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Some of the slides reproduced in this syllabus contain animation in the power point version. This cannot be seen in the printed version.
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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)™ Physicians should only claim credit commensurate with the extent of their participation in the activity.
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](image)

Grooteman et al, GIE 2017

**Location**

- Stomach
- Duodenum
- Small bowel (jejenum 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

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Caustic ingestion

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

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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)
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%


**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)


**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>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No lesion</td>
</tr>
<tr>
<td>1</td>
<td>3 aphthous lesions</td>
</tr>
<tr>
<td>2</td>
<td>5 aphthous lesions with normal mucosa between the lesions, or slip area of larger lesions, or lesions confined to the ileocolic anastomosis</td>
</tr>
<tr>
<td>3</td>
<td>Diffuse aphthous lesions with diffuse inflamed mucosa</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse inflammation with already larger ulcers, nodules, and/or narrowing</td>
</tr>
</tbody>
</table>


---

Post-operative recurrence


---

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

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

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
Urgent: Call the ED re: Patient with GI BLEEDING

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

2. Pant et al. CMRO, 2014
4. Lerner et al. JPGN, 2014

Low Volume of Hemostatic Procedures in Pediatric GI Centers
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

- Undetermined: 11%
- Non-GI: 2%
- No obvious bleeding: 20%
- Esophagitis/Gastritis/Duodenitis: 30%
- Esophageal Varices: 6%
- Mallory-Weiss Tears: 4%
- Gastric Ulcers: 11%
- Prolapse Gastropathy: 13%
- Intralesional Ulcers: 8%
- Duodenal Ulcers: 8%
- Erosive Esophagitis: 5%


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
Sheffield scoring system to predict need for endoscopic/surgical therapy [30].

<table>
<thead>
<tr>
<th>Score</th>
<th>History taking</th>
<th>Clinical assessment</th>
<th>Laboratory findings</th>
<th>Management or resuscitation</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Significant presenting condition</td>
<td>HR &gt; 20 from the mean HR for age</td>
<td>Prolonged capillary refill</td>
<td>Need for a fluid bolus</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Presence of melena</td>
<td>History of large amount of hematemesis</td>
<td></td>
<td>Need for blood transfusion (1 h of &lt; 80 g/L)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Need for other blood product</td>
<td>4</td>
</tr>
</tbody>
</table>

Cut-off = 8.

PPV: 91% (95% CI 73–97)

Sensitivity: 90% (95% CI 73–96)

Specificity: 91% (95% CI 73–97)

Notes: Based on n = 69 patients, admitted to single centre over 3 year period divided into intervention (n = 30) and no intervention required (n = 39).

---

Timing of endoscopy

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

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
## Diagnostic yield of lower GI exam


Yield 74-100%

Yield 10%

### Urgent endoscopy suite

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

Luh, et al., Gastrointest Endosc Clin N Am, 2016
Active Bleeding:
- 55–100% 40–50%
- 20–30% 10% 5%

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

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.
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.

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.

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.
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 diulafay 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.

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.

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.
Management of Pancreatic Fluid Collections

Matthew Giefer MD
Seattle Children’s
Director of Endoscopy
NASPGHAN Post-Graduate Course
November 2, 2017

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

Acute Peripancreatic Fluid Collection (APFC)

Acute Necrotic Collection (ANC)
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
Medical Management – Acute Phase

- Appropriately aggressive rehydration, pain control and enteral feeds.

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


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.


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.

Indications for Intervention

**Infection**

- 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.

**Obstruction**

Interventions: Percutaneous 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.

Interventions: Surgical Drainage

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

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.

Case: WON from Necrotizing Gallstone Pancreatitis
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

Michelle Pietzak, MD
Division Head, Los Angeles County Hospital
Pediatric Gastroenterology
University of Southern California Keck School of Medicine
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 ESPGHAN guidelines for the diagnosis of celiac disease
3. Understand the rationale for the recent modifications of the ESPGHAN guidelines
4. Know the differences in NASPGHAN 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 ticks or bread cut thin and well toasted on both sides
**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)


**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

**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
- Expert opinions: 1 primary care pediatrician, 1 clinical epidemiologist/ primary care pediatrician, 8 pediatric GI, 1 adult GI
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 confirmation 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

ESGPHAN 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 novel >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
  - If 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
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

Gluten-free Diet

• Increasing recognition that celiac disease is common
• Trendy to be gluten-free, ~30% of US adults "limiting" gluten
  – 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

---

Why do consumers buy Gluten-free?

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\(^2\)

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

---

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


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)

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

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

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

---

**My Plate**

![MyPlate Kids' Place](https://www.choosemyplate.gov)

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**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

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

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 Pediatrics and Physiology
University of Toronto

Conflict of Interest
- Nothing to disclose

Learning Objectives
Understand updated guidelines for:
- Who to test
- How to test
- How to treat
*H. pylori* infection in children
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?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer disease</td>
<td>Yes - Strong recommendation</td>
</tr>
<tr>
<td>Functional abdominal pain</td>
<td>No - Strong recommendation</td>
</tr>
<tr>
<td>Asymptomatic children</td>
<td>No - Strong recommendation</td>
</tr>
<tr>
<td>Family history of gastric CA</td>
<td>Yes - Strong recommendation</td>
</tr>
<tr>
<td>MALT lymphoma</td>
<td>Yes - Strong recommendation</td>
</tr>
</tbody>
</table>

New ESPGHAN/NASPGHAN 2016 recommendations
Who to test: extra-intestinal disease?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency anemia</td>
<td>No</td>
</tr>
<tr>
<td>Unexplained refractory iron deficiency anemia</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic ITP</td>
<td>Yes</td>
</tr>
<tr>
<td>Short stature</td>
<td>No</td>
</tr>
</tbody>
</table>

New ESPGHAN/NASPGHAN 2016 recommendations

How to test- initial diagnosis?

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI endoscopy and biopsy</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-invasive tests</td>
<td></td>
</tr>
<tr>
<td>Urea breath tests</td>
<td>No</td>
</tr>
<tr>
<td>Stool antigen tests</td>
<td>No</td>
</tr>
<tr>
<td>Serologic assays</td>
<td>No!</td>
</tr>
</tbody>
</table>

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 |

**Should H. pylori be eradicated?**

A. Yes  
B. No

**Who to treat?**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer disease</td>
<td>Yes</td>
</tr>
<tr>
<td><em>H. pylori</em> without peptic ulcer disease</td>
<td>consider</td>
</tr>
<tr>
<td>Unexplained refractory iron deficiency anemia</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic ITP</td>
<td>Yes</td>
</tr>
<tr>
<td>Family history of gastric CA</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*New ESPGHAN/NASPGHAN 2016 recommendations*
How to treat 1st line?

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


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

How to treat 1st line?

- Proton pump inhibitor 7-14d
  amoxicillin
  metronidazole

- Proton pump inhibitor 7-14d
  amoxicillin
  clarithromycin

- Bismuth salts 7-14d
  amoxicillin
  metronidazole

- Sequential therapy 10d


Efficacy of sequential therapy

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

Efficacy of sequential therapy


Efficacy of sequential therapy in treatment-naive children


**Efficacy of sequential therapy in treatment-naive children**


**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

**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
How to treat-first line? New guidelines

CLA resistance or prior CLA therapy?

Yes

No

Resistant to MET

New ESPGHAN/NASPGHAN 2016 recommendations
How to treat-first line?
New guidelines

<table>
<thead>
<tr>
<th>CLA resistance or prior CLA therapy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>PPI-AMO-CLA 2 weeks</td>
</tr>
<tr>
<td>CLA: High dose PPI-AMO-MET 2 weeks</td>
</tr>
<tr>
<td>or bismuth-based</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Resistant to MET</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>PPI-AMO-MET 2 weeks</td>
</tr>
<tr>
<td>CLA: High dose PPI-AMO-MET 2 weeks</td>
</tr>
<tr>
<td>or bismuth-based</td>
</tr>
</tbody>
</table>

New ESPGHAN/NASPGHAN 2016 recommendations

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How to treat-first line?
New guidelines

<table>
<thead>
<tr>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLA: High dose PPI-AMO-MET 2 weeks or bismuth-based</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Resistant to MET</td>
</tr>
<tr>
<td>Yes</td>
</tr>
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</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

New ESPGHAN/NASPGHAN 2016 recommendations

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Case presentation- cont’d

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

<table>
<thead>
<tr>
<th>Non-invasive tests</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea breath tests</td>
<td>Yes</td>
</tr>
<tr>
<td>Stool antigen tests</td>
<td>Yes</td>
</tr>
<tr>
<td>Serologic assays</td>
<td>No!</td>
</tr>
</tbody>
</table>

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

Case presentation- cont’d

- Urea breath testing shows the child is no longer \textit{H. pylori} positive

How to manage treatment failure?

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

Thanks for your attention!
Biliary Atresia: Update on Biomarkers of Disease and Therapeutic Interventions

Cara L. Mack, MD
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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)

- 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

Schwarz et al. Hepatology 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)


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

Biliary Atresia Subjects

Ng et al. J Pediatr 2014

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

- Bilirubin < 2 mg/dL
- Bilirubin ≥ 2 mg/dL


Th1 Infiltrates and Fibrosis in BA

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

- Change in bilirubin
- Change in IL-8
- Day 90 post-HPE

- IL-8 and outcome

- 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
  - LPC
  - lysophosphatidylcholine
  - lysophosphatidic acid

- HEPATIC STELLATE CELLS
  - Migration
  - Proliferation
  - Production of secreted factors
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

![Graph showing growth in length and head circumference over weeks for both enteral and oral feeding methods.](image1)

Macias-Rosales R et al. JPGN 2016;62

Arm fat area

Enteral P= 0.001
Oral P= 0.9

Arm muscle area

Enteral P= 0.11
Oral P= 0.98

Macias-Rosales R 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

Sullivan JS et al. Liver Transp 2012(18)

<table>
<thead>
<tr>
<th>Time at HPE</th>
<th>Time at Listing</th>
<th>Time at Clinical Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC (mean±SEM)</td>
<td>TNP (mean±SEM)</td>
<td>MAC (mean±SEM)</td>
</tr>
</tbody>
</table>

MAC: mid arm circumference (protein stores)
TNP: triceps skin fold (fat stores)

Fat Soluble Vitamin Deficiencies in BA

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

Vitamin Sufficiency Rates

**Target Fat Soluble Vitamin Levels and Replacement Regimens**

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Target range</th>
<th>Supplementation strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (retinol)</td>
<td>19 – 77 µg/dL, retinal/serum ratio &gt; 0.8</td>
<td>Increment of 5000 IU/day to 25 – 50,000 IU/monthly or intramuscular administration of 50,000 IU</td>
</tr>
<tr>
<td>D (25-hydroxy vitamin D)</td>
<td>15 – 45 ng/ml</td>
<td>Increment of 1200 to 8000 IU orally daily of cholecalciferol or ergocalciferol</td>
</tr>
<tr>
<td>E (alpha tocopherol)</td>
<td>3.8 – 20.3 µg/ml</td>
<td>Increment of 25 IU/kg of TPOS orally daily to 100 IU/kg/day</td>
</tr>
<tr>
<td>K (thymol)</td>
<td>INR&lt;1.2</td>
<td>1.2 &lt; INR&lt;1.5, 25-50 mg vitamin K orally daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.5 &lt; INR&lt;2.0, 5-10 mg vitamin K intramuscular and 25 mg vitamin K orally daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INR&gt;2.0, 10-25 mg vitamin K intramuscular and 50 mg vitamin K orally daily</td>
</tr>
</tbody>
</table>
**Cholangitis: Prophylactic Antibiotics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lally et al.</th>
<th>Wu et al.</th>
<th>deVries et al.</th>
<th>Bu et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>U.S.</td>
<td>Taiwan</td>
<td>Netherlands</td>
<td>Taiwan</td>
</tr>
<tr>
<td>Study Design</td>
<td>Retrospective cohort</td>
<td>Retrospective cohort</td>
<td>Retrospective cohort</td>
<td>Randomized (2 Antibiotics)</td>
</tr>
<tr>
<td>Sample Size</td>
<td>Abx: 34</td>
<td>No Abx: 7</td>
<td>Abx: 12</td>
<td>No Abx: 21</td>
</tr>
<tr>
<td>Prophylactic Abx (duration)</td>
<td>TMP/SMX; amoxicillin; cephalosporins (1- several mons.)</td>
<td>TMP/SMX; neomycin (unknown)</td>
<td>TMP/SMX; neomycin/colistin; ciprofloxacin (unknown)</td>
<td>TMP/SMX; neomycin (until 36 mons. age)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1-72 months</td>
<td>6-59 months</td>
<td>1-263 months</td>
<td>Age 36 mos.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Incidence of cholangitis</td>
<td>Incidence of cholangitis</td>
<td>Incidence of cholangitis</td>
<td>Recurrence rate cholangitis</td>
</tr>
<tr>
<td>Results</td>
<td>Abx: 15%</td>
<td>No Abx: 57%</td>
<td>Abx: 53%</td>
<td>No Abx: 47%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Abx: 15%</th>
<th>No Abx: 51%</th>
<th>Ctrl: 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>62.5%</td>
<td>51.7%</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>62.5%</td>
<td>51.7%</td>
<td></td>
</tr>
</tbody>
</table>


**Recent clinical trials: ChiLDReN**

*Original Investigation*

**Use of Corticosteroids After Hepatopancreatobiliary Infants With Bilary Atresia**

The START Randomized Clinical Trial

Bezerra et al. JAMA 2014;311(17)

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

![Graph showing results of subjects with total bilirubin <1.5 mg/dL and with native liver 6 months post- Kasai.](https://example.com/graph)

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

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
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; bilirubin 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: R01NASH 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

Schwimmer JB et al. *Pediatrics* 2006

![](image1)

**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/m² (99 ± 0.8 percentile)

Patton H et al. *Gastroenterology* 2008

![](image2)

**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* 2013
Ekstedt et al. *Hepatology* 2006

![](image3)
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)

<table>
<thead>
<tr>
<th>Glucose Status</th>
<th>NASH, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>1.9 (1.2-2.9)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>3.1 (1.5-6.2)</td>
</tr>
</tbody>
</table>

• 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

Age 11
BMI 28 kg/m²
ALT 134 U/L
Stage 1c fibrosis
5 years
Age 16
BMI 35 kg/m²
ALT 172 U/L
Stage 3/4 fibrosis

84
How should I screen for NAFLD?

Imaging studies?
Liver biopsy?
Degree of liver enzyme elevation?
Treatment?

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

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. Gastroenterology 2010

Schwimmer JB et al. Aliment Pharmacol Ther 2013
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 ethnicity
- 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)

---

### 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

---

### 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
  – 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/m² 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%)

**Selection criteria for adolescent weight loss surgery**

<table>
<thead>
<tr>
<th>BMI</th>
<th>Comorbidities</th>
</tr>
</thead>
</table>
| ≥ 35 | • Type 2 DM  
  • moderate-severe OSA (AHI ≥ 15 events/hr)  
  • pseudotumor cerebri  
  • severe NASH |
| ≥ 40 | • Mild OSA (AHI ≥ 3 events/hr)  
  • HTN  
  • Insulin resistance/IGT  
  • Dyslipidemia  
  • impaired QOL or ADL |

**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%
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

Xanco M et al. J Pediatr 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)

Fibrosis Prevalence

Xanthakos et al. Gastroenterology 2015

ALT outcomes in Teen LABS at 3 years

Approximately 2/3 bypass, 1/3 sleeve recipients

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?

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 (~% 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)

Famsuri et al JPN 2017
Ahi 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 often 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
  - 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

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

Andrew B. Grossman MD
Co-Director, Center for Pediatric Inflammatory Bowel Disease
Associate Professor of Clinical Pediatrics
Division of Gastroenterology, Hepatology, and Nutrition

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

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)
**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)

**Suggested Algorithm: Proactive and Reactive TDM**

- Proactive TDM: Check IFX trough at week 14 and/or if LOR
- Reactive TDM: Monitor IFX trough level during induction phase
- Continue IFX trough level monitoring

**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

PR: Week 54 remission (PCDAI, CDAI, or partial Mayo); no IFX dose escalation
Week 10 IFX Level and Duration of Response
Prospective cohort, pediatric Crohn disease (n=77)

<table>
<thead>
<tr>
<th>Week 10 IFX (n=66)</th>
<th>IFX IN (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.82 ± 2.04 mg/L</td>
<td>1.36 (0.60 to 2.10)</td>
<td>0.01</td>
</tr>
<tr>
<td>E73 (n=20)</td>
<td>6.73 (4.08 to 9.98)</td>
<td>0.01</td>
</tr>
<tr>
<td>IFX trough</td>
<td>4.38 (2.23 to 7.90)</td>
<td>1.36 (0.60 to 2.10)</td>
</tr>
<tr>
<td>IFX trough</td>
<td>4.38 (2.23 to 7.90)</td>
<td>1.36 (0.60 to 2.10)</td>
</tr>
</tbody>
</table>

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)

Concentration of Infliximab Associated with Subsequent Efficacy in Adult UC

Remission but subtherapeutic IFX trough ➔ Less likely to maintain remission

SONIC Trial

Corticosteroid-Free Clinical Remission at Week 50

<table>
<thead>
<tr>
<th>AZA + placebo</th>
<th>IFX + placebo</th>
<th>IFX + AZA</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.2</td>
<td>39.6</td>
<td>55.6</td>
</tr>
</tbody>
</table>

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

Variables Affecting Clearance of Biological Therapies
Factors Affecting Pharmacokinetics of Monoclonal Antibodies

- Presence of ADA
- Gender
- High baseline CRP
- Patient weight

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)

Proactive and Reactive TDM
**Trough Concentration Adapted InfliXImab Treatment**

**Dose optimization phase**

- **Eligibility**
  - Maintenance IFX ≥ 14 weeks
  - Full or partial responder
  - No ATI > 8 µg/ml
  - Stable dose immunomodulators

**Dose Optimization Phase**

148/263 (56.3%) required dose optimization

- 51.4% Dose escalation
- 48.6% Dose reduction

**Maintenance Phase**

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

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

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)

What is Our Target??

- Vary based on study; agreed upon targets not established
- Possibly different based on indication/goal
  - Mucosal healing may require higher trough1
  - Perianal fistula closure improved with IFX trough >10 2
  - Acute severe UC flare vs. maintenance of mucosal healing
- Mucosal levels?

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
  - 71.3% in active disease, 33.3% in remission (p=0.03)

Patients with active disease may have low tissue anti-TNF despite good serum levels
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=0.04)
  - No difference in clinical remission

**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 10.1 (p=0.02)
    - CRP: VDZ > 5.1 more likely to be in CRP remission
      - OR: 2.9, 95%CI 1.2-5.1 overall
      - OR: 2.5, 95%CI 1.3-4.5 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)
Future – Individualized Dashboards

PK Dashboard Optimizing IFX

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

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
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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Vice-Chair for Faculty Development, Diversity and Promotion, Dept. of Peds.
The Johns Hopkins University School of Medicine
Baltimore, MD

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
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

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)
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

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

Adapted from Springer TA, Cell 1994
### GEMINI 1: Vedolizumab for UC
#### Clinical Response at week 6

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N=149)</th>
<th>Vedolizumab (N=225)</th>
<th>Percentage-Point Difference (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical response</td>
<td>38 (25.5%)</td>
<td>106 (42.1%)</td>
<td>21.7 (11.6-31.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical remission</td>
<td>8 (5.4%)</td>
<td>38 (16.9%)</td>
<td>11.5 (4.7-18.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mucosal healing</td>
<td>37 (24.8%)</td>
<td>92 (40.9%)</td>
<td>16.1 (6.4-25.9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>


### GEMINI 1: Vedolizumab for UC
#### Clinical Outcomes at week 52

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N=126)</th>
<th>Vedolizumab every 8 wk (N=122)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>15.9%</td>
<td>41.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Steroid-free remission</td>
<td>13.9%</td>
<td>31.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mucosal healing</td>
<td>19.8%</td>
<td>51.6%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


### Gemini 2: Vedolizumab for CD
#### Primary endpoint at week 6

- **Clinical Remission**
  - Placebo (N=149): 6.8%
  - Vedolizumab (N=220): 14.5%
- **CDAI-100 Response**
  - Placebo (N=149): 25.7%
  - Vedolizumab (N=220): 31.4%

GEMINI 2: Vedolizumab for CD
Clinical Outcomes at Week 52


GEMINI 2: Vedolizumab for CD
Remission at Week 52

Patients in Clinical Remission (%)


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%

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)

Feagan B et al, NEJM 2013
Sandborn W et al, NEJM 2013
Willett W et al, Ctr Gastroenterol Hepatol 2016
Ungaro R et al, Gastroenterology 2017 abs S-385

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

<table>
<thead>
<tr>
<th></th>
<th>No biological therapy (n=172)</th>
<th>Anti-TNF (n=126)</th>
<th>Vedolizumab (n=94)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any post-op Complication</td>
<td>57 (33%)</td>
<td>36 (28%)</td>
<td>50 (53%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Non-SSI Infections</td>
<td>10 (16%)</td>
<td>6 (5%)</td>
<td>7 (7%)</td>
<td>&lt;0.11</td>
</tr>
<tr>
<td>All SSIs</td>
<td>22 (13%)</td>
<td>13 (10%)</td>
<td>35 (37%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>dSSIs</td>
<td>11 (6%)</td>
<td>5 (4%)</td>
<td>20 (21%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>sSSIs</td>
<td>11 (6%)</td>
<td>6 (5%)</td>
<td>13 (14%)</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Anastom. leak</td>
<td>1 (1%)</td>
<td>4 (3%)</td>
<td>2 (2%)</td>
<td>&lt;0.24</td>
</tr>
<tr>
<td>MCS</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>7 (7%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBO/ileus</td>
<td>20 (12%)</td>
<td>12 (10%)</td>
<td>9 (10%)</td>
<td>&lt;0.79</td>
</tr>
<tr>
<td>Re-admission</td>
<td>17 (10%)</td>
<td>12 (10%)</td>
<td>15 (16%)</td>
<td>&lt;0.24</td>
</tr>
<tr>
<td>Return to OR</td>
<td>8 (5%)</td>
<td>10 (8%)</td>
<td>8 (9%)</td>
<td>&lt;0.37</td>
</tr>
</tbody>
</table>

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

---

### Ustekinumab Blocks IL-12 and IL-23 Signaling

![Ustekinumab Blocks IL-12 and IL-23 Signaling](image)

---

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

![UNITI-1 & 2: Primary Outcome Clinical Response at Week 6](image)
IM-UNITI: Ustekinumab Maintenance for CD Primary and Secondary Endpoints


IM-UNITI: Ustekinumab Maintenance for CD Remission by Subgroups


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 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

Cameron FD 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

Tilki 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 µg/mL associated with endoscopic response and lower CRP
- Anti-drug antibodies ~2-5%

Bakel R et al, Clin Gastroenterol Hep 2017
Most Commonly Reported AEs in CD Patients in UNITI Trials

Vertocott 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

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 psoriasisiform rashes
Other Drugs in Phase II-III Development

- JAK kinase inhibition
  - Tofacitinib¹ (Xeljanz²): oral small molecule
- Anti-integrins
  - Etrolizumab² (subcutaneous) targets α4β7 and αEβ7
- Anti IL-23
  - Brazikumab³
  - Risankizumab⁴
- Anti-SMAD7
  - Mongersen⁵: oral antisense RNA

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

²Vermeire S et al, Lancet 2014
³Sands BE et al, Gastroenterology 2017
⁴Fegan B et al, Lancet 2017
Prevention of Postoperative Crohn's Disease

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Professor of Medicine & Translational Research
Associate Chief, Education
IBD Clinical Medical Director
Senior Medical Lead of Specialty Medical Homes
University of Pittsburgh Medical Center

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

Recurrence is clinically silent initially

Within 1 week
Histologic
70-90% by 1yr
Tissue damage
30% 3yr
60% 5yr
50% by 5yrs

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

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

Requeiro 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.


Endoscopic Recurrence Reduced in Infliximab Treated Patients

Endoscopic Recurrence defined as endoscopic scores of 2, 3, or 4.
<table>
<thead>
<tr>
<th>PO- Endo Recur</th>
<th>antiTNF</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorrentino1 (MTX/IFX v SASA 2yr)</td>
<td>0%</td>
<td>100% (SASA)</td>
</tr>
<tr>
<td>Requeiro2 (IFX vs PBO RCT 1 yr)</td>
<td>9%</td>
<td>85% (PBO)</td>
</tr>
<tr>
<td>Yoshida3 (IFX vs PBO Open 1 yr)</td>
<td>21%</td>
<td>81% (SASA)</td>
</tr>
<tr>
<td>Armuzi4 (IFX vs AZA Open 1 yr)</td>
<td>9%</td>
<td>40% (AZA)</td>
</tr>
<tr>
<td>Fernandez-Blanco 5 (ADA)</td>
<td>10%</td>
<td>N/A</td>
</tr>
<tr>
<td>Papamichael6 (ADA 6m)</td>
<td>0%</td>
<td>N/A</td>
</tr>
<tr>
<td>Savarino7 (ADA 3yr)</td>
<td>0%</td>
<td>N/A</td>
</tr>
<tr>
<td>Aguas8 (ADA 1 yr)</td>
<td>21%</td>
<td>N/A</td>
</tr>
<tr>
<td>De Cruz9 (ADA vs AZA 6mos)</td>
<td>6%</td>
<td>38% (AZA)</td>
</tr>
<tr>
<td>Savarino10 (ADA vs AZA vs SASA 2 yrs)</td>
<td>6%</td>
<td>65% (AZA), 83% (SASA)</td>
</tr>
</tbody>
</table>

...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)


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 of cyclosporine or azathioprine (AZA, 6-MP, or MTX).
Secondary Endpoint
Endoscopic Recurrence

---

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=150)</th>
<th>Infliximab 5 mg/kg (N=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of Subjects (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopic Recurrence Only Based on Endoscopic Criteria (i.e., Rutgeerts score ≥ 2)</td>
<td>51.3</td>
<td>60.6</td>
</tr>
<tr>
<td>Endoscopic Recurrence with Treatment Failure Rule and Other Data Handling Rules Applied</td>
<td>22.4</td>
<td>30.6</td>
</tr>
</tbody>
</table>

P <0.001†

†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., ADA, 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


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

By scoping at 6 mos and intensifying rx 18% lower rate of endoscopic recurrence
 Prevent vs. Wait for Recurrence?

When should we start anti-TNF?

<table>
<thead>
<tr>
<th>Method</th>
<th>1 week</th>
<th>70-90% by 1 yr</th>
<th>Tissue damage</th>
<th>30% 3 yr</th>
<th>60% 5 yr</th>
<th>50% by 5 yrs</th>
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</thead>
<tbody>
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<td>Histologic</td>
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</table>

Surgery

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

Too late = irreversible damage

<table>
<thead>
<tr>
<th>Method</th>
<th>1 week</th>
<th>70-90% by 1 yr</th>
<th>Tissue damage</th>
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<tr>
<td>Surgical</td>
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</tbody>
</table>

Surgery

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, MD1*; Fernando Velayos, MD2*; Julia B. Greer, MD, MPH1; Christina Bougatsos, MPH3; Roger Chou, MD3; Shahnaz Sultan, MD, MHSc4; Siddharth Singh, MD, MS5

.....this AGA Technical Review informed.....
American Gastroenterological Institute Guideline for the Management of Crohn’s Disease after Surgical Resection

Geoffrey C. Nguyen,1 Edward V. Loftus Jr2, Ikuo Hirano3, Yngve Falck-Ytter4, Siddharth Singh5, Shahnaz Sultan6, and the AGA Institute Clinical Guidelines Committee

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

Within 1 week

Tissue damage

50% by 5 yrs

Treat Here .......... not Here
#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 suggests AGAINST using mesalamine (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

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

Need to consider risk for recurrence of CD after surgery

<table>
<thead>
<tr>
<th>AGA Illustrative Risk Groups</th>
<th>Clinical Characteristics</th>
<th>Hypothetical Risk of Clinical Recurrence (&gt;18m after surgery)</th>
<th>Hypothetical Risk of Endoscopic Recurrence (&gt;18m after surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Risk</td>
<td>Older patient (&gt;50y); non-smoker; 1st surgery for a short segment of fibrostenotic disease (&lt;10-20cm); disease duration &gt;10 years</td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td>Higher Risk</td>
<td>Younger patient (&lt;30y); smoker; ≥2 prior surgeries for penetrating disease, with or without perianal disease</td>
<td>50%</td>
<td>80%</td>
</tr>
</tbody>
</table>
AGA Illustrative risk groups

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Hypothetical risk of clinical recurrence (&gt;18m after surgery)</th>
<th>Hypothetical risk of endoscopic recurrence (&gt;18m after surgery)</th>
</tr>
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<td>Lower Risk</td>
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</tr>
<tr>
<td>Higher risk</td>
<td>Younger patient (&lt;30y); smoker; ≥2 prior surgeries for penetrating disease, with or without perianal disease</td>
<td>50%</td>
</tr>
</tbody>
</table>

So….after all of these years....... 

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

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

Pulmonary/ORL Differential Diagnosis
- GERD
- 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

7% have EoE
Rosen and Nurko, Am J Gastro, 2004

Full Column Reflux Matters
Jadcherla et al Am J Gastro 2008

<table>
<thead>
<tr>
<th>Extent of Refluxate (# AREs)</th>
<th>Composite SSI</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharynx (N = 30)</td>
<td>77% (22/30)</td>
<td>47% (14/30)</td>
</tr>
<tr>
<td>Proximal esophagus (N = 36)</td>
<td>50% (18/36)</td>
<td>22% (8/36)</td>
</tr>
<tr>
<td>Middle esophagus (N = 36)</td>
<td>50% (18/36)</td>
<td>28% (10/36)</td>
</tr>
<tr>
<td>Distal esophagus (N = 409)</td>
<td>27% (109/409)</td>
<td>11% (44/409)</td>
</tr>
</tbody>
</table>

SSI value >10% was considered to be abnormal.

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
Reflux episode

Patients record only 48% of all coughs—and cough precedes reflux 58% of the time
Rosen et al JPGN 2013

Insensitivity of Exhaled Breath Condensate

Biomarkers other than pH?
- Redness
- LLMI
- Pepsin
- Bile
No Relationship between Erythematous Airways and Reflux Parameters
Rosen et al Journal of Pediatrics 2017

<table>
<thead>
<tr>
<th></th>
<th>Erythema score=0</th>
<th>Erythema score=1</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Reflux Episodes</td>
<td>24±14</td>
<td>25±17</td>
<td>0.8</td>
</tr>
<tr>
<td>Number of Acid Reflux Episodes</td>
<td>47±26</td>
<td>49±28</td>
<td>0.7</td>
</tr>
<tr>
<td>Number of Nonacid Reflux Episodes</td>
<td>23±23</td>
<td>23±23</td>
<td>0.9</td>
</tr>
<tr>
<td>% Episodes that are Full Column</td>
<td>47±18</td>
<td>46±21</td>
<td>0.8</td>
</tr>
<tr>
<td>% Time pH&lt;4</td>
<td>4.5±5.6</td>
<td>5.0±5.6</td>
<td>0.7</td>
</tr>
<tr>
<td>% Time Proximal Reflux</td>
<td>0.7±0.7</td>
<td>0.7±0.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

LLMI: No relationship with Reflux by Impedance
Rosen et al Pediatrics 2008

LLMI: No Relationship with Aspiration
Reiley et al Laryngoscope 2011
Sensitivity of Pepsin in Children
Rosen et al Neurogastro 2011

<table>
<thead>
<tr>
<th>Sensitivity of Pepsin</th>
<th>Specificity of Pepsin</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Abnormal EGD</td>
<td>67%</td>
</tr>
<tr>
<td>If Abnormal pH probe</td>
<td>45%</td>
</tr>
<tr>
<td>If Abnormal MII</td>
<td>71%</td>
</tr>
<tr>
<td>If Any Abnormal Test</td>
<td>57%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pepsin – (n=29)</th>
<th>Pepsin + (n=21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal pH-metry</td>
<td>11 (38%)</td>
<td>8 (38%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Abnormal Impedance</td>
<td>8 (17%)</td>
<td>6 (29%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Total reflux episodes</td>
<td>43.0 (32.0, 53.0)</td>
<td>46.0 (19.0, 91.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>No. of acid reflux episodes</td>
<td>26.0 (8.0, 38.0)</td>
<td>19.0 (11.0, 46.0)</td>
<td>0.69</td>
</tr>
<tr>
<td>No. of non-acid reflux episodes</td>
<td>11.0 (5.0, 26.0)</td>
<td>14.0 (8.0, 33.0)</td>
<td>0.77</td>
</tr>
<tr>
<td>% of time pH&lt;4</td>
<td>0.4 (0.3, 0.7)</td>
<td>0.3 (0.2, 0.9)</td>
<td>0.88</td>
</tr>
<tr>
<td>% of proximal reflux</td>
<td>4.0 (1.3, 7.4)</td>
<td>2.0 (0.3, 13.6)</td>
<td>0.70</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>6 (21%)</td>
<td>8 (38%)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

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

Relationship between Bile and Reflux Events
Blondeau et al, J Heart Lung Transplant 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

Just once I would like to read a medication label that says: WARNING: May cause permanent weight loss, remove wrinkles and increase energy.

RCT of Lansoprazole in Infants with crying...and extraesophageal symptoms
Orenstein et al J Peds 2009

<table>
<thead>
<tr>
<th>Lansoprazole double-blind (26 weeks, n = 81)</th>
<th>Placebo double-blind (26 weeks, n = 81)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy: Responder rate, n (%)</td>
<td>44 (54%) 44 (54%)</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinued due to inefficacy, n (%)</td>
<td>28 (23%) 29 (23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Individual symptoms:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crying, % of feed/week (Appendix 2)</td>
<td>–30 –30</td>
<td>NS</td>
</tr>
<tr>
<td>Regurgitation, % of feed/week</td>
<td>–14 –14</td>
<td>NS</td>
</tr>
<tr>
<td>Stool feed, % of feed/week</td>
<td>–7 –8</td>
<td>NS</td>
</tr>
<tr>
<td>Feed refusal, % of days/week</td>
<td>–14 –10</td>
<td>NS</td>
</tr>
<tr>
<td>Crying back, % of days/week</td>
<td>–30 –10</td>
<td>NS</td>
</tr>
<tr>
<td>Coughing, % of days/week</td>
<td>–0 –9</td>
<td>NS</td>
</tr>
<tr>
<td>Wheezing, % of days/week</td>
<td>–5 –6</td>
<td>NS</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2 5</td>
<td>NS</td>
</tr>
</tbody>
</table>

USA safety statement:
- Patient improved at week 4: 45 (54%) 41 (51%) NS
- Patient improved at week 8: 46 (55%) 40 (49%) NS
RCT of Lansoprazole for Asthma
ALA Clinical Research Centers, JAMA 2012

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>No. of Participants</th>
<th>Placebo</th>
<th>Lansoprazole</th>
<th>Placebo</th>
<th>Lansoprazole</th>
<th>Placebo</th>
<th>Lansoprazole</th>
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<td>24-Hour Score</td>
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<td>Range</td>
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</table>

PPIs increase risk of pneumonia in adults with aspiration
Takatori et al J Gastro 2013

Lansoprazole

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)

Turco et al, APT 2010, Turrin et al 2012

Fig. 5 Kaplan-Meier curve showing probability of freedom from pneumonia in the 3 groups: continuous line, control group; dashed line, Lansoprazole group; dotted line, Mesalazine group. The survival rate of the Lansoprazole group is significantly different from the control group (p = 0.001).

Stomach acid drugs increase risk of bacterial infections, FDA warns

142
Motility Agents

- Cisapride
- Tagaserod
- Reglan

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

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

<table>
<thead>
<tr>
<th>Erythromycin (n = 13)</th>
<th>Placebo (n = 11)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to full feeds (days)*</td>
<td>24.9 ± 2.9</td>
<td>30.8 ± 4.1</td>
</tr>
<tr>
<td>Age birth weight regained (days)</td>
<td>12.8 ± 4.4</td>
<td>16.8 ± 6.2</td>
</tr>
<tr>
<td>Age full feeds attained (days)</td>
<td>46.6 ± 18.0</td>
<td>52.1 ± 17.5</td>
</tr>
<tr>
<td>Total parenteral nutrition (days)</td>
<td>50.4 ± 13.8</td>
<td>34.3 ± 18.3</td>
</tr>
<tr>
<td>Cholestatic jaundice</td>
<td>4/13 (31%)</td>
<td>7/11 (64%)</td>
</tr>
<tr>
<td>Glycemic suspense used***</td>
<td>1.5 ± 0.4</td>
<td>2.0 ± 1.0</td>
</tr>
<tr>
<td>Reflux index before study (%)</td>
<td>5.2 ± 15.5</td>
<td>13.6 ± 17.3</td>
</tr>
<tr>
<td>Reflux index after study (%)</td>
<td>4.3 ± 7.1</td>
<td>0.3 ± 0.6</td>
</tr>
<tr>
<td>Reflux reduction</td>
<td>3/13 (23%)</td>
<td>4/11 (36%)</td>
</tr>
<tr>
<td>Duration of hospitalization (9 days)</td>
<td>98.3 ± 35.9</td>
<td>99.0 ± 58.6</td>
</tr>
</tbody>
</table>

* Values are mean ± SD, unless otherwise noted. ** mean ± SEM.
Azithromycin reduces bothersome lung symptoms in children

Macrolide use and risk of asthma at age 3
Metsala et al Clin & Exp Allerg 2015

<table>
<thead>
<tr>
<th></th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>2.35</td>
<td>2.1-2.63</td>
</tr>
<tr>
<td>Macrolides</td>
<td>2.74</td>
<td>2.5-2.99</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>1.91</td>
<td>1.76-2.07</td>
</tr>
</tbody>
</table>

Fundoplication

“Okay, folks, that’s a wrap!”
Extraesophageal symptoms relapse quickly after Fundoplication

Krill et al CGH 2017

Fundoplication does not reduce hospitalizations

Barnhart et al JAMA Peds 2013

Hospitalization after Fundoplication

Lee et al J Peds Surg 2008
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
Swallow dysfunction is a significant driver of BRUEs

Duncan et al JPGN 2016

- 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

38% of EoE patients have eosin 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
Bob’s Lung Aspiration Sauce

It’ll Burn your Friggin’ Lungs Out!

Made with fresh morning expectorate, handpicked nostril phlegm, and a tooth of some “stuff.”

For anyone smoking Bob’s Lung Sauce, or online at www.bobs.com

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For information write to Sunflower Press, 6488 S. Narrow Lane, Denver, CO 80214.
POTS AND JOINT HYPERMOBILITY, WHAT DO THEY HAVE TO DO WITH FUNCTIONAL DISORDERS?

Miguel Saps, MD
Professor of Pediatrics
University of Miami, Miller School of Medicine
Division of Pediatric Gastroenterology, Hepatology and Nutrition
Holtz Children’s Hospital, Jackson Health Systems

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)

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.


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

ORTHOSTATIC INTOLERANCE  POTS  HEART RATE

Beighton Score

One point for each thumb
One point for each finger = 10°
One point for each elbow = 10°
One point for each knee = 15°
One point for each ankle = 15°
BEIGHTON SCORE

JOINT HYPERMOBILITY

Beighton Score

+ "Brighton Score"

Hypermobility Ehlers-Danlos Syndrome

**Beighton Score**


<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Beighton score of 5/9 or greater (either currently or historically)</td>
<td>• Brighton score of 5, 6 or 7/9</td>
</tr>
<tr>
<td>• Arthralgia for longer than 3 months in 4 or more joints</td>
<td>• Arthralgia (&gt; 3 months) in 1-3 joints or back pain (&gt; 3 months), spondylitis, spondylolisthesis, spondylolisthesis</td>
</tr>
<tr>
<td></td>
<td>• Dislocation/subluxation in &gt;3 joints, or in one joint on more than one occasion</td>
</tr>
<tr>
<td></td>
<td>• Soft tissue rheumatism, &gt; 3 lesions (e.g. epicondylitis, tenosynovitis, bursitis)</td>
</tr>
<tr>
<td></td>
<td>• Marfanoid habitus (tall, thin, span/height ratio &gt;1.03, upper/lower segment ratio less than 0.85, arachnodactyly)</td>
</tr>
<tr>
<td></td>
<td>• Abdominal skin: striae, hyperextensibility, thin skin, papyraceous scarring</td>
</tr>
<tr>
<td></td>
<td>• Eye signs: drooping eyelids or myopia or antimongoloid slant</td>
</tr>
<tr>
<td></td>
<td>• Varicose veins or hernia or uterine/rectal prolapse</td>
</tr>
</tbody>
</table>

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

Why Do We Seem To See So Many?

• Selection bias?
• Recall bias?
• True association?
Functional Gastrointestinal Disorders

- POTS: 29%
- hEDS: 1/1000


Joint Hypermobility


<table>
<thead>
<tr>
<th>Functional Gastrointestinal Disorders</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brighton Score ≥4</td>
<td>28.7%</td>
<td>27.9%</td>
</tr>
</tbody>
</table>

OR = 1.03 (95% CI: 0.59-1.81, p=0.89)

GASTROINTESTINAL SYMPTOMS

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


SELECTION BIAS
Comorbidities in POTS and Hypermobile Ehlers-Danlos Syndrome

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


RECALL BIAS

Gastrointestinal symptoms reproduced - 89%
Electrogastrography (EGG)

Kuth KL. Exp Brain Res. 2014;232:2053-61
Electrogastrography (EGG)

Non-POTS


Antroduodenal Manometry

<table>
<thead>
<tr>
<th>Tilt Test Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurogenic intestinal dysmotility</td>
</tr>
<tr>
<td>Antral hypomotility</td>
</tr>
<tr>
<td>Abnormal gastric emptying studies</td>
</tr>
</tbody>
</table>


Hypermobile Ehlers-Danlos Syndrome

IBS and functional constipation are frequent.

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

Hypermobile Ehlers-Danlos Syndrome

- 49% - POTS
- 31% - Orthostatic intolerance

HEDs-Abnormal cardiovascular autonomic profile

Children/Adolescents

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

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

- Beta blockers, pyridostimine

POTS - Prognosis

- 2 years - 76% improved

- 5 years

  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

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

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
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
  
JPHN 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

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.

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, projectile 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
  - Prior abdominal surgery,
  - Foreign body ingestion,
  - Abnormal bowel sounds,
  - 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%.
- Sonogram is not a helpful diagnostic tool in children with FAP.
- Low risk
- Consider in children with specific findings


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
- Negative predictive value 97.4%
- Advantages
  - diagnosing extra-enteric lesions
  - No radiation risk
- Disadvantage
  - Cost

1. EA Zimmerman, Gut 2011
2. AR Kantar, Case Reports in Gastroenterology 2015
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.

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
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

Protozoa and CAP

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

G F 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
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.
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.


Hindgut Motility: Function

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First line treatment is Polyethylene 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......

**CONSTIPATION**

---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.

---

175
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.

Freedman 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

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?
  - Outlet dysfunction
  - Slow transit constipation
  - Organic constipation

- Don’t use AXR to diagnose IBS vs FC
- Non-retentive fecal soiling

Outlet dysfunction
- Increased evacuation
- Rectal hypersensitivity
- Megacolon
- Rectal hypercompliance
- Decreased anal tone

Overflow fecal incontinence
- Rectal incontinence
- Rectal pseudo-obstruction
- Rectovaginal fistula

Outlet dysfunction
- Rectal incontinence
- Rectovaginal fistula
- Rectal pseudo-obstruction

Achalasia
- Cardiac dysfunction
- Increased esophageal pressure
- Distal esophageal dilation

Hyper trophy
- Increased abdominal wall
- Fundal hernia

Achalasia
- Cardiac dysfunction
- Increased esophageal pressure
- Distal esophageal dilation

Hypertrophy
- Increased abdominal wall
- Fundal hernia
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

Intractable constipation

- Do you have right diagnosis?
- Outlet dysfunction
- Non-retentive fecal soiling
- Stimulant laxatives
- Consider biofeedback in older children

• Don’t use AXR to diagnose

- Organic constipation
- Slow transit constipation
- IBS vs FC
- 70%

180
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)
**Intractable constipation**

- Do you have a right diagnosis?
- Don’t use AXR to diagnose IBS vs FC
- Non-retentive fecal soiling
- Consider biofeedback in older children
- Outlet dysfunction
- Stimulant laxatives
- Slow transit constipation
- Prosecreatory Agents
- Organic constipation

**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
Anorectal Manometry May Identify Children With Spinal Cord Lesions

A. Isakoff, Rachel Hava, and Samuel Farber

(Reproduced from J Pediatr Gastroenterol Nutr. 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

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

Consensus Review of Best Practice of Transanal Irrigation in Children

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

May prevent surgical intervention

Moiaella G et al. JPGN 2017

186
Transanal irrigation in the Treatment of Children With Intractable Functional Constipation

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

Koppant I et al. JPIG 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 medical 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 I et al. Neurogastroenterol Motil 2013
Intractable constipation

- Do you have right diagnosis?
- Don’t use AXR for diagnosis
- IBS vs FC
- Non-retentive fecal soiling

Outlet dysfunction

- Consider biofeedback in older children
- Slow transit constipation

- Consider laxatives
- Prosecretory Agents

- Organic constipation
- Evaluate anatomy

- Laxatives and bulking
- Low threshold for enemas

POOP JOKES AREN'T MY FAVORITE KIND OF JOKES, BUT THEY'RE A SOLID NUMBER TWO.