricture refractory to balloon dilation
- Doppler US-guided needle-knife therapy

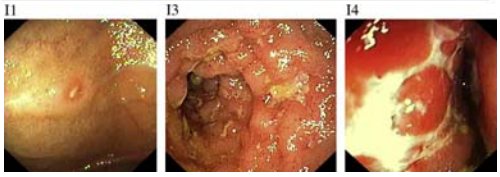
- Other technique being explored is stent placement with or without endoscopic suturing

Li et al. Endoscopy, 2011.

Post-operative recurrence

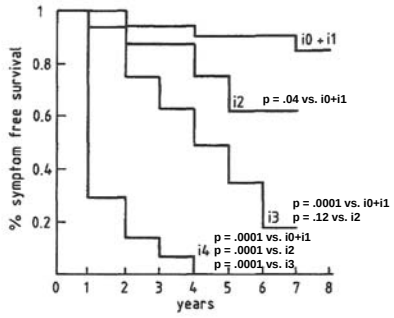
Table 1
Endoscopic recurrence score*

Endoscopic Score	Definition
i0	No lesions
i1	≤5 aphthous lesions
i2	>5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions, or lesions confined to the ileocolic anastomosis
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with already larger ulcers, nodules, and/or narrowing



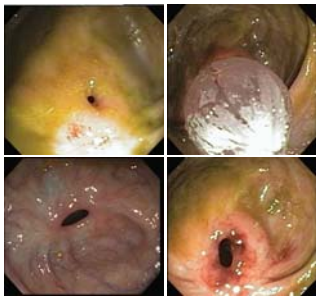
Rutgeerts et al. Gastroenterology 1990.

Post-operative recurrence



Rutgeerts et al. Gastroenterology 1990.

Post-operative dilation



Video- postoperative Crohn disease balloon dilation

Pouch

- Strictures after IPAA (ileal pouch-anal anastomosis) reported at 10-17%
- Study from Cleveland Clinic on 3,707 patients post IPAA
- Cumulative early and late stricture- 5% and 11%, respectively
- Causes include pelvic sepsis, anastomotic tension, ischemia, NSAID use and CD
- Techniques include balloon dilation and stricturotomy

Bharadwaj et al. GIE, 2017.

Complications

- Perforation
- Bleeding

Complications- perforation

- A meta-analysis showed rate of 1.9% with therapeutic procedures
- The perforation rate with pouch stricture dilation reported at 0.46%
- Conservative treatment
- Endoscopic therapy with clip and over-the-scope clip placement, and stent placement
- Surgical repair

Paine et al. GIE, 2013.

Complications- bleeding

- Frequency reported up to 1.4% of dilations
- Most can be successfully managed with cautery or hemoclip placement

Conclusions

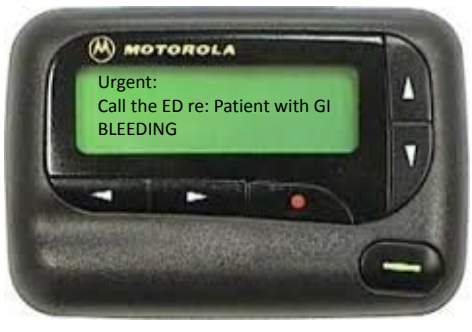
- Multi-disciplinary approach
- Understand the anatomy and utilize fluoroscopy
- Be comfortable with various techniques
- Be prepared in event of complication (bleeding and perforation) including back-up

Children's Hospital of Wisconsin
MEDICAL COLLEGE OF WISCONSIN
Children's Specialty Group

GI Bleeding

Diana Lerner, MD
Assistant Professor
Pediatric Gastroenterology, Hepatology and Nutrition

No disclosures

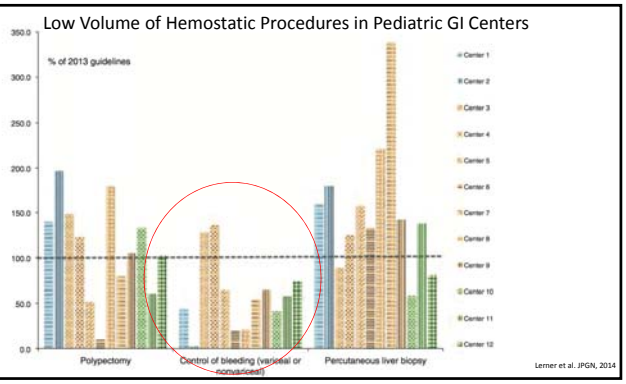


GI bleed in pediatrics are rare

- Incidence of GI bleeding in hospitalized children is low
  - 0.5% of all hospitalizations
    - Upper GI bleeding 22.2/10,000
    - Lower GI bleeding 6.8/10,000
  - UGI bleeding occurred in 10% of ICU patients
    - 1.6% or 16 patients had a clinically severe bleed

1. Henderson et al. Gut, 2014
2. Pant et al. CMRO, 2014
3. Chaibou, Pediatrics 1998

Low Volume of Hemostatic Procedures in Pediatric GI Centers



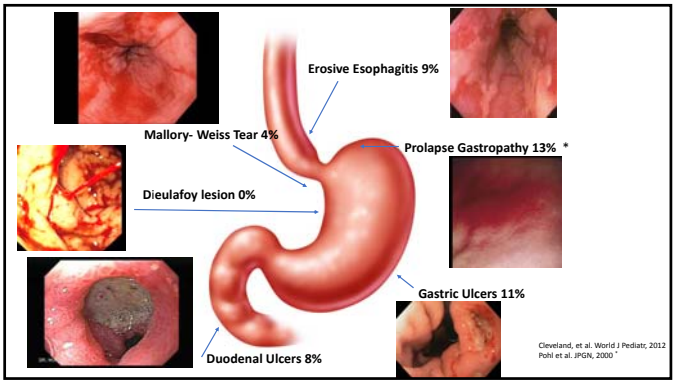
Lerner et al. JPGN, 2014

Objectives

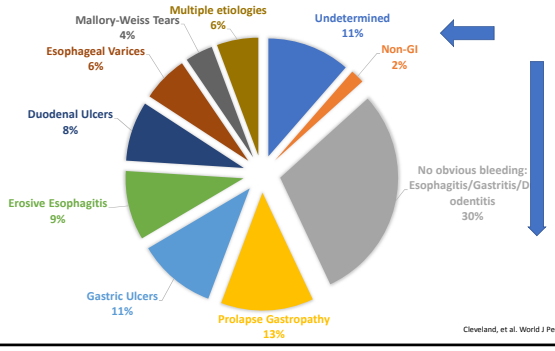
- Review acute management of a child with non-variceal GI bleeding
- Review the etiology of GI bleeding in children
- Recognize risk factors and endoscopic stigmata for severe GI bleeding
- Review available techniques for GI hemostasis
- Discuss appropriate patient disposition after GI bleed

Acute Management

- Patient is stable
  - Review the history
  - Labs (CBC, retic count, coagulation, type and screen, liver enzymes, BUN/Cr)
  - Gastric aspirate
  - IV PPI
  - +/- motility agents (erythromycin)
  - Octreotide for variceal bleed only
- Patient is unstable
  - transfuse and consider referral to IR or for surgical exploration

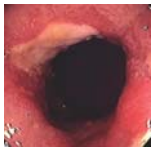


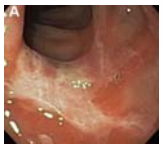
Etiology of Upper GI Bleeding in Children



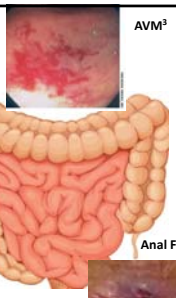
Cleveland, et al. World J Pediatr, 2012

Anastomotic Ulcer[5]



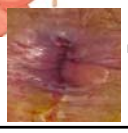


Solitary Rectal Ulcer[4]

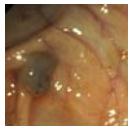


AVM[3]

Anal Fissure [2]



Blue Rubber Bleb Syndrome[4]

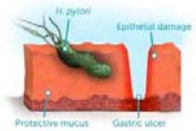


Polyp and post polypectomy bleed[4]

1. http://project-acj2021.blogspot.com/2015/11/small-and-large-intestine-adam-jonas.html
2. Myhre, et al. Child Abuse, 2013
3. Panikin, et al., Consultant, 2003
4. Sahn et al, Gastrointest Endoscopy Clin N Am, 2016
5. Colon, Abd Key, 2017

Risks of severe gastrointestinal bleed

- NSAID use/Anticoagulant
- H Pylori infection
- Organ failure
- Trauma
- ICU admission
- High Ventilator settings



1. Owensby, JABFM, 2015
2. Deerojanawong, et al. Pedatr Crit Care Med, 2009

Sheffield scoring system to predict need for endoscopic/surgical therapy [20].

		Score
History taking	Significant preexisting condition	1
	Presence of melena	1
	History of large amount of hematemesis	1
Clinical assessment	HR >20 from the mean HR for age	1
	Prolonged capillary refill	4
Laboratory findings	Hb drop of >20 g/l	3
Management and resuscitation	Need for a fluid bolus	3
	Need for blood transfusion (Hb of <80 g/L)	6
	Need for other blood product: 4	4
Total score 24		
Using cut-off = 8,		
Sensitivity: 89% (95% CI 73–97)	PPV: 91% (95% CI 76–98)	
Specificity: 91% (95% CI 76–98)	NPV: 88% (95% CI 73–97)	

Notes: Based on n = 69 patients, admitted to single center over 3 year period divided into intervention (n = 35) and no intervention required (n = 34).

Thomson, et al. JPGN, 2015

Timing of endoscopy

- Less than 48 hours
  - Improved diagnostic yield
- Urgent Endoscopy <24h
  - Benefit
    - Transfusion
    - Re-bleeding
    - Need for surgery

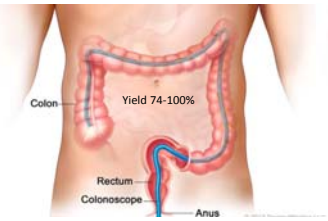
1. Cleveland, et al, World J Pediatr, 2012
2. Thomson, et al J. Pedsurg. 2016

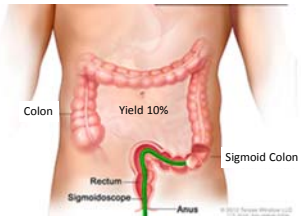
Timing of endoscopy

- Emergent Endoscopy <6-12h
  - Suspected varices
  - Hg <8 g/L
  - Hg fall of > 2 g/L
  - Suspected liver disease
- No known benefit
  - Mortality
  - Re-bleeding
  - Need for surgery

Thomson, et al J. Pedsurg. 2016

Diagnostic yield of lower GI exam





1. https://www.niddk.nih.gov/health-information/diagnostic-tests/colonoscopy
2. Lhewa, et al. World J Gastroenterol. 2012

Patient Weight	Endoscope	Working Channel/Outer Diameter range, mm	Hemostatic Accessory
<5 kg	Ultrathin gastroscope	2.0/4.9-5.9	Injection needle 23, 25G **APC 5-Fr probe** Polypectomy snare <30 mm **Bipolar 5-Fr probe**
5-15 kg	Standard gastroscope	2.8/8-11.6	Injection Needle 19-22 G Bipolar 7 –Fr probe APC 7 – Fr probe Through the scope clips
>15 kg	Pediatric or adult colonoscope	3.2-3.8 mm/11.5-13.2	Injection needle 19-22G Bipolar 7-10 Fr APC 7-10 Fr Through the scope clips
Older child	Ultra-slim colonoscope, dual-channel therapeutic upper/lower scope	2.8-3.2, 3.7-3.8, 9.5-13.7	Injection needle 19-22G Bipolar 7-10 Fr APC 7-10 Fr Through the scope clips

Sahn, et al., **Gastrointest Endosc Clin N Am, 2016**

Rensburg et al., Peptic Ulcer Disease, 2011

Bleeding Therapy

- Video to be imbedded (following slides are the script to video)
  - Injection
  - Endoscopic clip
  - Multipolar/bipolar probe
  - Heater probe
  - Argon Plasma Coagulation
  - Use of transparent cap

Excerpt was used with permission by ASGE

Injection Therapy (Video)

- Epinephrine is used for transient vasoconstriction and tamponade
- Recommended concentration is 1:10,000
- The scope and the needle should be positioned in proximity to the bleeding area with the goal of injecting 0.5 to 2 ml per site for up to 10 ml in young children. Adult data suggest that volumes up to 20 ml are safe and most efficacious.
- Due to the transient nature of epinephrine, once epinephrine is injected, another modality such as endoscopic clip or electrocautery should be used for definitive treatment.
- Recent of ongoing cardiac ischemia is a contraindication to epinephrine use

Excerpt was used with permission by ASGE

Barkun et. al, Annals of Int. Med, 2010
Park, et. al Gastrointest. Endosc., 2007

Endoscopic Clip (video)

- It is important to familiarize yourself with the clipping mechanism
- Clips on the market vary in ability to re-position, rotate, opening widths, lengths and price
- Ulcers are amendable to clipping if they are easy to access, are not fibrotic and are smaller than 2 cm in size
- Clips should be placed on the bleeding target area and proximal and distal to the site to clamp feeding vessels

Excerpt was used with permission by ASGE

Bipolar Electrocoagulation (video)

- Electrical energy is converted to heat energy at the tip
- There is no need for a grounding pad with this modality as the circuit is closed within the device
- Settings are based on indication, but for a stomach ulcer 15-20 watts with moderate-firm pressure for 5-10 seconds is recommended
- Settings should be lower in thinner tissue such as small bowel
- To prevent significant fluctuations in voltage, newer electrosurgical units are capable of detecting changes in voltage that happen due to changes in impedance. Settings vary and are not standard so be familiar with your electrosurgical unit.

Excerpt was used with permission by ASGE

ASGE Technology Committee, GIE, 2013

Argon plasma coagulation (video)

- This is a non-contact device and is positioned 1-2 mm away from target tissue. APC uses argon gas which turns into argon plasma after its ionized by the voltage from the generator.
- Settings are based on indication and range from 30-60 W at a flow rate of 1-1.5 L/m
- This modality is particularly helpful to treat arteriovenous malformations but can also be used for gastric antral vascular ectasia (watermelon stomach) and more diffuse superficial bleeding.

Excerpt was used with permission by ASGE

ASGE Technology Committee, GIE, 2013

Heater Probe (video)

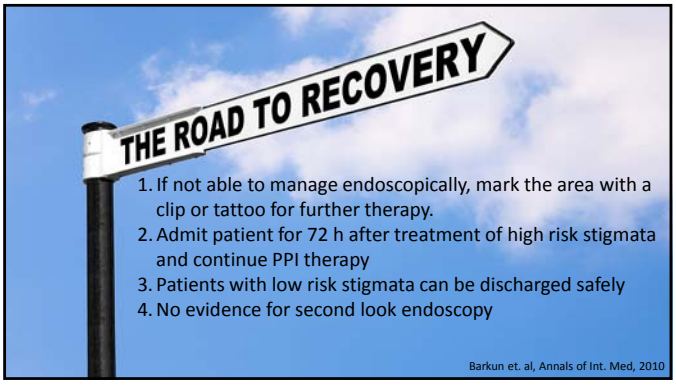
- Heater probe delivers heat directly to the tissue
- Settings are in joules and the time of delivery is predetermined by the power settings.
- For stomach ulcer bleed or dieulafoy lesion settings of 15-30 joules over 2-4 applications prior to removing the probe is recommended
- 15 joules is adequate for most other indications
- This is one modality which is safe to use in an un-prepped colon as there is no risk of a bowel explosion

Excerpt was used with permission by ASGE

Helpful tips (video)

- When bleeding source is difficult to isolate. Placing the bleeding area under water can help to identify area of active oozing.
- Transparent caps can be used at the tip of the scope to expose the bleeding site and target therapy for difficult to reach areas.

Excerpt was used with permission by ASGE



1. If not able to manage endoscopically, mark the area with a clip or tattoo for further therapy.
2. Admit patient for 72 h after treatment of high risk stigmata and continue PPI therapy
3. Patients with low risk stigmata can be discharged safely
4. No evidence for second look endoscopy

Barkun et. al, Annals of Int. Med, 2010

Management of Pancreatic Fluid Collections

Matthew Giefer MD
Seattle Children's
Director of Endoscopy

NASPGHAN Post-Graduate Course
November 2, 2017

Seattle Children's

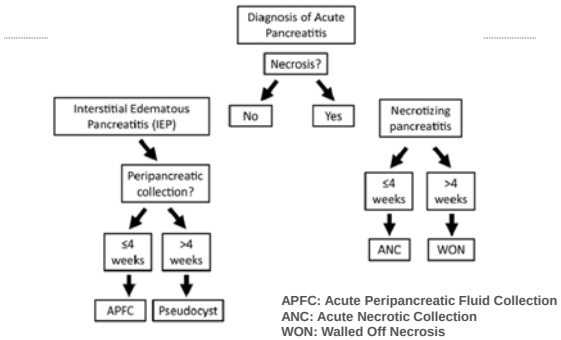
Disclosures

- I (and my family members) have no financial interest, arrangement or affiliation with medical/pharmaceutical or equipment companies.
- I (and my family members) have no financial interest, arrangement or affiliation with corporate organizations which offer research or financial support.

Outline

- Definitions of pancreatic fluid collections
- Diagnosis
- Natural History
- Medical management
- Indications for intervention
- Types of intervention
  - Percutaneous
  - Surgical
  - Endoscopic
- Example case

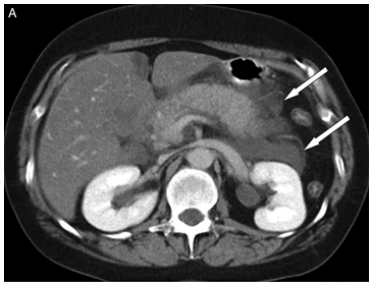
Definitions



APFC: Acute Peripancreatic Fluid Collection
ANC: Acute Necrotic Collection
WON: Walled Off Necrosis

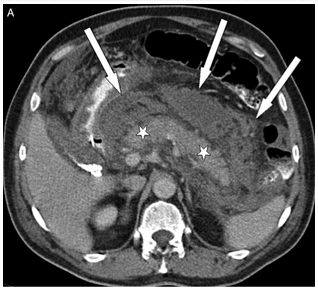
Bryan R. et al; *RadioGraphics* **2016,** 36, 675-687.

Acute Peripancreatic Fluid Collection (APFC)



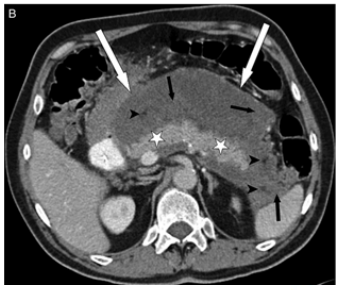
Banks, PA et al; *Gut* **2013,** 62, 102-111.

Acute Necrotic Collection (ANC)



Banks, PA et al; *Gut* **2013,** 62, 102-111.

Walled-off Necrosis (WON)



Banks, PA et al; *Gut* **2013,** 62, 102-111.

Diagnosis of Local Complications

- Early Phase of Acute Pancreatitis
  - Driven by inflammatory cytokine release
  - End organ dysfunction may occur
  - Local complications may be identified by are not the key drivers of severity or outcome
- Late Phase of Acute Pancreatitis
  - Persistent systemic inflammation may occur but is less common
  - Local complications evolve and may lead to complications

Key point: Imaging done around time of diagnosis may miss the development or extent of pancreatic fluid collections.

Natural History of Pancreatic Fluid Collections

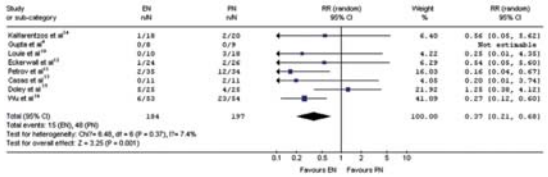
- Good natural history studies for WON and pseudocysts are lacking
  - Revised Atlanta Criteria should help separate populations for future study.
- Most patients (87-96%) with APFC do not develop pseudocysts.
- Those with pseudocysts, tend to have them shrink (58%) or resolve (26%) over time.
- Most patients (56-65%) with ANC develop WON.

Cui, ML et al; *Dig Dis Sci* **2014**, 59:1055-1062.
Manrai, M et al; *Ann Surg* **2016**, Nov Epub.

Medical Management – Acute Phase

- Appropriately aggressive rehydration, pain control and enteral feeds.

Key point: Pancreatic fluid collections are not a contraindication to enteral feeds.



Yi, F. *Intern Med*. **2012** 51(6):523-30.

Medical Management – Late Phase

- Monitor for signs of:
  - **Infection** (fever, leukocytosis, increasing abdominal pain)
  - **Feeding intolerance** (nausea, vomiting, decreased appetite, weight loss)
- Presence of any of these symptoms warrant cross sectional imaging to examine for development or progression of local complications.
- Keep in mind that 20-30% of acute pancreatitis patients will have transient or permanent pancreatic exocrine dysfunction.

Yadav, D et al. *Pancreas* **2014** 43:630-637.

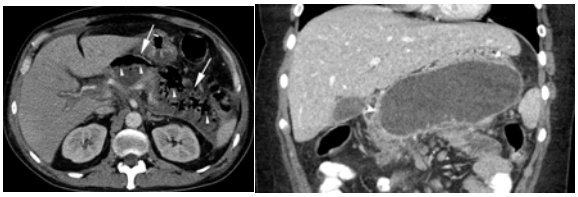
Indications for Intervention

- It is important to distinguish between complicated and uncomplicated fluid collections.
- Infection of walled-off necrosis is the most common complication and indication for drainage.
  - Empiric broad spectrum antibiotics
- Gastric, duodenal or biliary obstruction are other complications where drainage may be necessary.
- Uncomplicated collections (regardless of fluid collection size), do not typically require intervention.

Forsmark CE et al. *NEJM* **2016** 375:1972-81.

Indications for Intervention

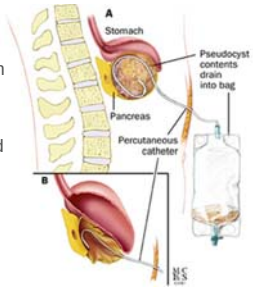
Infection **Obstruction**



Left image: Banks, PA et al; *Gut* **2013,** 62, 102-111.

Interventions: Percutaneous Drainage

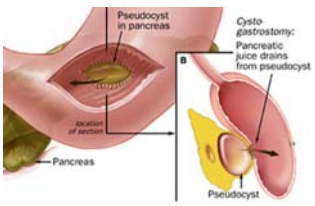
- Flexible percutaneous catheter placed in lumen of collection.
- Drains fluid component of collection but direct debridement of solid component is not possible.
- Long term success: 33-35%.
- Complications include bleeding and catheter obstruction. Up to 27% develop persistent fistulae from collection to skin.
- Often used for infected fluid collections in patients who are not good candidates for endoscopic therapy.



Van Santvoort HC et al. *NEJM* **2010** 362:1491-1502.
Horvath K et al. *Arch Surg* **2010** 145:817-825.
Illustration Copyright© 1998-2003 Johns Hopkins. Used with permission.

Interventions: Surgical Drainage

- Allows for direct debridement of cavity but now rare due to availability of minimally invasive techniques.
- Technical success: ~90%
- Complication: 34-95%
- Mortality: 6-25%
- Typically reserved for difficult anatomy.



Van Santvoort HC et al. *NEJM* **2010** 362:1491-1502.
Howard TJ et al. *J Gastro Surg* **2007** 11:43-49.
Illustration Copyright© 1998-2003 Johns Hopkins. Used with permission.

Interventions: Endoscopic Drainage

- Now considered the first-line approach for symptomatic pancreatic fluid collections
- Technical success: ~90%
- Complication (bleeding, stent migration, sepsis): 10-15%
- Compared to surgical cyst-gastrostomy, endoscopic drainage procedures are:
  - Equally effective
  - Have fewer complications
  - Associated with shorter hospitalization (6 days vs. 2 days)
  - Less expensive ($15,000 vs. $7,000)
  - Associated with better quality of life

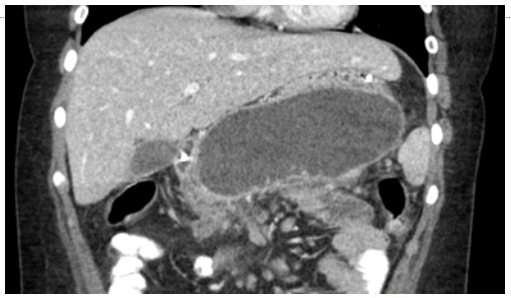
Thiruvengadam M et al. *J Clin Gastro* **2017** 54:19-33.
Varadarajulu S et al. *Gastro* **2013** 145:583-90.
Nabi Z et al. Gut and Liver **2017** 11(4):474-80.

Endoscopic Drainage Techniques

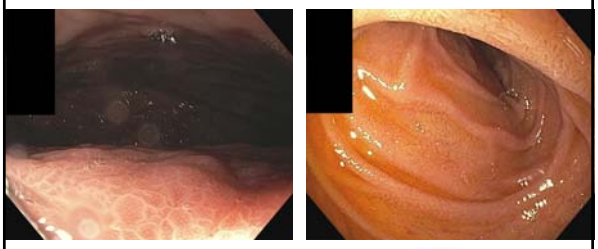
- Transmural drainage of fluid collection by creating a tract through the gastric or duodenal wall followed by balloon dilation of the tract and stent placement.
- A mature wall of the fluid collection is required. This "walling off" of the collection takes about 4 weeks.
- Can be accomplished with any therapeutic endoscope, however, EUS guided techniques are favored to allow for visualization of surrounding structures.
- Allows for direct endoscopic necrosectomy.

Thiruvengadam M et al. *J Clin Gastro* **2017** 54:19-33.
Bang JY et al. *Dig Endosc* **2015** 27:486-98.
Shah RJ et al. *Clin Gast Hep* **2015** 13:747-52.

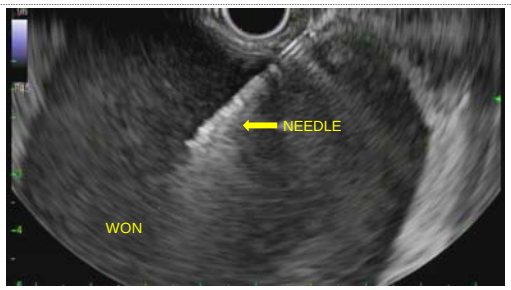
Case: WON from Necrotizing Gallstone Pancreatitis



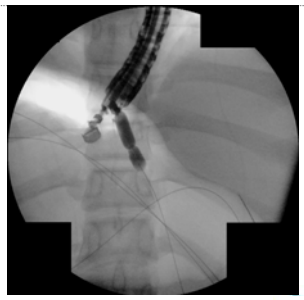
WON Endoscopic Drainage



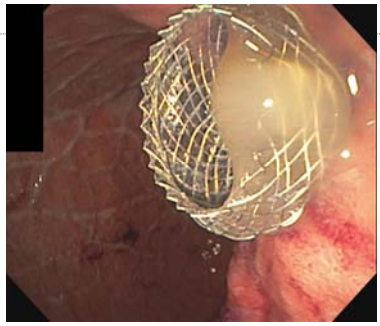
WON Endoscopic Drainage with LAMS



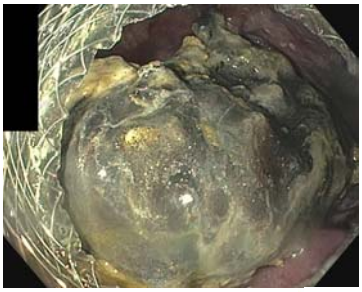
WON Endoscopic Drainage with LAMS



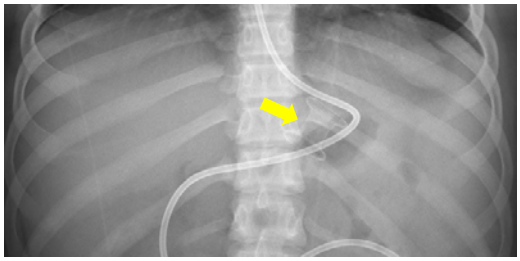
WON Endoscopic Drainage with LAMS



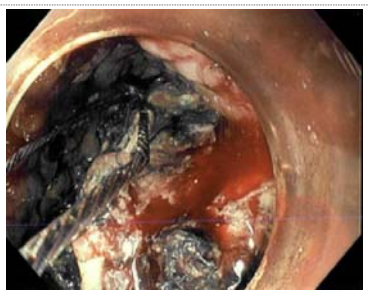
WON Endoscopic Drainage with LAMS



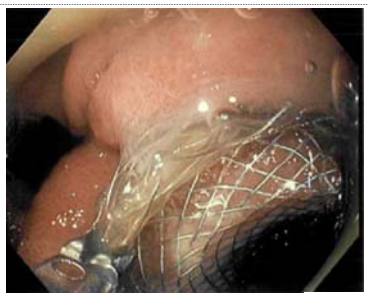
WON Endoscopic Drainage with LAMS



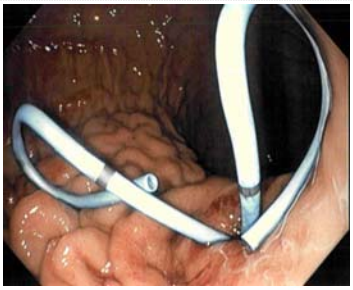
Endoscopic Necrosectomy through LAMS



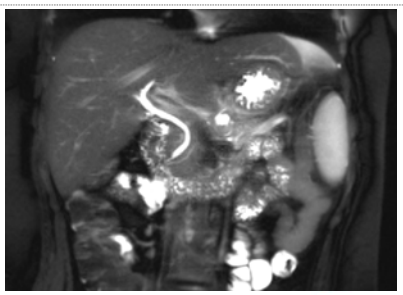
Removal of LAMS



Double Pigtail Plastic Stents



1 year follow up



Summary

- A **majority** of patients with necrotizing pancreatitis develop acute necrotic collections and subsequent walled off necrosis.
- A **minority** of patients with interstitial edematous pancreatitis develop acute pancreatic fluid collections and subsequent pseudocysts.
- Uncomplicated fluid collections should be monitored over time and do not typically require drainage.
- Complicated fluid collections (associated infection, gastrointestinal obstruction) may benefit from a drainage procedure.
- Endoscopic drainage procedures are effective and have fewer complications compared to surgical or percutaneous drainage techniques.

Thank you!

CELIAC DISEASE DIAGNOSIS: ESPGHAN VS. NASPGHAN GUIDELINES

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Director, Celiac and Gluten Resources and Treatment (GREAT) Clinic
Children's Hospital Los Angeles

DISCLOSURES

- Nestlé Nutrition North America (Gerber)
  - Scientific Advisory Board
  - Speaker's Bureau
  - Consultant
- Prometheus Labs
  - Consultant

OBJECTIVES

Following the conclusion of this lecture, participants will have been able to:

1. Explore a brief history on the discovery of celiac disease and its treatment
2. Learn the initial ESPHGAN guidelines for the diagnosis of celiac disease
3. Understand the rationale for the recent modifications of the ESPHGAN guidelines
4. Know the differences in NASGPHAN guidelines
5. Understand that mucosal healing can be incomplete on a gluten free diet on repeat biopsies

HISTORY: ARETAEUS

- Greek physician Aretaeus, the Cappadocian in the 2nd century A.D. is credited with the first written description of Celiac Disease:
- "a wasting illness associated with diarrhea, debility, and atrophy of the body"
- He also described several other diseases like asthma, diabetes, epilepsy, diphtheria, tetanus, and pneumonia

HISTORY: GEE

English pediatrician, Dr. Samuel Jones Gee, 1888

Described celiac disease as:

"A combination of a potbelly and thin buttocks, with proximal arm and thigh muscle wasting"

ON THE COELIAC AFFECTION

-Chronic indigestion which is met with in persons of all ages
-Especially apt to affect children between one and five years old

-Errors in diet may perhaps be a cause,
-Why, out of a family of children all brought up in much the same way, should one alone suffer?

-To regulate the food is the main part of treatment
-The allowance of farinaceous food must be small
-Highly starchy food, rice, sago, corn-flour are unfit
-Malted food is better, also rusks or bread cut thin and well toasted on both sides

Gee S. St Bart Hosp Rep 1890

HISTORY: HAAS AND BANANA BABIES

- In 1924, Dr. Sidney V. Haas tried a banana diet in children with celiac disease following his successful treatment of anorexia with this regime
- He excluded bread, crackers, potatoes, and cereals
- Bananas were gradually added back to the diet in the 4-8th day
- In 1951, Dr. Haas and his son, Dr. Merrill P. Haas, published their book "Management of Celiac Disease," which detailed the doctors' years of success in using this diet

HISTORY: WWII

- The connection between gluten and "celiac sprue" was made in the late 1940's by observant Dutch Pediatrician Willem K. Dicke
- He noted that his patients with Celiac Sprue improved during the food shortages of WWII and relapsed when cereal supplies were restored

"CLASSIC" CELIAC DISEASE

Most common age of presentation:
6-24 months

Symptoms:
- Chronic or recurrent diarrhea
- Abdominal distension
- Anorexia
- Failure to thrive or weight loss
- Abdominal pain
- Vomiting
- Constipation
- Irritability

Celiac Disease in London, 1938

ESPGAN
FIRST DIAGNOSTIC CRITERIA FOR CD 1970

- Main requirement: subtotal villous atrophy in the small bowel mucosa in patients consuming gluten
- Clinical and histological improvement on gluten-free diet
- Recurrence of the typical mucosal lesion after gluten challenge demonstrated by two more biopsies
- Debated:
  - Gluten challenge inciting clinical symptoms
  - Required deterioration in the histological lesion upon gluten-challenge
  - Need for a third biopsy

Meuwisse GW. Acta Paediatr Scand 1970

ESPGAN 1990

- Diagnosis based on typical findings in the small bowel biopsy specimen
- Full clinical remission after withdrawal of gluten from the diet
- Supportive:
  - Serum anti-gliadin (AGA) and antiendomysium (EMA) Ab and their disappearance on a gluten-free diet
  - Immunohistochemical analysis (particularly an increased infiltration of intraepithelial lymphocytes)

Walker-Smith JA et al. Arch Dis Child 1990

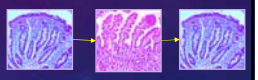
ESPGAN 1990

- Mandatory: control biopsy to verify the consequences of the gluten-free diet on the mucosal architecture in patients
  - with equivocal response to the diet
  - in asymptomatic patients at first presentation
- Encouraged: gluten challenge followed by small bowel biopsy when there are doubts
  - regarding the initial diagnosis
  - as to the adequacy of the clinical response to GFD
- In children under 2 years of age, a gluten challenge may be advisable, preceded and followed by a small bowel biopsy

Walker-Smith JA et al. Arch Dis Child 1990

ESPGAN SUMMARY: THE INTESTINAL BIOPSY IS THE "GOLD STANDARD"

- 1970: 3 biopsies
  - Damage at initial presentation
  - Healing on gluten-free diet
  - Damage after a gluten challenge



- 1990: 1 biopsy
  - Diagnosis definitive in those > 2 years of age
  - Characteristic histologic findings (serology suggestive)
  - Clinical resolution of symptoms on GFD
  - Repeat biopsy not necessary

ADVANCES SINCE REVISED 1990 ESPGAN CRITERIA

- Development of tissue transglutaminase antibody
- Increasing use of HLA typing in clinical practice
- Awareness of different clinical manifestations outside of the GI tract
- Recognition of a wide spectrum of histological alterations:
  - Villous atrophy is not always considered necessary
  - Minor degrees of mucosal damage (crypt hyperplasia or infiltrative lesion) also considered consistent with the disease

NASPGHAN 2005

- Developed by NASPGHAN Celiac Disease Guideline Committee
- First "evidence-based guidelines" for the evaluation and treatment of CD in children
- Systematic review of the medical literature 1966 – Feb. 2003 in PubMed, DARE and Cochrane Database
- Expert opinions: 1 primary care pediatrician, 1 clinical epidemiologist/ primary care pediatrician, 8 pediatric GI, 1 adult GI

JPGN 40:1-19, 2005

NASGPHAN 2005: RECOMMENDATIONS

Children and adolescents with symptoms or an increased risk for CD:

- Initial testing: human recombinant TTG IgA
- Consider total IgA in symptomatic children, if low check TTG IgG
- If TTG elevated, refer for an intestinal biopsy
- If characteristic histopathology, treat with a strict gluten-free diet
- "It is recommended that conf rmation of the diagnosis of CD require an intestinal biopsy in all cases."

JPGN 40:1-19, 2005

ESGPHAN 2012: DEVELOPMENT

- A panel of 17 experts defined CD and developed new diagnostic criteria based on the Delphi process
- Two groups of patients were defined with different diagnostic approaches to diagnose CD:
  - Group 1: children with symptoms suggestive of CD
  - Group 2: asymptomatic children at increased risk for CD
- Evidence-based recommendations on CD-specific antibody testing:
  - The 2004 National Institutes of Health/Agency for Healthcare Research and Quality report
  - A systematic literature search on antibody tests for CD in pediatric patients from 2004 to 2009

Husby S et al. JPGN 2012

ESPGHAN 2012: RECOMMENDATIONS

- Group 1 (symptomatic)
  - Diagnosis is based on symptoms, positive serology, and histology
  - If tTG IgA >10 times the upper limit of normal, option is to diagnose CD without biopsy if EMA IgA+ and HLA+
  - Rationale: in children and adolescents with signs or symptoms suggestive of CD and high anti-TG2 titers with levels >10 times ULN, the likelihood for villous atrophy (Marsh 3) is high
- Group 2 (asymptomatic but at-risk)
  - Diagnosis is based on positive serology and histology
  - HLA-DQ2 and HLA-DQ8 as first line testing is valuable because CD is unlikely if both haplotypes are negative
  - tTG IgA < 3 times ULN should be confirmed with EMA+

Husby S et al. JPGN 2012

ESGPHAN 2012: CONCLUSIONS

- "The aim of the new guidelines was to achieve a high diagnostic accuracy and to reduce the burden for patients and their families"
- "The performance of these guidelines in clinical practice should be evaluated prospectively"

Husby S et al. JPGN 2012

WHAT ARE OUR ADULT COLLEAGUES DOING?

- AGA Institute Technical Review on the Diagnosis and Management of CD 2001, updated 2006:
  - "A small intestinal mucosal biopsy is the current gold standard for the diagnosis of CD and must be used to confirm positive serologic test results before introduction of a lifelong dietary modification"
  - Noted:
    - Disease can be patchy, take multiple biopsies
    - Similar histology can be seen in other diseases
    - Marsh grade I or II lesions require support of serology and/or HLA testing
    - Persistently positive serology with normal histology may indicate latent disease

Gastro 2001, 2006

WHAT ARE OUR ADULT COLLEAGUES DOING?

- ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease, 2013
- GRADE system was used to evaluate the quality of supporting evidence
  - TTG IgA preferred single test over age 2 years
  - Under age 2, combine TTG IgA with DGP IgG and DGP IgA
  - If IgA deficient, check TTG IgG and/or DGP IgG
  - If suspicion of CD is high, biopsy even if serology is negative
  - All diagnostic testing should be done on a gluten-containing diet
  - Confirmation of diagnosis based on a combination of medical history, physical examination, serology, and upper endoscopy with histological analysis of multiple biopsies of the duodenum

Rubio-Tapia Am J Gastroenterol 2013

SHOULD WE REPEAT BIOPSIES?

- Adult literature
  - 390 adults on GFD for 2-22 years:
    - 33% mild and 24% severe damage on repeat biopsy (therefore 57% with some damage)
    - Correlated with education and compliance with GFD
  - 241 adults at Mayo Clinic:
    - Kaplan-Meier rate of confirmed mucosal recovery
      - 34% at 2 years
      - 66% at 5 years
    - Trend toward an association between achievement of mucosal recovery and a reduced rate of all-cause mortality

Ciacci C et al. Digestion 2002
Rubio-Tapia A et al. Am J Gastroenterol 2010

SHOULD WE REPEAT BIOPSIES?

- Pediatric literature:
  - 19% of children with Marsh III lesions at diagnosis had persistent enteropathy on repeat biopsy after 1 year GFD
  - Did not correlate with:
    - tTG IgA level
    - age at diagnosis
    - reported adherence to GFD
    - symptoms (diarrhea, weight loss)

Leonard M et al. JPGN 2017

SUMMARY

- All societies agree that tTG IgA is a highly sensitive and specific means of first-line screening for celiac disease in symptomatic and at-risk individuals
- NASPGHAN, AGA and ACG all recommend small bowel biopsy to confirm this lifelong condition
- The ESPGHAN 2012 revised guidelines state that a symptomatic child with tTG IgA> 10x ULN, EMA+, HLA+ with response to GFD does not need a biopsy
- The performance of these guidelines in clinical practice should be evaluated prospectively
- Children, adolescents and adults on the gluten free diet for several years often demonstrate continued enteropathy on repeat biopsy

Fad Diets: The Good, the Bad and the Just Plain Ugly

Mark R. Corkins, M.D.
Le Bonheur Children's/University of TN Health Science Center

Financial Disclosure

- I have nothing to disclose
- Wife a member of the Abbott speakers bureau
- No discussion of an unapproved/investigative use of a commercial product/device in this presentation

Objectives

1. The attendees will know the dietary philosophies that define the common fad diets.
2. The learners will be aware of the potential nutritional deficiencies and components that can cause harm with common fad diets utilized by pediatric patients.
3. The learners will know methods to work with families and guide them to a nutritionally complete diet regimen.

General Principles

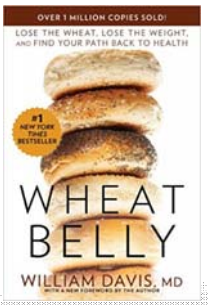
- Response to increased levels of obesity
- Fad diets tend to isolate a single nutritional component to increase, reduce, or eliminate
- The title "diet" is challenging
  - Implies temporary
  - Neglects the addition of regular activity or exercise to improve weight and health

Stratbucker W. . Pediatr Rev. August 2016;37(8):357-359

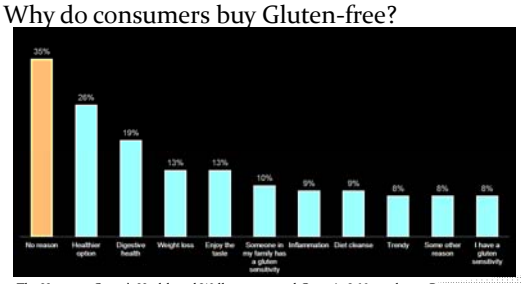
Gluten-free Diet

- Increasing recognition that celiac disease is common
- Trendy to be gluten-free, ~30 % of US adults "limiting" gluten[1]
  - Many not sure what gluten is
  - Done without "proof"
- Done for weight loss—Wheat Belly by William Davis, MD
- Autism—anecdotes, no studies support
- Autoimmune diseases/Anti-inflammation
  - Patients with celiac on diet for 10 years less likely to develop another autoimmune disease[2]

1. Hill et al. JPGN. July 2016;63(1):156-165 2. Cosnes et al. Clin Gastro Hepatol. 2008;6(7):753-758



Why do consumers buy Gluten-free?



The Hartman Group's Health and Wellness 2015 and Organic & Natural 2014 Reports. http://www.hartman-group.com/acumenPdfs/gluten-free-2015-05-03.pdf Used with permission. Accessed 8/23/2017

Gluten-free Diet

- Alter the diet by eliminating gluten, fewer choices
- Can result in weight gain if increase intake of refined carbohydrates or processed foods
- Gluten-containing grains a primary source of FODMAPs, may be why abdominal pain improves[1]
- Gluten-free foods not fortified
  - Deficiencies: fiber, thiamine, folate, vitamin A, magnesium, calcium, iron[2]

1. Leonard et al. JAMA. August 2017;318(7):647-656 2. Hill et al. JPGN. July 2016;63(1):156-165

Food-Focused Diets

- Grapefruit diet or cabbage soup diet
  - Eat at every meal
  - No proof that contain any special "enzyme"
- Raw food diet
  - No cooked, processed, microwaved, irradiated, genetically engineered or any exposed to pesticides or herbicides
- Result in reduced intake but not sustainable

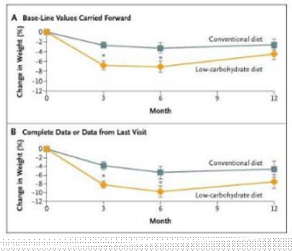
Carbohydrate-limiting

- Atkins
  - High intake of protein, fiber, vitamins and minerals
  - Low amounts of sugars and no trans fats
- South Beach
  - Three phases, gradually less restrictive
  - Emphasis on "good" carbohydrates and fats, avoiding "bad" carbs

Carbohydrate-limiting Issues

- Problem for children since low nutrient intake and kilocalories to support growth
- Not sustainable, result in quick weight loss due to water loss
- Usually end up with a high fat intake
  - Hard on heart and brain
  - Long-term increase in coronary heart disease
- Increased nitrogen waste and increased risk of kidney stones
- Decrease in calcium balance, bone loss and osteoporosis

Comparison of Standard Versus Low-carbohydrate Diet Outcomes (Adult)



Khawandanah et al. J Food Res. 2016;5(6):80-94

Fat-limiting

- Pritikin and Dean Ornish Diets
- Originally for treatment of heart disease, adopted for weight loss
- Limit fat intake to 10% of calories
- Limit simple sugars, high fiber intake
- Very restrictive, requires extensive meal planning

Fat-limiting

- Paleo
  - Diet of hunter-gatherers: high protein, high fiber
  - Lean meats, eggs, fish, fruits, vegetables/fruits, nuts and seeds
  - No processed foods
  - No wheat/grains, legumes, dairy, potatoes, salt, refined sugar, refined vegetable oils

Fat-limiting Issues

- Fats are very energy dense and also role in many tissues
  - Fat <10% of daily energy intake, risk essential fatty acid deficiency
- Potential deficiencies in pediatrics due to no dairy, grains and legumes
  - Low calcium intake
- Low intake of micronutrients
- Intake consists of poor quality proteins
  - Iron and zinc deficiency

Comparison High Protein Versus High Carbohydrate

Diets	Pros	Cons
High protein: Adkins, South Beach	Rapid weight loss Increased satiety Decreased TG Decreased cholesterol	High fat content Nutrient deficiency Detrimental to brain and heart Increased risk for CHD
High carbohydrate (low fat): Ornish, Pritikin, Paleo	Reduction of cardiovascular disease risk	Increased TG Decreased HDL-C Micronutrient deficiency

De-tox or Cleansing Diets

- Belief that body builds up toxins over time
- Need to do smoothies or some other "cleansing" food periodically
- Very limited intake of calories-fatigue, weakness and nausea
- Fluid imbalance with high output
- Liver and kidney don't need to de-tox, that is their function in the first place!

Explaining The Issues to Families

- Diet implies temporary
- Concept of a balanced diet: need a variety of nutrients, skewing makes no sense
  - Explain we need protein, fat and carbohydrates
- Weight loss by malnutrition is not healthy
- Diets designed for adults and not growing children
  - Nutrient needs different and greater
  - Pick the greatest shortfall and recommend adding it back
  - Gradually add back towards the ideal diet

Working Towards Normal

- Point to work by the dietary guidelines group
  - Experts but not government employees
- Recommendations for lifetime eating patterns
  - U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at http://health.gov/dietaryguidelines/2015/guidelines/.

My Plate

www.choosemyplate.gov

Intervention Program Success

- Meta-analysis of 52 pediatric studies, N=28,236
- Compared change in BMI, overall effect size was 0.068
- Most effective programs:
  - Interventions with physical activity and nutritional changes
  - Parent participation
  - Intervention lasted a year

Vasques et al. J Phys Act Health. 2014;11(2):426-444

Summary

- Fad diets work by a focus on eliminating or increasing something
- Promise a quick fix, often a quick response due to short-term water loss or severe caloric reduction
- If not in dietary balance, something is invariably lacking
- Families understand that children have greater nutritional needs, focus on this to guide back to a more balanced intake

Fad Diet Reviews

- Khawandanah et al. J Food Res. 2016;5(6):80-94
- Christie et al. Chapter 26 in ASPEN Pediatric Nutrition Support Core Curriculum, 2nd edition, ed. Corkins, M, publisher ASPEN, Silver Spring, MD
- Amidor, T. Today's Dietitian. 2016;18(1):8

What's new for clinical guidelines for *H. pylori* infection in children?

NASPGHAN Postgraduate Course 2017

Nicola L. Jones, MD, FRCPC, PhD

Division of GI, Hepatology and Nutrition
SickKids Toronto
Professor of Paediatrics and Physiology
University of Toronto

1

Conflict of Interest

- Nothing to disclose

2

Learning Objectives

Understand updated guidelines for:

- Who to test
- How to test
- How to treat
  H. pylori infection in children

3

Case presentation

- 12 year old girl referred for second opinion from GP
- Mother thinks a blood test showed the child was infected with *H. pylori*
- Symptoms of epigastric pain with some night time wakening
- Physical exam and labs including Hb normal

What is the next step?

A. Treat with triple therapy and encourage adherence
B. Perform a urea breath test and treat if positive
C. Perform an upper endoscopy and treat if *H. pylori* positive

Who to test?

Peptic ulcer disease	Yes	Strong recommendation
Functional abdominal pain	No	Strong recommendation
Asymptomatic children	No	Strong recommendation
Family history of gastric CA	Yes	
MALT lymphoma	Yes	

New ESPGHAN/NASPGHAN 2016 recommendations

6

Who to test: extra-intestinal disease?

Iron deficiency anemia	No	Strong recommendation
Unexplained refractory iron deficiency anemia	Yes	Weak recommendation
Chronic ITP	Yes	Weak recommendation
Short stature	No	Strong recommendation

New ESPGHAN/NASPGHAN 2016 recommendations

7

How to test- initial diagnosis?

Invasive Diagnostic test	**Recommendation**
GI endoscopy and biopsy	Yes
Non-invasive tests	**Recommendation**
Urea breath tests	No
Stool antigen tests	No
Serologic assays	No!

New ESPGHAN/NASPGHAN 2016 recommendations

What is the next step?

A. Repeat treatment with triple therapy and encourage adherence

B. Perform a urea breath test and treat if positive

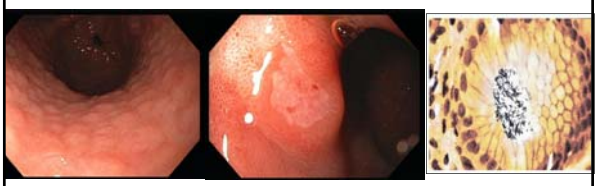
C. Perform an upper endoscopy and treat if *H. pylori* positive

Case presentation

- upper endoscopy is performed

Upper endoscopy findings

Pathologic findings



10

Should *H. pylori* be eradicated?

A. Yes

B. No

11

Who to treat?

Peptic ulcer disease	Yes
H. pylori without peptic ulcer disease	consider
Unexplained refractory iron deficiency anemia	Yes
Chronic ITP	Yes
Family history of gastric CA	Yes

New ESPGHAN/NASPGHAN 2016 recommendations

12

How to treat-1st line?

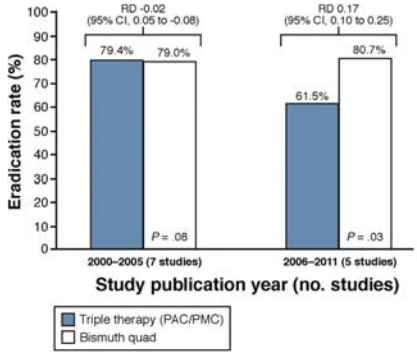
- Proton pump inhibitor amoxicillin metronidazole — 7-14d
- Proton pump inhibitor amoxicillin clarithromycin — 7-14d
- Bismuth salts amoxicillin metronidazole — 7-14d
- Sequential therapy — 10d

*Joint ESPGHAN/ NASPGHAN Consensus Guidelines : J Pediatr Gastroenterol Nutr. 2011[13]

What is the best choice of therapy?

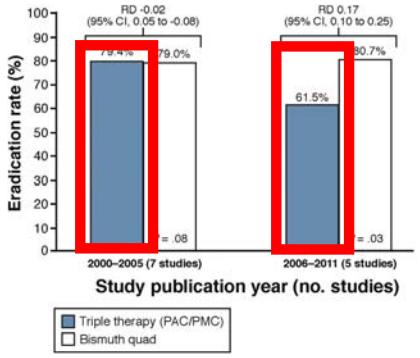
A. Triple therapy
B. Sequential therapy
C. Bismuth-based

Changes in eradication rates over time



Fallone et al., Gastroenterology 2016;151: 51-69

Changes in eradication rates over time



Fallone et al., Gastroenterology 2016;151: 51-69

How to treat-1st line?

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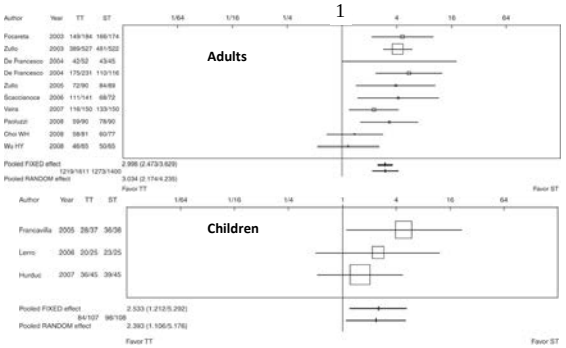
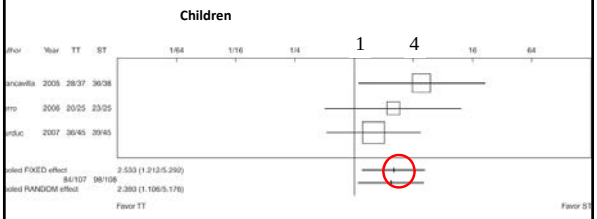
*Joint ESPGHAN/ NASPGHAN Consensus Guidelines : J Pediatr Gastroenterol Nutr. 2011 [17]

Efficacy of sequential therapy



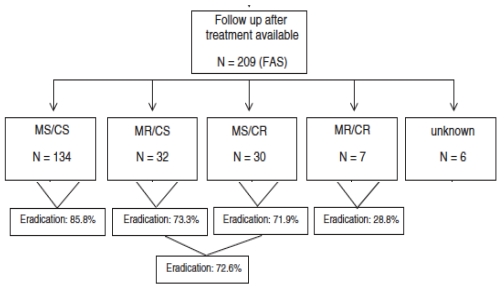
Gatta et al. Am J Gastroenterol 2009: 104:3069-79

Efficacy of sequential therapy



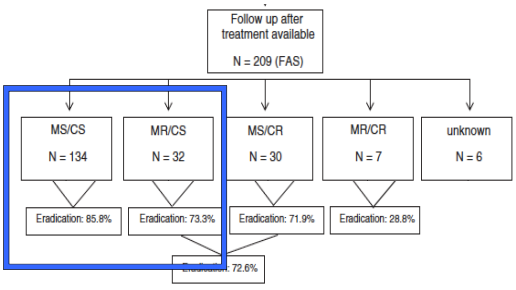
Gatta et al. Am J Gastroenterol 2009: 104:3069-79

Efficacy of sequential therapy in treatment- naïve children



Schwarzer et al. Helicobacter 2016: 21:106-13

Efficacy of sequential therapy in treatment- naïve children



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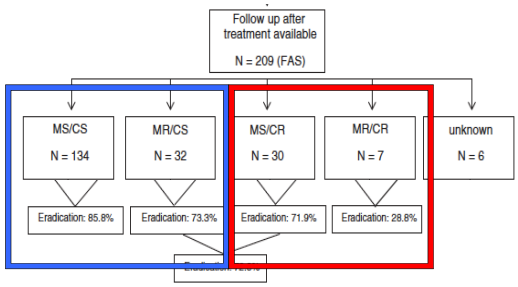

Schwarzer et al. Helicobacter 2016: 21:106-13

Recommendation:

We recommend that the antimicrobial susceptibility be obtained for the infecting *H. pylori* strain(s), and, the anti-*H. pylori* treatment tailored accordingly.

Grade: Strong recommendation

Agreement: 86%

New ESPGHAN/NASPGHAN 2016 recommendations

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Recommendation:

We recommend that the physician explain to the family the importance of adherence to the anti-*H. pylori* therapy to enhance treatment success.

Grade: strong recommendation

Agreement: 86%

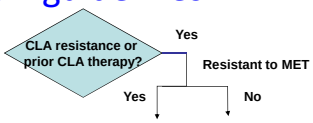
New ESPGHAN/NASPGHAN 2016 recommendations

24

How to treat-first line? New guidelines

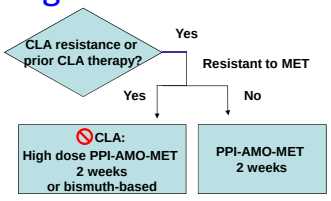
New ESPGHAN/NASPGHAN 2016 recommendations

How to treat-first line? New guidelines



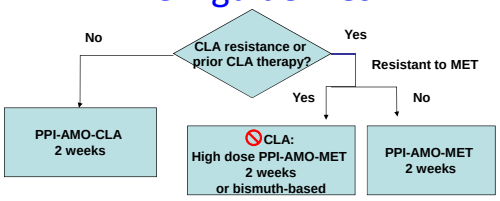
New ESPGHAN/NASPGHAN 2016 recommendations

How to treat-first line? New guidelines



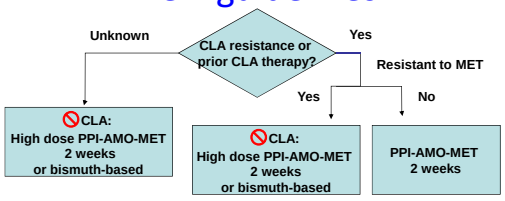
New ESPGHAN/NASPGHAN 2016 recommendations

How to treat-first line? New guidelines



New ESPGHAN/NASPGHAN 2016 recommendations

How to treat-first line? New guidelines



New ESPGHAN/NASPGHAN 2016 recommendations

Case presentation- cont'd

- Receives eradication therapy
- Continues to have intermittent pain
- Should you confirm eradication?
  - –Yes
  - –No

30

How to test ? –confirm eradication

Non-invasive tests	Recommendation
Urea breath tests	Yes
Stool antigen tests	Yes
Serologic assays	No!

***confirmation testing should be performed at least 4-8 weeks after stopping therapy**

31

Case presentation- cont'd

- Urea breath testing shows the child is no longer *H. pylori* positive

32

How to manage treatment failure?

- Modify therapy-add/change antibiotic, bismuth, change dose/ duration
- Culture and susceptibility testing to guide therapy

33

Summary

- In children the goal of testing is to diagnose the cause of symptoms- NOT detect *H. pylori* infection
- Therapy should be guided by antibiotic resistance rates when available
- Choose the best initial therapy to avoid treatment failure

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Thanks for your attention!

Biliary Atresia: Update on Biomarkers of Disease and Therapeutic Interventions

Cara L. Mack, MD
Professor of Pediatrics
Medical Director of Pediatric Liver Center
Director of Pediatric GI, Hepatology & Nutrition Fellowship Training Program
Children's Hospital Colorado, University of CO School of Medicine

Disclosures

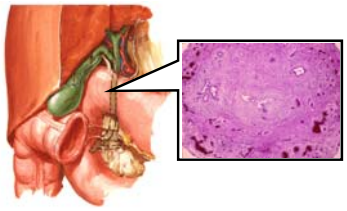
- I have no financial disclosures or conflicts of interest

Objectives

- Educate audience on diagnostic and prognostic biomarkers in BA
  - --Diagnosis: bilirubin
  - --Prognosis: bilirubin, inflammatory and fibrosis markers
- Summarize recent studies on nutritional and medical interventions in BA
  - --Nutrition and fat soluble vitamin supplementation
  - --Cholangitis prophylaxis
  - --Clinical trials involving immunosuppression

Biliary Atresia (BA)

- Progressive inflammatory sclerosing process of biliary tract with obstruction by age 3 months
- Incidence per live births: Taiwan- 1:5,600, U.S.- 1:12,000, Europe- 1:18,000



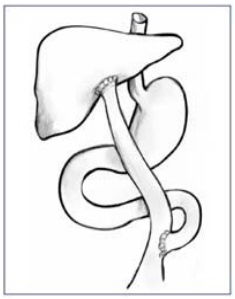
Childhood Liver Disease Research Network (ChiLDReN)

BA Classifications (ChiLDReN)

- Isolated (perinatal; acquired): 84% of cases
- Syndromic BA associated with laterality defects (abdominal heterotaxy) and spleen anomalies: 10% of cases
  -- rare in China (0.5%)
- BA with other anomalies but not laterality (i.e. cardiac): 6%
- Cystic BA

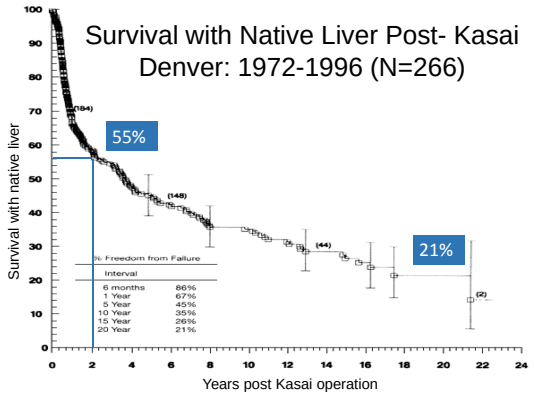
Zhan et al. Asian J Surg 2016
Schwarz et al. Hepatolgoy 2013;58(5)

Kasai Portoenterostomy



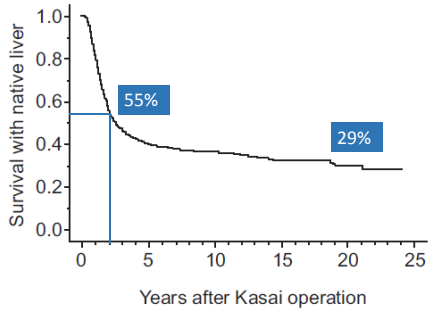
- Better outcomes if:
  1. Performed before 45 days of age
  2. Performed at high volume centers
  3. Isolated BA vs. Syndromic
  4. No cholangitis episodes

Survival with Native Liver Post- Kasai
Denver: 1972-1996 (N=266)



Altman RP et al. Ann Surg 1997

Survival with Native Liver Post- Kasai
France: 1986-2009 (N=1,044)



Chardot et al. J Hepatol 2013

Medical Status of Children with BA Surviving with Native Liver (ChiLDReN)

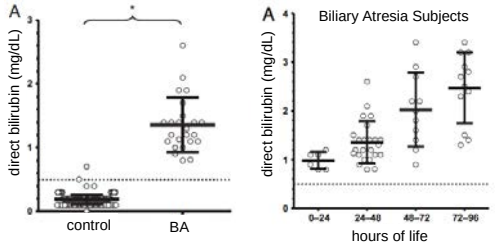
- Analysis of outcome 10.5 years after successful Kasai (range 5-18 yrs) (N=219)
- Chronic liver disease: 90%
- "Ideal" outcome: 1.8% of patients
  - -normal liver tests
  - -no signs of chronic liver disease
  - -no liver-specific medications
  - -normal quality of life

Ng et al. J Pediatr 2014

Diagnostic Biomarker: Newborn Bilirubin

Newborn Direct or Conjugated Bilirubin Measurements As a Potential Screen for Biliary Atresia

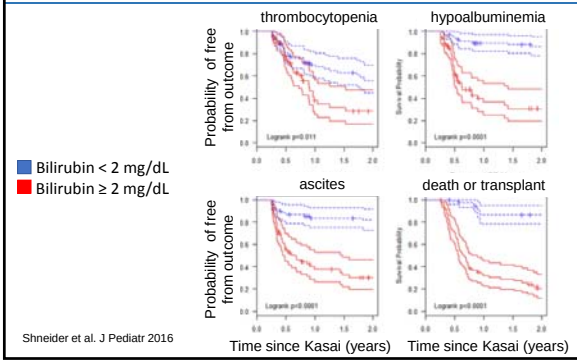
*Sanjiv Harpavat, *Ramya Ramraj, †Milton J. Finegold, ‡Mary L. Brandt, *Paula M. Hertel, ‡Sara C. Fallon, *Ross W. Shepherd, and *Benjamin L. Shneider



Harpavat et al. Pediatrics 2011

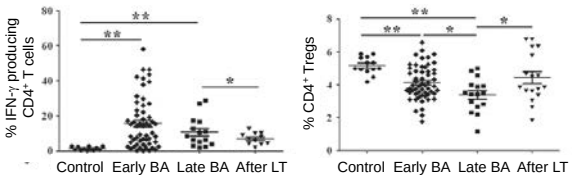
Prognostic Biomarkers

Serum Bilirubin 3 Months post- Kasai Predicts Outcome in BA (ChiLDReN)



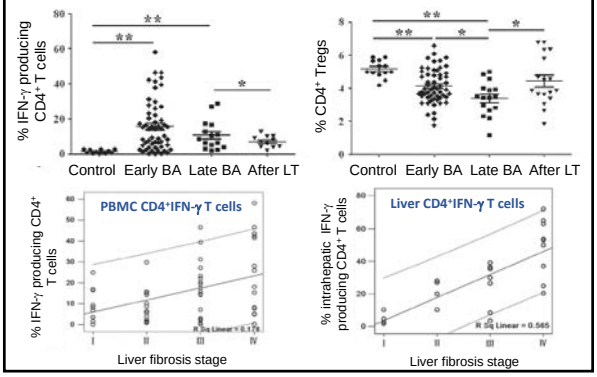
Shneider et al. J Pediatr 2016

Th1 Infiltrates and Fibrosis in BA



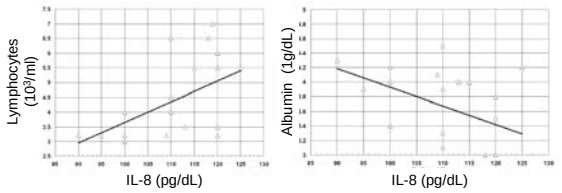
Wen J et al. Cell Death Differentiation 2017;1-10

Th1 Infiltrates and Fibrosis in BA



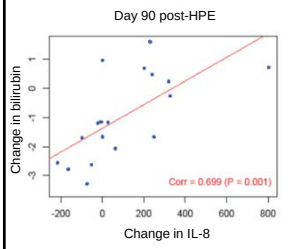
IL-8 and Outcome in BA

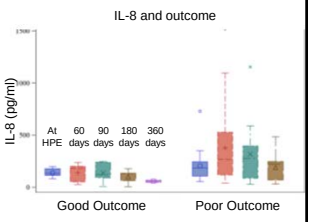
- IL-8: neutrophil chemotaxis and activation



El Faramawy et al. Tropical Gastro 2011;32(1)

IL-8 and short term outcomes in BA

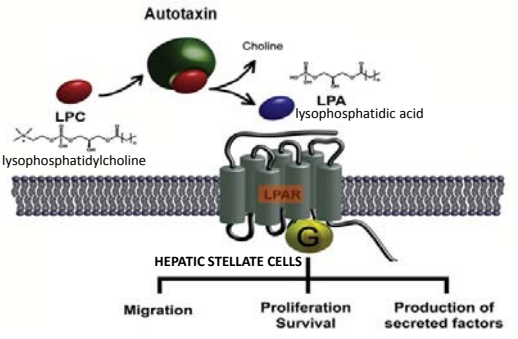




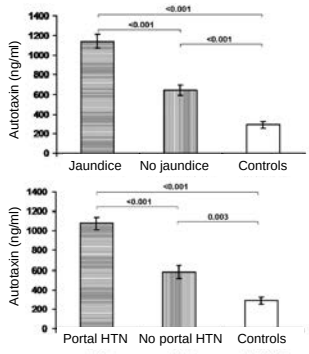
Good Outcome: total bilirubin < 1.5 mg/dL and transplant-free survival
Poor Outcome: total bilirubin > 1.5 mg/dL or liver transplant

Mack et al. Poster presentation NASPGHAN 2017

Autotaxin Predicts Outcome in BA

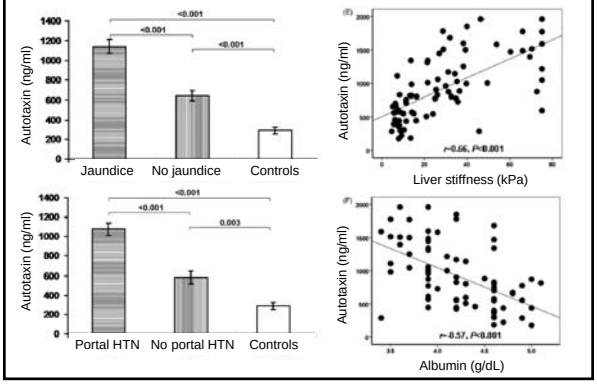


Autotaxin Predicts Outcome in BA



Udomsinprasert W et al. Biomarkers 2015;20(1)

Autotaxin Predicts Outcome in BA



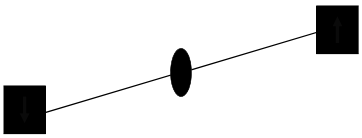
Summary of Biomarkers in BA

- BA patients have direct/ conjugated bilirubin elevation in the first 72 hours of life
- Further research on universal newborn screening with direct bilirubin is warranted
- Many biomarkers are associated with progression of disease
- Potential for combining biomarkers to predict outcome in BA

Therapeutic Interventions

Causes of Nutrient Imbalance in BA

Increased energy expenditure and protein catabolism



--Decreased protein and lipid synthesis, amino acid utilization and gluconeogenesis

--Decreased tissue delivery (portal shunts)

--Decreased absorption (cholestasis)

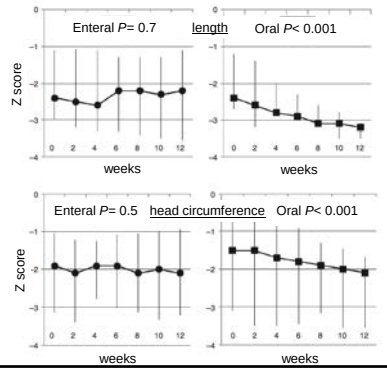
--Decreased appetite

Shepherd RW et al. J Gastro Hepatol 1996

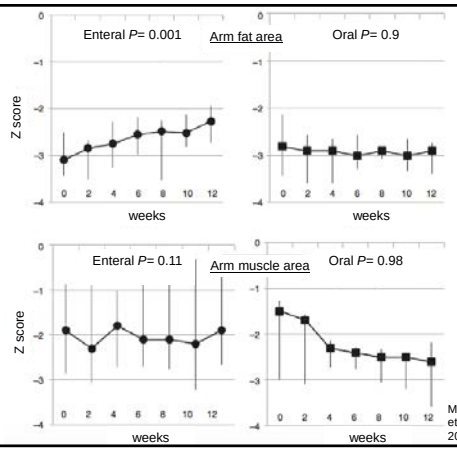
Nutritional Support

- Choose infant formula with moderate/ high MCTs, adequate EFAs
- Breast milk alone may be inadequate for cholestatic infant growth
- Aim for 130-160 kcal/ kg IBW and 20-30 gm/ day of weight gain
- May need NG feedings or TPN for growth

NG Feeds Maintains Growth in BA



Macias-Rosales R et al. JPGN 2016;62

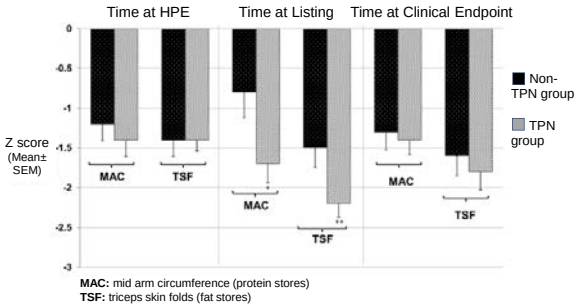


Macias-Rosales et al. JPGN 2016;62

Nutritional Support: Parenteral Nutrition

- Pros:
  - --bypasses malabsorption to deliver calories
  - --provides route of administration of nutrition in setting of failure to tolerate NG feeds (emesis, diarrhea)
  - --maximizes nutrition while awaiting transplant
- Cons:
  - --risk inherent to central lines (infection, clot)
  - --potential for TPN-related cholestasis
  - --higher costs

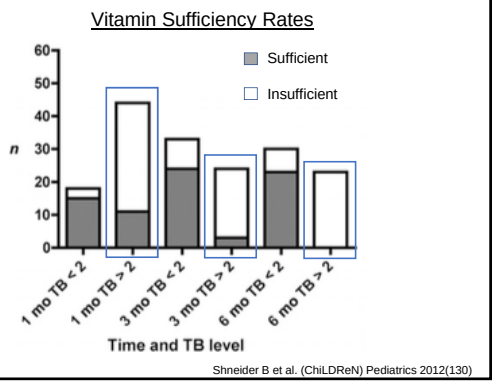
TPN Use in BA Patients Awaiting Liver Transplant



MAC: mid arm circumference (protein stores)
TSF: triceps skin folds (fat stores)

Sullivan JS et al. Liver Transp 2012(18)

Fat Soluble Vitamin Deficiencies in BA



Shneider B et al. (ChiLDReN) Pediatrics 2012(130)

Target Fat Soluble Vitamin Levels and Replacement Regimens

Vitamin	Target range	Supplementation strategy
A(retinol)	19 – 77 μg/dL retinol:retinol binding protein molar ratio > 0.8	Increments of 5000 IU(up to 25 – 50,000 IU/day) orally or monthly intramuscular administration of 50,000 IU
D (25-hydroxy vitamin D)	15 – 45 ng/ml	Increments of 1200 to 8000 IU orally daily of cholecalciferol or ergocalciferol Alternatively calcitriol at 0.05 to 0.20 μg/kg/day
E (alpha tocopherol)	3.8 – 20.3 μg/ml Vitamin E:total serum lipids ratio > 0.6 mg/g	Increments of 25 IU/kg of TPGS orally daily(to 100 IU/kg/day)
K (phytonadione)	INR≤1.2	1.2 < INR≤ 1.5 2.5 mg vitamin K orally daily 1.5 < INR≤ 1.8 2.0 – 5.0 mg vitamin K intramuscular and 2.5 mg vitamin K orally daily INR > 1.8 2.0 – 5.0 mg vitamin K intramuscular and 5.0 mg vitamin K orally daily

Cholangitis: Prophylactic Antibiotics

Characteristics	Lally et al.	Wu et al.	deVries et al.	Bu et al.
Location	U.S.	Taiwan	Netherlands	Taiwan
Study Design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Randomized (2 Antibiotics)
Sample Size	Abx: 34 No Abx: 7	Abx: 16 No Abx: 21	Abx: 124 No Abx: 80	Abx: 19 No Abx: 18
Prophylactic Abx (duration)	TMP/ SMX; amoxicillin; cephalosporins (1-several mons.)	TMP/ SMX; neomycin (unknown)	TMP/ SMX; neomycin/colistin; ciprofloxacin (unknown)	TMP/ SMX; neomycin (until 36 mons. age)
Follow-up	1-72 months	6-59 months	1-263 months	Age 36 mons.
Outcome Measured	Incidence of cholangitis	Incidence of cholangitis	Incidence of cholangitis	Recurrence rate cholangitis
Results: incidence of cholangitis	Abx: 15% No Abx: 57%	Abx: 53% No Abx: 47%	Abx: 62% No Abx: 51%	Ctrl: 1 TMP/ SMX: 0.5 Neomycin: 0.4

Dechuran et al. Clin Pediatr 2016;55(1)

Recent clinical trials: ChiLDReN

Research

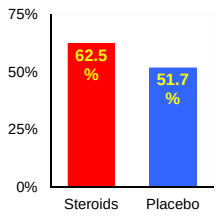
JAMA. 2014;311(17):1750-1759

Original Investigation

Use of Corticosteroids After Hepatoportoenterostomy for Bile Drainage in Infants With Biliary Atresia
The START Randomized Clinical Trial

Jorge A. Bezerra, MD; Cathie Spino, DSc; John C. Magee, MD; Benjamin L. Shneider, MD; Philip Rosenthal, MD; Kasper S. Wang, MD; Jessi Erlichman, MPH; Barbara Haber, MD; Paula M. Hertel, MD; Saul J. Karpen, MD; Nanda Kerkar, MD; Kathleen M. Loomes, MD; Jean P. Molleston, MD; Karen F. Murray, MD; Rene Romero, MD; Kathleen B. Schwarz, MD; Ross Shepherd, MD; Frederick J. Suchy, MD; Yumirle P. Turmelle, MD; Peter F. Whitington, MD; Jeffrey Moore, MS; Avarell H. Sharker, MD, FRCP(C); Patricia R. Robuck, PhD, MPH; Ronald J. Sokol, MD; for the Childhood Liver Disease Research and Education Network (ChiLDREN)

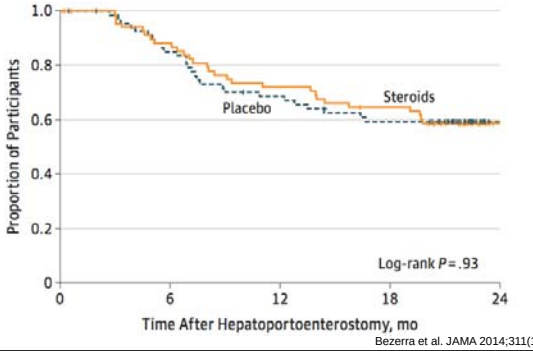
Subjects with total bilirubin <1.5 mg/dL and with native liver 6 months post- Kasai



Adjusted RR [95% CI]: 1.14 [0.81, 1.61] *P=0.44*

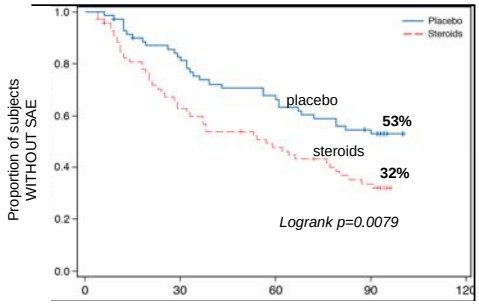
Bezerra et al. JAMA 2014;311(17)

Kaplan-Meier survival with native liver



Bezerra et al. JAMA 2014;311(17)

Serious Adverse Events (SAE): Steroid group had more frequent SAEs and earlier time to SAE

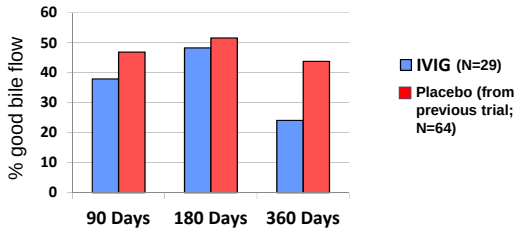


IVIg Therapy

Anti-inflammatory activities of intravenous immunoglobulin (IVIg)

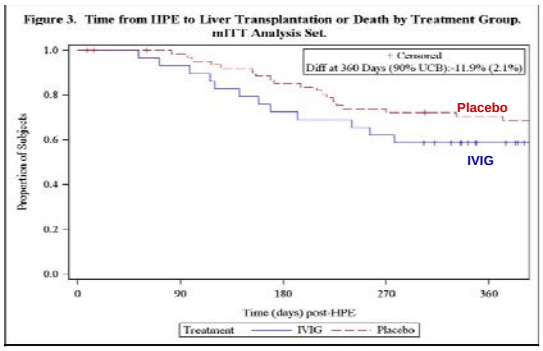
- Decreases function of FcγR on innate immune cells (i.e. macrophages) & ↓ pro-inflammatory cytokines
- Interferes with complement cascade activation
- Neutralizes autoantibodies
- Inhibits antigen presentation (preventing T cell activation)
- Increases number and function of Tregs

% With Good Bile Drainage



Mack et al. submitted to Jrl Peds Sept 2017, under review

Time from Kasai to transplant or death



Conclusions

- BA is a devastating disease of unknown etiology that results in cirrhosis and liver transplant in the vast majority
- Multiple potential diagnostic and prognostic biomarkers; bilirubuin most promising
- Close attention to nutritional support essential to health of BA patients
- Currently no therapeutic options that delay progression of disease


Thank You

Diagnosis and Management of Pediatric NAFLD in 2017

Stavra Xanthakos, MD, MS

Associate Professor of Pediatrics
Director, Steatohepatitis Center
Medical Director, Surgical Weight Loss Program for Teens

Disclosures

- **Funding sources**
  - NIH/NIDDK: R01**NASH Clinical Research Network (NASH CRN), Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS)**
  - Target NASH
- **I will be discussing some non-FDA approved investigational treatments**

Learning objectives

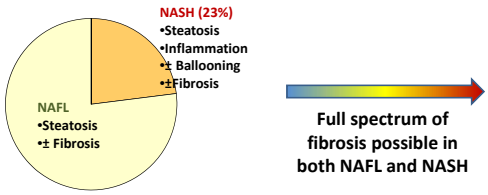
1. Understand **advantages and limitations of available diagnostic tools** for NAFLD in children
2. Describe and implement **available treatments** for NAFLD in children
3. Review **status of emerging therapeutic options** for pediatric NAFLD

Prevalence of pediatric NAFLD in USA

2008 San Diego County autopsy study of 742 children, ages 2-19 years, 1993-2003:

~10% prevalence of NAFLD in all children

38% prevalence in obese children

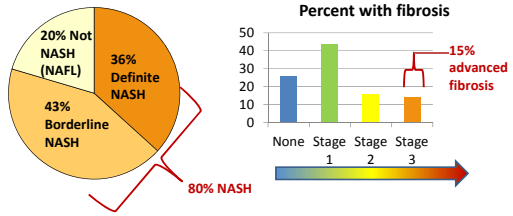


Full spectrum of fibrosis possible in both NAFL and NASH

Schwimmer JB et al. Pediatrics 2006

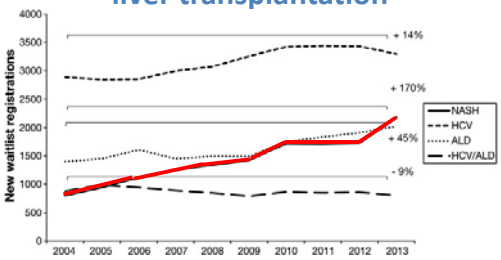
NASH in pediatric GI/Liver centers

- 176 children from 8 NASH CRN sites in USA, mean age 12 (6-17 yrs)
- Mean BMI 33 ± 5 kg/m^2 (99 ± 0.8 percentile)



Patton H et al. Gastroenterology 2008

NASH now 2nd indication for adult liver transplantation



- **Predicted to be # 1 cause for adults by 2030**
- **NASH also associated with increased mortality in adults**

Wong RJ et al. Gastroenterology 2015
Ekstedt et al. Hepatology 2006

Natural history of pediatric NAFLD

- **122 children in NASH CRN trials 2005-2015, standard lifestyle counseling q3 months + placebo x 52 or 96 wks**
  - **28% had worsening in fibrosis or NASH and 7% had both**
  - NASH progression associated with
    - higher ALT, AST, GGT, total cholesterol, LDL-c at baseline, and increasing BMI z score over time
  - Fibrosis progression associated with
    - white race, worsening ALT, GGT and A1C over time.
  - **T2DM developed in 8% at IR 44.3/1000**
    - **>300 fold incident T2DM rate in children overall**

Xanthakos et al for NASH CRN. AASLD October 2017

Cardiometabolic risk factors common in children with NASH

- **Prediabetes (23%) and type 2 diabetes (6.5% in NASH CRN)**

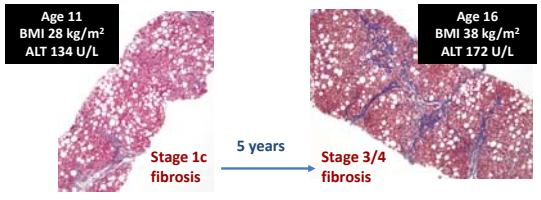
Glucose Status	NASH, OR (95% CI)
Normal glucose	1 [reference]
Prediabetes	1.9 (1.2-2.9)
Type 2 diabetes	3.1 (1.5-6.2)

- **High blood pressure (36% in NASH CRN)**
- **Dyslipidemia**
  - High triglycerides, TG/HDL-C & LDL-C/HDL-C ratios
- **Obstructive sleep apnea**

Schwimmer JB et al. PLOS One 2014
Newton KP et al. JAMA Pediatrics 2016

Long-term outcomes of NAFLD and comorbid conditions unknown

- **Hepatic outcomes:** fibrosis progression, end-stage liver disease, transplantation rate, hepatocellular carcinoma
- **Non-hepatic outcomes:** cardiovascular events, diabetes incidence and complications, all-cause and specific mortality



How should I screen for NAFLD?

ALT still optimal initial screening tool

- **Inexpensive, universally available**
- **Use biologically-derived upper limits of normal (ULN)!**
  - Regional labs ULN median **53 U/L** (range 30-90 U/L)
  - Actual sex-specific biological ULN much lower **<30 U/L**

In NHANES, ages 12-17 years:
Girls: 22 U/L
Boys: 26 U/L
In Canada,
Ages **1-12 years: 30 U/L**
Ages 13-19 years, 24 U/L

Colantonio DA et al. Clin Chem 2012
Schwimmer JB. Gastroenterology 2010

Limitations of ALT

- **ALT ≥ 50 for boys and ≥ 44 for girls** (2 x sex-specific ULN) **88% sensitive but only 26% specific for detecting NAFLD**
  - **NASH more common if ALT ≥ 80 U/L (41% VS. 21% prevalence)**
- **Need to exclude multiple other possible etiologies ($$$)**
  - Viral hepatitis
  - Autoimmune hepatitis
  - Genetic/storage disorders (alpha 1 antitrypsin, Wilson, hemochromatosis, lysosomal acid lipase)
  - Endocrine (hypothyroidism)
- **Significant NASH can be present with normal or mild ↑ ALT**
  - 9% children with ALT <44 or 50 U/L had ≥ stage 3 fibrosis (NASH CRN)

Schwimmer JB et al. Aliment Pharmacol Ther 2013
Molleston JP et al. J Pediatric 2014

NASPGHAN 2017 Clinical Practice Guidelines for Pediatric NAFLD:

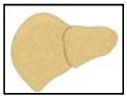
Screening recommendations

- Screen **obese children** (BMI ≥ 95th%ile) & **overweight children** (BMI ≥ 85th – 94th %ile) with risk factors, beginning age 9-11 years
  - Severe obesity, family history of NAFLD/NASH, hypopituitarism, OSA, prediabetes, Hispanic ethnity
- Consider earlier screening if risk factors
- Consider screening siblings and parents of children with NAFLD if risk factors

Vos MB et al. JPGN 2017

Can imaging replace biopsy?

Routine ultrasound limitations

- **Pros:**
  - **Non-invasive**
  - **Less costly**
  - **More widely available**
- **Cons**
  - **Poor sensitivity and specificity for NAFLD**
  - **Cannot differentiate between**
  - **NAFL**  **and NASH** 

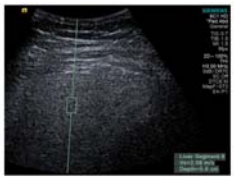
US elastography imaging

Transient Elastography- Fibroscan

- AUROC 0.99 for predicting ≥ stage 2 fibrosis in Italian cohort with NAFLD (mean age 14)

Acoustic Radiation Force Imaging (ARFI) shear wave elastography

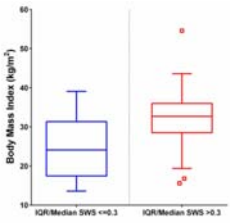
- AUROC 0.97 for predicting ≥ stage 2 fibrosis in Italian cohort with NAFLD (mean age 13)



Nobili V et al. Hepatology 2008
Alkhouri et al. Liver International 2012
Garcovich M et al. Radiology 2017

Caveats of US-based elastography

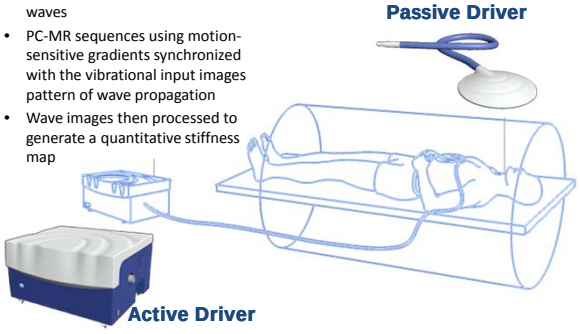
- **Both techniques not validated in large, multicenter cohorts**
  - Children with NAFLD more obese in USA
  - More shear wave measurement dispersion as BMI rises >30 kg/m² and anterior abdominal wall thickness increases
- **Further validation needed** to determine cut-offs and accuracy in children with NAFLD
- **Longitudinal correlation** with disease progression and outcomes lacking



Trout AT et al. Radiology 2016

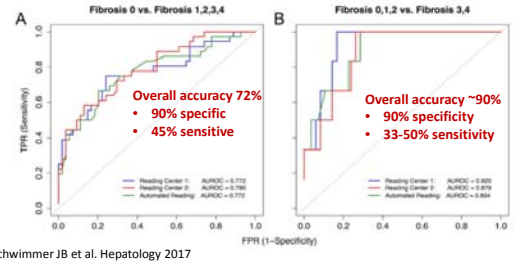
MR Elastography (MREL)

- 60 Hz vibration frequency shear waves
- PC-MR sequences using motion-sensitive gradients synchronized with the vibrational input images pattern of wave propagation
- Wave images then processed to generate a quantitative stiffness map



MREL in Pediatric NAFLD

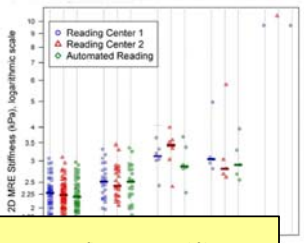
- Prospective cohort of 114 children, age 8-17 at 2 NASH CRN centers
- 90 children successfully completed MRE



Schwimmer JB et al. Hepatology 2017

MRI: Current Pros and Cons

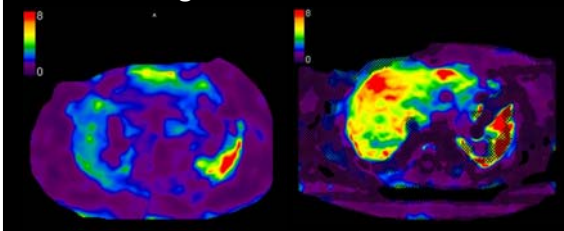
- **Pros**
  - Optimal to detect and measure liver steatosis
  - ≤ 30 min, no IV needed
  - Low failure rate (<5% usual)
- **Cons**
  - Expensive
  - Not widely available
  - Sedation for very young
  - Poor discrimination of lower



Future directions
- Add novel MRI measures to assess inflammation and fibrosis more accurately (multi-parametric MRI)
- Study correlation of changes in MRI with clinical outcomes

Xanthakos et al. Hepatology 2017

Longitudinal ability to detect histologic change unknown in children



Age 8
Mean liver stiffness 2.2 kPa
Stage 1 fibrosis on biopsy

Age 12
Mean liver stiffness 5.5 kPa
Cirrhosis on biopsy

Biopsy remains "gold standard"

- **PROS**
  - **Can** distinguish between NAFLD and NASH
  - Clinical prognosis depends on histology
    - NASH 25-30% risk of progression
    - Early onset pediatric fibrosis more aggressive?
  - Rule out other liver diseases (AIH, Wilson)
  - Intensify Rx and assess response
- **CONS**
  - Risk 1:10,000 risk of death (in adults)
  - Sampling error
  - Expense

My patient has NAFLD, but how do I treat it?

NASPGHAN 2017 Clinical Practice Guideline for Pediatric NAFLD

- **Lifestyle modification to improve diet and increase activity recommended as first-line treatment**
- **No current medications/supplements are recommended**
  - None proven to benefit majority of patients with NAFLD

Challenging to offer lifestyle intervention programs in US

- More **obesogenic environment**
- High proportion of **severe obesity**
- **Poor insurance coverage** for comprehensive weight management treatment
- Disease is often silent
- Patient have little incentive to change behaviors

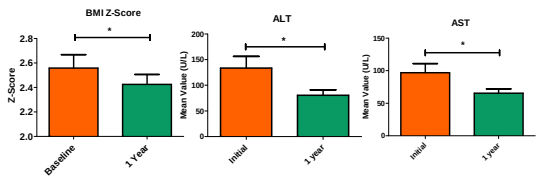
Feasible NASH Clinic Model

- **Pre-clinic planning and initial visit**
  - Screen for related obesity co-morbidities
  - Testing for other causes of liver disease
  - Lifestyle modification advice (RD necessary, psychologist optimal)
- **Every 3-6 month follow up visits**
  - Labs and weight management progress reviewed
  - Liver biopsy as indicated
    - Concern for other disease
    - Concern for progressive or severe NASH

Xanthakos S, Kohli R. Clinical Liver Disease; 1:(4).

Steatohepatitis Center: Outcomes

Only ~50% return for 1 year follow-up
Those with liver biopsy more likely to return



Significant reduction in BMI, ALT and AST (*p<0.05).

Kohli R et al. JPGN 2013

Lifestyle advice

- **Diet:**
  - **Decrease/avoid sugar sweetened beverages and foods (< 6 tsp added sugars per day)**
  - Reduce take out/fast food meals
  - Increase fruits and vegetables to 5/day
- **Activity:**
  - Increase physical activity 1 hr/day
  - Reduce screen time < 2 hs/day
- **Hepatotoxins**
  - **Alcohol counseling** in teens
  - **Hepatitis A and B** vaccination

No established pharmacotherapy in children with NAFLD (large RCT)

- **Metformin**
  - Ineffective at low dose (1000 mg/day) in children
- **Cysteamine bitartrate**
  - Improved ALT significantly, but not histological outcomes
- **Vitamin E**
  - Possibly effective at 800 IU per day
  - % with **histological NASH resolution** at 96 week follow up biopsy:
    - 28% with placebo
    - **58% with vitamin E** (*P* = .006)

Vitamin E remains controversial

- **Caveats**
  - **Secondary analysis (N of 39 with NASH in trial)**
    - Predominantly due to reduced ballooning
    - No effect on steatosis, inflammation or fibrosis
  - **CVD and prostate cancer risk in adults taking high dose vitamin E**
    - Not seen in 2 year NASH CRN studies
    - But not studied in type 2 DM patients
  - **If using it, recommend biopsy pre-treatment to stage disease severity and consider post-treatment biopsy to reassess**

Sobering facts about pediatric NASH in the U.S. and lifestyle intervention

- **Many children with NASH are severely obese**
  - **Mean BMI of 33-34kg/m^2** common in USA studies
- **Treatment of severe obesity is more difficult**
  - Only 2-4% of severely obese kids reduced BMI in intensive treatment trials
  - Vast majority regained lost weight
  - High attrition rates (>50%)

ASMBS guidelines

ASMBS pediatric committee best practice guidelines

Marc Michalsky, M.D., F.A.C.S., F.A.A.P.[a,e], Kirk Reichard, M.D., F.A.C.S., F.A.A.P.[b], Thomas Inge, M.D., F.A.C.S., F.A.A.P.[c], Janey Pratt, M.D., F.A.C.S.[d], Carine Lenders, M.D., F.A.A.P.[e]

Selection criteria for adolescent weight loss surgery

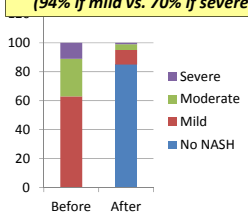
BMI	Comorbidities
≥ 35	• Type 2 DM • moderate-severe OSA (AHI ≥ 15 events/hr) • pseudotumor cerebri • severe NASH
≥ 40	• Mild OSA (AHI>5 events/hr) • HTN • Insulin resistance/IGT • Dyslipidemia • impaired QOL or ADL

SOARD 2012;8:1-7

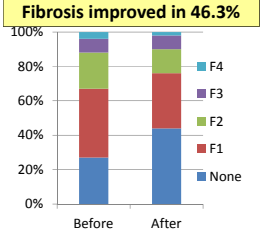
Adult data suggest high remission of NASH after bariatric surgery

N=109 adults (mean BMI 48.9) with NASH

85% Remission of NASH
(94% if mild vs. 70% if severe)



Fibrosis improved in 46.3%



Lassailly et al. Gastroenterology 2015

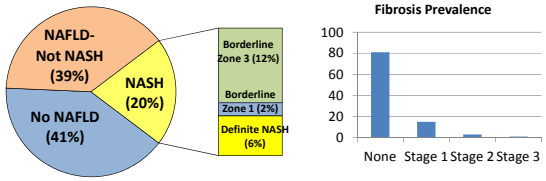
One year outcome after sleeve gastrectomy (SG) in teens with NAFLD

- 20 adolescents underwent SG and 53 non-surgical lifestyle intervention (NSWL)
- At 12 months, **weight loss -21.5% after SG** vs. **gain of +1.75%** after NSWL **(53% attrition)**
- NAFLD resolved in 75% and fibrosis stage 2 resolved in 90%
  - 100% of patients with NASH (6/6) resolved completely
- No significant histological or metabolic improvement after NSWL
- **Caveats:**
  - No advanced fibrosis, only 19% prevalence of NASH
  - Type 2 DM prevalence?
  - Small N

Manco M et al. J Pediatri 2017

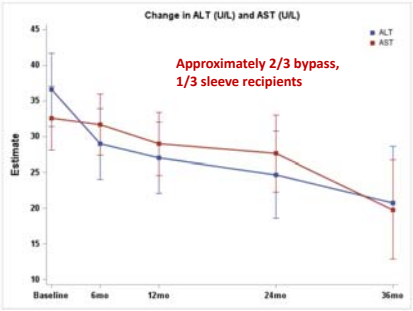
Low prevalence of NASH in adolescents in Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS)

157 teens with intraoperative liver biopsies (BMI 52 kg/m², age 15)
16 excluded due to medications (13) or insufficient tissue (3)



Xanthakos et al. Gastroenterology 2015

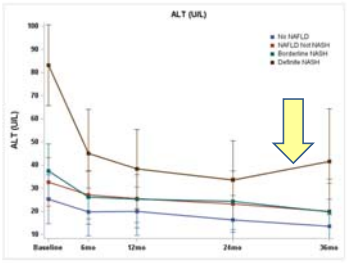
ALT outcomes in Teen LABS at 3 years



Xanthakos et al. Teen LABS Manuscript in preparation

Long term outcomes unknown after bariatric surgery

- **Most studies short term to date**
  - **1-3 years in adults**
  - **1-2 years in teens**
  - **Small N in teens**
  - **Remission vs. Cure?**



Xanthakos et al. Teen LABS Manuscript in preparation

Additional Barriers for Bariatric Surgery as Treatment for NASH

- **Not available to everyone**
  - **Cost? (need cost-effectiveness studies)**
- **Not appropriate for everyone**
  - Not all are severely obese (~ ½ of kids with NASH)
  - Younger age - most appropriate for 13+ years
  - Psychosocial barriers/poor adherence
  - Not interested (surgical risk)

More pediatric clinical trials needed!

- **Nutritional supplements** (various combinations)
  - Fish oil (mixed results to date)
  - DHA+ vitamin E + choline (reduced steatosis by US)
  - DHA + vitamin D (improved NAFLD activity score)
  - Vitamin E + hydroxytyrosol (olive oil phenol) – not published yet
- **Probiotics (variety of organisms)** ALT and US improvement in one study
- **Low sugar diet** (in progress at 2 sites)
- **Intensive lifestyle intervention vs. sleeve gastrectomy** in U.S. cohort (in progress, single site)

Della Corte C. PLoS One 2016
Famouri et al JPGN 2017
Alisi A et al. Aliment Pharmacol Ther 2014

Limitations of many pediatric NAFLD intervention studies to date:

- **Uncertain generalizability and reproducibility**
  - Single center, smaller cohorts (40-60 patients)
  - Lack of validation in larger independent cohorts
  - Limited # with advanced fibrotic liver disease
  - Limited # of patients with type 2 diabetes
  - Varying prevalence and degree of severe obesity
- **Problematic outcome measures**
  - Histological outcomes o. en lacking (↓ ALT may not = improvement)
  - Imaging outcomes using US are not optimal
- **Duration may be too short to detect meaningful change**
  - 2-6 months

Options for patients ≥ 18 years

- **Obeticholic acid phase 3 study**
  - 45% improved NAFLD and 22% resolved NASH in phase 2 RCT
  - Can raise LDL-c and lower HDL-c
- **If type 2 diabetes (not FDA-approved for NASH):**

  Pioglitazone - 18 month RCT 45 mg vs. placebo
  - 51% vs. 19% NASH resolution, p<0.001
  - Mild weight gain vs. placebo, no difference in adverse events

  Liraglutide – GLP 1 agonist approved for T2DM and weight loss, 1.8 mg daily x 48 weeks
  - 39% resolution of NASH vs. 9% placebo, p<0.05 in 52 adults
  - Decreased fibrosis progression

Armstrong MJ Lancet. 2016 Feb 13; 387(10019):679-90.
Cusi K. Ann Intern Med 2016;165(5):305

Take-Home Messages (1)

- **Screen for NAFLD**
  - Normal or overweight children with metabolic risk factors
  - All obese children
- **More data support MRI to quantify steatosis and detect advanced fibrosis in children than current US methods**
  - But expensive and not widely available
  - Validated thresholds for Fibroscan and ARFI lacking for pediatric NAFLD

Take-Home Messages (2)

- **Lifestyle intervention always first line**
- **Vitamin E controversial** – not recommended in recent guidelines until further validation
- **Consider weight loss surgery** if meeting medical criteria
- **More well-designed clinical trials** in children with NAFLD urgently needed

Therapeutic Drug Monitoring in Pediatric IBD

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Disclosures

- No relevant disclosures

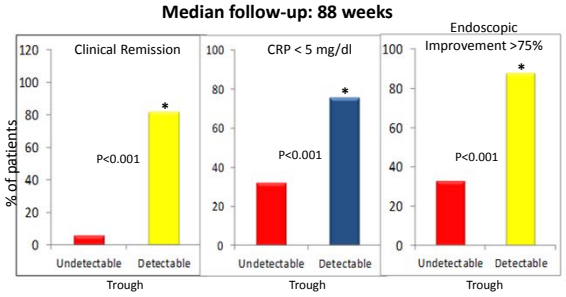
Objectives

- Review role of therapeutic drug monitoring (TDM) for biological therapy in treatment of pediatric IBD
- Describe optimization of therapies via **reactive TDM**
- Explore role for **proactive TDM**

Predictive Value of Trough/Anti-Drug Antibody (ADA)

Higher Infliximab (IFX) Levels Associated with Better Outcomes

Prospective cohort (n=105)
Median follow-up: 88 weeks



Maser EA, *et al. Clin Gastroenterol Hepatol* 2006;4:1248–54.

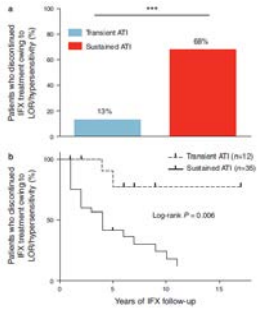
IFX Trough Levels Predict Future Loss of Response (LOR)

- 90 adult IBD patients (59% with known ATI)
- Retrospectively measured 1,232 serum IFX levels via mobility shift-assay (HMSA)
- Greatest predictor of IFX failure
  - Any IFX trough < 0.91 µg/ml
- IFX trough <2.2 µg/ml at week 14 predicts
  - Develop ATI (p<0.0001)
  - Discontinue IFX for LOR/hypersensitivity (p=0.003)

Vande Casteele N et al. *Am J Gastroenterol* 2013; 108(6):962-71

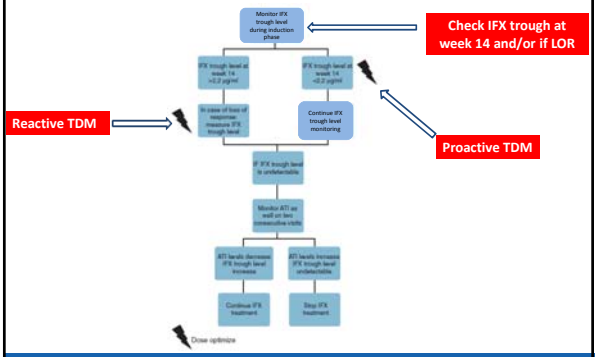
Antibody to IFX (ATI) Can Be Transient

- ATI was **transient** in 28%
- ATI could be overcome by escalating therapy
  - ATI > 9.1 U/mL → risk of failure (LR 3.6)



Vande Casteele N et al. *Am J Gastroenterol* 2013; 108(6):962-71

Suggested Algorithm: Proactive and Reactive TDM



Vande Casteele N et al. *Am J Gastroenterol* 2013; 108(6):962-71

Early Infliximab Trough Associated with Persistent Remission in Pediatric IBD

- Prospective observational cohort (n=58) of pediatric patients (<21 yo) starting IFX
  - 50/58: Primary responders; entered maintenance phase
- 60% (30/50) achieved persistent remission (PR)
- Median infliximab trough at week 14
  - Persistent remission: **4.7 µg/ml**
  - Not persistent remission: **2.6 µg/ml**

p<0.03

PR: Week 54 remission (PCDAI, CDAI, or partial Mayo); no IFX dose escalation

Singh N, et al. *Inflamm Bowel Dis* 2014; 20: 1708-1713

Week 10 IFX Level and Duration of Response

Prospective cohort, pediatric Crohn disease (n=77)

	On IFX (n = 60)	Off IFX (n = 17)	*P*
s-IFX, μg/mL			
10 wk s-IFX	20.40 (11.20 to 35.00)	8.70 (0.90 to 16.90)	0.01
6 mo s-IFX trough	4.00 (1.20 to 7.90)	1.30 (0.90 to 4.90)[a]	0.28
Detectable ATI			
10 wk, n (%)	0 (0)	3 (18)	0.008
6 mo, n (%)	6 (10)	2 (22)[a]	0.30

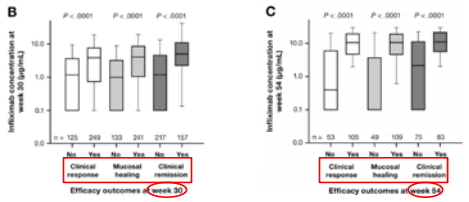
	Sensitivity, %	Specificity, %	PLR	NLR	AUC (95% Confidence Interval)	*P*[a]
10 week s-IFX ≥ 9.10 μg/mL	80.70	60.00	2.02	0.32	0.71 (0.54–0.88)	0.00
Δs-TNF-α 0–10 wk ≤ −3.60 pg/mL	81.48	66.67	2.44	0.28	0.74 (0.58–0.91)	0.00

[a]Fisher's exact test used to test the association between each cutoff and ongoing therapy at 12 months.

Stein R, et al. *Inflamm Bowel Dis* 2016; 22: 1370-1377

Concentration of Infliximab and Efficacy in Adult UC

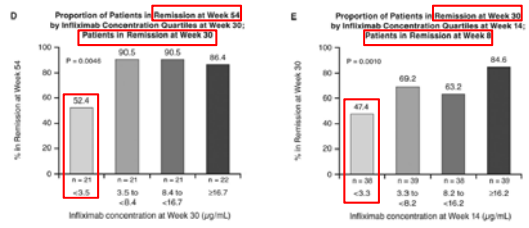
Post-hoc analysis of ACT-1 and ACT-2



(Regardless of 5 mg/kg or 10 mg/kg)

Adedokun EA, et al. *Gastroenterology* 2014; 147:1296–1307

Concentration of Infliximab Associated with Subsequent Efficacy in Adult UC

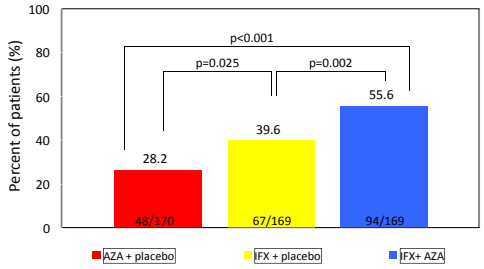


Remission but subtherapeutic IFX trough → Less likely to maintain remission

Adedokun EA, et al. *Gastroenterology* 2014; 147:1296–1307

SONIC Trial

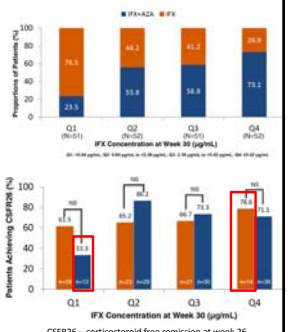
Corticosteroid-Free Clinical Remission at Week 50



Colombel JF et al. *N Eng J Med*. 2010; 362:1383-1395

SONIC Post Hoc – Combination Therapy Benefit Primarily Due to Improved IFX Levels

- Exposure-response within IFX concentration ranges evaluated
  - With & without azathioprine (AZA)
  - N=206 from SONIC
- Combination therapy associated with higher IFX troughs
- Within quartiles, no benefit to combination therapy
- **Conclusion:** Benefit of combination therapy primarily due to AZA's influence on PK of IFX



CSFR26 – corticosteroid free remission at week 26

DDW 2017: Colombel et al. , Abstract 134

Variables Affecting Clearance of Biological Therapies

Factors Affecting Pharmacokinetics of Monoclonal Antibodies

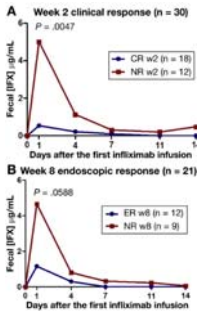
	Impact on pharmacokinetics
Presence of ADAs	Decreases serum (mAbs) Threefold-increased clearance Worse clinical outcomes
Concomitant use of IS	Reduces ADA formation Increases serum (mAbs) Decreases mAbs clearance Better clinical outcomes
High baseline (TNF-α)	May decrease (mAbs) by increasing clearance
Low albumin	Increases clearance Worse clinical outcomes
High baseline CRP	Increases clearance
Body size	High body mass index may increase clearance
Gender	Males have higher clearance

ADA, antidrug antibody; CRP, C-reactive protein; IS, immunosuppressive agent; mAb, monoclonal antibody; TNF-α, tumor necrosis factor-α. Terms in parentheses refer to serum concentration.

Ordas I et al. *Clin Pharmacol Ther.* 2012;91:635

Fecal Loss of IFX Contributes to Lack of Response in Acute Severe Colitis

- Moderate to severe UC, anti-TNF naïve (n=30)
  - Fecal samples collected within first 14 days following 1st IFX (5 mg/kg)
- During 1st 2 weeks of treatment
  - 83% had detectable IFX in feces
  - Peak concentrations: Day 2
- Non-responders:
  - Higher fecal IFX at Day 1 (p=0.02)
  - Lower serum IFX at Day 14 (p=0.03)



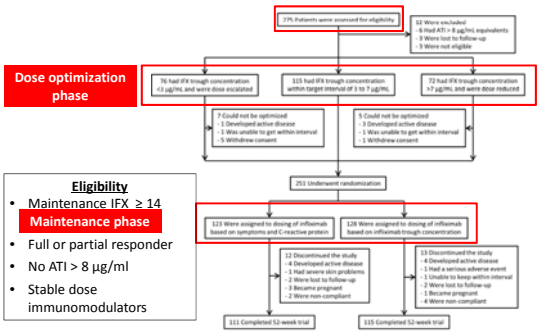
Clinical response: Simple Clinical Colitis Activity Index 4 points, or drop of 50% from the baseline value
Endoscopic response: Mayo score improvement of at least 1 point

Brandse JF et al *Gastroenterology* 2015; 149:350-355

Proactive and Reactive TDM

TAXIT

Trough Concentration Adapted InfliXImab Treatment



Vande Casteele N et al. *Gastroenterology* 2015;148:1320-1329

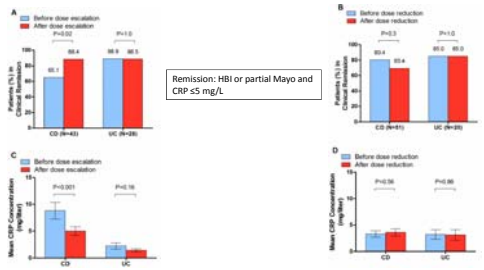
TAXIT

Dose Optimization Phase

148/263 (56.3%) required dose optimization

51.4% → Dose escalation

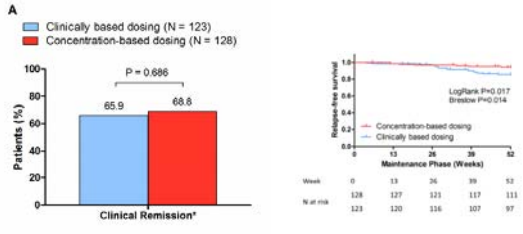
48.6% → Dose reduction



Vande Casteele N et al. *Gastroenterology* 2015;148:1320-1329

TAXIT

Maintenance Phase



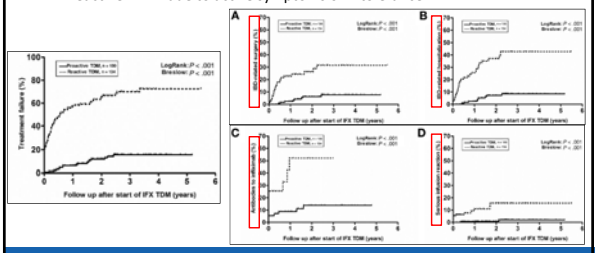
- Clinically based vs. concentration-based:
  - More relapses
  - Required more rescue therapy
  - Had lower IFX troughs/more ADA

Vande Casteele N et al. *Gastroenterology* 2015;148:1320-1329

Proactive vs. Reactive TDM in Clinical Practice

Multi-center, retrospective cohort of adult IBD patients (n=264) who responded to IFX induction therapy

- Proactive: TDM prior to active disease; titrate to goal trough
- Reactive: TDM due to active symptoms or intolerance



Papamichael R, et al. *Clin Gastroenterol Hepatol* 2017; epub ahead of print

Official AGA Recommendations on TDM

- In adults with active IBD treated with anti-TNF agents, the AGA suggests **reactive TDM** to guide treatment changes (conditional, very low quality of evidence)
- In adults with clinically quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of **routine proactive TDM**
  - Knowledge gap and need for further studies

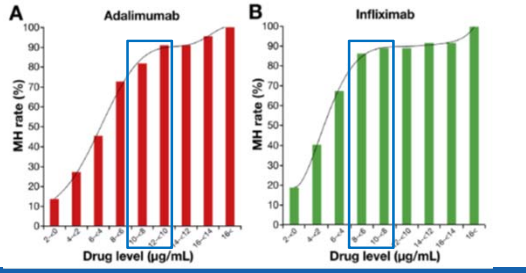
American Gastroenterological Association

Feuerstein JD et al. *Gastroenterology* 2017; epub ahead of press

Identifying Targets

Assessing Optimal Anti-TNF Levels for Mucosal Healing

Retrospective, observational cohort adult study (n=145; 78 IFX, 67 adalimumab; 111 CD; 34 UC)



Ungar B et al. *Clin Gastroenterol Hepatol* 2016; 14:550-557

What is Our Target??

- Vary based on study; agreed upon targets not established
- Possibly different based on indication/goal
  - Mucosal healing may require higher trough[1]
  - Perianal fistula closure improved with IFX trough >10 [2]
  - Acute severe UC flare vs. maintenance of mucosal healing
- Mucosal levels?

1. Rakowsky S et al. DDW 2017, Abstract Sa1882
2. Yarur AJ et al. *Aliment Pharmacol Ther* 2017; epub ahead of press

Tissue Anti-TNF Levels and Endoscopic Disease Activity

- Cross-sectional, adult IBD on IFX or ADA (n=30)
- TNF and anti-TNF measured from serum and tissue
  - Generally good correlation
  - Higher levels of both in more inflamed tissue
- Serum/tissue anti-TNF mismatch
  - 73.3% in active disease, 33.3% in remission (p=0.03)

Table 2 Correlation of serum anti-tumour necrosis factor (TNF) with tissue anti-TNF

Correlation	Spearman r	p Value
All samples		
Anti-TNF in serum and tissue	0.39	0.002*
Non-inflamed		
Anti-TNF in serum and tissue	0.50	<0.001*
Inflamed		
Anti-TNF in serum and tissue	0.19	0.54
Ileum samples		
Anti-TNF in serum and tissue	0.34	0.049*
Colon samples		
Anti-TNF in serum and tissue	0.44	0.026*
Infliximab samples		
Anti-TNF in serum and tissue	0.51	0.017*
Adalimumab samples		
Anti-TNF in serum and tissue	0.23	0.174

*Statistically significant.

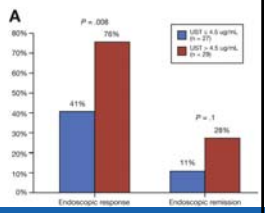
Patients with active disease may have low tissue anti-TNF despite good serum levels

Yarur AJ, et al. *Gut* 2015; 65: 249-255

TDM for Other Biologics

Ustekinumab (UST) Trough Associated with Endoscopic Response

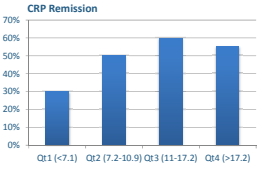
- 62 adult CD patients
  - Longitudinal and cross-sectional
  - Induction: 90 mg SQ weeks 0,1,2
  - Maintenance: 90 mg q 4 or 8 weeks
  - UST trough/ADA week ≥26
- Week ≥ 26 trough > 4.5 µg/ml
  - Higher endoscopic response
  - Lower mean CRP (12.6±21.1 vs 23.9±34.1 mg/L; p=04)
  - No difference in clinical remission



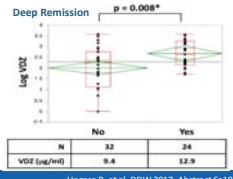
Battat R, et al. *Clin Gastroenterol Hepatol* 2017; epub ahead of print

Association Between Vedolizumab Levels and Remission Rates

- Retrospective, cross-sectional study[1]
  - n=180 (50% CD), 38% combination therapy
  - VDZ levels higher in:
    - Clinical remission (p=NS)
    - **CRP remission**, 11.7 vs 10.0 (p=0.02)
      - VDZ >7.1 more likely to be in CRP remission
        - » **OR: 2.5**, 95%CI 1.2-5.1 overall
        - » **OR 3.7**, 95%CI 1.3-10.5 in CD



- Prospective, cross-sectional study[2]
  - n=56 (73% CD), 36% combination therapy
  - 43% with deep remission (DR)
  - VDZ levels ≥5.1 more likely to be in DR (**OR:6.6**, 95%CI 1.6-45.8] p=0.009)



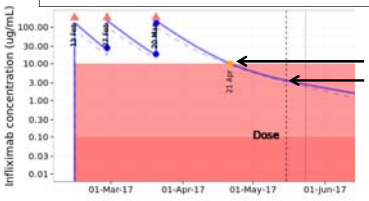
	No	Yes
N	32	24
VDZ (µg/ml)	9.4	12.9

Ungaro R, et al. DDW 2017. Abstract Sa1891
Yarur, et al. DDW 2017. Abstract Sa1906

Future – Individualized Dashboards

PK Dashboard Optimizing IFX

Input: Age, gender, weight, albumin, disease activity, previous dose, levels, etc.



Expected target IFX=10 0n **4/21** (4 wk, 4 d)

First maintenance if 8 weeks from Inf#3: **5/15** Predicted IFX level ~ 3.48

Inf#	Date	Dose	ALB	CRP	Pre-IFX	Post-IFX	ATI
1	2/13	5 mg/kg	3.6	4.7	-	-	-
2	2/27	5 mg/kg	4.0	0.2	27.1	-	<3.1
3	**3/20**	**5 mg/kg**	**4.4**	**4.0**	**18.1**	**129.2**	**<3.1**

Units: Albumin levels in g/dL, C-reactive protein levels in mg/dL, IFX levels in ug/mL

Courtesy of Marla Dubinsky MD

Conclusions

- Measureable drug levels → Better outcomes
  - Less risk of ADA
- Standard dosing regimen often inadequate
- **Reactive TDM** should be utilized
- **Proactive TDM** makes sense, but need more data
  - Optimization vs. maintenance phase
- Target trough may vary
- Personalized dosing may be the future

Thank you

Types of Assays

- **ELISA**
  - Most commonly utilized
  - Commercially available
  - Cannot measure ADA in presence of drug
- Fluid-phase radioimmunoassay (**RIA**)
- High-Pressure liquid chromatography-based homogeneous mobility shift assay (**HMSA**)
  - Dissociates drug-ADA complexes
  - Can measure ADA in presence of drug

What if Anti-TNFs FAIL?

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JOHNS HOPKINS MEDICINE

Disclosures

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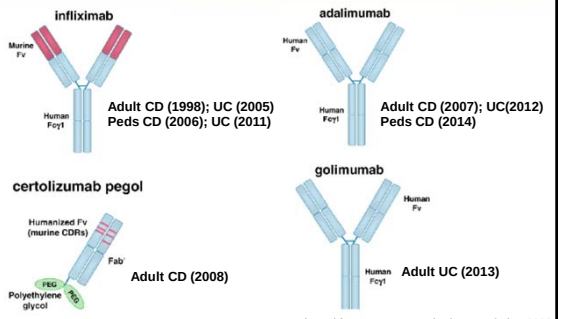
- Prometheus—research grant
- Nestle Nutrition—educational grant
- Hoffman LaRoche--consultant

Objectives

- Review why anti-TNF medications may fail
- Discuss the efficacy and safety profiles of newer biologic therapies in the treatment of IBD
  - vedolizumab and ustekinumab

Commercially Available Anti-TNFs for IBD



Adapted from Tracey D et al, Pharmacol Ther 2008

Primary Nonresponse to Anti-TNF

- Occurs in 10-15% children; up to 30% adults
- Symptoms may not due to IBD
- Non-TNFα mediated mechanisms of inflammation
- Inadequate drug levels from rapid clearance

Hyams JS et al, Gastoenterology
Ordas I et al. Clin Pharmacol Ther 2012

Secondary Loss of Response to Anti-TNFs

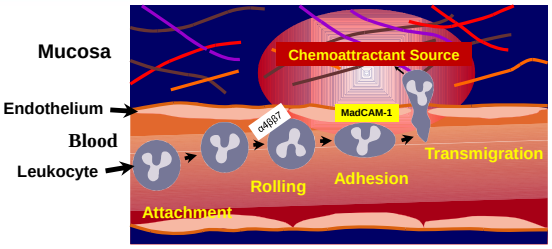
- Occurs in 10-20% of patients per year
- Inability to maintain adequate serum drug levels
  - Inadequate dose, anti-drug antibodies, rapid clearance
- Anatomic issue (e.g. stricture, fistula, abscess)
- Symptoms not from IBD (e.g. IBS, *C. difficile* infection)

Ordas I et al. Clin Pharmacol Ther 2012

Options Beyond Anti-TNFs

- Is surgery the best next step?
  - Ulcerative colitis: colectomy with/without pouch
  - Crohn's disease: limited resection, diversion, colectomy
- Is long term nutritional therapy an option?
- What other medications are now available?

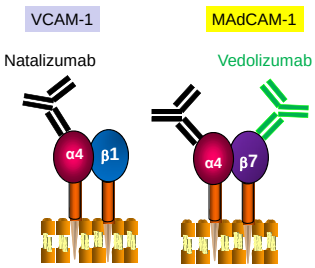
Leukocyte Transmigration is an Important Component of Inflammation



Adapted from Springer TA, Cell 1994

Anti-integrin Biologic Agents

- **Natalizumab**
  - Binds α4 subunits
  - Interferes with lymphocyte surveillance of central nervous system
  - >200 cases of progressive multifocal leukoencephalopathy
- **Vedolizumab**
  - Binds β7 subunit
  - Increased gut specificity



GEMINI 1: Vedolizumab for UC Clinical Response at week 6

	Placebo (N=149)	Vedolizumab (N=225)	Percentage-Point Difference (95% CI)	P-Value
Clinical response	38 (25.5%)	106 (42.1%)	21.7 (11.6-31.7)	<0.001
Clinical remission	8 (5.4%)	38 (16.9%)	11.5 (4.7-18.3)	0.001
Mucosal healing	37 (24.8%)	92 (40.9%)	16.1 (6.4-25.9)	0.001

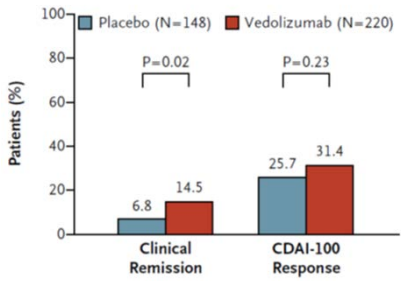
Feagan BG et al, N Eng J Med 2013

GEMINI 1: Vedoliuzmab for UC Clinical Outcomes at week 52

Outcome	Placebo (N=126)	Vedolizumab every 8 wk (N=122)	P Value
Remission	15.9%	41.8%	<0.001
Steroid-free remission	13.9%	31.4%	<0.01
Mucosal healing	19.8%	51.6%	<0.001

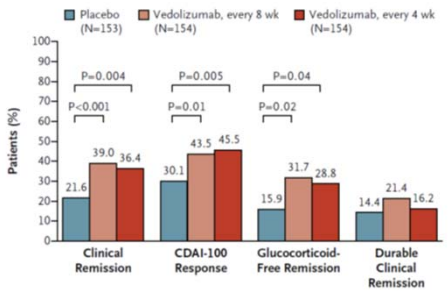
Feagan BG et al, N Eng J Med 2013

Gemini 2: Vedolizumab for CD Primary endpoint at week 6



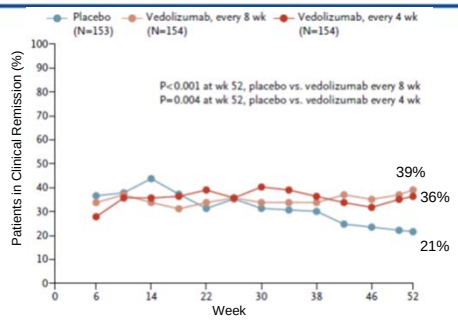
Sandborn W et al, N Eng J Med 2013

GEMINI 2: Vedolizumab for CD Clinical Outcomes at week 52



Sandborn W et al, N Eng J Med 2013

GEMINI 2: Vedolizumab for CD Remission at Week 52



Sandborn W et al, N Eng J Med 2013

Vedolizumab Pediatric Retrospective Studies

- **Singh N et al, Inflamm Bowel Dis 2016**
  - 52 patients (58%CD/42%UC)
  - 90% failed ≥1 anti-TNF
  - Clinical remission at week 14: 76% UC, 42% CD (p<0.05)
- **Conrad MA et al Inflamm Bowel Dis 2016**
  - 21 patients (76% CD/ 34% UC or IBD-U)
  - 100% failed ≥1 anti-TNF
  - Clinical response: 31.6% at wk 6; 57.9% at wk 22
  - Steroid free remission: 5% at wk 6, 15% at wk 14, 20% at wk 22
- **Ledder O et al, J Crohns Colitis 2017**
  - 64 patients (36% CD/ 64% UC or IBD-U)
  - 100% failed ≥1 anti-TNF
  - Steroid free remission at week 14: 37% UC, 14% CD (p=0.06)
  - 10 patients needed surgery; 6 colectomy

Vedolizumab Dosing

- FDA approval May 2014 for adults with moderate to severe UC or CD
- Induction regimen is not weight based in adults:
  - 300 mg infusion at weeks 0, 2 and 6
- Maintenance
  - 300 mg q 8 weeks
- Pediatrics
  - "Smaller patients" 5-6 mg/kg/dose (Singh et al 2016)

Therapeutic Drug Monitoring with Vedolizumab

- Higher trough drug levels reported in responders and seen more commonly with mucosal healing
- GEMINI Trials: During maintenance, trough mean levels ~11-13 µg/ml q 8 week dosing; ~32-34 µg/ml with q 4 week dosing
- Trough levels during maintenance >7 ug/mL (using drug tolerate assay) more likely to be associated with remission
- Anti-drug antibodies ~3-4%

Feagan B et al, NEJM 2013
Sandborn W et al, NEJM 2013
Williet N et al, Clin Gastroenterol Hepatol 2016
Ungaro RC et al, Gastronetrology 2017 abs S-385

Vedolizumab Safety: Encouraging Signs But Ongoing Monitoring Required

No increased risk of:

- Adverse events in patients assigned to drug in clinical trials
  - Most commonly reported AEs was headache, URIs, arthralgia
- Infection (including serious infection)
- Malignancies
- Progressive multifocal leukoencephalopathy (PML)

Infusion reactions low (<5% patients)

Colombel JF et al Gut 2016
Bye WA et al, Aliment Pharmacol Ther 2017

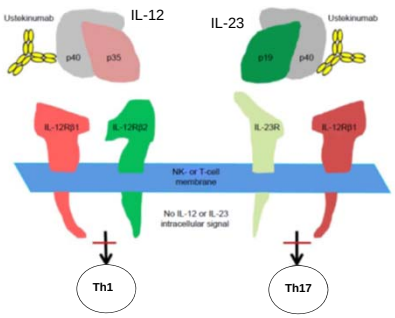
30-Day Post-Operative Complications in IBD Patients Undergoing Abdominal Surgeries

	No biological therapy (n=172)	Anti-TNF (n=126)	Vedolizumab (n=94)	P-value
Any post-op Complication	57 (33%)	35 (28%)	50 (53%)	<0.01
Non-SSI Infections	10 (16%)	6 (5%)	7 (7%)	<0.71
All SSIs	22 (13%)	13 (10%)	35 (37%)	<0.01
sSSIs	11 (6%)	5 (4%)	20 (21%)	<0.01
dSSIs	11 (6%)	6 (5%)	13 (14%)	<0.03
Anastom. leak	1 (1%)	4 (3%)	2 (2%)	<0.24
MCS	1 (1%)	1 (1%)	7 (7%)	<0.01
SBO/ileus	20 (12%)	12 (10%)	9 (10%)	<0.79
Re-admission	17 (10%)	12 (10%)	15 (16%)	<0.24
Return to OR	8 (5%)	10 (8%)	8 (9%)	<0.37

SSI: surgical site infection (s-superficial; d-deep)
MCS: mucocutaneous separation; SBO: small bowel obstruction

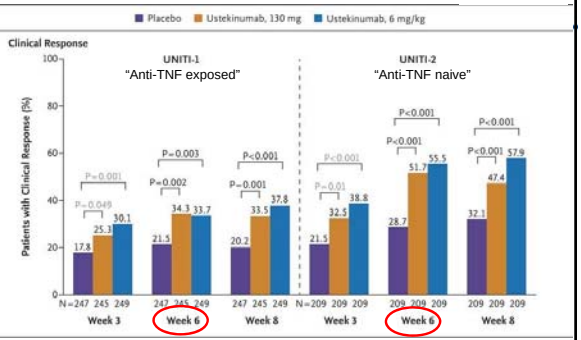
Lightner AL J Crohn's Colitis 2017

Ustekinumab Blocks IL-12 and IL-23 Signaling



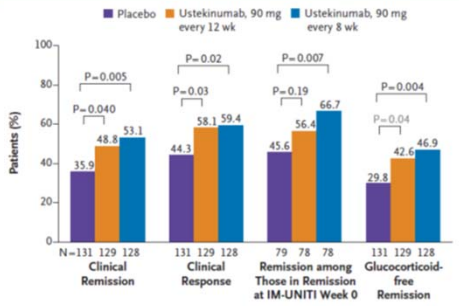
Deepak P & Loftus EV, Drug Design Develop 2016

UNITI-1 & 2: Primary Outcome Clinical Response at Week 6



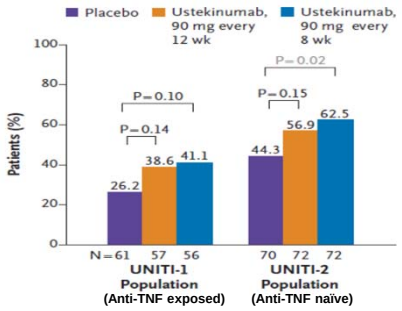
Feagan BG et al, N Eng J Med 2016

IM-UNITI: Ustekinumab Maintenance for CD Primary and Secondary Endpoints



Feagan BG et al, N Eng J Med 2016

IM-UNITI: Ustekinumab Maintenance for CD Remission by Subgroups



Feagan BG et al, N Eng J Med 2016

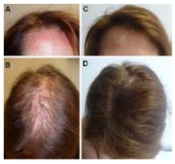
Ustekinumab Case Reports in Pediatric Crohn's Disease

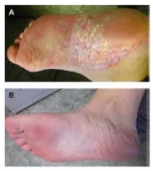
- 4 patients:12-17 yrs (2 perianal disease)
  - Failed Aza, MTX, 1-3 anti TNFs
  - 2 patients clinically improved
- 16 yo with ileocolonic disease
  - Failed Aza, MTX, 2 anti-TNFs including combo therapy
  - Failed ustekinumab and required requiring colectomy
- 7 yo with active colitis, chronic arthritis (symptoms started 9 months of age)
  - Failed Aza, MTX, 2 anti-TNFs
  - Responded to 3 SC doses of ustekinumab and transitioned back to Aza
  - In clinical and biochemical remission at 1 year

Bishop C et al, J Pediatr Gastroenterol Nutr 2016
Cameron FL et al, J Pediatr Gastroenterol Nutr 2016
Rinawi F et al, J Pediatr Gastroenterol Nutr 2016

Ustekinumab for Anti-TNF Induced Psoriasiform Rashes

- 14 adults with CD and anti-TNF induced rash: 11 (79%) clinical improvement of CD at 3 months and 13 (93%) improvement of rash
- 9 adults with CD had significant improvement in rash and alopecia





Wils P et al, Clin Gastro Hepatol 2016
Tillack C et al, Gut 2014

Ustekinumab Dosing

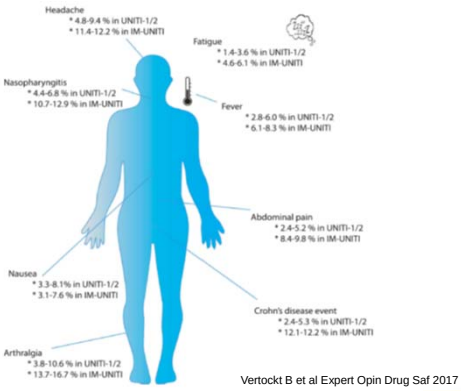
- FDA approval Sept 2016 for adults with moderate to severe Crohn's disease
- Induction regimen is weight based (vials 130 mg):
  - 260 mg IV for <55 kg
  - 390 mg IV for 55-85 kg
  - 520 mg IV for >85 kg
- Maintenance 8 weeks after initial dose, 90 mg SC q 8W
- Pediatrics
  - 3 mg/kg induction, then 90 mg (1.5 mg/kg) SC (Cameron et al 2016)
  - 7 yo 22.5 mg (1.3 mg/kg) at months 0, 1 and 3 (Rinawi et al 2016)

Therapeutic Drug Monitoring with Ustekinumab

- In substudy of UNITI patients, proportion achieving endoscopic response increased with higher trough levels >0.5 µg/mL, >1.39 µg/mL, >2.67 µg/mL
- Maintenance trough concentrations of >4.5 ug/mL associated with endoscopic response and lower CRP
- Anti-drug antibodies ~2-5%

Sandborn W et al, N Engl J Med 2012
Battat R et al, Clin Gastroenterol Hep 2017

Most Commonly Reported AEs in CD Patients in UNITI Trials



Vertockt B et al Expert Opin Drug Saf 2017

Ustekinumab Safety: Psoriasis Data Reassuring But Longer Term IBD Data Required

- Extensive adult safety data exists for psoriasis treatment (Psoriasis Longitudinal Assessment and Registry (PSOLAR)
  - Extensive safety data; 12,093 patients (40,388 patient years)
  - No increased risk of malignancy, serious infection, mortality, or major adverse cardiovascular events
- Phase III RCT pediatric psoriasis trial (CADMUS)
  - 12-17 years
  - No significant increase in AEs in drug compared to placebo
  - Common AEs similar to adults
- Difficult to extrapolate safety data to other indications and dose

Papp K et al J Drugs Dermatol 2015
Landells I et al J Am Acad Dermatol 2015

Positioning Emerging Biologics in the Pediatric IBD Treatment Paradigm

Vedolizumab	✓ May be used as 1st-line therapy; efficacy >UC vs CD ✓ May be reasonable next step after anti-TNF failure for CD (especially colonic) ✓ Consider use in patients at risk/history of malignancy, serious infection
Ustekinumab	✓ 2nd-line for moderate to severe CD refractory/unresponsive to anti-TNFs ✓ May be preferable in CD patients with anti-TNF-induced psoriasiform rashes

Other Drugs in Phase II-III Development

- JAK kinase inhibition
  - Tofacitinib[1] (Xeljanz®): oral small molecule
- Anti-integrins
  - Etrolizumab[2] (subcutaneous) targets α4β7 and αEβ7
- Anti IL-23
  - Brazikumab[3]
  - Risankizumab[4]
- Anti-SMAD7
  - Mongersen[5]: oral antisense RNA

[1]Sandborn WJ et al, N Engl J Med 2017
[2]Vermeire S et al, Lancet 2014
[3]Sands BE et al, Gastroenterology 2017
[4]Fegan B et al, Lancet 2017
[5]Monteleone G et al, N Engl J Med 2015

Key Points

- ✓ Options for pediatric patients not responding to or failing anti-TNFs have recently expanded to include anti-integrin and anti IL-12/23 medications
  - ✓ These new medications may becoming increasingly positioned as first line therapies along with anti-TNFs
  - ✓ Medical evidence remains limited in the pediatric population
  - ✓ Safety profiles are reassuring but post-marketing surveillance will be critical

Prevention of Postoperative Crohn's Disease

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Professor of Medicine & Translational Research
Associate Chief, Education
IBD Clinical Medical Director
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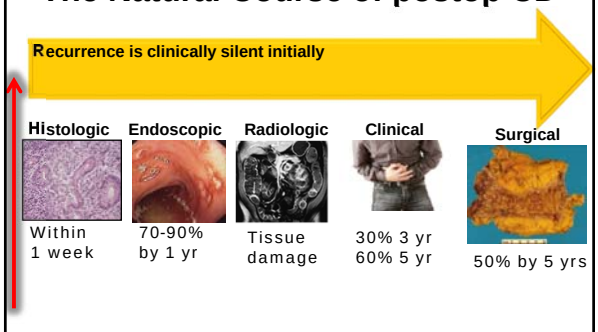
Disclosures

Consultant:
- Abbvie
- Amgen
- Janssen
- Miraca laboratories
- Pfizer
- Takeda
- UCB

Research Grants:
- Abbvie
- Janssen
- Takeda

Unlabeled/Unapproved use of meds (postop):
- Infliximab, adalimumab, vedolizumab

The Natural Course of postop CD



[1] D'Haens G, et al Gastroenterology 1998.
[2] Olaison G, et al Gut 1992.
[3] Rutgeerts P, et al Gastroenterology 1990.
[4] Sachar DB. Med Clin North Am 1990.

Until recently no postop guidelines, but 2 approaches

1. Early treatment for most
2. Endoscopic guidance to decide on treatment

Early Treatment:

Medications for Preventing Postoperative Crohn's Disease

Summary of Postop RCTs

5ASA, Nitroimidazoles, AZA/6MP

Postop Prevention RCTs	Clinical Recurrence	Endoscopic recurrence
Placebo	25% – 77%	53% - 79%
5 ASA	24% - 58%	63% - 66%
Budesonide	19% - 32%	52% - 57%
Nitroimidazole	7% - 8%	52% - 54%
AZA/6MP	34% – 50%	42 – 44%

Regueiro M. *Inflammatory Bowel Diseases*. 2009

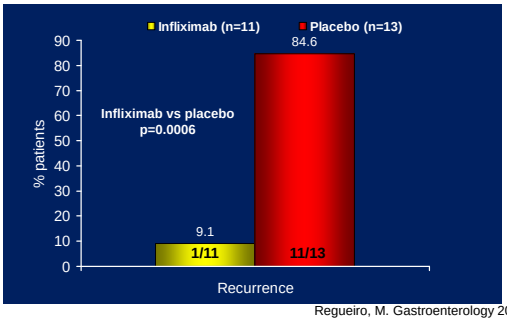
What about Postop antiTNF?

RCT: Infliximab Prevents Crohn's Disease Recurrence after Ileal Resection

Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, Harrison J, Plevy SE.

Gastroenterology 2009;136:441-50.

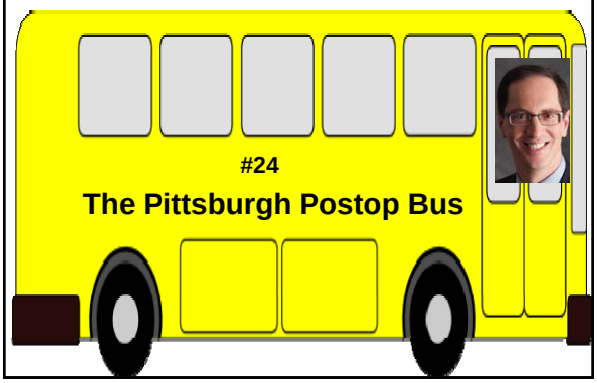
Endoscopic Recurrence Reduced in Infliximab Treated Patients



Regueiro, M. Gastroenterology 2008

Endoscopic Recurrence defined as endoscopic scores of i2, i3, or i4.

The Pittsburgh (Postop) Bus



PO- Endo Recur	antiTNF	Control
Sorrentino[1] (MTX/IFX v 5ASA 2yr)	0%	100% (5ASA)
Regueiro[2] (IFX vs PBO RCT 1 yr)	9%	85% (PBO)
Yoshida[3] (IFX vs PBO Open 1 yr)	21%	81% (5ASA)
Armuzzi[8] (IFX vs AZA Open 1 yr)	9%	40% (AZA)
Fernandez-Blanco [4] (ADA)	10%	N/A
Papamichael[5] (ADA 6m)	0%	N/A
Savarino[6] (ADA 3yr)	0%	N/A
Aguas[7] (ADA 1 yr)	21%	N/A
De Cruz[9] (ADA vs AZA 6mos)	6%	38% (AZA)
Savarino[10] (ADA vs AZA vs 5ASA 2 yrs)	6%	65% (AZA), 83%(5ASA)

…and most recently the large international postop trial…

The PREVENT Study

Infliximab for Prevention of Recurrence of Post-Surgical Crohn's Disease Following Ileocolonic Resection: a Randomized, Placebo-Controlled Study (PREVENT)

M Regueiro[1], BG Feagan[2], B Zou[3], J Johanns[3], M Blank[4], M Chevrier[3], S Plevy[3], J Popp[4], F Cornillie[5], M. Lukas[6], S. Danese[7], P Gionchetti[8], M Molenda[4], SB Hanauer[9], W Reinisch[10], WJ Sandborn[11], D Sorrentino[12], P Rutgeerts[13]

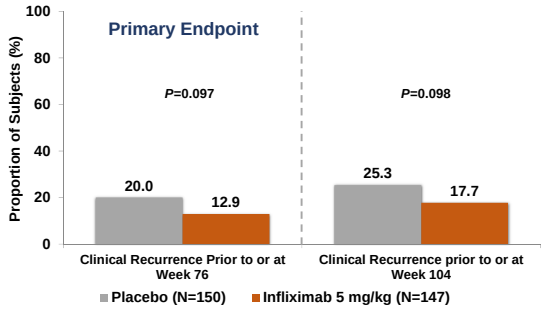
[1]University of Pittsburgh Medical Center, [2]Robarts Research Institute, University of Western Ontario, [3]Janssen Research and Development, LLC., [4]Janssen Scientific Affairs, LLC., [5]MSD International, [6]Charles University, [7]Istituto Clinico Humanitas, [8]DIMEC, S. Orsola-Malpighi Hospital, University of Bologna, [9]Northwestern Feinberg School of Medicine, [10]McMaster University, [11]University of California San Diego, [12]Virginia Tech Carilion School of Medicine, [13]Catholic University of Leuven

This study was supported by Janssen Scientific Affairs, LLC.

Primary Endpoint

Clinical Recurrence

Subjects with Clinical Recurrence Prior to or at Week 76 and Week 104



P-values based on the Cochran-Mantel-Haenszel chi-square test stratified by the number of risk factors for recurrence of active CD (1 or >1) and baseline use (yes/no) of an immunosuppressive (i.e., AZA, 6-MP, or MTX).

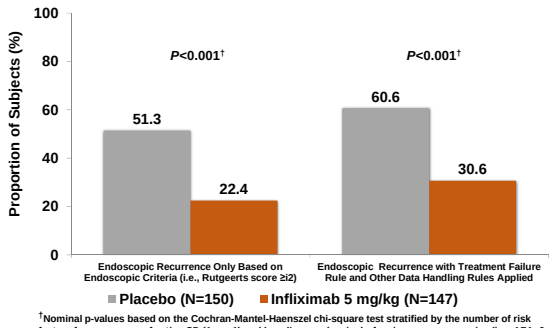
Secondary Endpoint

Endoscopic Recurrence

PREVENT

17

Secondary Endpoint: Subjects with Endoscopic Recurrence Prior to or at Week 76



†Nominal p-values based on the Cochran-Mantel-Haenszel chi-square test stratified by the number of risk factors for recurrence of active CD (1 or >1) and baseline use (yes/no) of an immunosuppressive (i.e., AZA, 6-MP, or MTX).

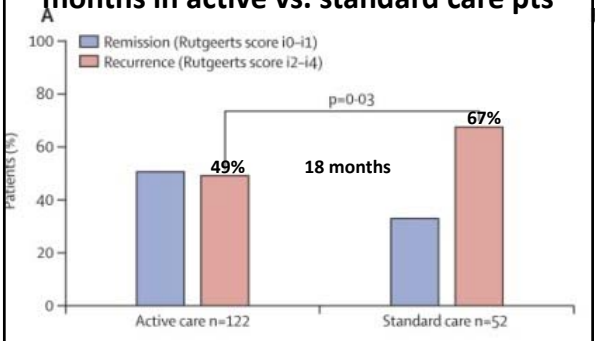
…ok, that was the *early treatment* approach, but what about…

***Watchful Waiting* and Treat Postoperative Crohn's recurrence?**

Crohn's disease management after intestinal resection: a randomized (postoperative Crohn's endoscopic recurrence POCER) trial

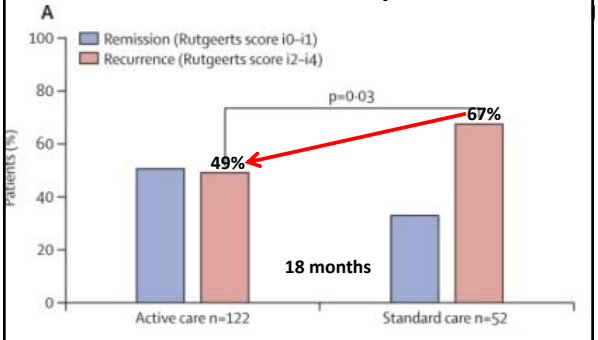
De Cruz P, Kamm M, et al. Lancet 2014

49% vs. 67% endoscopic recurrence at 18 months in active vs. standard care pts



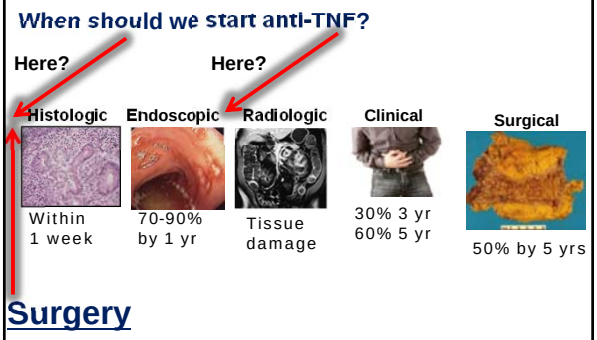
De Cruz, P. Lancet 2014

By scoping at 6 mos and intensifying rx 18% lower rate of endoscopic recurrence

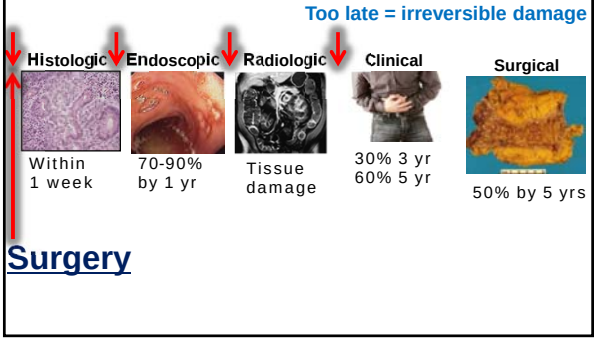


De Cruz, P. Lancet 2014

Prevent vs. Wait for Recurrence?



Ultimate question: when is it too late to start a biologic and when is it just right?



So…the question still remains: How should we manage a Crohn's ds pt who recently had surgery?

Are there better evidence based data or guidelines to help us?

Postop Crohn's disease Guidelines

2017

American Gastroenterological Association Technical Review of the Management of Crohn's Disease after Surgical Resection

Miguel Regueiro, MD[1]*; Fernando Velayos, MD[2]*; Julia B. Greer, MD, MPH[1]; Christina Bougatsos, MPH[3]; Roger Chou, MD[3]; Shahnaz Sultan, MD, MHSc[4]; Siddharth Singh, MD, MS[5]

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.....this AGA Technical Review informed…..

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American Gastroenterological Institute Guideline for the Management of Crohn's Disease after Surgical Resection

Geoffrey C. Nguyen,[1] Edward V. Loftus Jr[2], Ikuo Hirano[3], Yngve Falck-Ytter[4], Siddharth Singh[5], Shahnaz Sultan[6], and the AGA Institute Clinical Guidelines Committee

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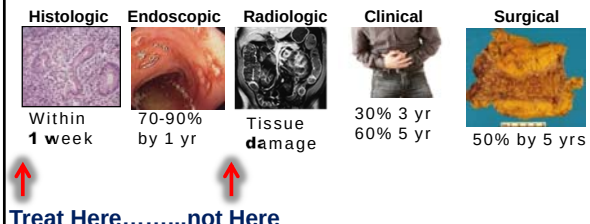
Why guidelines?

"These guidelines are intended to reduce practice variation and promote high-value care."

- AGA Guidelines committee 2016

#1 The AGA Recommends: "early pharmacological prophylaxis over endoscopy-guided pharmacological treatment"

Conditional recommendation, very low quality of evidence

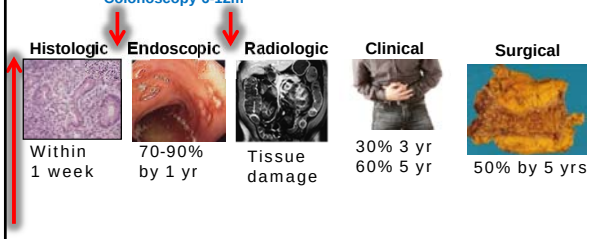


#2 "In patients with surgically induced remission of CD, the AGA suggests using anti-TNF therapy and/or thiopurines over other agents" *Conditional recommendation, moderate quality of evidence*

#3: "In patients with surgically induced remission of CD, the AGA <u>suggests AGAINST using mesalamine</u> (or other 5-aminosalicylates), budesonide or probiotics. *Conditional recommendation, low quality of evidence*

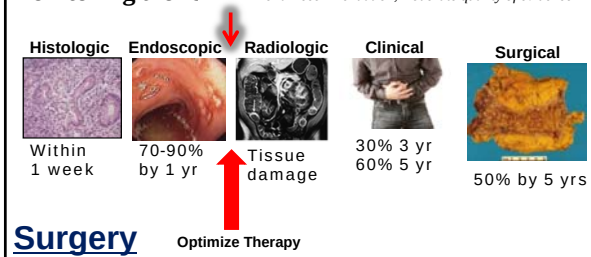
#4: the AGA suggests routine postoperative endoscopic monitoring at 6 to 12 months over no monitoring.

Conditional recommendation, moderate quality of evidence



<u>Surgery</u>

#5 Pts with asymptomatic endoscopic recurrence, the AGA suggests initiating or optimizing anti-TNF and/or thiopurine therapy over continued monitoring alone. *Conditional recommendation, moderate quality of evidence*



<u>Surgery</u>

Ok, so after all of that, how should we manage post op CD?

Need to consider risk for recurrence of CD after surgery

AGA Illustrative risk groups	Clinical Characteristics	Hypothetical risk of clinical recurrence (>18m after surgery)	Hypothetical risk of endoscopic recurrence (>18m after surgery)
Lower Risk	Older patient (>50y); non-smoker; 1st surgery for a short segment of fibrostenotic disease (<10-20cm); disease duration >10 years	20%	30%
Higher risk			

AGA Illustrative risk groups	Clinical Characteristics	Hypothetical risk of clinical recurrence (>18m after surgery)	Hypothetical risk of endoscopic recurrence (>18m after surgery)
Lower Risk			
Higher risk	Younger patient (<30y); smoker; ≥2 prior surgeries for penetrating disease, with or without perianal disease	50%	80%

AGA Illustrative risk groups	Clinical Characteristics	Hypothetical risk of clinical recurrence (>18m after surgery)	Hypothetical risk of endoscopic recurrence (>18m after surgery)
Lower Risk	Older patient (>50y); non-smoker; 1st surgery for a short segment of fibrostenotic disease (<10-20cm); disease duration >10 years	20%	30%
Higher risk	Younger patient (<30y); smoker; ≥2 prior surgeries for penetrating disease, with or without perianal disease	50%	80%

So….after all of these years.....

……my final slide and my approach to postoperative Crohn's disease has not changed.

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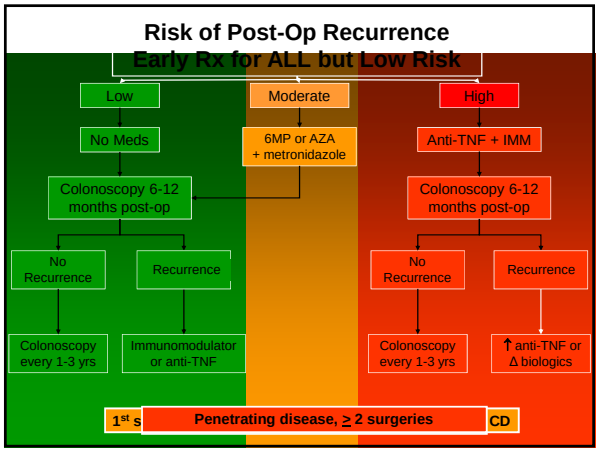


Thank you

Diagnosis and Treatment of Extraesophageal Reflux Disease

Rachel Rosen, MD
Center for AeroDigestive Disorders
Center for Motility and Functional Gastrointestinal Disorders

Disclosures

- Research funding through the NIH
- Consultant for Janssen Pharmaceutical (pulmonary drug development)

What are examples of extraesophageal signs and symptoms?

- Cough
- GERD
- Regurgitation
- Feeding difficulties
- Asthma
- Croup
- Otitis media
- Retching
- Desaturations
- Fevers
- Pneumonia
- Aspiration
- Sinusitis
- Bronchiectasis
- Lung transplant failure
- Hoarseness
- Post-nasal drip
- Emesis
- ALTES/BRUEs
- Nasal congestion
- EVERYTHING

Scope of the Problem

Francis et al Am J Gastro 2013

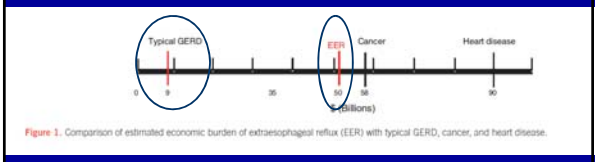


Figure 1. Comparison of estimated economic burden of extraesophageal reflux (EER) with typical GERD, cancer, and heart disease.

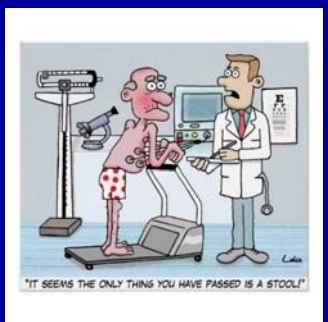
Cost is being driven by:
-Medication costs
-Diagnostic tests
-Side effects from therapy

Pulmonary/ORL Differential Diagnosis

- GERD
- GERD
- GERD
- GERD
- GERD
- GERD
- GERD

GI Differential Diagnosis

- Oropharyngeal dysphagia
- Cricopharyngeal dysfunction
- Esophageal obstruction
- Esophageal dysmotility
- Eosinophilic esophagitis
- Gastroparesis
- GERD
- Anatomic (fundo, strictures, fistulae)
- NON-GI CAUSES



TESTING

- Pharyngeal pH monitoring
- **pH-MII**
- BRAVO
- pH probe
- **Exhaled Breath Condensate**
- **Cough catheters**
- **Biomarkers**

58% of patients undergoing GI evaluation have abnormal testing by EGD or pH-MII

Rosen et al Peds Pulm 2014

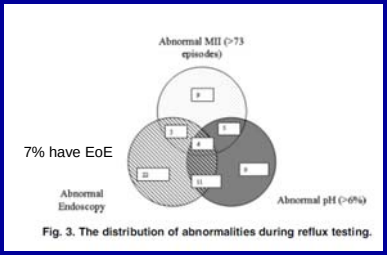


Fig. 3. The distribution of abnormalities during reflux testing.

Full Column Reflux Matters

Jadcherla et al Am J Gastro 2008

Extent of Refluxate (# AREs)	Composite SSI	Respiratory
Pharynx (N = 30)	77% (23/30)	47% (14/30)
Proximal esophagus (N = 36)	50% (18/36)	22% (8/36)
Middle esophagus (N = 36)	50% (18/36)	28% (10/36)
Distal esophagus (N = 409)	27% (109/409)	11% (44/409)

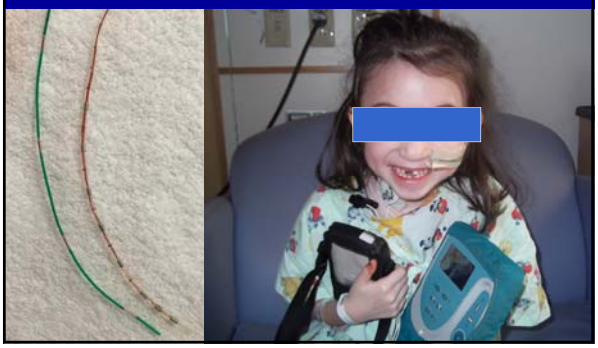
SSI value >10% was considered to be abnormal (8).

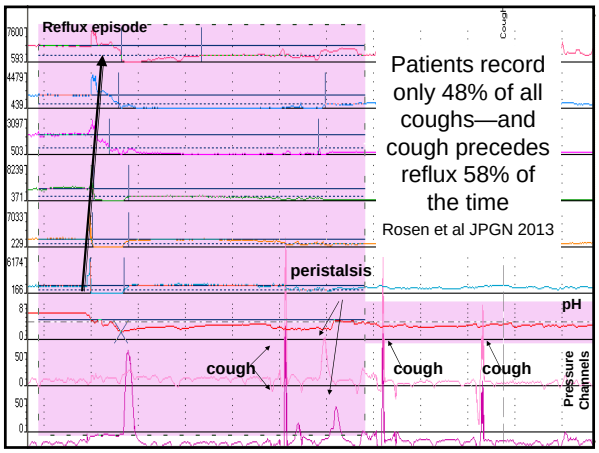
SSI: Symptom Sensitivity Index

Full column reflux and nonacid reflux are associated with cough in older children as well

Rosen and Nurko, Am J Gastro, 2004

Esophageal Pressure Recording or Acoustic Recording with Impedance





Insensitivity of Exhaled Breath Condensate

Fitzpatrick et al *J Allergy Clin Immunol Pract*. 2014

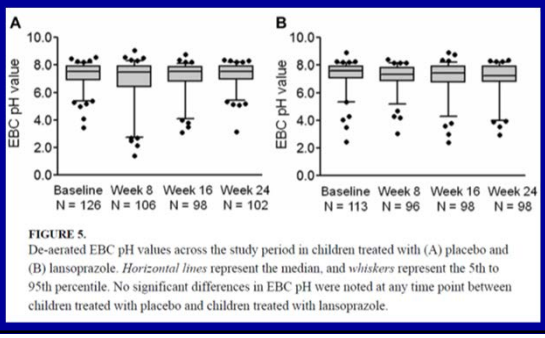


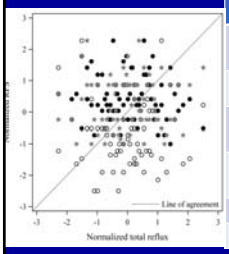
FIGURE 5.
De-aerated EBC pH values across the study period in children treated with (A) placebo and (B) lansoprazole. *Horizontal lines* represent the median, and *whiskers* represent the 5th to 95th percentile. No significant differences in EBC pH were noted at any time point between children treated with placebo and children treated with lansoprazole.

Biomarkers other than pH?

- Redness
- LLMI
- Pepsin
- Bile

No Relationship between Erythematous Airways and Reflux Parameters

Rosen et al Journal of Pediatrics 2017



	Erythema <4	Erythema score=4	P Value
Total Number of Reflux Episodes	24±14	25±17	0.8
Number of Acid Reflux Episodes	47±26	49±28	0.7
Number of Nonacid Reflux Episodes	23±23	23±23	0.9
% Episodes that are Full Column	47±18	46±21	0.8
% Time pH<4	4.5±5.6	5.0±5.6	0.7
% Time Proximal Reflux	0.7±0.7	0.7±0.8	0.7

LLMI: No relationship with Reflux by Impedance

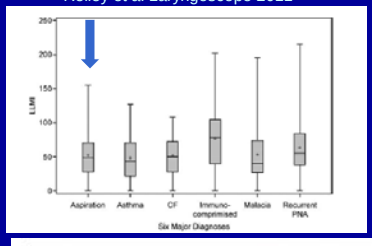
Rosen et al Pediatrics 2008

TABLE 2 Spearman Correlations to Determine the Relationship Between the LLMI and Reflux Parameters Detected by pH-MII

Variable	*r*	*P*
No. of acid events	−0.20	.200
No. of nonacid events	−0.15	.300
No. of pH-only events	−0.18	.200
Percentage of time reflux in esophagus by pH-MII	−0.19	.200
Percentage of time pH <4	−0.37	.008
Percentage of full-column reflux	−0.13	.400

LLMI: No Relationship with Aspiration

Reiley et al Laryngoscope 2011



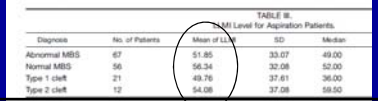


TABLE III.
LLMI Level for Aspiration Patients.

Diagnosis	No. of Patients	Mean of LLMI	SD	Median
Abnormal MBS	67	51.85	33.07	49.00
Normal MBS	56	56.34	32.08	52.00
Type 1 cleft	21	49.76	37.61	36.00
Type 2 cleft	12	64.08	37.08	59.50

Sensitivity of Pepsin in Children

Rosen et al Neurogastro 2011

	Sensitivity of Pepsin	Specificity of Pepsin
If Abnormal EGD	67%	59%
If Abnormal pH probe	45%	56%
If Abnormal MII	71%	60%
If Any Abnormal Test (pH/MI/EGD)	57%	65%

100% of critically ill patients have pepsin in tracheal secretions, Hallal et al Chest 2015

No relationship between salivary pepsin and reflux parameters

Dy et al J Peds 2016

Measure	Pepsin – (n=29)	Pepsin + (n=21)	P
Abnormal pH-metry	11 (38%)	8 (38%)	0.99
Abnormal Impedance	5 (17%)	6 (29%)	0.49
Total reflux episodes	43.0 (32.0, 53.0)	45.0 (19.0, 91.0)	0.55
No. of acid reflux episodes	26.0 (6.0, 38.0)	19.0 (11.0, 46.0)	0.69
No. of non-acid reflux episodes	11.0 (5.0, 26.0)	14.0 (6.0, 33.0)	0.77
% Proximal reflux	0.4 (0.3, 0.7)	0.3 (0.2, 0.9)	0.88
% of time pH<4	4.0 (1.3, 7.4)	2.0 (0.3, 13.6)	0.70
Esophagitis	6 (21%)	8 (38%)	0.18

Pepsin has been found in tonsils, middle ear fluid, sinuses, tracheal secretions, and bronchoalveolar lavage fluid.

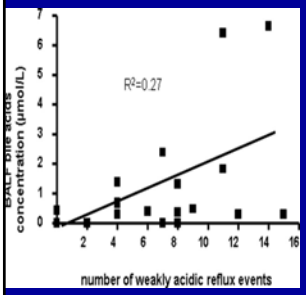
Pepsin may not just be a biomarker

- Pepsin increases neutrophil migration across the lung epithelium
- Pepsin results in monocyte activation in tonsils and has been associated with tonsillar hypertrophy
- Pepsin has been associated with increased IL8 in middle ear fluid and may predict a worse prognosis from a TM and hearing perspective

O'Reilley et al JAMA OTO 2015, Kim el al PLOS One 2016, Luo et al Int J Ped Oto 2014, Hurley et al Submitted for publication

Relationship between Bile and Reflux Events

Blondeau et al J Heart Lung Transpl 2009



Bile in bronchoscopy fluid has been associated with increased lung rejection

Bile acids and Lung Transplant Survival

Mertens et al, American J Transplantation 2011

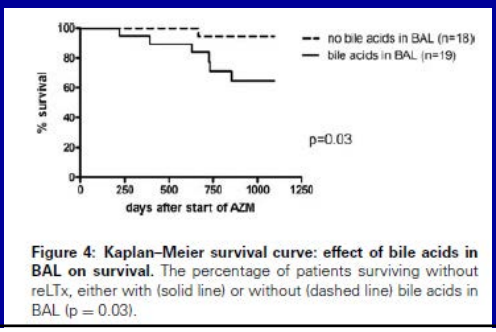
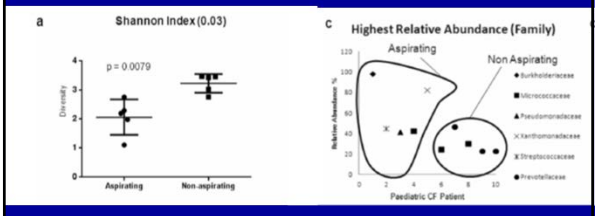


Figure 4: Kaplan–Meier survival curve: effect of bile acids in BAL on survival. The percentage of patients surviving without reLTx, either with (solid line) or without (dashed line) bile acids in BAL ($p = 0.03$).

Bile: More than a Biomarker

Reen et al Eur J Clin Microbiol Infect Dis 2014



Testing Summary

- There is no single test that can make the diagnosis of extraesophageal reflux disease
- Studies are limited based on a lack of data in healthy children and a lack of a clear gold standard test to diagnose reflux

Acid Suppression

RCT of Lansoprazole in Infants with crying…and extraesophageal symptoms

Orenstein et al J Peds 2009

	Lansoprazole double-blind (≤4 weeks, n = 81)*	Placebo double-blind (≤4 weeks, n = 81)*	P value†
Primary efficacy: Responder rate, n (%)	44 (54%)	44 (54%)	NS
Discontinued due to nonefficacy, n (%)	28 (35%)	29 (36%)	NS
Individual symptoms‡			
Cry, % of feeds/week (Appendix 2)	−20	−20	NS
Regurgitate, % of feeds/week	−14	−11	NS
Stop feed soon, % of feeds/week	−7	−8	NS
Feed refusal, % of days/week	−14	−10	NS
Arching back, % of days/week	−20	−18	NS
Coughing, % of days/week	0	−9	NS
Wheezing, % of days/week	−5	−6	NS
Hoarseness	2	−5	NS
Global severity assessment§			
Parent: Improved at week 4	45 (56%)	41 (51%)	NS
Physician: Improved at week 4	44 (55%)¶	40 (49%)	NS

RCT of Lansoprazole for Asthma

ALA Clinical Research Centers, JAMA 2012

Questionnaires	No. of Participants[a]	Mean (95% CI) 24-Week Score: Placebo	24-Week Score: Lansoprazole	Score Change From Baseline: Placebo	Score Change From Baseline: Lansoprazole	Treatment Effect, Difference in Change, Lansoprazole vs Placebo[b]	P Value: Treatment Effect[c]	P Value: Interaction With GER[d]
Asthma control								
Asthma Control Questionnaire	306	1.0 (0.9 to 1.1)	1.1 (0.9 to 1.2)	−0.2 (−0.4 to −0.1)	−0.1 (−0.2 to 0.1)	0.2 (−0.0 to 0.3)	.12	.50
Asthma Symptom Utility Index	306	0.88 (0.86 to 0.90)	0.86 (0.83 to 0.88)	0.06 (0.03 to 0.09)	0.03 (0.01 to 0.06)	−0.03 (−0.07 to 0.01)	.14	.38
Asthma Control Test for ages 12-17 y	142	20.2 (19.4 to 21.1)	20.2 (19.3 to 21.1)	1.6 (0.5 to 2.7)	1.0 (0.2 to 1.7)	−0.6 (−1.9 to 0.7)	.37	.86
Asthma Control Test for ages 6-11 y	164	21.9 (21.1 to 22.8)	20.9 (19.9 to 21.9)	2.0 (1.0 to 2.9)	1.2 (0.3 to 2.1)	−0.7 (−2.0 to 0.6)	.27	.33
Pulmonary function								
Prebronchodilator, FEV_1, L	306	2.3 (2.1 to 2.4)	2.2 (2.1 to 2.4)	0.0 (−0.0 to 0.1)	0.0 (−0.0 to 0.1)	0.0 (−0.1 to 0.1)	.99	.27
FEV_1 bronchodilator response, %	120	10.8 (7.7 to 14.0)	10.7 (7.0 to 14.5)	2.2 (−1.2 to 5.7)	−0.1 (−4.0 to 3.9)	−2.3 (−7.6 to 2.9)	.38	.002
Prebronchodilator, FVC, L	306	2.9 (2.7 to 3.1)	2.9 (2.7 to 3.0)	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)	0.0 (−0.1 to 0.1)	.68	.22
PC_{20}, mg/mL	119	2.5 (1.7 to 3.4)	2.6 (2.0 to 3.3)	0.0 (−0.9 to 1.0)	0.1 (−0.8 to 1.1)	−0.8 (−2.1 to 0.4)	.20	.80

PPIs increase risk of pneumonia in adults with aspiration

Takatori et al J Gastro 2013

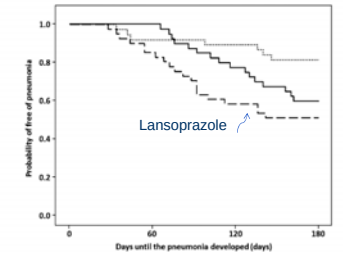


Fig. 5 Kaplan–Meier curve showing probability of freedom from pneumonia in the 3 groups (*continuous lines*: control group, *dashed lines*: Lansoprazole group, *dotted lines*: Mosapride group). The mosapride group showed a significant difference as compared with the lansoprazole group ($p < 0.05$)

Risk of Infections in PPI-treated children

- Upper respiratory infections (RR: 1.3)
- Pharyngitis (RR: 1.3)
- Pneumonia (OR: 6.3)
- Gastroenteritis (OR: 3.5)
- C. Difficile (OR: 4.5)
- NEC (OR: 6.6)

ALA Clinical Research Centers, Jama 2012, Canani et al, Pediatrics 2006
Turco et al, APT 2010, Turrin et al 2012

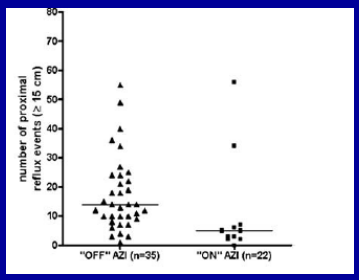
Motility Agents

Macrolides

- Increase antral contractility
  - Improvement in gastric emptying?
  - Improvement in reflux?
- Anti-inflammatory effect
- Antimicrobial effect

Azithromycin Reduces Proximal Reflux

Mertens et al Dig Dis Sci 2009



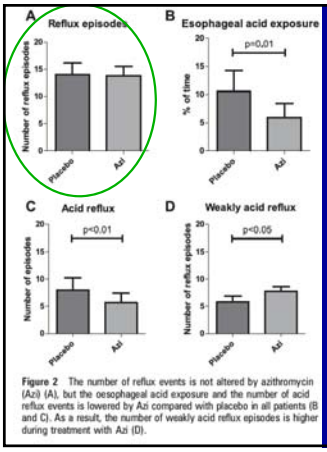


Figure 2 The number of reflux events is not altered by azithromycin (Azi) (A), but the oesophageal acid exposure and the number of acid reflux events is lowered by Azi compared with placebo in all patients (B and C). As a result, the number of weakly acid reflux episodes is higher during treatment with Azi (D).

Azithromycin and its effect on reflux

Rohof et al Gut 2012

But….proximal extent of reflux was significantly reduced in the AZI group compared with placebo ($p<0.01$)

RCT:Erythromycin (5 mg/kg/dose Q8) and GER in preterm infants

Ng et al JPGN 2003

	Erythromycin (n = 13)	Placebo (n = 11)	*P* value
Time to full feeds (days)**	24.9 ± 2.9	30.8 ± 4.1	0.17
Age birth weight regained (days)	12.8 ± 4.4	16.8 ± 6.2	0.106
Age full feeds attained (days)	46.6 ± 18.0	52.1 ± 17.5	0.371
Total parenteral nutrition (days)	39.4 ± 13.8	43.3 ± 18.3	0.743
Cholestatic jaundice	4/13 (31%)	7/11 (64%)	0.113
Glycerin suppositories used**	1.5 ± 0.4	2.9 ± 1	0.282
Reflux index before study (%)	7.3 ± 15.5	13.6 ± 17.3	0.715
Reflux index after study (%)	4.3 ± 7.1	0.3 ± 0.6	0.068
Reflux reduction	3/13 (23%)	4/11 (36%)	0.565
Duration of hospitalization (9 days)	98.3 ± 35.9	99.6 ± 58.6	0.675

* Values are mean ± SD unless otherwise noted; **mean ± SEM.

Azithromycin reduces bothersome lung symptoms in children

Stokholm et al Lancet Resp Med 2016

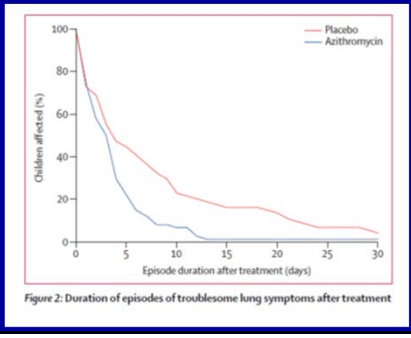


Figure 2: Duration of episodes of troublesome lung symptoms after treatment

Macrolide use and risk of asthma at age 3

Metsala et al Clin & Exp Allerg 2015

	Adjusted OR	95% CI
Amoxicillin	2.35	2.1-2.63
Macrolides	2.74	2.5-2.99
Cephalosporins	1.91	1.76-2.07

Fundoplication

"Okay, folks, that's a wrap!"

Extraesophageal symptoms relapse quickly after Fundoplication

Krill et al CGH 2017

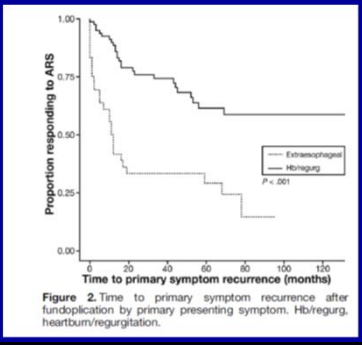


Figure 2. Time to primary symptom recurrence after fundoplication by primary presenting symptom. Hb/regurg, heartburn/regurgitation.

Fundoplication does not reduce hospitalizations

Barnhart et al JAMA Peds 2013

Table 3. Reflux-Related Hospitalizations During the First Year After Fundoplication

Cause of Admission	Hospitalizations, Mean (95% CI)	
	GT Placement Only	Fundoplication and GT Placement
All	0.92 (0.91-1.00)	1.02 (0.93-1.10)
Aspiration pneumonia	0.08 (0.07-0.09)	0.08 (0.06-0.10)
Gastroesophageal reflux disease	0.65 (0.60-0.70)	0.53 (0.63-0.76)
Esophagitis	0.00 (0.00-0.01)	0.00 (0.00-0.00)
Requirement for mechanical ventilation	0.29 (0.27-0.32)	0.38 (0.33-0.42)
Pneumonia	0.18 (0.16-0.20)	0.23 (0.19-0.26)

Abbreviation: GT, gastrostomy tube.

Hospitalization after Fundoplication

Lee et al J Peds Surg 2008

Table 1 Number of patients requiring hospital admissions for aspiration pneumonia, other pneumonia, respiratory distress, and FTT before and after Nissen fundoplication

	Before Nissen	After Nissen		
	Total no. of patients admitted	Total no. of patients admitted	No. of patients admitted with previous admission	No. of patients admitted with no previous admission
Aspiration pneumonia	24	23	3	20
Other pneumonia	86	90	47	43
Respiratory Distress	129	120	65	55
FTT	127	118	72	46

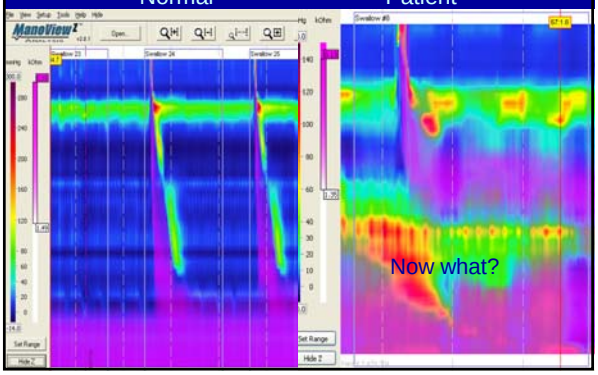
Therapy Summary

- The treatment algorithm of extraesophageal reflux symptoms differs from typical reflux symptoms with a reduced reliance on acid suppression and antireflux surgery

Masqueraders of Extraesophageal Reflux

Esophageal Stasis from Dysmotility presents like EERD

Normal Patient



Swallow dysfunction is a significant driver of BRUEs

Duncan et al JPGN 2016

Table 4: ALTE Testing Results

Test	EKG	CXR	EEG	VFSS
% (n) of patients tested	70% (131)	64% (120)	18% (33)	29% (55)
% (n) abnormal	3% (4)	5% (10)	12% (4)	72% (40)

-And despite this, 30% of patients went home on a proton pump inhibitor
-The sensitivity of an observed feeding to diagnose aspiration is only 43%

Patients with EoE have airway inflammation

Yawn et al Oto Head Neck Surg 2015

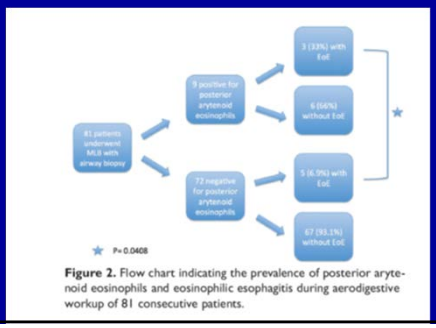
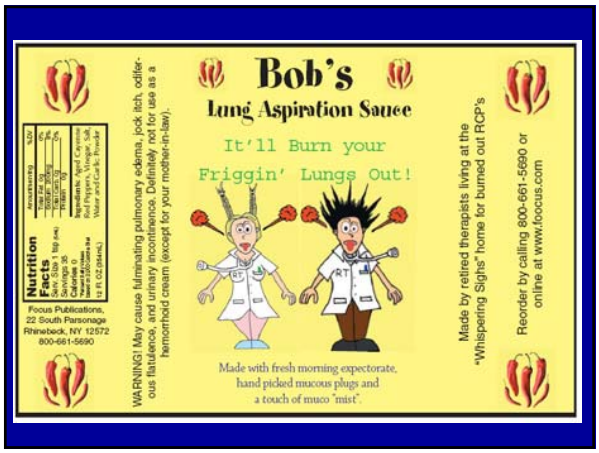


Figure 2. Flow chart indicating the prevalence of posterior arytenoid eosinophils and eosinophilic esophagitis during aerodigestive workup of 81 consecutive patients.

38% of EoE patients have eos in the larynx versus 8% in non-EoE patients

Conclusions

- It is very hard to prove that symptoms are reflux related
- The differential diagnosis of extraesophageal symptoms large and reflux is rarely the sole driver of these symptoms
- Acid suppression and fundoplication, while helpful for typical symptoms, have a very limited role in atypical symptoms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Made with fresh morning expectorate, hand picked mucous plugs and a touch of muco "mist".
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800-661-5690

POTS AND JOINT HYPERMOBILITY, WHAT DO THEY HAVE TO DO WITH FUNCTIONAL DISORDERS?

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Disclosures

Consultant

QOL Medical, Ardelyx, Nutricia, Forest, Quintiles, IM HealthScience, Sucampo

Objectives

- Define postural orthostatic tachycardia syndrome (POTS), and joint hypermobility (JH).
- Review the prevalence of POTS and JH in patients with functional gastrointestinal disorders.
- Discuss the management of patients with functional gastrointestinal disorders and POTS

Case

- 16 years old previously healthy, history of viral infection 6 months ago.
- Abdominal pain that improves with bowel movements.
- Nausea, dizziness, lightheadedness, headaches.
- Gymnastics team, chronic fatigue.
- Physical exam-Diffuse abdominal tenderness.

- Joint hypermobility
- Benign joint hypermobility syndrome
- Joint hypermobility syndrome
- Ehlers-Danlos syndrome
- Ehlers-Danlos syndrome hypermobility type
- Ehlers-Danlos Syndrome Type III
- Hypermobile Ehlers-Danlos syndrome

- Orthostatic intolerance
- POTS

Orthostatic Intolerance

- Inability to tolerate standing or upright. Relieved by recumbency.
- Exercise intolerance, lightheadedness, diminished concentration, tremulousness, nausea and recurrent syncope (may be incorrectly labeled as having panic disorder or chronic anxiety)

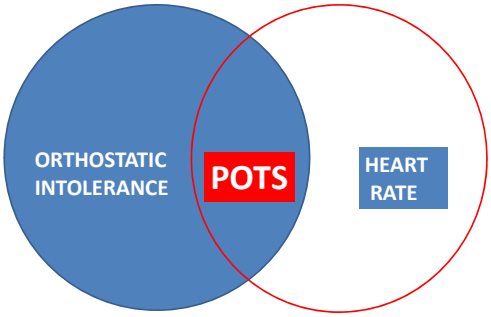
Low PA et al. Neurology. 1995; 45:S19–S25

Postural Orthostatic Tachycardia Syndrome

- Sustained heart rate increment of 40 beats/ minute within 10 min of standing or head-up tilt in the absence of orthostatic hypotension.

Stewart J, et al. Pediatrics. 2017. In Press.

- Orthostatic symptoms: dizziness, palpitations, headaches, sweating, nausea, tremulousness, anxiety, sensation of near-syncope, fatigue and light-headedness.



Beighton Score

BEIGHTON SCORE

JOINT HYPERMOBIILITY

Beighton Score
+
Brighton Score

Hypermobile Ehlers-Danlos Syndrome

Brighton Score

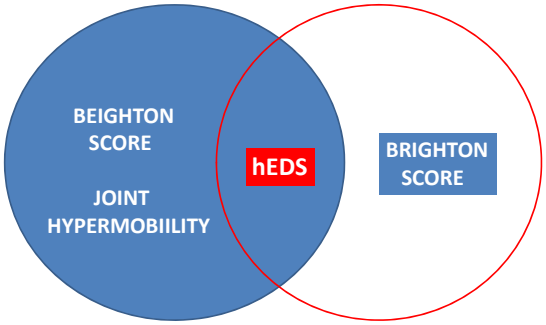
Grahame R, et al.J Rheumatol. 2000;27:1777-9.

Major Criteria	Minor Criteria
• Beighton score of 5/9 or greater (either currently or historically) • Arthralgia for longer than 3 months in 4 or more joints	• Beighton score of 1, 2 or 3/9 • Arthralgia (> 3 months) in 1-3 joints or back pain (> 3 months), spondylosis, spondylolysis/spondylolisthesis. • Dislocation/subluxation in >1joint, or in one joint on more than one occasion. • Soft tissue rheumatism. > 3 lesions (e.g. epicondylitis, tenosynovitis, bursitis). • Marfanoid habitus (tall, slim, span/height ratio >1.03, upper: lower segment ratio less than 0.89, arachnodactyly • Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring. • Eye signs: drooping eyelids or myopia or antimongoloid slant. • Varicose veins or hernia or uterine/rectal prolapse.

JHS - two major criteria, or one major and two minor criteria, or four minor criteria.
Two minor criteria sufficed where there was an unequivocally affected first-degree relative

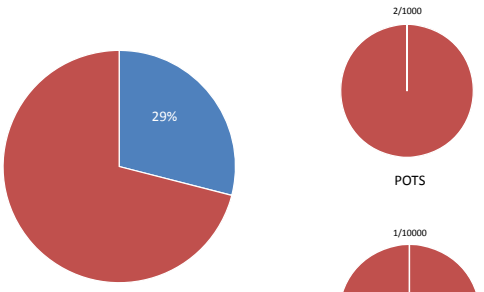
- Joint hypermobility syndrome
- Ehlers-Danlos syndrome hypermobility type
- Ehlers-Danlos Syndrome Type III
- Hypermobile Ehlers-Danlos Syndrome (hEDS)

Malfait et al. Am J Med Genet C Semin Med Genet. 2017;175:8-26.



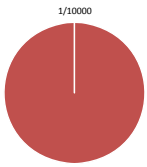
Why Do We Seem To See So Many?

- **Selection bias?**
- **Recall bias?**
- **True association?**



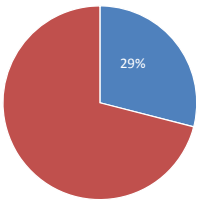
Functional Gastrointestinal Disorders

POTS



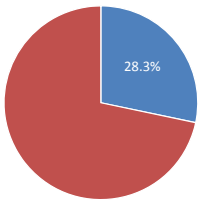
hEDS

Saps M, et al. J Pediatr. 2014;164:542-45
Schondorf R, et al. J Auton Nerv Syst 1999;75:192-201
Am J Med Genet A. 2010b;152A:2406–8.



Functional Gastrointestinal Disorders

Saps M, et al. J Pediatr. 2014;164:542-45



Joint Hypermobility

Saps M, et al. J Pediatr Gastroenterol Nutr. In Press.

Functional Gastrointestinal Disorders			
	Yes	No	
Beighton Score ≥4	28.7%	27.9%	OR = 1.03 (95% CI: 0.59-1.81, p=0.89)

GASTROINTESTINAL SYMPTOMS

POSTURAL ORTHOSTATIC TACHYCARDIC SYNDROME
80%
HYPERMOBILE EHLERS DANLOS SYNDROME
57%

Ojha A. , et al. J Pediatr. 2011;158:20-3.
Nelson AD, et al. Neurogastroenterol Motil. 2015;27:1657-66.

SELECTION BIAS

Comorbidities in POTS and Hypermobile Ehlers-Danlos Syndrome

- Gastrointestinal symptoms
- Bladder disorders
- Migraines
- Fibromyalgia
- Anxiety
- Chronic fatigue
- Sleep problems
- Brain fog

Ojha A. , et al. J Pediatr, 158 (2011), pp. 20–23

Ross AJ, et al. Clin Auton Res. 2013;23:305-11

RECALL BIAS

Gastroenterol Res Pract. 2009;2009:868496. doi: 10.1155/2009/868496. Epub 2009 May 5.

Autonomic testing in functional gastrointestinal disorders: implications of reproducible gastrointestinal complaints during tilt table testing.

Safder S[1], Chelimsky TC, O'Riordan MA, Chelimsky G.

POTS and functional abdominal pain replicated - 42%

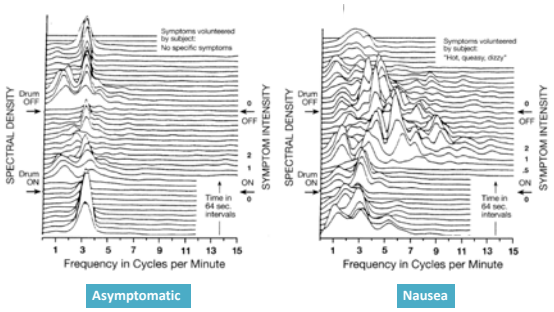
J Pediatr Gastroenterol Nutr. 2016 Sep;63(3):329-35. doi: 10.1097/MPG.0000000000001150.

Antroduodenal Manometry Is Abnormal in Children Presenting With Orthostatic Intolerance and Gastrointestinal Symptoms.

Moak JP[1], Fabian RR, Clarke LC, Hanumanthaiah S, Desbiens J, Darbari A.

POTS- Gastrointestinal symptoms reproduced - 89%

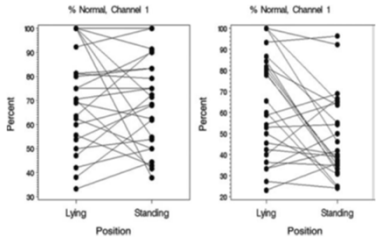
Electrogastrography (EGG)



Asymptomatic **Nausea**

Koch KL. Exp Brain Res. 2014;232:2553-61

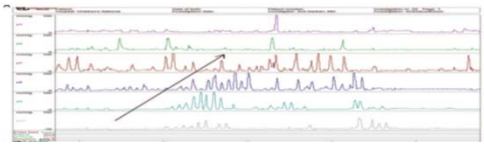
Electrogastrography (EGG)



Non-POTS | POTS

Safder S, et al. J Pediatr Gastroenterol Nutr. 2010;51:314-8.

Antroduodenal Manometry



Tilt Test Table	
Neurogenic intestinal dysmotility	48%
Antral hypomotility	13%
Abnormal gastric emptying studies	52%

Moak JP et al. J Pediatr Gastroenterol Nutr. 2016;63:329-35.

Hypermobile Ehlers-Danlos Syndrome

IBS and functional constipation are frequent.

More likely to have GERD, functional dyspepsia.
More likely if they have POTS.

Fikree et al. Clin Gastroenterol Hepatol. 2014.
Fikree et al. Neurogastroenterol Motil. 2017.

Hypermobile Ehlers-Danlos Syndrome

- 49% - POTS
- 31% - Orthostatic intolerance

HEDs-Abnormal cardiovascular autonomic profile

Celletti C, et al. Biomed Res Int. 2017;2017:9161865.

Children/Adolescents

Chelimsky G, et al. J Pediatr. 2016;177:49-52.

Interdisciplinary Rehabilitation Program

- Education
- Regular meals and sleep schedule
- Drink water prior to rising
- Progressive and regular exercise program
- Compression stockings
- Psychological support- behavioral strategies

Treatment

Enhancement of vascular volume

Increase oral fluid and salt intake

Treatment

- Fludrocortisone- mineralocorticoid
  Promotes intravascular volume expansion
  Improvement- dizziness, flushing, nausea, abdominal pain

Fortunato JE. J Pediatr Gastroenterol Nutr. 2014;59:39-43.

- Midodrine- alpha-1-agonist
  Peripheral vasoconstriction, reduces venous pooling

Ross AJ, et al. Clin Sci (Lond). 2014;126:289-96.

- Beta blockers, pyridogstimine

POTS - Prognosis

- 2 years- 76% improved

Lai CC, et al. Pacing Clin Electrophysiol 2009;32:234-8.

- 5 years

Bhatia R, et al. J Pediatr. 2016;173:149-53.

57% limitation climbing more than 1 flight of stairs
50% accomplished less than they would like to

86% symptoms improved or resolved
Majority were in college or had completed college

Take Home Message

- POTS and hEDS are rare disorders.
- Patients with functional gastrointestinal disorders, POTS and hEDS have frequent comorbidities.
- Treatment is multidisciplinary: GI symptoms, regular meals and sleep schedule, salt, fluids, medications and psychological support.
- Most patients improve but limitations frequently persist.

Do I need to test that C.R.A.P?

Rina Sanghavi, MBBS, MD, FAAP
Director, Pediatric GI Motility Program & Pediatric Neurogastroenterology
Children's Medical Center Dallas
UTSW Medical Center Dallas

UT SOUTHWESTERN MEDICAL CENTER

children's health

Financial Disclosure

- Nothing to disclose

Objectives

- Recurrent versus chronic abdominal pain (CAP)
- Indications for testing in CAP
- Evidence regarding usefulness of various tests for CAP

Recurrent Abdominal Pain in Childhood

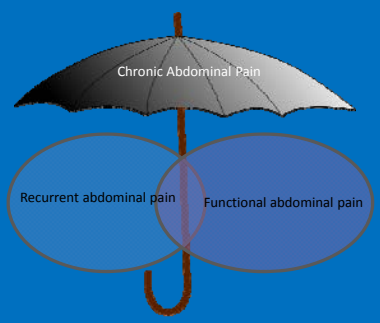
- Apley - three episodes of abdominal pain occurring in the space of three months, severe enough to affect daily activities

J R Soc Med. 2005
Apley, *Arch Dis Child*. 1958

Chronic Abdominal Pain

- Continuous or intermittent abdominal discomfort for at least 6 months
- Caused by a wide variety of etiologies ranging from organic to functional

L. Kapural (ed.), *Chronic Abdominal Pain: An Evidence-Based, Comprehensive Guide to Clinical Management*, 2015



Do not use interchangeably

- AAP and NASPGHAN guidelines recommend that:

" the term 'recurrent abdominal pain' should not be used as a synonym for functional, psychological, or stress-related abdominal pain.

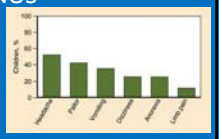
Functional Abdominal pain, which is the most common cause of chronic abdominal pain must be distinguished from other sources of abdominal pain"

JPGN and AAP Technical Report 2005

Functional Abdominal Pain

Can manifest with symptoms typical of

- functional dyspepsia,
- irritable bowel syndrome
- abdominal migraine
- functional abdominal pain NOS



ROME IV criteria
Functional Abdominal Pain NOS

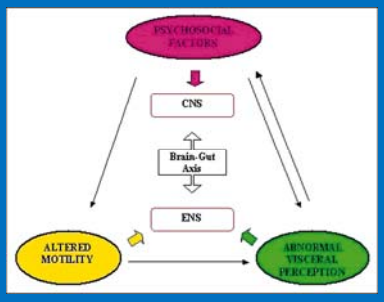
Must be fulfilled at least 4 times/month and include ALL of the following

1. Episodic or continuous abdominal pain that does not occur solely during physiologic events(e.g. eating, menses)
2. Insufficient criteria for IBS, functional dyspepsia or abdominal migraine
3. **After appropriate evaluation**, the abdominal pain cannot be fully explained by another medical condition.

Criteria fulfilled for at least 2 months prior to diagnosis

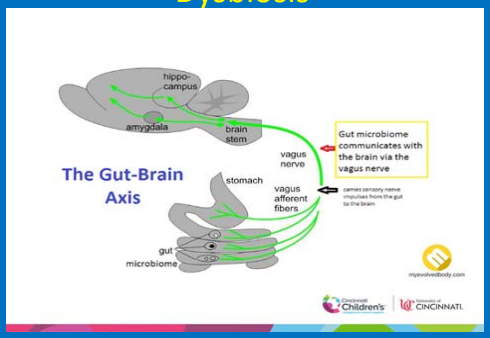
Drossman,D (Ed.) ROME IV 4th edition 2016

Pathophysiology of Functional Abdominal Pain(FAP)



Collins, BS et al, *Pediatrics in Review* 2007

Dysbiosis



Slide courtesy Ajay Kaul, MD

Evaluation of a patient with CAP

- History
- Examination
- Selective use of diagnostic testing

History

- Helps to reassure the patient and family
- 4 questions to ask parents
  - -what do you think is causing the pain
  - - what are they worried could be causing the pain
  - -What concerns would they like addressed
  - -What course of therapy are they hoping for?
- Establish a therapeutic alliance early in the course of evaluation and treatment.

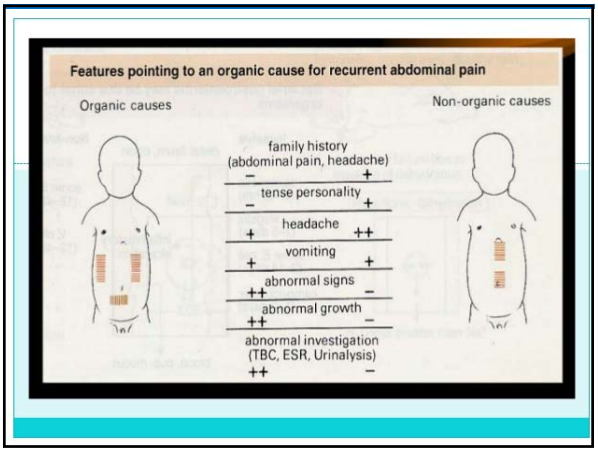
Boyle JT. In : Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management, 4th ed, Walker WA et al , (Eds), 2004.

Examination

- Carnett sign - If the focal tenderness increases or remains during abdominal muscle contraction
- Helpful in distinguishing deep visceral pain from abdominal wall pain
- Abdominal wall pain
  - -hernia
  - -hematoma
  - -abdominal wall musculature

Examination

- Rectal exam
  - - constipation
  - - perianal signs
- Stool Guaiac testing



Evaluation and Diagnosis

ALARM *SYMPTOMS* USUALLY NEEDING FURTHER INVESTIGATIONS

- Pain that wakes up the child from sleep
- Persistent right upper or right lower quadrant pain
- Significant vomiting (bilious vomiting, protracted vomiting, cyclical vomiting or worrisome pattern to the physician)
- Unexplained fever
- Genitourinary tract symptoms
- Dysphagia
- Chronic severe diarrhea or nocturnal diarrhea
- Gastrointestinal blood loss
- Involuntary weight loss
- Deceleration of linear growth
- Delayed puberty
- Family history of inflammatory bowel disease, celiac disease, and peptic ulcer disease

Do you need to order at least some diagnostic tests in everyone?

- Additional diagnostic evaluation is not required without alarm symptoms.
- A 2005 systematic review found little or no evidence to suggest that ultrasonography, endoscopy, or esophageal pH monitoring increases the yield of organic disease in the absence of "alarm findings"

Pediatrics March 2005

Repeating tests already done?

- If already negative – do not repeat
- Can provoke anxiety in child and family
- Child may start thinking that the physician is unable to find a cause of the symptoms and a rare and unusual disease" Zebra" is being missed.

Some tests to consider

- Radiology
  - -Plain x-ray
  - -Sonogram
  - -CT
  - -MRE
- Stool tests
  - -Fecal calprotectin
  - -Stool tests for Giardia and H. pylori
- Endoscopy and Capsule endoscopy
- Breath tests
- Psychological testing

Plain X-ray in CAP

- 82% -either normal, incidental or misleading
- High-yield criteria - > 90% sensitivity for the examination
  - o Prior abdominal surgery,
  - o foreign body ingestion,
  - o abnormal bowel sounds,
  - o abdominal distention or peritoneal signs.

SG Rothrock. *Pediatr Emerg Care.* 1991

Ultrasound in Children with CAP

- Without alarm symptoms, abnormalities found in fewer than 1% [1]
- Sonogram is not a helpful diagnostic tool in children with FAP. [2,3]
- Low risk
- Consider in children with specific findings

1 Yip,Wc *J Clin Ultrasound.1998*
2.A Shannon, *Pediatrics. 1990*
3 SB van der Meer *Pediatr Radiol. 1990*

Computed Tomography in CAP

- In 2012–13 - $146 million.
- ~ 5% of abdominal CT scans will detect 'incidentalomas' - > more tests, further risk, anxiety and cost.
- Radiation burden
- Not routinely recommended

AL Hryhorczuk, *Radiology*, June 2012

MR Enterography for CAP

- Little published data [1,2]
- Negative predictive value 97.4% [3]
- Advantages
  - diagnosing extra-enteric lesions
  -No radiation risk
- Disadvantage
  -Cost

1.EM Zimmerman, *Gut* 2011
2 .AS Kumar, *Case Reports in Gastro Med* 2015
3 .Watanabe,Y et al; Pediatrics International 2014

Endoscopy in CAP

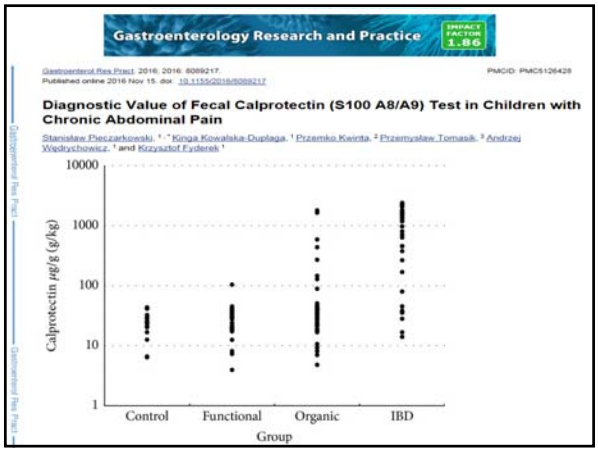
- A technical report by NASPGHAN - in the evaluation of CAP, there is **little evidence** to suggest that the use of endoscopy and biopsy in the absence of alarm symptoms has a significant yield of organic disease

Chronic abdominal pain in children: a technical report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2005

Is Capsule endoscopy useful in children with CAP?

- Lymphoid nodular hyperplasia -? Significance [1]
- CE does not provide useful information without other symptoms [2]
- Although possibly useful in rare, isolated cases, routine use of CE in children with CAP w/o other symptoms cannot be supported

1.R.Shamir et al, *JPGN* 2007
2.Arguielles- Arias F et al, *An Pediatr Barc* 2007



Use of Fecal Calprotectin in CAP

- Differentiation between inflammatory and functional GI disorders.
- High Fecal Calprotectin due to
  - -IBD
  - -Inflammatory intestinal disorders
  - -EXCLUDES functional disorders

H.Pylori testing and CAP

- No association
- Testing for H.Pylori is not recommended

MM Mansour *Trop Gastroenterol* 2012.

Protozoa and CAP

- Protozoa were found as the cause of pain in 6% to 11% of children with CAP.

CF Gisbers. *J Pediatr Gastroenterol Nutr* 2013

Lactose intolerance and CAP

- Lactose intolerance nor fructose intolerance could be established as causes of RAP, according to preset criteria including elimination, open provocation and DBPC provocation.

CF Gijsbers *Acta Paediatrica* 2012

Testing for psychological disorders in CAP

- Children with CAP and their parents- more anxious or depressed
- The presence of anxiety, depression, behavior problems or recent negative life events does not appear to be useful in distinguishing between functional abdominal pain and abdominal pain attributable to organic disease
- Ongoing debate on the role of psychological questionnaires

JPGN 2005

Summary of testing in CAP

- Diagnosis- clinical criteria
- Testing – if criteria for classical FAP- no testing is needed
- Tests – adults vs pediatric
- In children investigations are common, costs are substantial, and yield is minimal.

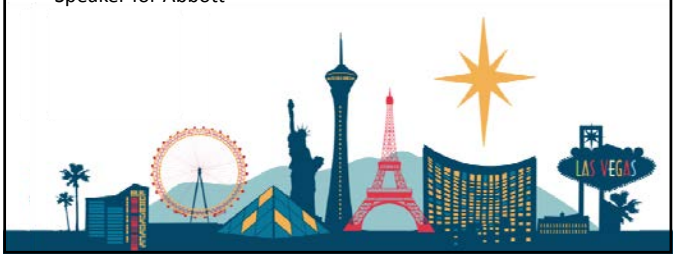
G Dhroove *JPGN* 2010

The child with refractory constipation

Jose M Garza MD. MS
Gi Care for Kids
Medical Director Neurogastroenterology and Motility
Children's Healthcare of Atlanta

Disclosure

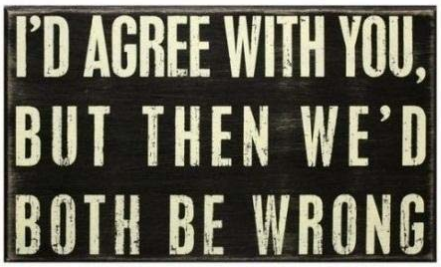
Speaker for Abbott



Objectives

- Recognize common causes of treatment failure in constipation
- Establish a diagnostic approach to children with refractory constipation
- Identity alternative treatments for refractory constipation

Disclaimer




Journal of Pediatric Surgery

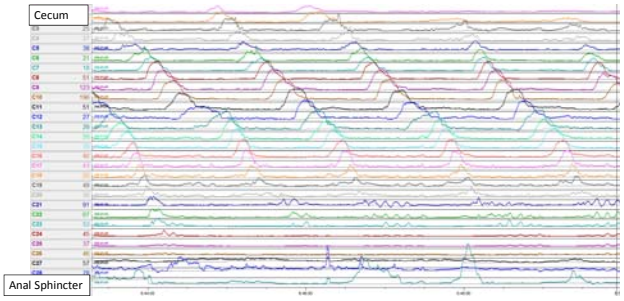
Surgical decision-making in the management of children with intractable functional constipation: What are we doing and are we doing it right?

Diagnostic and therapeutic approach towards children with intractable functional constipation differs considerably even among physicians with interest and expertise in the fields of pediatric surgery and pediatric gastroenterology

Colon

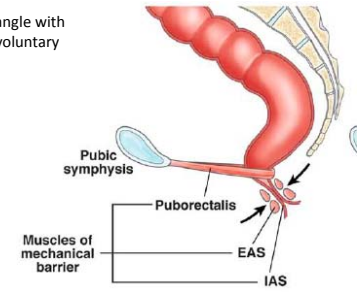
- Reabsorbs water and electrolytes
- Serves as temporary storage
- Motor activity divided into:
  - Segmental
  - Propagated Activity

High Amplitude Propagated Contractions



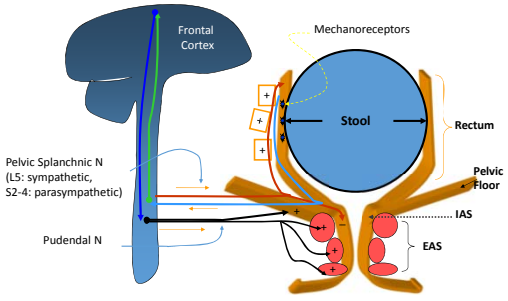
The anal canal forms a 90-degree angle with the axis of the rectum and during voluntary squeeze it becomes more acute

IAS: 70% to 85% of the resting sphincter pressure primarily responsible for maintaining anal continence at rest



Schey R, et al. Am J of Gastroenterol 2012

Hindgut Motility: Function



First line treatment is Polyetylene Glycol (PEG)

Complete bowel evacuation is the first step

High dose (PEG) has been proven safe and effective when given at doses of 1 to 1.5g/kg per day for 3 to 6 days

For maintenance therapy:

Enough medication should be used to reach a goal of regular, soft, and painless bowel movements and avoid re-accumulation of stool in the rectum

Tabbers M et al. JPGN 2014

- Maintenance treatment should continue for at least 2 months. All symptoms of constipation should be resolved for at least 1 month before discontinuation of treatment
- Treatment should be decreased gradually
- Medication should only be stopped once toilet training is established

Tabbers M et al. JPGN 2014

Intractable Constipation

- Severe and long-lasting symptoms that respond poorly to conventional behavioral, dietary and pharmacological management
- Functional constipation unresponsive to optimal conventional treatment for at least 3 months

50% of children referred to a pediatric gastroenterologist are still symptomatic after 5 years and 20% still struggle with symptoms after 10 years.

Tabbers M et al. JPGN 2014

One symptom……..

…….numerous etiologies

Intractable constipation

- Do you have right diagnosis?
- Outlet dysfunction
- Slow transit constipation
- Organic constipation

After failed medical management diagnostic testing is necessary to understand underlying anorectal and or colonic pathophysiology

No single test provides a comprehensive assessment

An abdominal X-ray should not be used to diagnose constipation.

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Delayed Diagnoses in Children with Constipation: Multicenter Retrospective Cohort Study

Stephen B. Freedman, MDCM, MSc[1], Jonathan Rodean, MPP[2], Matthew Hall, PhD[3], Elizabeth R. Alpern, MD, MSCE[3], Paul L. Aronson, MD[4], Harold K. Simon, MD, MBA[5], Samir S. Shah, MD, MSCE[6], Jennifer R. Marin, MD[7], Eyal Cohen, MD, MSc[8], Rustin B. Morse, MD, MMM[9,10], Yiannis Katsogridakis, MD, MPH[11], Jay G. Berry, MD, MPH[12], and Mark I. Neuman, MD, MPH[13]

- Abdominal radiographs are performed in up to 70% of children diagnosed with constipation in emergency department
- Among children diagnosed with constipation abdominal radiograph performance is associated with an increased risk of a revisit with a clinically important alternate related diagnosis

Freedmam SB et al. J Pediatr 2017

Is it Constipation or IBS ?

Functional Constipation - Rome IV

- 2 or fewer defecations in the toilet per week in a child with a developmental age of at least 4 years
- At least 1 episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large diameter stools that can obstruct the toilet

2 or more at least once per week, for a minimum of 1 month and insufficient criteria for diagnosis of IBS

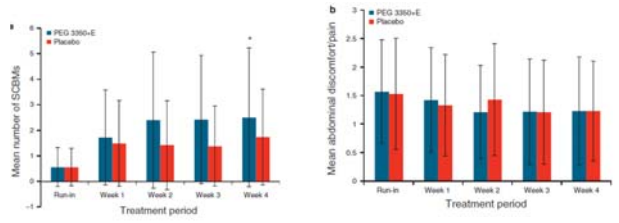
Hyams JS et al. Gastroenterology 2016

IBS - Rome IV

- Abdominal pain at least 4 days per month associated with one or more of the following:
  - Related to defecation
  - A change in frequency of stool
  - A change in appearance of stool
- In children with constipation, the pain does not resolve with resolution of the constipation
- After evaluation, the symptoms cannot be fully explained by another medical condition

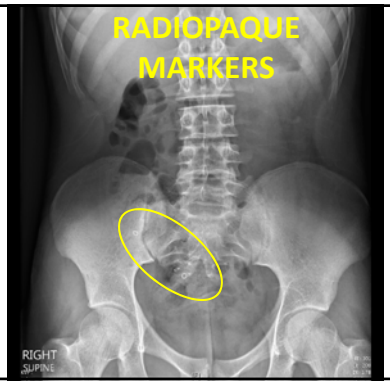
Hyams JS et al. Gastroenterology 2016

Randomized Clinical Trial: Macrogol/PEG 3350 Plus Electrolytes for Treatment of Patients With Constipation Associated With Irritable Bowel Syndrome



Chapman et al. Am J Gastroenterol 2013

What about the 15 year old female that has not had a bowel movement in the past 30 days despite all sorts of laxatives?

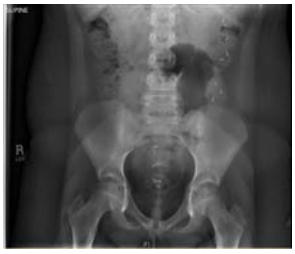


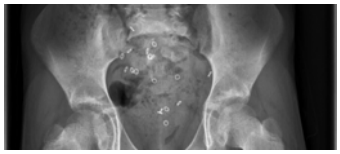
Radiopaque Markers

- Patients must be willing to stop all laxatives for 5 days during the procedure
- Unknown effect of bowel cleansing vs not prepared on transit time
- Different protocols
  - The most simple is an X-ray on day 5 only

Koughnett JAM et al. Gastroenterol Clin N AM 2013

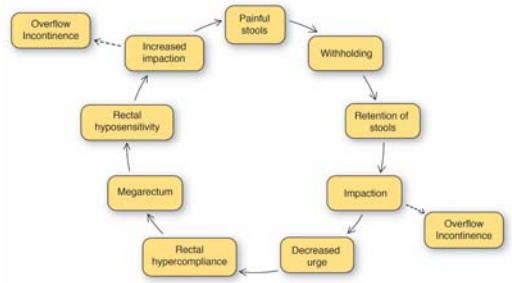
A normal colonic transit study equates to the passage of at least 80% of the markers (19 of the 24 markers) at 5 days

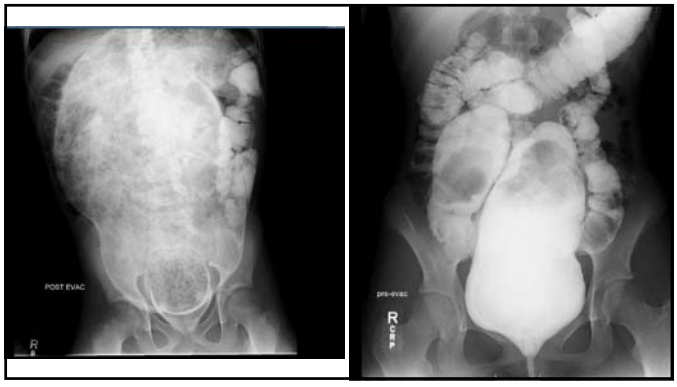




Intractable constipation

- Do you have right diagnosis?
  - Don't use AXR to diagnose
  - IBS vs FC
  - Non retentive fecal soiling
- Outlet dysfunction
- Slow transit constipation
- Organic constipation



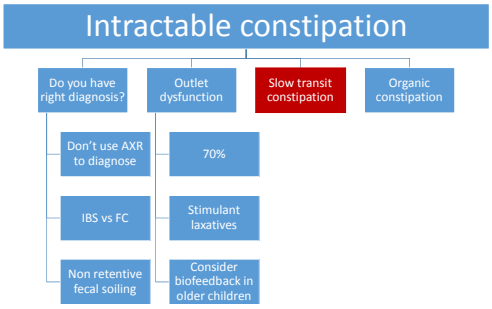


Stimulant laxatives (senna and bisacodyl) are widely available and likely underutilized

3 rules of treatment

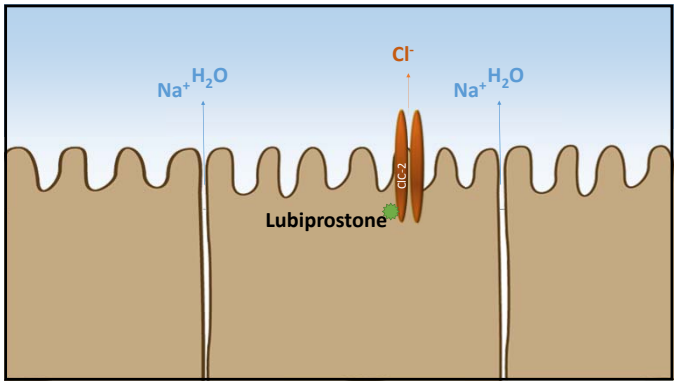
1. Take the medicine EVERY DAY at the SAME TIME
2. Sit on the toilet after breakfast, after dinner and if belly cramps
3. Call to adjust regimen if any accidents, no stool in 48 hours, too hard or too loose

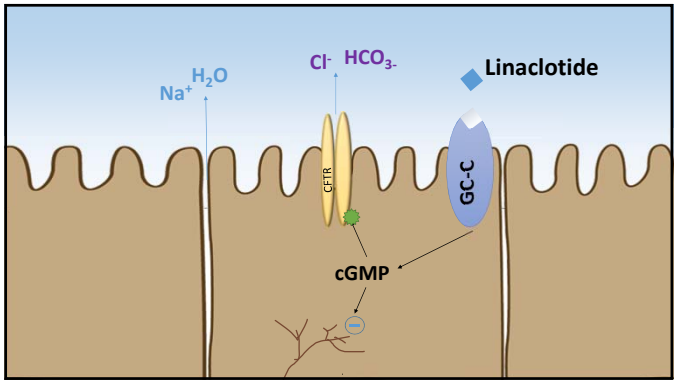
- Once doing well I continue treatment for 6 months and then follow up with a slow wean

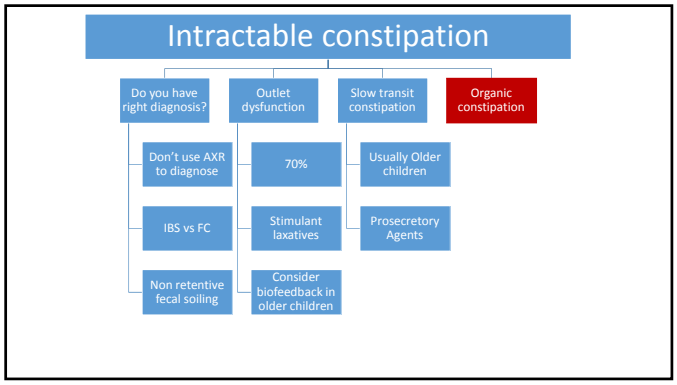


Prosecretory agents

- Chloride secretion is the major determinant of mucosal hydration throughout the gastrointestinal tract
  - 2 specific chloride channels ClC-2 (chloride channel protein 2) and CFTR have been validated as targets for treatment of constipation
  - Lubiprostone
  - Linaclotide
  - Plecanatide
    - Analog of uroguanylin (activates GC-C receptor)







Received: 10 May 2016 | Accepted: 18 August 2016
DOI: 10.1111/nmo.12944

REVIEW ARTICLE

WILEY

An ANMS-NASPGHAN consensus document on anorectal and colonic manometry in children

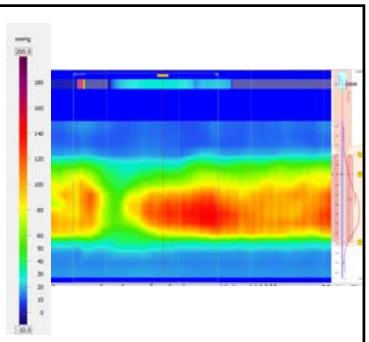
L. Rodriguez[1] | M. Sood[2] | C. Di Lorenzo[3] | M. Saps[3]

Anorectal Manometry

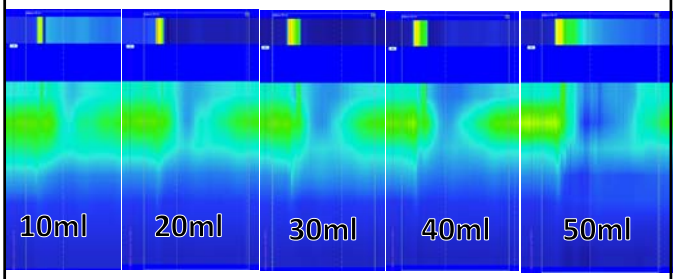
- Superior to barium enema for the diagnosis of Hirschsprung's disease
- Studies suggest may be as sensitive as rectal biopsy
  - although false-negative results may occur, particularly within the neonatal period.
  - Diagnosis should be confirmed via biopsy in all patient with an abnormal barium enema or suggestive ARM
- Contrast enemas ARE NOT a valid alternative to rectal biopsy or anorectal manometry to exclude or diagnose Hirschsprung's disease, helpful to identify anatomical abnormalities (megarectum, megasigmoid)

RAIR

- Rectal distension is associated with a decrease in anal resting pressure, known as the rectoanal inhibitory reflex (RAIR)
- Mediated by the myenteric plexus



Dose Response



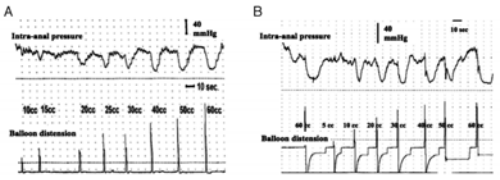
Spina bifida

- Myelomeningocele most common spinal abnormality
- There are children who have only tethered cord without any signs of spinal dysraphism presenting with urinary or fecal incontinence, or intractable constipation.
- Patulous anal tone, dilated or impacted rectal vault, inability to control bowel movements.
- Anorectal manometry
  - Prolonged IAS relaxation and duration, decreased or absent sensation and squeeze, presence of spasms

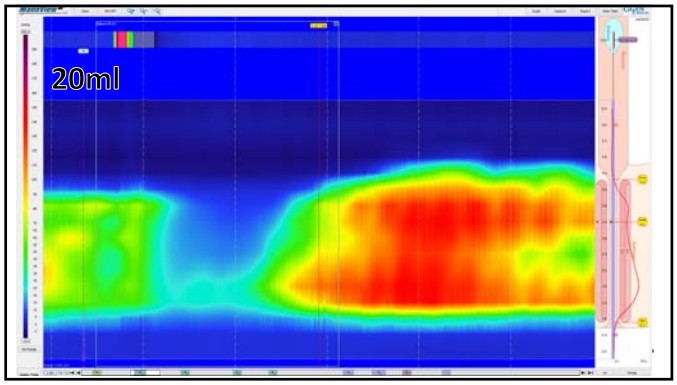
ORIGINAL ARTICLE: GASTROENTEROLOGY

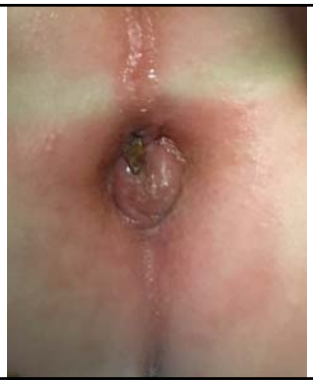
Anorectal Manometry May Identify Children With Spinal Cord Lesions

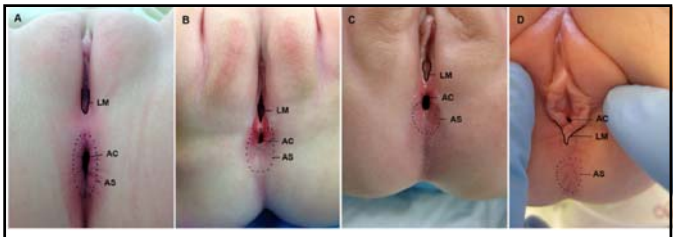
Anees Siddiqui, Rachel Rosen, and Samuel Nurko



JPGN November 2011







The distance between anal orifice and the labia minus is an unreliable approach to identify a mild version of CARM

Jonker JE et al. J Pediatr 2017


Journal of Pediatric Surgery

Effectiveness of senna vs polyethylene glycol as laxative therapy in children with constipation related to anorectal malformation

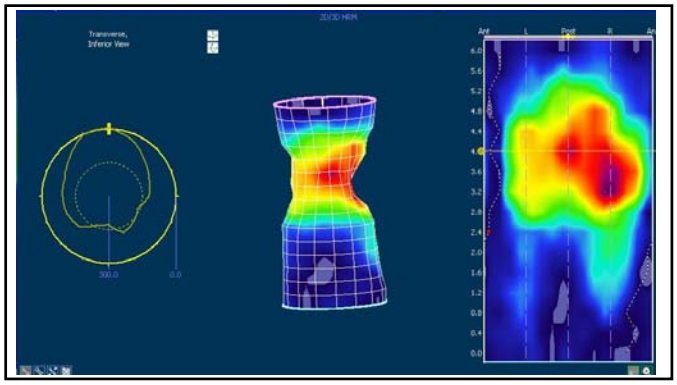
Karla Alejandra Santos-Jasso, José Luis Arredondo-García, Jorge Maza-Vallejos, Pablo Lezama-Del Valle

Polyethylene glycol causes liquid stool and increases frequency of accidents or soiling

Santos-Jasso K et al. J Pediatr Surg 2017

Anorectal malformations

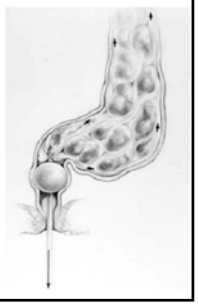
- Was repair done properly?
- MRI of the spine to r/o tethered cord
- Maintain right consistency of stool
  - Soluble fiber: pectin, psyllium and gum
- For slow transit…..Stimulant laxatives are preferred
  - Senna and Bisacodyl offer more effective emptying
- For fast transit……Loperamide
  - Decreases small bowel and colonic transit, increases internal anal sphincter tone and improves rectal perception and urgency



If nothing else is working time to try Rectal therapy

Offers predictable rectosigmoid emptying

- Suppositories
- Enemas
  - Cone or Foley 20-24Fr
  - Normal saline
  - 10 to 20ml/kg max 1000ml
  - Can add glycerin, castile soap, Bisacodyl



CHOA Pediatric Neurogastroenterology & Motility

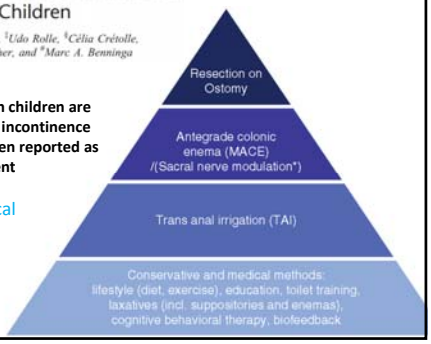
GI CARE FOR KIDS

Consensus Review of Best Practice of Transanal Irrigation in Children

*Giovanni Mosiello, †David Marshall, ‡Udo Rolle, §Célia Crétolle, ||Bruno G. Santacruz, ¶Jason Frischer, and #Marc A. Benninga

Average success rates of TAI in children are estimated to be 78% for fecal incontinence and constipation. And 84% when reported as overall improvement

May prevent surgical intervention



Moisello G et al. JPGN 2017

Transanal Irrigation in the Treatment of Children With Intractable Functional Constipation

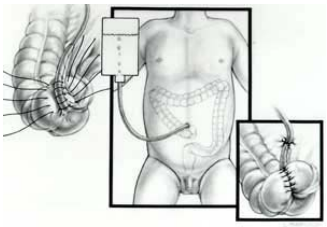
*Ilan J.N. Koppen, *Sophie Kuizenga-Wessel, *Heleen W. Voogt, †Marijke E. Voskuil, and *Marc A. Benninga

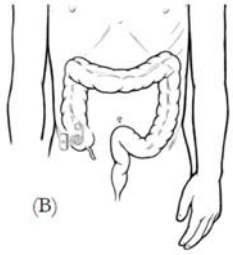
Do not recommend for children with anxiety problems, or those with poor adherence as is likely to fail because is time consuming

TAI can be a valuable tool in the management of children with intractable functional constipation and renders high parental satisfaction

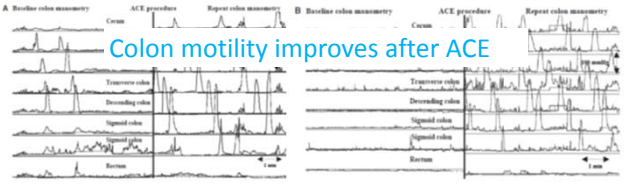
Koppen I et al. JPGN 2017

Surgery should be considered a treatment of last resort and is generally performed with a step up approach. Only considered in severe cases when maximal medial therapies have failed, appropriate work up has been done and symptoms significantly affect the child's quality of life



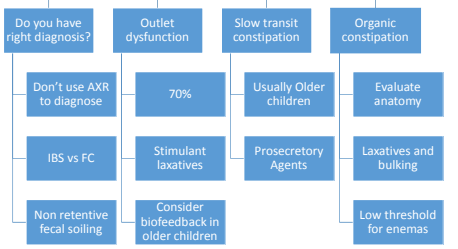


Colon motility improves after ACE



Rodriguez L et al. Nerogastroenterol Motil 2013

Intractable constipation



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