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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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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 live activity for a maximum of 8 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Satisfactory Completion
For MOC credit, learners must pass the post-test with a score of 60% or higher and complete an evaluation form to receive a certificate of completion.

If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

Nurses
In support of improving patient care, this activity has been planned and implemented by Amedco LLC and NASPGHAN. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Amedco LLC designates this live activity for a maximum of 8 contact hours for nurses. Learners should claim only the credit commensurate with the extent of their participation in the activity.

ABP MOC Part 2 Credits
Successful completion of this CME activity, which includes participation in the activity, with individual assessments of the participant and feedback to the participant, enables the participant to earn 8 MOC Part 2 points for the Post-Graduate Course in the American Board of Pediatrics’ (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider’s responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit. Participant must complete the assessment within 30 days of the activity. Participant information will be uploaded to ABP 30 days post activity.
Module 1 – Endoscopy
Moderators: Gary A Neidich, MD and Jennifer Strople, MD

8:00am – 8:20am  Management of foreign bodies
David Brumbaugh MD, Children’s Hospital Colorado
Learning objectives:
1. Understand epidemiology, symptoms and management of common gastrointestinal foreign body ingestions in children
2. Review new poison control guidelines for pre-hospital and in-hospital management of swallowed button batteries
3. Discuss clinical management of high-powered magnet ingestions

8:20am – 8:40am  Advanced endoscopic techniques for gastrointestinal bleeding
Petar Mamula MD, Children’s Hospital of Philadelphia
Learning objectives:
1. Briefly discuss existing techniques for treatment of gastrointestinal bleeding
2. Discuss new techniques available for treatment of GI bleeding
3. Discuss endoscopy training in the these techniques

8:40am – 9:00am  Cancer screening top to bottom
Srinadh Komanduri MD, Northwestern Medicine
Learning objectives:
1. Recognize current recommendations for screening for CRC in specific populations and identify novel diagnostic tools for screening
2. Understand the role of Barrett’s Esophagus in development in esophageal adenocarcinoma and the role of screening in GERD
3. Identify specific populations who need screening for pancreaticobiliary malignancies

Module 2 – Potpourri
Moderators: Terry Sigman MD, FRCPC and Maria Oliva-Hemker, MD

9:00am – 9:20am  Celiac disease: Beyond diagnosis
Alessio Fasano MD, MassGeneral Hospital for Children
Learning objectives:
1. Review current celiac disease diagnostic criteria and critically review the need for an upper endoscopy to confirm diagnosis
2. Discuss the best approach to monitor compliance with the gluten free diet
3. Provide an overview of ongoing clinical trials aimed at identifying novel target for treatments alternative/complementary to the gluten free diet

9:20am – 9:40am  The role of the gastroenterologist and hepatologist in Cystic Fibrosis (CF) care today
Meghana Sathe MD, UT Southwestern Medical Center
Learning objectives:
1. Understand the management of pancreatic replacement enzyme therapy
2. Become familiar with Cystic Fibrosis Transmembrane Receptor (CFTR) Modulators and the potential impact on GI manifestations of CF
3. Recognize how to differentiate between Distal Intestinal Obstruction Syndrome (DIOS) and constipation and understand variations in management

9:40am – 10:00am  Update on C. difficile
Sonia Michail MD, Children’s Hospital Los Angeles
Learning objectives:
1. Understand the manifestations and risks of development of clostridium difficile infection
2. Update on treatment of clostridium difficile infection
3. Understand options in difficult to treat cases

10:00AM – 10:20am What the pediatric GI provider needs to know about cannabis
Ed Hoffenberg MD, Children’s Hospital Colorado
Learning objectives:
1. Describe how endocannabinoid system modulation may impact GI disorders
2. Identify complications and risks of cannabis use
3. Develop your own approach to discussing cannabis use with your patients

Module 3 – Functionality/Motility
Moderators: Anil Darbari, MD and Maria Oliva-Hemker, MD

10:40am – 11:00am   Testing for functional disorders: The indispensable, the useless, the dangerous
Carlo Di Lorenzo MD, Nationwide Children’s Hospital
Learning objectives:
1. When testing is needed in the child presenting with symptoms of IBS/FAP
2. Emphasize how to effectively provide reassurance in the office setting
3. Discuss the dangers and relevance of the incidental findings
4. Address any concerns which may mimic pain predominant functional disorders

11:00am – 11:20am  Achalasia
Peter Kahrilas MD, Northwestern Medicine
Learning objectives:
1. Review the sub-classification of achalasia and related syndromes
2. Understand the limitations of pneumatic dilation and Heller myotomy in treating spastic achalasia (type III)
3. Appreciate the advantages and disadvantages of pneumatic dilation, per oral endoscopic myotomy (POEM) and laparoscopic Heller myotomy

11:20am – 11:40am Evaluation and treatment strategies in NERD and functional dyspepsia
Julie Khlevner MD, Morgan Stanley Children’s Hospital
Learning objectives:
1. Discuss the criteria for diagnosing NERD and functional dyspepsia
2. Understand the current concepts in pathogenesis of NERD and functional dyspepsia
3. Review evidence based approach to therapy in pediatric NERD and functional dyspepsia

11:40am – 12:00pm  The role in diet in managing IBS
Robert J. Shulman MD, Texas Children’s Hospital
Learning objectives:
1. Describe mechanisms whereby diet can induce symptoms
2. Enumerate pros and cons of different diets
3. Describe limitations of research on diet therapy
12:10pm – 1:35pm  PG Course Learning Lunches (see tickets for room assignments)

1. Challenging celiac disease cases
Moderator: Iona Monterio, MD
Alessio Fasano, MD and Maureen Leonard, MD

2. Comprehensive treatment of functional disorders: Difficult cases
Moderator: Tanaz Danialifar, MD
Carlo Di Lorenzo, MD and Rob Shulman, MD

3. Complicated IBD
Moderator: Jeanne Tung, MD
Anne Griffiths, MD and David Rubin, MD

4. Management of chronic cholestasis
Moderator: Henry Lin, MD, MBA
Saul Karpen MD, PhD and Sanjiv Harpavat MD, PhD

5. Chronic pancreatitis
Moderator: Gary Galante, MD
Sohail Husain, MD and Jaimie Nathan, MD

6. NERD and dyspepsia: real world treatment
Moderator: Kelly Fair Thomsen, MD, MSCI, CNSC
Julie Khlevner, MD and Diana Lerner, MD

7. Foreign body management in practice
Moderator: Alex Koral, MD
David Brumbaugh, MD and Petar Mamula, MD

8. How to approach your patient who wants to use a medical marijuana product
Moderator: Ellen Mitchell, MD
Ed Hoffenberg, MD and Ann Ming Yeh, MD

9. Eosinophilic GI disease
Moderator: Garrett Zella, MD
Edaire Cheng, MD and Nathalie Nguyen, MD
Module 4 – Liver/Pancreas
Moderators: Nadia Ovchinsky, MD, MBA and Jennifer Strople, MD

1:40pm – 2:00pm  New news in NAFLD  
*Miriam Vos MD, MSPH, Emory University*  
Learning objectives:  
1. Understand current concepts in pathogenesis  
2. Update on diagnostic tools for NAFLD  
3. Discuss clinical management of pediatric NAFLD

2:00pm – 2:20pm  New therapies for chronic cholestatic diseases  
*Saul J. Karpen MD, PhD, Emory University School of Medicine/Children’s Healthcare of Atlanta*  
Learning objectives:  
1. Know the array of new agents that target bile acid based hepatotoxicity of cholestatic diseases  
2. Understand the approach to therapy for genetic forms of cholestatic diseases based upon specific genes and variants – chaperones and potentiators  
3. Know the current status of the field regarding treatments for biliary atresia

2:20pm – 2:40pm  Diagnosing drug-induced pancreatitis  
*Sohail Husain MD, Stanford Children’s Hospital*  
Learning objectives:  
1. Recognize the burden of drug-induced pancreatitis in children and the commonly associated drugs  
2. Evaluate the causality indices for drug-induced pancreatitis  
3. Review management guidelines for drug-induced pancreatitis in children

2:40pm – 3:00pm  Pediatric pancreatic masses: Steroids, surgery or surveillance?  
*Jaimie D. Nathan MD, FACS, Cincinnati Children’s Hospital Medical Center*  
Learning objectives:  
1. Recognize the presentation of pancreatic masses in children  
2. Understand the workup and evaluation of pediatric pancreatic masses  
3. Recognize the different etiologies and outcomes of pancreatic masses in children

3:00pm – 3:20pm  Break

Module 5 – Intestinal Inflammation
Moderators: Deborah Neigut, MD and Jennifer Strople, MD

3:20pm – 3:40pm  Positioning the new IBD therapies: Merging experience with evidence  
*David T. Rubin MD, University of Chicago*  
Learning objectives:  
1. Choose therapies based on prognosis and confirm effectiveness  
2. Identify targets of treatment that are individualized based on patient symptoms and objective measure of disease activity  
3. Understand risks and benefits of considering de-escalation and restart protocols in management
3:40pm – 4:00pm  Immunosuppressive therapy in IBD: Can we de-escalate therapy?
Anne Griffiths MD, FRCPC, Hospital for Sick Children
Learning objectives:
1. Advise families concerning the likelihood of (and factors predictive of) successful
discontinuation of biologic therapies
2. Utilize therapeutic drug monitoring to plan de-escalation of combination therapy with
biologics
3. Initiate and utilize biologic therapies in a way most likely to allow long-term
effectiveness while balancing risks

4:00pm – 4:20pm  When it is not IBD ... Rare forms of intestinal inflammation
Stacy Kahn MD, Boston Children’s Hospital
Learning objectives:
1. Learn to recognize and diagnose intestinal inflammation not due to IBD
2. Understand the natural history of a variety of rare forms of intestinal inflammation
3. Learn how to treat rare forms of intestinal inflammation

4:20pm – 4:40pm  Eosinophilic inflammation beyond the esophagus
Edaire Cheng MD, UT Southwestern Medical Center
Learning objectives:
1. Understanding the diagnostic criteria for eosinophilic gastrointestinal diseases (EGIDs)
2. Recognizing the clinical presentations for eosinophilic gastrointestinal diseases
3. Understanding the relationship between EoE and EGIDs
Objectives

• Understand epidemiology, symptoms, and management of common gastrointestinal foreign body ingestions in children.

• Review new poison control guidelines for pre-hospital and in-hospital management of swallowed button batteries.

• Discuss clinical management of high-powered magnet ingestions.
Foreign Bodies - Epidemiology

• Estimated 759,000 FB ingestions in children <6yo between 1995-2015. Rate of FB ingestion increased 91% over measurement period.


Foreign Bodies - Epidemiology

• Children 1-3yo accounted for two-thirds of FB ingestions.
• 10% of FB ingestions resulted in hospitalization.
• Coins represented 62% of FB ingestions.
• Batteries represented 0.14% of ingestions in 1995 and 8.4% in 2015.


Consumer Product Safety improvement Act
• Mandated screw closure for batteries.
• Banned small toys representing choke hazards
When to Not be On-Call

Christmas Decoration Ingestions


Key Anatomic Locations For Impaction
60%: UES
10%: Aortic Arch
30%: LES

Anatomy of Esophageal FB

Ginsberg. Gastro Endoscopy: 1995 (41)

Foreign Bodies – Symptoms

• Many children are asymptomatic!
• Early symptoms
  • Drooling
  • Gagging
  • Chest pain
  • Choking/spit up
  • Inappetence
• After a week, respiratory symptoms predominate
  • Coughing
  • Wheezing
  • Respiratory distress

### Timing of Endoscopic Intervention

<table>
<thead>
<tr>
<th>Type</th>
<th>Location</th>
<th>Symptoms</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Button</td>
<td>Battery</td>
<td>Yes or No</td>
<td>Emergent</td>
</tr>
<tr>
<td></td>
<td>Esophagus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastric/SB</td>
<td>Yes</td>
<td>Emergent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urgent (if age &lt; 5 and BB ≥20 mm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Elective (if not moving on serial X-ray)</td>
</tr>
<tr>
<td>Magnets</td>
<td>Esophagus</td>
<td>Yes</td>
<td>Emergent (if not managing secretions, otherwise urgent)</td>
</tr>
<tr>
<td></td>
<td>Gastric/SB</td>
<td>Yes</td>
<td>Emergent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urgent</td>
</tr>
<tr>
<td>Sharp</td>
<td>Esophagus</td>
<td>Yes</td>
<td>Emergent (if not managing secretions, otherwise urgent)</td>
</tr>
<tr>
<td></td>
<td>Gastric/SB</td>
<td>Yes</td>
<td>Emergent (if signs of perforation then with surgery)</td>
</tr>
<tr>
<td>Food Impaction</td>
<td>Esophagus</td>
<td>Yes</td>
<td>Emergent (if not managing secretions, otherwise urgent)</td>
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<tr>
<td></td>
<td>Gastric/SB</td>
<td>Yes</td>
<td>Urgent</td>
</tr>
<tr>
<td>Long Object</td>
<td>Esophagus</td>
<td>Yes or No</td>
<td>Urgent</td>
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<tr>
<td>Absorptive Object</td>
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</tr>
<tr>
<td></td>
<td>Gastric/SB</td>
<td>Yes or No</td>
<td>Urgent</td>
</tr>
</tbody>
</table>

Timing:
- Emergent (< 30 Min)
- Emergent (< 2 hours)
- Urgent (<8 Hours)
- Elective (<24 Hours)

Courtesy Rob Kramer, MD

### Preparation for FB Removal

- **Venue**: Endoscopy unit, OR
- **Team members**: Anesthesiologist, circulating RN/endoscopy technologist
- **Practice ex-vivo if an unusual foreign body**
- **Foreign body box**

### Button Batteries

Source: National Capital Poison Center www.poison.org
Button Batteries – Structures at Risk

- Vocal Cord Paralysis
- Tracheo-oesophageal Fistula
- Discitis
- Aorto-oesophageal Fistula
- Esophageal perforation
- Esophageal stricture
- Pneumothorax

Source: Personal files

Button Battery Management – Murky Areas

- Can we mitigate injury?
- How do we monitor patients post-ingestion?
- What do we do about those gastric batteries?

NEW DATA!

Mechanism of Battery Injury

- NaCl
- H2O
- Na+ + H+ + OH-
- Cl- - e-

Negative Pole: 2H+ + 2e- \rightarrow H2

Positive Pole: HCl

Mitigation Strategies

• Series of six patients receiving 150ml irrigation of 0.25% Acetic Acid immediately post-battery removal. No immediate or delayed complications at >4 months.

Mitigation Strategies

• 

Mitigation Strategies

• 

Mitigation Strategies

• 

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Mitigation Strategies

Live piglet model – Button Battery in place x 60 mins


Our Expert

https://i.pinimg.com/originals/b1/c9/99/b1c999a1b3a6939498491ce1cf989dc3.jpg

New Poison Control Recommendations
For Witnessed/Suspected BB Ingestion

• Administer 10ml honey every 10 minutes until reaching ED.
  • Children >12 months of age.
  • Max doses: 6

• Continue honey or sucralfate 10ml every 10 minutes.
• Immediate x-ray to confirm location.
• If esophageal, remove emergently (rapid sequence intubation).
• Post-removal, irrigate area of impaction with 50-150ml of 0.25% acetic acid. Suction fluid from stomach.
• only when low suspicion of perforation

Source: National Capital Poison Center
www.poison.org
Post-Ingestion Monitoring

- What are structures at risk?
  - Based on location and orientation of battery, duration of impaction.
  - Post-removal imaging? MRI versus other modalities
  - Follow-up endoscopy/direct laryngoscopy?
  - How long do we keep in the hospital?

Gastric Batteries – What to do?

- Serious outcomes are rare.
- Gastric erosions and superficial ulcers are commonly seen. Are these dangerous?
- Could battery have injured esophagus during transit?
- Symptomatic patients with gastric batteries: always remove.
- Asymptomatic patients with gastric batteries: is battery likely to pass?
  - Consider esophageal assessment and prompt removal if patient <5yo and battery >20mm
  - If observing, repeat x-ray in 2-4 days for batteries >20mm and 10-14 days for batteries <20mm. Remove if still intragastric.

Rare Earth Magnets

Complications:
- Entero-enteric fistulae
- Volvulus/obstruction
- Perforation/abscess
Rare Earth Magnets

Consumer Product Safety Commission Intervention

At presentation

At endoscopy

Next day

Rare Earth Magnets - Approach

Single magnet
- Be certain there is one. 2 views are mandatory.
- Observation OK if low risk for subsequent ingestion.

Multiple magnets
- Remove immediately if accessible in stomach
- If beyond stomach and asymptomatic, serial x-rays to ensure progression.
- If symptomatic OR failure to progress, consult pediatric surgery
- Consider balloon enteroscopy or elective laparoscopy for removal if failure to progress.

Case Example – Rare Earth Magnets
Case Example – Rare Earth Magnets

Small Bowel Enteroscopy with Magnet Removal

An Emerging Hazard

Gauge Earrings

9 month old with recurrent croup-like presentation.
  • Repeat x-rays did not show a radio-opaque FB
Summary

- The incidence of foreign body ingestion may be increasing in the United States.
- New Poison Control recommendations for pre-hospital and pre-removal management of button batteries include administration of honey/sucralfate. Dilute acetic acid irrigations can be used post-removal for faster normalization of tissue pH.
- Neodymium magnets are again widely available for purchase. Immediate removal of multiple magnets is recommended. If past stomach, rent a rents to follow passage. If stuck - remove using advanced endoscopic techniques or laparoscopy.

Would you go after it?

THANKS!
ADVANCED ENDOSCOPIC
TECHNIQUES FOR
GASTROINTESTINAL BLEEDING

Petar Mamula, MD
Division of Gastroenterology, Hepatology and Nutrition
Children’s Hospital of Philadelphia

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

Objectives

• To discuss endoscopy training for treatment of gastrointestinal bleeding
• To discuss existing GI bleeding treatment techniques
• To discuss new techniques
Epidemiology

- GI bleeding requiring treatment in pediatrics is uncommon
  - Hematemesis accounts for only 5% of EGD indications in children
    (Bancroft et al. Gastrointest Endosc, 2003)
  - PICU setting – 6% with UGI bleeding
    (Chaibou et al. Pediatrics, 1998)

- Retrospective 6-year study of 12,737 EGDs
  - Variceal bleeding represented 2.5% of cases
  - Non-variceal bleeding only 0.1% of cases


How good are we when it comes to GI bleeding treatment?

- Survey of 20 tertiary pediatric GI training centers in UK
  - 80% responded and only 19% felt that all consultants are capable of treating GI bleeding
  - 19% felt that none of the consultants had these skills
  - 50% were able to provide off hours service, but 69% of those were covered by surgeons

How about available training?

- 2009-11 study based on CPT codes for therapeutic procedures
- 12 centers with 81/296 (27%) fellows in training
- NASPGHAN training guidelines (15 bleeding cases)

Lerner et al. JPGN, 2014

How about available training?

Additional training options

- Simulators (mechanical and virtual reality)
- Hands-on Courses (animal models)
- Educational materials (print and videos)
- Additional training at an adult GI program
How does one predict who will need an endoscopy?

Scoring system

- Retrospective pediatric case series at a tertiary care center during a 3-year period
- 69 cases of upper GI bleeding
- Wide range of clinical parameters - statistical modelling

Sheffield scoring system
Who will need therapy during endoscopy?

Forrest classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Re-bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aa</td>
<td>Non Bleeding</td>
<td>90 - 95%</td>
</tr>
<tr>
<td>Ab</td>
<td>Adherent Clot</td>
<td>30 - 50%</td>
</tr>
<tr>
<td>Acr</td>
<td>Fat spot in ulcer crater</td>
<td>7 - 10%</td>
</tr>
<tr>
<td>B</td>
<td>Clean Base Ulcer</td>
<td>3 - 5%</td>
</tr>
</tbody>
</table>

GI Bleeding Therapies

- Endoscopic
  - If two attempts failed, move on to next level therapy

- Interventional Radiology

- Surgery
## Endoscopic Therapy Techniques

- **Injection therapy**
- **Thermal devices:**
  - Contact: Heater probe, Mono-, Bi/Multi-polar electrocautery, Hemostatic grasper
  - Non-contact: Argon plasma coagulator
- **Ligation devices: Clips and loops**
- **Hemopowders**
- **Stents and endoscopic suturing devices** (OverStitch, Apollo Endosurgery, Austin, TX)

## Equipment

- Whenever possible use therapeutic-size endoscope:
  - large working channel (2.8 - 6 mm) or two channels available
  - allows for simultaneous cleaning/suctioning
- In neonates and small infants:
  - injection therapy and cautery catheter fit 2.0 mm working channel

Barth et al. GIE, 2012.
Parsi et al. GIE, 2019.
ASGE Tech Talks
Single vs. Combination Therapy

• Epinephrine alone provides suboptimal efficacy
• No single therapy is superior to another
• Clips or thermal therapy should be used in high-risk lesions in combination with epinephrine injection


Thermal Therapy- Coaptive Coagulation (video)

Hemoclips
Active bleeding (video)
Argon Plasma Coagulation (APC) (video)

New Techniques

• Over-the-scope-clip (OVESCO®, Ovesco Endoscopy USA Inc, Cary, NC, and Padlock Clip®, US Endoscopy, Mentor, OH)

• Hemopowders

• Doppler probe

Over-the-scope-clip (OTSC)
OTSC

- Retrospective pediatric case series of both upper and lower GI bleeding
- 10 patients (5 ulcers, 2 polypectomy site bleedings, 1 post-sphincterotomy, 2 anastomotic ulcers)
- All achieved hemostasis
- Anastomotic ulcers required repeat therapy

Tran et al. JGPN. 2018.

OTSC (video)
• Literature search between 2010 and 2018 with 1,517 cases identified

• 559 cases for bleeding with 85% clinical success rate

Hemopowders

• Hemospray® (Cook Medical, LLC, Bloomington, IN)
  – Inorganic powder
  – FDA approved for hemostasis of non-variceal GI bleeding

• Ankaferd Blood Stopper (Erkan Medikal, Turkey)
  – Plant extract

• EndoClot® (EndoClot Plus Inc, Santa Clara, CA)
  – Polysaccharide
  – FDA- 510(k) clearance- device is substantially equivalent to legally marketed predicate devices

Hemospray®

• Inorganic biologically inert powder when placed in contact with moisture in the GI tract becomes adhesive serving as a mechanical barrier for hemostasis

• It may provide a scaffold, enhancing platelet aggregation and possibly activating clotting factors
Hemospray®

• Prospective study assessing need for hemostatic intervention with pediatric Sheffield AUGIB score >8/24

• A follow up endoscopy occurred in those deemed to have clinical need pre-discharge

• Comparison group of patients who received conventional hemostatic treatment in the preceding 24 months

Thomson et al. JPGN, 2018.

Hemospray®

• A total of 20 applications of hemospray in 17 patients (age range 2 days-18 y)
• 29 patients were enrolled in group two
• 100% initial hemostasis with 18% re-bleeding rate and 6% failure after re-application of hemospray
• In the conventional group, 24% re-bleeding rate with 7% failure necessitating surgical intervention

Thomson et al. JPGN, 2018.

Hemospray® (video)
Ankaferd Blood Stopper (ABS)

• Herbal extract derived from 5 different plants (*Thymus vulgaris*, *Glycyrrhiza glabra*, *Vitis vinifera*, *Alpinia officinarum*, and *Urtica dioica*)
• Mechanism of action unclear
• Limited data
• Available in Turkey
• Not FDA approved

EndoClot®

• Hemostatic polysaccharides derived from plant starch
• Adhesive and ultra hydrophilic
• Induces hemostasis by rapidly absorbing water from blood and thereby concentrating red cells, platelets, and coagulation factors at the bleeding site
• Limited data

Polysaccharide hemostatic powder

• 70 patients with acute GI bleeding
• 83% percent (58/70) of the patients had upper and 17% (12/70) had lower GI bleeding
• In the upper GI tract treatment success was achieved in 64% (30/47) after primary use and in all patients, when used after established techniques failed

Chen and Barkun, Gastrointest Endosc Clin N Am, 2015.
Doppler Endoscopic Probe

- Tangential probing of the ulcer bed in 4 directions used to detect blood flow and predict re-bleeding risk


Doppler Endoscopic Probe

- Single-blind randomized controlled trial
- 148 patients with non-variceal GI bleeding randomized to standard hemostasis or Doppler
- Primary outcome- re-bleeding at 30 days with 26% control vs. 11% Doppler group (odds ratio for re-bleeding with Doppler 0.35 with 7 NNT)


Future (video)
Summary

• Non-variceal GI bleeding in pediatrics is uncommon

• Exposure to therapeutic endoscopic techniques for GI bleeding during fellowship is limited and additional training requires multi-faceted approach

• There are several new endoscopic techniques available which may significantly improve our ability to treat life-threatening GI bleeding

Thank you
Disclosures

- Consultant: Boston Scientific, Medtronic, and EndoscopyNow

GI Cancer Screening

The Crossroads of Childhood and Adulthood

- Esophagus
  - Achalasia (SCC)
  - Barrett’s Esophagus (Adenoc)
- Stomach
  - H. Pylori
  - Hereditary Gastric Cancer
- Small Bowel
  - Hereditary Cancer syndromes (FAP)
  - Celiac Disease
- Colon
  - Early onset CRC
  - IBD
- Pancreaticobiliary
  - Pancreas Cancer Screening
  - Choledochal Cysts
  - PSC
Screening Program Success

• The target disease should be a common form of cancer
• The target disease should have a high associated morbidity and mortality
• Screening should decrease incidence and mortality of the disease being screened
• Cost effective
• Safe

Colorectal Cancer: Disturbing Trends

CRC Screening 2016 USPSTF Recommendations

<table>
<thead>
<tr>
<th>Test</th>
<th>Interval if negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool-based tests</td>
<td></td>
</tr>
<tr>
<td>1. Fecal Immunochemical test (FIT)</td>
<td>Annual</td>
</tr>
<tr>
<td>2. FIT and DNA</td>
<td>1 or 3 years</td>
</tr>
<tr>
<td>Structural Exam of Colon</td>
<td></td>
</tr>
<tr>
<td>1. Colonoscopy</td>
<td>10 years</td>
</tr>
<tr>
<td>2. Flexible Sigmoidoscopy (FS)</td>
<td>5 years</td>
</tr>
<tr>
<td>3. CT colonography (CTC)</td>
<td>5 years</td>
</tr>
</tbody>
</table>

* United States Preventive Services Task Force
What has changed over time?

- Obesity/Metabolic Syndrome
- Increased use of childhood antibiotics
- Food Industrialization
- Increased processed food and chemicals
- Inflammation
- Radiation exposure
- Environmental Exposures

CRC Screening Modalities

- Colonoscopy
- FOBT
- Fecal Immunochemical Testing (FIT): measures hemoglobin in the stool
  - Suggested q yr
  - Data suggests reduction in mortality from CRC (dependent of f/u)
  - Pooled sensitivity: 79%, Specificity: 94%
- Multitarget stool DNA tests (Cologuard)
  - Suggested q 3yr
  - Comprehensive molecular analysis (k-ras, methylation markers... along with a fecal immunochemical test (FIT) to test for hemoglobin from blood that may have been shed by colorectal lesions
- Comparative study with FIT

<table>
<thead>
<tr>
<th>TEST</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT</td>
<td>74%</td>
<td>95%</td>
</tr>
<tr>
<td>MT-sDNA</td>
<td>92%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Imperiale TF et al., NEJM 2014
Lee JK et al., Ann Intern Med 2014

Novel CRC Screening Tools

- Physician sends specimen to lab
- Patient collects blood at home
- Lab provides collection and shipping materials to patient
- Patient returns specimen to lab
- Stool DNA analysis is performed in lab and reported to physician
- Mutation identified: perform conventional colonoscopy
- No mutation identified: continue routine screening program
Colon Cancer

- The target disease should be a common form of cancer
  - Lifetime risk is 4.5% - YES
- High associated morbidity and mortality - YES
- Screening decreases incidence and mortality of the disease - YES
  - Death rates falling on average 2.7%/yr. (2004-2013)
  - New cases falling 3.2%/yr. (2004-2013)
- Cost-effective - YES
- Safe - YES

IBD and Colorectal Cancer

- Mean age of CRC is 40-50
- Odds of CRC is increased with OR of 7.0
- Risk Factors
  - Disease duration
  - Extent and severity of UC or CD
  - PSC (Earlier onset CRC)
  - Family history of CRC
- Most CRC from Polyps (adenoma or DALM (flat dysplasia))
- Colonoscopy with chromoendoscopy utilized for early dysplasia detection
- Screening for CRC 8-10 years after disease onset

IBD and Surveillance

<table>
<thead>
<tr>
<th>Society</th>
<th>Surveillance Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACG/ASGE 2016</td>
<td>Every 5 yr.</td>
</tr>
<tr>
<td>ACG 2015</td>
<td>Every 5 yr.</td>
</tr>
</tbody>
</table>
| ACG 2015 | Every 5 yr. | Asymptomatic, abnormal screening test, or positive surveillance (
- Colonoscopy with chromoendoscopy) |

Clarke WT et al, WJG 2019
### Polyposis and Endoscopic Surveillance

<table>
<thead>
<tr>
<th>Polyp type</th>
<th>Starting age</th>
<th>Surveillance interval</th>
<th>Intervention indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomatous/familial adenomatous polyposis</td>
<td>30-50 years</td>
<td>Every 1-3 years</td>
<td>Polypectomy, endoscopic mucosal resection (EMR)</td>
</tr>
<tr>
<td>Hereditary Non-Polyposis Colorectal Cancer (HNPCC)</td>
<td>30 years</td>
<td>Every 1-3 years</td>
<td>Polypectomy, endoscopic mucosal resection (EMR)</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>12 years</td>
<td>Every 1-3 years</td>
<td>Polypectomy, endoscopic mucosal resection (EMR)</td>
</tr>
</tbody>
</table>

| Barrett's esophagus | 12-15 years | Every 1-3 years | Endoscopic mucosal resection (EMR) |

| Barrett’s esophagus | 12-15 years | Every 1-3 years | Endoscopic mucosal resection (EMR) |

**Notes:**
- N/A: not applicable

---

### Evolution of Barrett’s

- Squamous esophagus
- Chronic inflammation
- Barrett’s metaplasia
- Low-grade dysplasia
- High-grade dysplasia
- Invasive adenocarcinoma

- Injury from acid & bile reflux, chronic nitrous oxide
- Genetic, Gender, race, other factors (COX-2)
- Accumulate Genetic Changes

---

### Current Standards for Barrett’s Diagnostics

- Visible BE on EGD
- HD/Videos
- Targeted biopsies of visible lesions
- Seattle Protocol Sampling
- Pathology Interpretation
- EET: Endoscopic EMR
- Surveillance

- Where does screening fit?
- Optical Chromo: NBI/NICE
- What is a visible lesion?
- Does this really make sense?
- How can we overcome IOV?
- Should we feel confident in this?
- Can we risk stratify and eradicate?
- When can we stop?
**Imaging and Barrett’s Esophagus**

- Surface Imaging
  - HD-WLE
  - Chromoendoscopy
  - Virtual Chromoendoscopy (NBI, FICE, iScan)
  - Magnification Endoscopy (Zoom, Near focus)
  - Autofluorescence Imaging (AFI)
- Subsurface Imaging
  - EUS
  - Confocal Endomicroscopy
  - Optical Coherence Tomography
  - Molecular Markers (WATS®)

**Beyond Seattle Protocol**

The Next Generation of Tissue Sampling in BE

- RCT of 16 centers of 160 patients to WATS then biopsy vs. Biopsy then WATS
- The addition of WATS to biopsy sampling yielded an additional 23 cases of HGD/EAC (14% increase)
- Of these 23, biopsies showed NDBE (n=11), LGD or IFD (n=12)
- Mean time of WATS procedure 4.5 min

**You cannot cure a disease we cannot find...**

![Proportion of EAC Patients with Known BE](image)

- Dulai GS, Gastroenterology 2002.
- Cooper GS, GIE, 2009.
Pancreatic Cancer

- Risk factors
  - Smoking
  - Diabetes
  - Chronic Pancreatitis
  - Hereditary pancreatic cancer syndromes
  - Familial pancreatic cancer (FPC)
Pancreatic Cancer Screening
Risk of Susceptibility Genes

<table>
<thead>
<tr>
<th>High-risk patient population</th>
<th>Mutation</th>
<th>Risk for developing PDAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian cancer</td>
<td>BRCA1</td>
<td>HR 2.55 (95% CI, 1.35-5.03)14</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>HR 2.13 (95% CI, 1.51-3.04)</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11</td>
<td>SIR 3.12 (95% CI, 4.4-26.1)11</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>ATM</td>
<td>RR 2.41 (95% CI, 0.38-1.71)9</td>
</tr>
<tr>
<td>Familial atypical multiple mole and melanoma syndrome</td>
<td>CDKN2A</td>
<td>SIR 13.3811</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>MSH1</td>
<td>HR 7.3 (95% CI, 2.4-23.0)71</td>
</tr>
<tr>
<td></td>
<td>MSH2</td>
<td>HR 10.9 (95% CI, 3.5-21.9)71</td>
</tr>
<tr>
<td></td>
<td>MSH6</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>PM2 2</td>
<td>NA</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>PKS81</td>
<td>SIR 5.3 (95% CI, 2.3-10.0)</td>
</tr>
</tbody>
</table>

Lo, W et al., J Surg Onc 2019

Pancreas Screening Studies

- 12 studies from 2002-12
- Diagnostic yield: precancerous changes or pancreatic cancer range from 1.3% - 43%
  - Largest US study was the CAPS 3 study that enrolled 225 high-risk patients – CT/MRI/EUS
  - 84 cysts, 3 Neuroendocrine tumors and 5 with dilated PD in 91 patients (42%)
  - 3/5 who underwent surgery had HGD in less than 3cm either main duct or SB IPMN’s
- Study conclusion: Screening efforts should focus on and removing high-risk precancerous changes of the pancreas not on detecting cancer

Pancreatic Screening Guideline

Lo, W et al., J Surg Onc 2019
Take Home Points

• Detection of GI cancers related to pediatric and adult genetic predisposition remains a dilemma
• Effective screening is dependent on incidence of disease
• Screening needs to demonstrate a reduction in mortality
• Endoscopic Techniques for GI cancer screening are improving and becoming minimally invasive
• Implementation of such tools across a primary care setting is a challenge but essential
• Collaborative efforts across pediatric and adult GI programs is needed to overcome and face the rising incidence of GI Cancers in younger age populations
Celiac Disease: Beyond Diagnosis

Alessio Fasano, M.D.
W. Allan Walker Chair in Pediatric Gastroenterology and Nutrition
Professor of Pediatrics Harvard Medical School
Professor of Nutrition Harvard T.H. Chen School of Public Health
Mucosal Biology and Immunology Research Center
And Center for Celiac Research
Massachusetts General Hospital for Children

Disclosures

<table>
<thead>
<tr>
<th>Company</th>
<th>Relationship</th>
<th>Content Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba Therapeutics</td>
<td>Stock Holder</td>
<td>Alternative treatments to gluten free diet for celiac patients</td>
</tr>
<tr>
<td>Inova Diagnostics</td>
<td>Consultant</td>
<td>Diagnosis celiac disease</td>
</tr>
<tr>
<td>Viome</td>
<td>SAB</td>
<td>Role of microbiome in CID</td>
</tr>
<tr>
<td>Mead Johnson Nutrition</td>
<td>Speaking Agreement</td>
<td>Role of Nutrition on CID</td>
</tr>
<tr>
<td>Takeda Pharmaceuticals</td>
<td>Sponsored Research</td>
<td>Alternative treatments to gluten free diet for celiac patients</td>
</tr>
</tbody>
</table>

Objectives

– Review current celiac disease diagnostic criteria and critically review the need for an upper endoscopy to confirm diagnosis;
– Discuss the best approach to monitor compliance with the gluten free diet;
– Provide an overview of ongoing clinical trials aimed at identifying novel target for primary prevention and treatments alternative/complementary to the gluten free diet
Celiac Disease as a Unique Model of Autoimmunity

- The only autoimmune disease in which specific MHC class II HLA (DQ2 and/or DQ8) are present in >95% of patients;
- The auto-antigen (tissue Transglutaminase) is known;
- The environmental trigger (gluten) is known;
- Elimination of the environmental trigger leads to a complete resolution of the autoimmune process that can be re-ignited following re-exposure to gluten.

Revised Diagnostic Criteria

[Diagram showing the revised diagnostic criteria]

Is not Happening!!!
Paradigm Of Celiac Disease
Pathogenesis And Management

Necessary and Sufficient

HLA DQ2 and/or DQ2 necessary but not sufficient

Current Management: Follow Up

• Follow up 6 months after diagnosis to check:
  • Symptoms;
  • Serology (not validated for monitoring but recommended by current guidelines);
  • Compliance difficulties with the implementation of the GFD;
  • Check for Hep B Ab;
  • Check thyroid function (T4 and TSH);
  • If problems, follow up in 3 months, otherwise:
• Follow up 12 months after diagnosis to check:
  • Symptoms;
  • Serology (not validated for monitoring but recommended by current guidelines);
  • Compliance difficulties with the implementation of the GFD
        Currently a repeated endoscopy is not routinely recommended in Pediatrics unless patients still experience CD-associated symptoms despite good compliance to the GFD

What is The Efficacy of the GFD In Controlling CD?

Out of 1,000 CD Patients

700 CD Patients Respond to the GFD

300 CD Patients Do Not Respond to the GFD, 200 of Them For Poor Compliance

100 Non-Responsive CD Cases

Type 1

5 RCD

Type 2

10 RCD
70% of Celiac Disease Patients Have Known Gluten Exposure on GFD

Reported intentional and inadvertent gluten consumption (n=269)


Current Management:
Compliance to the GFD

One of the most challenging issues related to the treatment of CD is proper compliance to strict gluten free diet for life.

Beside facing the same issues that adult CD patients experience, including risk of cross-contamination while traveling, vacationing, eating out, etc, pediatric patients have unique challenges that make the compliance to the GFD extremely difficult

Unique Challenges for Compliance to the GFD in Pediatrics

- Birthday parties
- School lunch
- Sleepovers
- Peer pressure
- Lack of appreciation for long term consequences for specific behavior;
- Transitioning to college lifestyle
Is Persistent Villous Atrophy in Children an Issue?

- More than 40% of adults with CD on a gluten free diet have persistent villous atrophy after 2-5 years;
- 4%-19% of children with CD have persistent villous atrophy after a median of 1.4-2.4 years

Age and Persistent Villous Atrophy

Factors Not Correlated with Persistent Villous Atrophy:

- Adults:
  - Symptoms
  - Celiac Serology
- Children:
  - Symptoms
  - Celiac Serology
Serology Cannot Predict Compliance or Remission Status

Adult Data
• tTG and EMA do not correlate with dietary compliance
• Hopper et al.
  – 7/16 of Adult pts on a GFD >1 year
  – Normal tTG and EMA
  – Persistent villous atrophy

Pediatric Data

Serology Tests Are Accurate At Diagnosis But Not Follow-Up

Factors Associated with Persistent Villous Atrophy

• Adults
  – Risk Factors
    • Males
    • Older age
    • Use of PPI, NSAIDS, SSRIs
  – Protective Factors
    • Longer period of time on a GFD
    • Higher educational level

• Children

References:
- Leonard et al., JPGN, 2017
- Fasano et al., NEJM, 2012
- Vehadi et al., Am J Gastro 2003

51
Controversy and Mucosal Recovery #1: What Is The Treatment Endpoint?

- Symptom Improvement
  - 30% of patients may be asymptomatic at diagnosis
  - Studies show symptoms do not correlate with mucosal damage
- Normalization of Serology
  - Negative tests poorly correlate with mucosal outcome and GFD adherence
- Mucosal Recovery
  - Only objective marker is endoscopy*


Controversy and Mucosal Recovery #2: What are the Clinical Consequences of Persistent Villous Atrophy?

- Morbidity:
  - Increased rates of osteoporosis
  - Increased hypothyroidism
  - Lower BMI
  - Nutritional deficiencies
  - Increased Lymphoma*Persistent VA
  - Increased risk of developing other autoimmune disease
- Mortality:
  - No increase in mortality in undetected CD compared to the general population (US, UK)
  - 4-fold increased risk of death
  - Persistent VA has been linked to increased mortality


Controversy and Mucosal Recovery #2A: Are there Any Clinical Consequences to Persistent Villous Atrophy in Children?

- Growth failure
- Nutritional Deficiencies
- Other
  - School performance;
  - Cognition and attention level;
  - Peripheral neuropathy;
  - Dental enamel defects.
Controversy and Mucosal Recovery #3: Why Diagnose Persistent Villous Atrophy If There Are No Treatment Options?

Currently Available Treatment Options
- Gluten Contamination Elimination Diet
- Budesonide

Possible Future Treatment Options
- Polymeric Binder
- Enzymes
- Zonulin Inhibitor
- Induction of Tolerance

Patient reported treatment burden is high compared to other chronic diseases
>65% of Patients with CD want alternative treatments

Branchi, Digestion, 2016.

Alternative/Integrative Approaches To The Gluten Free Diet

Prevention
- Primary Prevention
  (Microbiome Modification)

Alternative Treatments
- Development of genetically modified grains
- Inhibitors of tissue transglutaminase
- Cytokines and/or cytokine receptors inhibitors
- Deactivation of immunogenic gliadin peptides via oral peptidase supplementation
- Oral, parenteral, or intra-nasal celiac vaccines to induce tolerance
- Inhibitors of the effects of zonulin on intestinal permeability

Alternative/Integrative Treatment To The GFD

www.clinicaltrials.gov (Updated August 19th, 2019)

Diagnosis: 60
Dietary intervention: 32
Treatment alternative To GFD: 52
NCGS: 31
Others (co-morbidities, behavior, QOL): 20

Completed: 37
Registered Clinical Trials: 195

Treatment: 46
(9 technologies: 6)

Prevention: 6

Glutenases: 11 Trials
Nexvax2: 4 Trials (last trial failed)
J45: 2 Trials (last trial failed)
IgG4: 1 Trial

Enzymatic/Polymers: 3 Trials
Princess Alexandra Hospital, Brisbane, Australia
Inoculation Hookworm N. Americanus: 2 Trials

Active: 9

ChemoCentryx
CCR9 antagonist: 1 Trial

Alvine Pharmaceuticals
ALV003: 6 Trials (last trial failed)

Nexpep Pty
Nexvax2: 4 Trials

Glutenases: 11 Trials

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Primary Prevention
Celiac Disease Genomic Environmental Microbiome and Metabolomic Study

Take Home Messages:
- The diagnosis of celiac disease is based on the presence of suggestive clinical symptoms and/or belonging to risk groups, positive celiac disease serology screening, and confirmatory EGD with histology showing typical celiac enteropathy;
- Based on revised ESPGHAN criteria, EGD can be avoided if specific criteria are satisfied (with many caveats);
- Celiac disease serology remains a robust tool for initial screening, but its performance for monitoring the disease is poor;
- Despite good compliance to the GFD, there are several patients showing persistent celiac enteropathy. Persistence of symptoms and/or positive celiac disease serology do not correlate with celiac enteropathy;
- Ongoing studies for primary prevention or treatment complementary to the GFD may open new paradigms for celiac disease management.

Key Open Questions:
- Best diagnostic strategies?
- Endoscopy yes/no for diagnosis?
- How to properly follow up CD patients?
- Should CD patients be actively screened for other autoimmune diseases?
- How to manage CD patients with discrepancies between serology and histology?
- Are POC tests useful/appropriate for diagnosis and/or management of CD?
- Is the GFD highly effective in controlling CD?
- How to properly check for gluten cross-contamination?
- Are there any alternative/complementary treatments to the GFD at the horizon?
Acknowledgments

The MIBRC Crew
Complications of Cystic Fibrosis

Meghana Sathe, MD
Associate Professor Pediatric Gastroenterology and Nutrition
Co-Director Cystic Fibrosis Clinic
University of Texas Southwestern / Children’s Health

Conflict of Interest
I have funding through the Cystic Fibrosis Foundation as part of the Clinical Scholars Research Program
I have funding through the Cystic Fibrosis Foundation for my involvement in both the GALAXY and BONUS studies

Objectives
At the conclusion of this activity, participants will be able to:

• Describe the state of Cystic Fibrosis (CF) disease in 2019
• Diagnose and manage Exocrine Pancreatic Insufficiency in patients with CF
• Understand the spectrum of liver disease in CF
• Recognize other common gastrointestinal manifestations of CF including Gastroesophageal Reflux (GERD), Distal Intestinal Obstruction Syndrome (DIOS), Constipation, and Small Bowel Bacterial Overgrowth (SBBO)
Genetic of Cystic Fibrosis

- Autosomal Recessive
- Located on chromosome 7

<table>
<thead>
<tr>
<th>Affected populations</th>
<th>Risk of CF Mutation (in %)</th>
<th>Risk of child with CF (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasians</td>
<td>1 in 25</td>
<td>1 in 3,500</td>
</tr>
<tr>
<td>Hispanics</td>
<td>1 in 25</td>
<td>1 in 8,000</td>
</tr>
<tr>
<td>African-Americans</td>
<td>1 in 25</td>
<td>1 in 13,300</td>
</tr>
<tr>
<td>Asian (e.g., Indian, Thai)</td>
<td>1 in 30</td>
<td>1 in 35,000</td>
</tr>
</tbody>
</table>

Cystic Fibrosis Transmembrane Regulator (CFTR)

Loss of CFTR Function

- Different patient mutations prevent normal CFTR function

Classic Clinical GI Manifestations of CF

- Pancreatic disease
- Respiratory disease
- Gastrointestinal disease
The Evolution of CF Care and Survival

Diagnosis of CF

- Newborn screening: Immunoreactive trypsinogen (IRT)
  - 70% of infants screen positive
  - False positives: Prematurity, stressful delivery, meconium ileus

- GOLD Standard follow-up testing: Sweat chloride
  - ≥60 mmol/L: positive
  - 30-59 mmol/L: intermediate
  - <30 mmol/L: negative

- Genetic testing: Modulator qualification
  - >2000 CFTR mutations
  - CFTR2.org (cfr2.org, Johns Hopkins, Sick Kids)
Pancreatic Insufficiency

**EXOCRINE INSUFFICIENCY**
- Ducts blocked
- Lack enzymes & bicarbonate
- Malabsorption
- Enzyme replacement
- +/- Acid suppression

**ENDOCRINE INSUFFICIENCY**
- Tissue fibrosis/loss
- Endocrine cell loss
- Diabetes
- Insulin replacement

Diagnosis of Exocrine Pancreatic Insufficiency (PI)
- Diarrhea – specifically steatorrhea, poor weight gain, gas and bloating
- Fecal elastase (FE) <200mcg/gm stool
  - Inaccurate in the setting of liquid stool
  - If normal < 6 months of age, should be repeated between 6-12 months of age and then annually in pancreatic sufficiency (PS)
  - Other less common measurement tools
    - Pancreatic stimulation test
    - Fecal fat balance studies (>7gm/day)
    - Serum Immunoreactive trypsinogen (<20ng/ml)
- Deficiencies in fat-soluble vitamins and essential fatty acid deficiency can be supportive

Pancreatic Enzyme Replacement (PERT)
- Oral enzyme replacement therapy (PERT) – extracts from porcine pancreas (pancrelipase)
  - Dependent on availability of pigs
  - Do not 100% mimic native enzymes
- Enteric coated microspheric preparations or non-coated
  - pH sensitive (Readily dissolve in a pH >5.5 to 6)
  - Nonenteric coated preparation are activated immediately
*All enzymes were required to be FDA approved between 2009-2012*

<table>
<thead>
<tr>
<th>Enzyme Brand</th>
<th>Commonalities</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creon, Zenpep, Pancrease</td>
<td>Lipase, amylase, protease</td>
<td>Variations in size of beads</td>
</tr>
<tr>
<td>Pertyze</td>
<td>Lipase, amylase, protease</td>
<td>Ursodiol binder and Bicarbonate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4000s FDA-approved for 14 Fr+ Gtube</td>
</tr>
<tr>
<td>Viokase</td>
<td>Lipase, amylase, protease</td>
<td>ONLY tablet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not enteric coated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recommend use of proton pump inhibitor (PPI) in conjunction</td>
</tr>
<tr>
<td>Relizorb</td>
<td>Lipase only</td>
<td>Lipase ONLY in-line cartridge for enteral tube feeding</td>
</tr>
</tbody>
</table>

CFF Consensus Guidelines for PERT Dosing

<table>
<thead>
<tr>
<th>Lipase units/kg/meal</th>
<th>Lipase units/kg/g of fat eaten</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 years of age: 1000-2500 lipase units/kg/meal</td>
<td>Infants on breast milk or formula: 2000-4000 lipase units/120 ml</td>
</tr>
<tr>
<td>½ for snack</td>
<td>Beyond infancy: 500-4000 lipase units/g of fat</td>
</tr>
</tbody>
</table>

Above 10,000 lipase units/day increasing risk of fibrosing colopathy

Do Modulators Eliminate Need For PERT?

- **Ivacaftor** for gating mutations
  - Stallings et al.
    - Improvement in weight due to change in REE (Resting Energy Expenditure), gut inflammation, and fat malabsorption
    - Improvements in FE improved most in PS.
  - Rosenfield et al. in ARRIVAL study evaluating 12 to <24 months old children
    - Improvements in FE, IRT, amylase and lipase suggesting potential may preservation or improve pancreatic function if started early enough in life.
  - Not as promising results with other modulators
  - PROMISE study will show what happens with HEMs

Nutritional counseling:
- Focus healthy fats
- Monitor need to decrease calorie goal

Rule of thumb: Check FE before stopping PERT
Spectrum of CF Liver Involvement

- Elevated liver enzymes: 30% by 20 years of age
- Elevated GGT: 20% by 20 years of age
- Imaging abnormalities on US: 18%
- Fatty steatosis: US imaging 25%, Liver biopsy 23-75%
- Focal biliary cirrhosis: 10-50% (autopsy reports)
- Multilobular cirrhosis: 7%
- Neonatal cholestasis: often associated with MI
- Cholangiopathy: more commonly adult onset

PATHOGENESIS
- Impaired secretory function
- Direct cholangiocyte injury
- Immune response

LIVER INJURY
- Mucins
- Altered intestinal microbiome
- Toxic bile acids
- Circulating cytokines
- Steatite cell activation
- Steatosis

MODIFIER GENE
- Z allele of SERPINA1 (encoding α1-antitrypsin)

The New Kids on the Block for Diagnosis of CFLD

BIOCHEMICAL Markers
- Asparate Aminotransferase-to-Platelet Ratio Index (APRI) [Hepatology 2015;62:179–89]
- Persistently elevated GGT [JPGN. 2015;61: 113–8]
- Decreasing platelet count
- Investigational: microRNAs and biomarkers of intestinal bile salt absorption [IPJN. 2015;60:247–54.]

IMAGING
- Heterogeneous increased liver echogenicity at ultrasound [J CF. 2008;7:215–21.]
- Fibroscan [JCF. 2015;14:169–77.]
- Liver Elastography
- Ultrasound
- Magnetic Resonance

Complications of CFLD

- Portal hypertension
- Decline in lung function
- Varices – GI bleeding
- Portopulmonary hypertension
- Ascites
- Worse fat-soluble vitamin deficiencies
- Hypersplenism (thrombocytopenia)
- Splenomegaly
- Malnutrition
- Increased risk of CF-related diabetes

Porto-Pulmonary Hypertension

Increased Risk CF-Related Diabetes
Management of Complications of CFLD

• Ursodeoxycholic Acid (UDCA)
  • Inadequate data

• GI Bleeding
  • Acute: Octreotide, endoscopic variceal band ligation – followed by secondary prophylactic banding or consideration of β-blocker use, emergent transjugular intrahepatic portosystemic shunt (TIPS)
  • Preventive = controversial

• Shunts – TIPS, Splenorenal

• Liver Transplantation +/- Lung Transplantation

DILI – Antibiotics & Modulators

LIVER INJURY
• Labs: Hepatocellular (elevated transaminases) +/- cholestatic (elevated alkaline phosphatase and bilirubin)
• Pathology: Steatohepatitis, fibrosis, vascular injury, autoimmune phenotype, and others

MEDICATIONS IMPLICATED
• Amoxicillin-clavulanate, nitrofurantoin, isoniazid, sulfa, and azithromycin fluoroquinolones
• Herbals and nutritional supplements
• Antidepressant or ADHD drugs

MODULATORS

Monitoring Liver Enzymes with Modulators

ROUTINE
• Liver enzymes are evaluated at baseline
• Every 3 months for the 1st
• Then annually

SPECIAL CIRCUMSTANCE
• Use with caution in patients with pre-existing liver disease, especially cirrhosis
• Skip if ALT >5 times ULN (use lower ALT if bilirubin is also elevated)
• Use caution to resume use of drug – consider starting 1/2 dose and then working up slowly
• Monitor reintroduction closely
• Metabolism via cytochrome P450 – be familiar with drug-drug interactions
• May require stopping temporarily when used with certain antibiotics
• Contraindication with certain seizure medications

Home Medical Package Insert for Ivacaftor, Lumacaftor-Ivacaftor, Tezacaftor-Ivacaftor
Diagnostic Considerations & Treatment Options

- Clinical symptoms vs pulmonary exacerbations due to presence of Enteric flora on CF culture

- Acidity
  - Empiric Treatment vs pH probe or impedance study
  - Histamine blockers, Proton pump inhibitors

- Motility
  - Gastric emptying scan
  - Azithromycin (often drug of choice due to Pseudomonas treatment), Erythromycin, Metoclopramide, Bethanechol

- Surgical options
  - Reserved for medical management failure: Nissen fundoplication

---

DIOS

Constipation
Management of DIOS

For partial obstruction:
- Polyethylene glycol – clean out
- Gastrograffin
  *Hyperosmolar solution via enema refluxing into terminal ileum (TI)
  *Oral preparation

For complete obstruction:
- Decompression with sump and surgical consult
- Once improving → treatment as noted for partial obstruction
- Most important – if not resolving with traditional management – consider alternate etiology

DIOS Differential Diagnosis

- Constipation (most common)
- Appendicitis
- Appendicular abscess
- Mucocele of the appendix
- Intussusception
- Crohn’s disease
- Adhesions
- Volvulus
- Fibrosing colonopathy
- Malignancy
- Anastomotic stricture (previous history of meconium ileus or DIOS surgery)

Management of Constipation

- Adequate PERT
- Hydration
- Stool softeners
  - Juice
  - Polyethylene glycol
  - Lactulose
  - Magnesium
- Stimulants
- Fiber?
- Medications
  - Lubiprostone – Adult CF Pilot study with only 7 patients
  - Linactolide and Plecanatide
  - CFTR modulators
Colon Cancer Risk

High Risk
- F508 x2 or severe functional mutation
- Male
- >30 years of age
- Lung transplantation

Other contributing factors
- Inflammatory
  - Intestinal microbiome
  - Disease influence
  - Antibiotic influence
- Non-inflammatory
  - Intestinal cell turnover
  - Alteration in mucin gene expression
  - Bile acid composition and exposure
  - Nutritional deficiencies
  - Immunosuppressive medications [transplant]
- CF-specific risk factors
  - Role of CFTR as oncogene

SBBO

Diagnosis & Management of SBBO

DIAGNOSIS
- 30-40% of CF patients
- Empiric treatment – most common
- Breath test – challenging due to chronic antibiotic use
- Luminal sampling of small bowel fluid +/- intestinal biopsies – uncommonly done as invasive

TREATMENT (for 10-14 days)
- Metronidazole
- Rifaximin
- Sulfamethoxazole-trimethoprim
- Amoxicillin-clavulanate
Take Home Points

• CF care has significantly evolved significant in the era of modulator therapy
• Traditional nutritional counseling practices will need to be altered
• Measurement of FE should continue to determine need for PERT
• CFLD is becoming better recognized with the acceptance of new biochemical markers and imaging modalities (elastography)
• DIOS and Constipation continue to be challenging to differentiate
• The risk of GI cancers in CF is significant and deserves recognition as the longevity is achieved

Opportunities and Studies in CF GI

DIGEST (Developing Innovative Gastroenterology Specialty Training)
• Training its 3rd cohort of pediatric and adult gastroenterologist

GALAXY (GI symptoms observational study)
• Based on James Lind Alliance recognition of need to address GI symptoms as #2 priority of persons with CF (June 2017)

PROMISE – evaluate of Highly Effective Modulatory Treatment (new triple combination)
• Liver disease, Pancreatic function, Nutrition, pH of GI tract, GI symptomology, Gut microbiome

QUESTIONS?
UPDATE ON CLOSTRIDIUM DIFFICILE INFECTION IN CHILDREN

Sonia Michail, MD, CPE, FAAP, AGAF
Professor of Clinical Pediatrics
University of Southern California
Los Angeles, California
Children’s Hospital of Los Angeles
10/17/2019

Disclosure

• Rebiotix: Medical Scientific Advisory
• NIH

Objective

• Update on clostridium difficile epidemicology
• Update on the management of clostridium difficile infections
• Update on the role of fecal microbial transplant and its safety
Outline

- Background and Epidemiology
- Risk factors and special populations
- Testing
- Management

Introduction: Epidemiology

Spore-forming Gram-positive anaerobe

Epidemiology

- Most common infectious cause of antibiotic-associated-diarrhea
- Related to production of toxins, primarily toxin B.
- Produce resistant spores
- Near doubling in incidence in US children
- Rate of community-associated clostridium difficile infection (CDI) in children is rising
**Gut Microbial changes in Clostridium Difficile**

**Distance-based redundancy analysis (15) of Bray–Curtis intersample distances**

**Epidemiology**

- A large multicenter study of hospitalized patients at 22 children’s hospitals in the US
- Near doubling in the incidence of *C. difficile* infection (CDI) between 2001 and 2006.
- Although classically identified as a healthcare-associated infection, 70-80% of pediatric cases of CDI identified as community-associated.

Toilets

- C. difficile was recoverable from air sampled at heights up to 25 cm above the toilet seat.
- The highest numbers were recovered from air sampled immediately following flushing, and then declined 8-fold after 60 min and a further 3-fold after 90 min.
- The mean numbers of droplets emitted upon flushing by the lidless toilets in clinical areas were 15-47, depending on design.
- C. difficile aerosolization and surrounding environmental contamination occur when a lidless toilet is flushed.

Best EL, J Hosp infection 2012

Colonization in infants

Jangi S, JPGN 2010
Risk factors

- Pediatric recurrent C. difficile infection (rCDI) risks are different than in adults
- Prior antibiotic use,
- Recent surgery,
- Malignancy,
- Tracheostomy tube,
- Concomitant use of non-CDI antibiotics during CDI treatment.

Davidovics et al. JPGN 2019

Risk factors-co-morbidities

- In a large pediatric database (>4000 patients).
- At least 2/3 had ≥1 complex chronic condition.
- Children with inflammatory bowel disease (IBD) have rates of CDI that far exceed the general population.
- A statewide database of hospital discharges from 2009 to 2012, shows prevalence of CDI in children with IBD to be 46 per 1000 versus 4.1 per 1000 (P < 0.001).
- 25% of pediatric CDI cases occur in children with cancer.
- Children with malignancy and CDI had longer hospital stays and more all-cause mortality (rr 2.29)

Davidovics et al. JPGN 2019

Microbiology

- Toxigenic strains: genes tcdA and tcdB produce Toxin A and B
- Nontoxigenic strains lack the tcdA and tcdB genes
- Toxin A ("enterotoxin") causes inflammation leading to mucosal injury and intestinal fluid secretion
- Toxin B ("cytotoxin") is essential for the virulence
- Hypervirulent strain (NAP1/B1/027) associated with:
  - More severe disease,
  - Lower cure rates,
  - Increased recurrence
  - Severity due to deletion in the tcdC gene (a negative regulator of toxin production) and produces a third toxin (binary toxin)

IDSA April 2018
Morbidity and mortality

- Severe CDI-related complications, including toxic megacolon, perforation, and the need for a surgical intervention, occurred in fewer than 2% of pediatric patients with CDI.
- Significant morbidity is less common in children, rates of rCDI in pediatric patients mirror that of adults.

Testing

- Recommend only in symptomatic (>3BM)
- IDSA suggest one strategy to optimize toxin assay sensitivity: a two-step method: Glutamate Dehydrogenase (GDH; highly sensitive for C. difficile but does not distinguish toxigenic from non-toxigenic C. difficile), and if positive, follow-up testing with either CCCNA or toxigenic stool culture (TC) as a confirmatory method.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens</th>
<th>Availability</th>
<th>Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAAT</td>
<td>High</td>
<td>Available</td>
<td>Toxin gene detection</td>
</tr>
<tr>
<td>GDH</td>
<td>High</td>
<td>Available</td>
<td>Detection of common antigens toxigenic and non-toxigenic</td>
</tr>
<tr>
<td>EIA toxin A/B</td>
<td>Low</td>
<td>Available</td>
<td>Detection of free toxin</td>
</tr>
<tr>
<td>CCCNA or TC</td>
<td>High</td>
<td>Limited availability</td>
<td>Detection of free toxin and culture of a toxigenic C. difficile strain, respectively</td>
</tr>
</tbody>
</table>
Age conscious suspicion of CDI

Test for CDI: consider combined testing including NAAT

Positive for toxigenic C. difficile

Repeatedly assess for possible misdiagnosis or underlying disease

Mild CDI
• Eliminate risk factors if possible, Consider vanco

Moderate CDI
• Consider hospitalization
  • vanco

Severe Complicated CDI
Hospitalization, Vanco or other, Consider surgical consultation

Hospitalization, Vanco or other, Consider surgical consultation

Davidovics et al JPN 2019
### IDSA 2018 recommendations

**What are important ancillary treatment strategies for CDI?**

- Discontinue therapy with the inciting antibiotic agent(s) *(strong recommendation, moderate quality of evidence)*.
- Antibiotic therapy for CDI should be started empirically for situations where a substantial delay in laboratory confirmation is expected, or for fulminant CDI *(weak recommendation, low quality of evidence)*. **IDSA April 2018**

### IDSA 2018 recommendations

Best treatments of initial CDI episode to ensure resolution of symptoms and sustained resolution for 1 month:

- Either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode of CDI. The dosage is vancomycin 125 mg orally 4 times per day or fidaxomicin 200 mg twice daily for 10 days *(strong recommendation, high quality of evidence)*.
- In settings where access to vancomycin or fidaxomicin is limited, we suggest using metronidazole for an initial episode of nonsevere CDI only *(weak recommendation, high quality of evidence)*. The suggested dosage is metronidazole 500 mg orally 3 times per day for 10 days. Avoid repeated or prolonged courses due to risk of cumulative and potentially irreversible neurotoxicity *(strong recommendation, moderate quality of evidence)*. **IDSA April 2018**
IDSA 2018 recommendations

What are the best treatments of fulminant CDI?

- For fulminant CDI, vancomycin administered orally is the regimen of choice (strong recommendation, moderate quality of evidence).
- If ileus is present, vancomycin can also be administered per rectum (weak recommendation, low quality of evidence).
- Vancomycin dose is 500 mg orally 4 times per day and 500 mg in approximately 100 mL normal saline per rectum every 6 hours as a retention enema.
- Intravenously administered metronidazole should be administered together with oral or rectal vancomycin, particularly if ileus is present (strong recommendation, moderate quality of evidence).
- Metronidazole dosage is 500 mg intravenously every 8 hours.

IDSA April 2018

IDSA 2018 recommendations

- Fulminant CDI, characterized by hypotension or shock, ileus, or megacolon.
- If surgical management is necessary, perform subtotal colectomy with preservation of the rectum (strong recommendation, moderate quality of evidence).
- Diverting loop ileostomy with colonic lavage followed by antegrade vancomycin flushes is an alternative approach (weak recommendation, low quality of evidence).

IDSA April 2018

Recurrent CDI treatment (IDSA)

- First recurrence options:
  - 10-day course vancomycin rather than second course of metronidazole if metronidazole was used for primary Rx
  - Oral vancomycin as a tapered and pulsed regimen rather than a second 10-day course
  - 10-day course of fidaxomicin rather than a standard 10-day course of vancomycin

IDSA April 2018
Recurrent CDI treatment (IDSA)

• More than one recurrence of CDI:
  – oral vancomycin therapy using a tapered and pulsed regimen (weak recommendation, low quality of evidence),
  – a standard course of oral vancomycin followed by rifaximin (weak recommendation, low quality of evidence),
  – fidaxomicin (weak recommendation, low quality of evidence).

Recurrent CDI treatment (IDSA)

• Fecal microbiota transplantation is recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments (strong recommendation, moderate quality of evidence).

Recurrent CDI treatment (IDSA)

• There are insufficient data at this time to recommend extending the length of anti–C. difficile treatment beyond the recommended treatment course or restarting an anti–C. difficile agent empirically for patients who require continued antibiotic therapy directed against the underlying infection or who require retreatment with antibiotics shortly after completion of CDI treatment, respectively (no recommendation).
Logistic regression of predictors of primary fecal microbiota transplantation (FMT) success for the treatment of *Clostridium difficile* infection (CDI) in children and young adults (N-323).1

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Odds ratio [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh (vs. frozen) donor stool</td>
<td>2.60 [1.37, 4.86]</td>
<td>0.004</td>
</tr>
<tr>
<td>Delivery by colonoscopy (vs. other)</td>
<td>3.34 [1.22, 4.48]</td>
<td>0.01</td>
</tr>
<tr>
<td>Feeding tube (vs. no feeding tube)</td>
<td>0.48 [0.23, 0.97]</td>
<td>0.04</td>
</tr>
<tr>
<td>No. of CDI episodes prior to FMT</td>
<td>0.83 [0.72, 0.96]</td>
<td>0.01</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n = 137)</th>
<th>Non-RCDI (n = 113)</th>
<th>RCDI (n = 24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic use after last FMT</td>
<td>61/137 (45%)</td>
<td>43/113 (38%)</td>
<td>18/24 (75%)</td>
<td>.0009</td>
</tr>
<tr>
<td>Antibiotic after FMT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>18/61 (30%)</td>
<td>9/34 (21%)</td>
<td>9/9 (50%)</td>
<td>.03</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>7/61 (11%)</td>
<td>6/43 (14%)</td>
<td>1/18 (6%)</td>
<td>.66</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>25/61 (41%)</td>
<td>15/43 (35%)</td>
<td>10/18 (56%)</td>
<td>.16</td>
</tr>
<tr>
<td>Penicillin</td>
<td>13/61 (21%)</td>
<td>9/34 (21%)</td>
<td>4/18 (30%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Probiotic use after last FMT</td>
<td>81/137 (45%)</td>
<td>46/113 (41%)</td>
<td>15/24 (62%)</td>
<td>.05</td>
</tr>
<tr>
<td>Surgery</td>
<td>41/130 (32%)</td>
<td>29/108 (27%)</td>
<td>12/22 (55%)</td>
<td>.01</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>54/131 (41%)</td>
<td>36/108 (33%)</td>
<td>18/23 (78%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>New symptom/diagnosis</td>
<td>45/134 (34%)</td>
<td>38/137 (28%)</td>
<td>7/16 (35%)</td>
<td>.81</td>
</tr>
<tr>
<td>Improved symptoms/diagnosis</td>
<td>15/138 (11%)</td>
<td>12/131 (11%)</td>
<td>3/24 (13%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Weight change, in pounds</td>
<td>5 (-5, 10)</td>
<td>5 (-5, 10)</td>
<td>0 (-9, 8)</td>
<td>.18</td>
</tr>
</tbody>
</table>

Mamo. Clinical Infectious Diseases; Volume 66, Issue 11, 17 May 2018, 1705–1711

Recurrent C diff post FMT

- 82% of patients had durable cure of CDI 22 months after FMT. Patients with recurrence had more post-FMT antibiotic exposure, underscoring the need for thoughtful antibiotic use and a potential role for prophylactic microbiome enrichment to reduce recurrence.

Mamo. Clinical Infectious Diseases, Volume 66, Issue 11, 17 May 2018, 1705–1711
**FDA warning regarding FMT**

June 13th, 2019: FDA recently became aware of two cases of serious multidrug-resistant organism (MDRO) infection, one fatal, in recipients of fecal microbiota for transplantation (FMT) following confirmed transmission of the MDRO from the FMT donor to the recipient and subsequent translocation of the organism from the GI tract into the bloodstream. In these cases, donor stool was not tested for the presence of MDROs.

https://www.fda.gov/medwatch-safety-alerts-human-medical-products-

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**FDA safety warning**

Donor screening
a. Health care workers
b. Persons recently been hospitalized or discharged from long term care facilities
c. Persons who regularly attend outpatient medical or surgical clinics
d. Persons who have recently engaged in medical tourism

https://www.fda.gov/medwatch-safety-alerts-human-medical-products-

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**FDA safety warning**

FMT donor stool testing must include MDRO testing should at minimum include extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, vancomycin-resistant enterococci (VRE), carbapenem-resistant Enterobacteriaceae (CRE), and methicillin-resistant Staphylococcus aureus (MRSA).

https://www.fda.gov/medwatch-safety-alerts-human-medical-products-
Summary

- Clostridium difficile infection can be difficult to treat or eliminate
- Antibiotic therapy recommendations have been recently modified
- Fecal transplant can be highly effective
- Recent FMT safety issues are related to screening and testing for MDROs

Thank you
What the pediatric GI provider needs to know about cannabis

Edward J Hoffenberg, MD
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UC Denver and Children’s hospital Colorado
edward.hoffenberg@childrenscolorado.org

Disclosures
CDPHE grant on the benefits of marijuana for adolescents and young adults with IBD
In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

Learning Objectives
At the end of this talk, you will be able to

1. Describe how endocannabinoid system modulation may impact GI disorders.
2. Identify complications and risks of cannabis use
3. Develop your own approach to discussing cannabis use with your patients.
• Describe endocannabinoid system
• Review approved uses and data for use in IBD
• Discuss
  Cannabis use disorder
  Cannabis withdrawal syndrome
  Cannabis hyperemesis syndrome
  Cannabis allergy
  Cannabis drug interaction concerns
Endocannabinoids
Endo-inside body
Arachidonic acid derivatives
Lipid mediators

Phytocannabinoids
Phyto-plant

CB1 Receptor
Neurons and epithelial cells

CB2 > CB1 Receptor
Immune cells

And other Receptors
(TRPV1 and GPR55…)

An Atmospheric Pressure Chemical Ionization MS/MS Assay Using Online Extraction for the Analysis of 11 Cannabinoids and Metabolites in Human Plasma and Urine

Unknown Importance

“…a reduction in motility, reduced inflammation, and reduced immune activation”
Fine tune metabolic, physiologic processes
Potential benefit in chronic diseases
CB2R Q63R variant is a risk for celiac and IBD
Strisciuglio J Clin Gastroenterol 2018;52:e37-43
An expanding set of interactions between cannabinoid receptors, ligands, and enzymes

Modulation of the endocannabinoid (EC) system in human disease
Desirable effects
- Pain, nausea/vomiting, appetite, mood
- Insulin resistance, inflammation, appetite, mood
- Peripheral, CB1, inhibition
- Path, anxiety, inflammation

Additional potential therapeutic areas
- GVHD
- Autism
- Inflammation
- Obesity/metabolic syndrome
- Diabetes
- Cardiovascular
- Liver
- Cancer

Fig. 1. Cannabinoid therapeutics: finding the right balance.
Pacher and Kunos, FEBS Journal, 2013,280,1918

What are cannabinoids effective for?

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There are 3 FDA approved products

- Synthetic THC (Dronabinol, Nabilone)
  - Nausea and vomiting from cancer chemotherapy
  - Anorexia with weight loss from AIDS
- CBD (plant based enriched in cannabidiol)
  - Severe childhood Seizures (Lennox Gastaut and Dravet syndromes)
    Does not work through known cannabinoid receptors

Syndros–liquid
Marinol‐capsule
Cesamet
Epidiolex
Syndros.com
cvs.com
gwpharm.com
Nabiximol (Sativex)

Oromucosal spray
  - 1:1 CBD: THC + other cannabinoids + non cannabinoids
  - 100 ul spray contains 2.5mg CBD and 2.7mg THC

Approved outside the US for spasticity associated with multiple sclerosis

Nabiximol
Syndros
Cesamet
Epidiolex
Syndros.com
cvs.com
gwpharm.com
Nabiximol

Cannabis for IBD

- Pediatric data: efficacy data absent
- Adult data:
  - 3 observational studies, about 300 subjects
    - Reports of symptom relief
    - Use > 6m associated with surgery
  - 1 trial of cannabis for Crohn’s:
    - ↑ appetite, ↓ pain, but no ↓ in inflammation measures.
  - 1 trial of CBD for UC:
    - less adherent and did not meet endpoint
  - 1 abstract of cannabis for UC
    - improved endoscopy score

Lal, Eur J Gastroenterol Hepatol, 2011, 23, 891
Naftali IBD, 2013, 11, 1276
Irving, IBD, 24, 4, 714, 2018
Naftali, DDW 2018
### Table 1. Summary of Studies on Medicinal Cannabis Use in IBD

<table>
<thead>
<tr>
<th>Year/Author*</th>
<th>Country</th>
<th>Study Design</th>
<th>Cannabis Type</th>
<th>Patients</th>
<th>IBD Diagnosis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018/Irving</td>
<td>UK</td>
<td>RCT</td>
<td>Oral CBD-rich</td>
<td>10mg CBD bid</td>
<td>UC</td>
<td>AE in T-group: no difference shown</td>
</tr>
<tr>
<td>2018/Naftali</td>
<td>Israel</td>
<td>BCT</td>
<td>Inhalation</td>
<td>23 mg THC</td>
<td>UC</td>
<td>Mayo score improved</td>
</tr>
</tbody>
</table>

Limited data on potential benefits of cannabis for IBD

In the USA, many States have defined medical uses for cannabis

So what about our patients with IBD?

In the image:

- Limited data on potential benefits of cannabis for IBD
- In the USA, many States have defined medical uses for cannabis
- Table 1. Summary of Studies on Medicinal Cannabis Use in IBD
- Popular demand, not evidence-based
N= 53  18‐21 yr on infliximab
70% ever used
47% current users (33% of 53)
29% daily users (20% of 53)
70% did not tell their GI providers

N= 99  13‐21 yr
32% ever used
50% current users (16% of 99)
28% daily users (9% of 99)
80% of ever users perceive no to low risk of harm with regular smoking

User vs non user: no difference noted for appetite, pain, anxiety, QOL

N = 30
* Self‐administered multiple routes:

<table>
<thead>
<tr>
<th>Products/routes of use</th>
<th>25 (83%)</th>
<th>15 (50%)</th>
<th>12 (40%)</th>
<th>9 (30%)</th>
<th>5 (17%)</th>
<th>1 (3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled as edible</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vape</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Motivations for use

Medical
n = 17 (57%)
Survey question: Do you think you use marijuana...
(check all that apply)
To relieve physical pain 16 (53%)
To relieve abdominal cramping 11 (37%)
To relieve nausea 8 (27%)
To improve appetite 7 (23%)
To help lose weight 1 (3%)
Cannabis Oil Use  n=15

Frequency
Median Past 30-day use: 25 days
30 times (1 a day)

Content  CBD 1-500mg
THC 1-50mg

CBD: THC
1:1  3
19:1  2
10:1  1
100:0.1  1
Unknown  2

Perceive safety and some benefit → that is hard to measure
Variety of dosing strategies and amounts
IBD ~10%+ use ~daily

Summary of Pediatric IBD Users

Health Kids Colorado Survey (HKCS)
Youth Risk Behavior Surveillance System (YRBSS)
Monitoring the Future 2018 8-10-12th graders
CBS.com
Freeworldmaps.net

Over labelling content on-line CBD Bonn-Miller JAMA 2017,318, 708
Risks for cannabis use disorder

- Frequent use
- Early use of cannabis, alcohol, nicotine
- Male
- Depression
- Poor school performance
- Antisocial, oppositional
- Other drugs

Consequences of adolescent use

Impairments in
- Cognition (learning, memory, attention)
- Academics
- Employment
- Income
- Social relationships

Cannabis Use Disorder DSM 5

11 Criteria

- Larger amounts and/or over a longer period
- Unable to reduce or control use
- Spending a lot of time to get, use, or recover from effects
- Craving
- Failing on obligations at work, school, or home
- Using despite social, interpersonal problems from use
- Missing out on activities
- Using when it is physically hazardous
- Tolerance: diminished effect, needing more
- Withdrawal: syndrome or using to avoid syndrome

Severity

- Mild: 2-3 symptoms
- Moderate: 4-5 symptoms
- Severe: 6+ symptoms
Cannabis withdrawal syndrome

**Criteria (≥ 3 within 1 wk abrupt stop)**

- Irritable
- Nervous/anxious
- Sleep difficulty
- Appetite, weight loss
- Depressed mood
- Physical symptoms: Abdominal pain  (± Nausea/vomiting)
  Shaking/tremors
  Sweating
  Fever
  Chills
  Headache

**GI Differential**

- Typical teenager?
- Eating disorder
- Abdominal migraine
- Autonomic dysfunction/POTS
- Hyperthyroid
- Celiac?

"Just Quit" may not work

Cannabis withdrawal syndrome- Treatment

**Lasts days to several weeks**

**Treatment**

- Severe cases: inpatient “detox”
- No approved medications
  - Anxiolytics
  - CB agonists: Dronabinol or Nabiximol
  - Gabapentin
  - (Antidepressants may worsen symptoms)

Cannabis hyperemesis syndrome

91
Cannabis Hyperemesis Syndrome

**Diagnosis Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GRAE Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe cyclic vomiting usually accompanied by abdominal pain</td>
<td>Rare</td>
</tr>
<tr>
<td>Symptoms present in a last visible cannabino use</td>
<td>Rare</td>
</tr>
<tr>
<td>Temporary relief of symptoms with hot tubbing</td>
<td>Low</td>
</tr>
<tr>
<td>Resolution of symptoms with cannabinoid cessation</td>
<td>Rare</td>
</tr>
<tr>
<td>Supporter factors male gender, cannabis use onset in teenage years, symptom onset in third decade of life</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**GI Differential**
- Cyclic vomiting
- Brain tumor, ↑ICP
- Psychogenic vomiting
- Other toxin
- ...

**Cannabis Hyperemesis Treatment**

Low Quality of Evidence for any treatment

- Abstinence
- Dopamine antagonists
- Avoidance of opiates
- Capsaicin cream to abdomen (or heat)

Dezieck L. Clin Toxicol 2017,55:908
Resolution of cannabis hyperemesis syndrome with topical capsaicin in the emergency department: case series
Capsaicin: Analgesic
Topical cream 0.025, 0.075, 0.1%
Patch 8%
Adverse effects: Skin irritation, burning, and cough

TRPV1: Endocannabinoid and endovanilloid system
Distribution similar to CB1
Activated by Heat
Capsaicin
Anandamide
May work by counterbalancing effects of CB1, mechanism unclear

Cannabis sativa allergy: looking through the fog. Allergy, 2016, 72, 205

Cannabis Allergy
Exposure: inhaled, ingested, skin
• User
• Occupational (work in grow facility)
• Environmental (passive) to MJ or Hemp
• Seeds, leaves, pollen (late August)

Cannabis-fruit/vegetable syndrome
Cross react with other lipid transfer proteins LTPs
peach, tomato, latex

Contaminants: fungus and mold (aspergillus); pesticides; fentanyl...

Cannabis Food Allergy (edibles)

Symptom
• Orthostatic hypotension, tachycardia
• Fatigue, dizziness,
• Dry mouth
• Vomiting
• Abdominal Cramping
• Anxiety
• Throat tingling

GI differential
• POTS/autonomic dysfunction
• Oral Allergy Syndrome
• Food allergy
• ?potential for eosinophilic gastrointestinal diseases??
Cannabis and Drug Interactions

- CBD: potent inhibitor of CYP2C, CYP2D6, and CYP3A
- Potential for clinically significant drug-drug interaction

- 3A: cyclosporine, tacrolimus
- 2C: NSAIDs
- 2D6: tricyclics, codeine,

Summary and practical comments

- Little data on efficacy
- Important to monitor patients on cannabis
  - risks of use
  - discourage from stopping standard therapies
- Ask (they want to tell you)

Denver first in U.S. to decriminalize psychedelic mushrooms

Policy change would remain illegal but would become police’s “lowest law enforcement priority”
Diagnosing Children with Functional Abdominal Pain in 2019: How Much Testing is Enough?

Carlo Di Lorenzo, M.D
Twitter: @carlodilorenzo1

Disclosure

I have the following financial relationships with the manufacturer(s) of commercial product(s) and/or provider of commercial services:

Consultant: Sucampo, Merck, QOL Inc., Mahana, Shire, Mallinckrodt, Allergan

I do not intend to discuss unapproved/investigative uses of commercial products/devices in my presentation.

Objectives

- Discuss pros and cons of diagnostic testing in children with FAP
- Emphasize problems related to the discovery of incidental findings
- Describe other poorly understood conditions which may present with abdominal pain
History
15 y.o. girl, developmentally normal
CC: Periumbilical abdominal pain every day
- Pain is present all the time but is worse after ingestion of fatty foods and pizza
- Tried “everything”, nothing helped
- Home schooled
- ROS: depressed

History
- Onset of pain at puberty
- No other medical problem
- SHx: Divorced parents; not able to be involved in sports because of the pain
- FHx: Mother with IBS
- Meds: Anticholinergics

Physical exam
- Overweight, claims to be in severe pain, says “nobody believes her”; answers most of the questions: “Sometimes”.
- Abdomen: Generalized tenderness, no masses, no rebound or guarding. Small amount stools in rectal vault.
Next step? How much testing does this child need?

You know what this child has!

The cost of referral to a specialist in FAP

- Children with FAP/IBS: 46 seen by pediatric GI vs 43 seen only by PCP
- Had similar symptoms, interference with activities and stool characteristics
- Mothers of children seen by specialists perceived more pain intensity
- Excluding cost of endoscopy, cost of care was 5-fold higher in children seen by the specialist

Lane MM et al. Pediatrics 2009; 123: 758
A Million Dollar Workup for Abdominal Pain. Is It Worth It?

122 consecutive children with pain predominant FGID. Everyone had some test
14% EGD - 10% “abnormal”: H. pylori, chemical gastritis, esophagitis
17% colonoscopy - 9.5% “abnormal”: rare fork crypts, lymphoid hyperplasia

Average cost per patient: $6,104.

Why testing?

1) To make sure you get the correct diagnosis
2) To reassure patient and family
3) To reassure yourself

In general, parental anxiety and physician insecurity determine the extent of the work-up
Does lack of training lead to more testing?

Barriers in Neurogastroenterology and Motility Training Experience for Pediatric Gastroenterology Fellows

Can Rome help?

Adolescent committee

Rome Criteria:

Diagnostic Criteria for Functional Abdominal Pain-NOS Must be fulfilled at least 4 times per 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 irritable bowel syndrome, 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 before diagnosis.
Rome Criteria: Functional abdominal pain

Diagnostic Criteria for Functional Abdominal Pain-NOS

How does this help the clinician?

1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g., eating, menses)
2. Insufficient criteria for irritable bowel syndrome, 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 before diagnosis.

Do we need to “rule out” an organic disease?

Why the fear of missing an “organic” disease and not the fear of missing a functional disorder or not diagnosing an anxiety disorder?

- We (and the family) can “see” the organic disease
- We can do “something” about the organic disease (poor training in functional disorders)
- Society and medical bias against mind/brain disturbances

Gastroenterology 2016;150:1456–1468

How does this help the clinician?

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Gastroenterology 2016;150:1456–1468
I have had patients complaining to me that I missed:
- "Chronic appendicitis"
- Gallbladder dyskinesia
- Median arcuate ligament syndrome
- "Mild IBD"
- Food allergy

I have NEVER had a parent complain that I missed IBS or an anxiety disorder.

How do we avoid missing “organic” disease?
- Red flags?
- “Constant” pain is always functional?
- Time as your ally?
- Tests?

Red (pink?) flags!
- Persistent right upper, or right lower quadrant pain
- Arthritis
- Nocturnal Pain
- Perirectal disease
- Dysphagia
- Persistent vomiting
- Involuntary weight loss
- Deceleration of linear growth
- Delayed puberty
- Gastrointestinal blood loss
- Nocturnal diarrhea
- Unexplained fever
- Family history of IBD, celiac disease or PUD
Waking from sleep or joint pain similar prevalence in patients with FGIDs and Crohn’s disease and are not “red flags.”

Are there “green flags”?

• Persistent pain that does not change with physiological activities
• Presence of several other somatic symptoms
• “Nothing works” (side effects with every medication)
• Co-existence of internalizing disorder
• Family history of IBS
• Anxious/catastrophizing parents

Diagnosis is usually in the history
Let them speak

In encounters in which clinicians elicited patient concerns, the clinician interrupted the patient after a median of 11 seconds (interquartile range 7-22; range 3 to 234 s).

Communication study

Effect of sitting vs. standing on perception of provider time at bedside: A pilot study


Sitting vs standing

Let's do some tests!

Mother / Child's Agenda

I hope he finds something

I hope he does not find anything

I do not know why I'm here

It is not in her head!

I hope it is not cancer

She loves school and has many friends

I want some tests!

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It is not in her head!

I hope it is not cancer

She loves school and has many friends

I want some tests!

How can you tell it is functional?

Negative screening tests!

- CBC plus differential
- Hb/MCV/leucinophils
- ESR/CRP
- Celiac testing
- Chem profile
  - BUN/Cr/TP, A/LFT's
- Stool
  - heme test, O&P, fecal leukocytes, culture, H. Pylori Ag, calprotectin

What about KUB (constipation!) abdominal US, pH studies, EGD, UGI, HIDA scans, CT, and on and on and on....
The only two tests that are cost-effective in the absence of red flags in children are celiac disease serologic testing and stool calprotectin.

No KUB to diagnose constipation, please!

CONCLUSIONS The prevalence of celiac disease among children with IBS is 4 times higher than among the general pediatric population. Rome III classification of abdominal pain–related functional gastrointestinal FGID might help to select children who deserve screening for celiac disease.
Delaying a diagnosis of a FGID

- Not cost effective
- No limit to diagnostic work-up
- Increase uncertainty
- Postpones treatment

Endoscopy?

Initial Diagnosis of Functional Gastrointestinal Disorders in Children Increases a Chance for Resolution of Symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male as a reference)</td>
<td>1.628</td>
<td>0.912-2.908</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.048</td>
<td>0.946-1.096</td>
</tr>
<tr>
<td>Functional diagnosis from the beginning</td>
<td>2.163</td>
<td>1.029-4.544</td>
</tr>
</tbody>
</table>

Binary logistic regression, corrected for diagnosis.
Ordering tests is like picking your nose

Don’t chase the incidental findings, minimize them….

Making a diagnosis has side effects!

Endoscopy to reassure?


- 301 patients with abdominal pain-related FGIDs
- Patients with endoscopies, 61% reported abdominal pain, those without endoscopies, 64% were symptomatic (p=0.76)
- Abdominal pain frequency, intensity, and child’s disability were similar in those with and without endoscopies
- The study does not suggest that a negative endoscopy improves the outcome of children with FGIDs

You may find this
The incidental H. Pylori

Unlike in adults, there is no evidence in children that H. pylori gastritis causes dyspeptic symptoms in the absence of duodenal ulcer.

Meta-analysis, 14 cross sectional studies found no association between recurrent abdominal pain and H. pylori infection in children

What could we be missing?

- Biliary dyskinesia: “My aunt had exactly the same symptoms and a cholecystectomy cured her”.
- Chronic appendicitis: Many case series in the surgical literature
- Abdominal wall pain: Elicit the Carnett sign
- Median arcuate ligament syndrome (MALS): Abdominal angina, MR angiography confirms it, rare in children
Conclusions: Hypokinetic gallbladders are no more likely to have gallbladder pathology than normal or hyperkinetic gallbladders in the setting of a patient with both a HIDA scan and a cholecystectomy. Care should be used when interpreting the results of HIDA scans in children and adolescents.
Median Arcuate Ligament Syndrome (MALS)


- Vascular compression syndrome with symptoms that overlap chronic functional abdominal pain.
- Celiac artery compression by duplex ultrasound and diagnosis was confirmed by computed tomography.
- Laparoscopic surgical release resulting in a significant improvement in blood flow through the celiac artery.

N=46
- 67% reported improvement of symptoms since surgery
- No deaths, 9 complications, 8 required secondary procedure

Take home messages

- Use history, red flags and green flags to direct testing
- Relieve parental anxiety
- Do not chase (minimize) incidental findings
- Diagnoses have side effects
Achalasia
2019

Peter J. Kahrilas, M.D.
Northwestern University
Chicago, USA

Financial disclosures: PJ Kahrilas 2019

In the past 12 months, I have had no relevant financial relationships with the manufacturer of any commercial product and/or provider of commercial services discussed in this CME activity.

Achalasia 2019
Lecture Objectives

• To review recent advances in achalasia related to:
  – Diagnostic criteria
  – Epidemiology
  – Pathophysiology
  – Treatment
**Esophageal Anatomy**

- Upper esophageal sphincter: Striated, 18-22 cm long
- Lower esophageal sphincter: Smooth

---

**The Chicago Classification of esophageal motility disorders, v3.0**

Kahrilas PJ et al, Neurogastroenterol Motil 2015;27:160-74

---

**Normal Esophageal Motility**

*Pressure topography plot with key metrics*

- Swallow
- Distal contractile integral: DCI<8,000 mmHg-cm
- IRP window: IRP<15 mmHg
- Latency: 15-45 sec
- Pressure: 0-150 mmHg
Interpreting Clinical EPT Studies

The tools of analysis

- IRP (Integrated Relaxation Pressure)
  - The best validated metric of deglutitive relaxation
  - Advantages of a sleeve-type recording
  - Accounts for both nadir and persistence of relaxation

The Chicago Classification v3.0

Hierarchical analysis

1. Achalasia
   - IRP ≥ ULN and not Type I-III achalasia
2. EGJ Outflow Obstruction / Nonachalasia-achalasia
   - Mechanical obstruction

Achalasia Subtypes

- Type I (classic) achalasia
- Type II (achalasia with compression)
- Type III (spastic) achalasia
- Type IV (achalasia with compression)
Previously reported achalasia incidence and prevalence

<table>
<thead>
<tr>
<th>City/Region</th>
<th>Time period</th>
<th>Incidence rate</th>
<th>Prevalence rate</th>
<th>Case inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venice, Italy</td>
<td>2001-2010</td>
<td>0.28</td>
<td>8.9</td>
<td>ICDO-3 code 151</td>
</tr>
<tr>
<td>Melbourne, Canada</td>
<td>2001-2006</td>
<td>1.64</td>
<td>10.6</td>
<td>ICDO-3 code 151 and ICDO procedure code 151-0010</td>
</tr>
<tr>
<td>action, UK</td>
<td>1998-2002</td>
<td>0.87</td>
<td>7.3</td>
<td>ICDO-3 code 151 and ICDO procedure code 151-0010</td>
</tr>
<tr>
<td>Ireland</td>
<td>1994-2002</td>
<td>0.67</td>
<td>7.8</td>
<td>ICDO-3 code 151 and ICDO procedure code 151-0010</td>
</tr>
<tr>
<td>Singapore</td>
<td>1991-1999</td>
<td>0.3</td>
<td>1.0</td>
<td>Prevalence study conducted to identify all patients with achalasia in a single hospital</td>
</tr>
<tr>
<td>London, UK</td>
<td>1994-2002</td>
<td>0.77</td>
<td>11.7</td>
<td>Prevalence study conducted to identify all patients with achalasia in a single hospital</td>
</tr>
<tr>
<td>Sydney, Australia</td>
<td>1994-2002</td>
<td>0.1</td>
<td>0.2</td>
<td>Prevalence study conducted to identify all patients with achalasia in a single hospital</td>
</tr>
<tr>
<td>Chicago, IL</td>
<td>1994-2000</td>
<td>0.23</td>
<td>11.7</td>
<td>Prevalence study conducted to identify all patients with achalasia in a single hospital</td>
</tr>
<tr>
<td>Washington, DC</td>
<td>1994-2000</td>
<td>0.67</td>
<td>6.6</td>
<td>Prevalence study conducted to identify all patients with achalasia in a single hospital</td>
</tr>
<tr>
<td>Virginia, United States</td>
<td>1991-1977</td>
<td>0.23</td>
<td>11.7</td>
<td>Prevalence study conducted to identify all patients with achalasia in a single hospital</td>
</tr>
<tr>
<td>London, UK</td>
<td>1994-2000</td>
<td>0.13</td>
<td>11.7</td>
<td>Prevalence study conducted to identify all patients with achalasia in a single hospital</td>
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<tr>
<td>Sydney, Australia</td>
<td>1994-2000</td>
<td>0.13</td>
<td>11.7</td>
<td>Prevalence study conducted to identify all patients with achalasia in a single hospital</td>
</tr>
</tbody>
</table>

Achalasia epidemiology in Chicago since the widespread use of HRM

Age distribution of incident achalasia cases

- Median age = 56
Estimated prevalence of achalasia in the era of HRM

Based on the assumption that we manage all cases!

Achalasia Incidence

Achalasia Prevalence

Evolution of achalasia over a 2-year period,
Myenteric plexus inflammation at LES

Proposed scheme of achalasia pathogenesis

Viral infection (HSV-1, …) + Susceptible immunogenetic background

Aberrant autoimmune response

Cytotoxic (CD8) immune response / anti-neuronal antibodies

Myenteric plexus inflammation

Progressive loss of myenteric neurons

EGI outflow obstruction

Type II achalasia

Type I achalasia

End-stage achalasia

Finally treated with laparoscopic Heller myotomy
Achalasia Treatments

General principles

- Early treatment is desirable
  - Prevents disease progression and complications
- Dysphagia responds to Rx better than chest pain
- Botox can be a useful temporizing measure
  - Doubt in diagnosis
  - Elderly, frail patient
- Pneumatic dilation and LHM are both highly effective and highly operator dependent procedures

Clinical scoring system for achalasia (Eckardt score)

<table>
<thead>
<tr>
<th>Score</th>
<th>Weight loss (kg)</th>
<th>Dysphagia</th>
<th>Retrosternal pain</th>
<th>Regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>&lt; 5kg</td>
<td>Occasional</td>
<td>Occasional</td>
<td>Occasional</td>
</tr>
<tr>
<td>2</td>
<td>5–10kg</td>
<td>Daily</td>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 10kg</td>
<td>Each meal</td>
<td>Each meal</td>
<td>Each meal</td>
</tr>
</tbody>
</table>
Pneumatic Dilators used for Treating Achalasia

Microvasive® Dilator (3.0, 3.5, or 4.0 cm) Passed over guidewire, imaged with fluoroscopy

Microvasive™ Pneumatic Dilation 35 mm dilator

“Waist” locating the LES

Microvasive™ Pneumatic Dilation 35 mm dilator

Effacement of “Waist”
Laparoscopic Heller Myotomy with Dor Fundoplication

Success rates of pneumatic dilation and laparoscopic Heller myotomy
*The European Achalasia Trial, 2 year results*

<table>
<thead>
<tr>
<th></th>
<th>Heller myotomy (n=106)</th>
<th>Pneumatic dilation (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful, ES&lt;3 (%)</td>
<td>90%</td>
<td>86%</td>
</tr>
<tr>
<td>Eckardts score</td>
<td>1.1 ± 0.1</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>LES pressure (mmHg)</td>
<td>14 ± 1</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>Timed barium swallow (cm)</td>
<td>3.4 ± 0.6</td>
<td>4.8 ± 0.7</td>
</tr>
</tbody>
</table>

*In the initial study protocol, the first dilation was performed with a 35 mm balloon and 4 of the first 13 patients were perforated (31%); these were excluded from the analysis*

*Subsequently, protocol changed to initial 30 mm balloon followed shortly by 35 mm with further dilation mandated by symptoms and 4% perforation rate experienced*

Per-Oral Esophageal Myotomy (POEM)
*Novel alternative to LHM or PD for achalasia*

1) Enter into the submucosa in the mid esophagus
2) Creation of submucosal tunnel = half esophageal circumference
3) Myotomy begun = 3 cm distal to entry, 7 cm above EGJ
4) Myotomy completion
5) Clipping
Pneumatic dilation outcome in the POEMA trial

RCT comparing PD to POEM in 1° achalasia

Ponds FA et al. JAMA 2019;322(2):134‐144

EMD #100 v6/21/19 PJK

30 mm PD
5 PSI for 1 minute then 8 PSI for 1 min

Eckardt score >3 at 3 wks or IRP > 10 mmHg on HRM?

Yes 76% received 35 mm PD
No

Treatment failure
29/63 (46%)

Eckardt score >3 within 2 yrs

Treatment success
34/63 (54%)

23 received 40 mm PD

9 (14% of initial group) received POEM

European RCT

POEMA RCT

LHM vs PD

POEM vs PD

Dilators utilized: 30, 35, 40 mm
30, 35 mm

Dilations done in 2 yrs: 2‐6
1‐2

Repeat dilations OK?: Yes No

Perforation rate: 4% 1.6%

PD "success" reported: 86% 54%

Meta-analysis of outcome after treatment for achalasia based on subtypes

• Studies utilizing Botox, pneumatic dilation, LHM, POEM
• Patients grouped according to Chicago classification
• 20 studies (1575 patients) included

Wide variability in PD efficacy among trials

Tradeoffs of risk, benefit, and willingness for repetition

120
Meta-analysis of outcome after treatment for achalasia based on subtypes

**Type I achalasia totals (random effects)**

- Botox: 0.18 (0.05-0.40)
- PD: 0.61 (0.54-0.68)
- LHM: 0.81 (0.75-0.86)
- POEM: 0.95 (0.88-0.98)

P = 0.03

**Type II achalasia totals (random effects)**

- Botox: 0.61 (0.38-0.88)
- PD: 0.84 (0.69-0.95)
- LHM: 0.92 (0.83-0.97)
- POEM: 0.97 (0.93-0.99)

NS

**Type III achalasia totals (random effects)**

- Botox: 0.21 (0.04-0.46)
- PD: 0.32 (0.17-0.49)
- LHM: 0.71 (0.51-0.87)
- POEM: 0.93 (0.88-0.97)

P = 0.007
Meta-analysis of outcome after treatment for achalasia based on subtypes

Commentary

• Success rates for lap Heller myotomy in type I, II and III achalasia were 81%, 92% and 71% respectively
  — Yes, subtype matters!
• Those for POEM were 95, 97 and 93 per cent respectively
  — No, this is not experimental!
• POEM was more successful than LHM for both type I (OR 2.97, p=0.03) and type III (OR 3.50, p <0.007)
  — LHM is on the way out
• Pneumatic dilation had lower but acceptable success rate compared with POEM or LHM in type II
  — Solid argument for PD in type II (and EGJOO)

POEM in pediatrics

Limited data: case reports and one uncontrolled series

• 27 pediatric patients age 6-17, median 13.8
• 96.3% successful POEMs
• 15-38 month follow-up, mean 24.6 months
• 100% treatment success gauged by Eckardt score ≤3
• 19.2% developed reflux

Opioid-Induced Esophageal Dysfunction

Chronic opiate user: none for >24 hrs
Chronic opiate user: EGJOO
Chronic opiate user: type II achalasia
Chronic opiate user: type III achalasia
Chronic opiate user: jackhammer
Achalasia 2019

Summary

• Widespread adoption of HRM and the Chicago Classification have revealed achalasia to be about 3 times more common than previously thought
• Pathophysiology: autoimmune attack on the esophageal myenteric plexus of susceptible host
  – At least 2 distinct phenotypes
• Standard treatments of pneumatic dilation and laparoscopic Heller myotomy are rapidly being replaced by per-oral endoscopic myotomy (POEM)
  – Early data suggest this is also effective in pediatrics
Evaluation and Treatment Strategies in Non-Erosive Reflux Disease and Functional Dyspepsia

Julie Khlevner, MD
Associate Professor of Pediatrics at Columbia University Medical Center
Director, Pediatric Gastrointestinal Motility Center
Division of Pediatric Gastroenterology, Hepatology and Nutrition

LEARNING OBJECTIVES

- Discuss the criteria for diagnosing Non-Erosive Reflux Disease (NERD) and functional dyspepsia (FD)
- Understand the current concepts in pathogenesis of NERD and FD
- Review evidence based approach to therapy in pediatric NERD and FD

DISCLOSURE

- In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) or any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity
CASE

12 y.o. boy with 6 months of intermittent post-prandial regurgitation and frequent heartburn attributed to gastroesophageal reflux. Prolonged trial of acid suppressive therapy (variety of brands and doses) was essentially ineffective. No evidence of rumination. Pt is well appearing on physical examination without abdominal tenderness.

- EGD nonrevealing

- What is the next step and possible diagnosis/treatment?

NON-EROSIVE REFLUX DISEASE (NERD)

- Heterogeneous disorder
- troublesome reflux-related symptoms in the absence of endoscopic esophageal erosions/breaks with increased reflux burden on pH-impedance monitoring
- prevalence of NERD in the general adult population is between 50% and 70%
- 27% in pediatrics
- Is pH-impedance monitoring essential?

```
<table>
<thead>
<tr>
<th>Classification</th>
<th>Distal esophageal adenocarcinoma</th>
<th>Symptoms correlation</th>
<th>Symptom severity: FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Increased</td>
<td>0</td>
<td>Good</td>
</tr>
<tr>
<td>NERD</td>
<td>Increased</td>
<td>0</td>
<td>Good</td>
</tr>
<tr>
<td>NERD</td>
<td>Normal</td>
<td>0</td>
<td>Good</td>
</tr>
<tr>
<td>Normal</td>
<td>Not increased</td>
<td>0</td>
<td>Poor</td>
</tr>
<tr>
<td>NERD</td>
<td>Not increased</td>
<td>0</td>
<td>Poor</td>
</tr>
</tbody>
</table>

*Eisenberg et al.* J Neurogastroenterol Motil 2010 Jan; 16(1): 8–21

PH-IMPEDEANCE MONITORING (PH-MII)

- Pediatric Indications:
  - Differentiate NERD, hypersensitive esophagus and functional heartburns in patients with normal endoscopy (strong recommendation)
  - Determine the efficacy of acid suppression therapy (weak recommendation)
  - Correlate persistent troublesome symptoms with acid and nonacid GER events (weak recommendation)
  - Clarify the role of acid and non-acid reflux in the etiology of esophagitis and other signs and symptoms suggestive for GERD (weak recommendation)


PATHOPHYSIOLOGY OF NERD

- Peripheral factors (luminal, mucosal, and sensory afferents) as well as central (psychological, stress, sleep, etc.)
- Role of microscopic esophagitis
- Proximal esophageal migration of a reflux event (acidic, weakly and nonacidic) has been shown to be an important predictor of symptom generation in NERD
- Higher prevalence of FGID—IBS, FD
**Non-erosive reflux disease (NERD):** patients with esophageal symptoms who lack evidence of reflux on endoscopy but do have an abnormal acid burden that may or may not trigger symptoms

**Reflux hypersensitivity:** patients with esophageal symptoms (heartburn and chest pain) who lack evidence of reflux on endoscopy or abnormal acid burden on reflux monitoring, but do have evidence that reflux events trigger symptoms

**Functional Heartburn:** patients with esophageal symptoms who lack evidence of reflux on endoscopy or abnormal acid burden on reflux monitoring, and do not have evidence that reflux events trigger symptoms

**Rome IV Gastroenterology 2016**

neither microscopic esophagitis nor PPI responsiveness can predict phenotype in pediatric patients
EGD has 3 roles in the evaluation of symptomatic children: to diagnose erosive esophagitis (EE), microscopic esophagitis, and other conditions mimicking GERD.

- In patients with GED, the likelihood of having erosive EE ranges from 15% to 71% among studies.
- GERD may be present despite normal endoscopic appearance as well as in the absence of histological abnormalities.

Adult guidelines suggest that patients undergo endoscopy off acid suppression therapy.

Pediatric prospective studies are clearly needed at this time there is lack of data to recommend a single approach.

ENDOSCOPY: ON OR OFF ACID SUPPRESSION?

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- Adult guidelines suggest that patients undergo endoscopy off acid suppression therapy.
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**TREATMENT**

- **PPIs are superior to H2RA**
  - Better response rate in patients with greater acid exposure
  - Adult patients with NERD are less responsive to proton pump inhibitors (PPIs) as compared with patients with erosive esophagitis by approximately 20–30% after 4 weeks of the treatment

<table>
<thead>
<tr>
<th>Study population</th>
<th>PPI response rate (%)</th>
<th>Placebo response rate (%)</th>
<th>Therapeutic gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult NERD</td>
<td>60% (59-61)</td>
<td>36% (35-37)</td>
<td>22% (22-23)</td>
</tr>
<tr>
<td>Adult Esophagitis</td>
<td>98% (96-100)</td>
<td>85% (84-88)</td>
<td>13% (13-14)</td>
</tr>
</tbody>
</table>

- **PPI non-responders**
  - Role of antireflux surgery in NERD has not been well established
  - Neuromodulators
  - Prokinetics

- **CTP2C19 polymorphism and proton pump inhibitors**
  - All PPIs are metabolized by CYP2C19 hepatic microsomal enzymes and have similar pharmacokinetic parameters
  - The CYP2C19 gene is polymorphic
  - Several loss-of-function alleles (e.g., CYP2C19*2 through CYP2C19*9) reduce drug clearance and significantly increase PPI plasma concentrations resulting in poor metabolizers (two mutant alleles)

- **Recommendations for proton pump inhibitor dosing based on CTP2C19 haplotype and metabolizer phenotype**

> **Moving towards personalizing medicine**
AZITHROMYCIN AND ITS EFFECTS ON REFLUX

MEDICAL MANAGEMENT: NOT FDA APPROVED

Antidepressants With the Best Evidence to Support Their Use in a Specific Esophageal Disorder With a Functional Component

<table>
<thead>
<tr>
<th>Esophageal disorder</th>
<th>Medication Class</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional chest pain</td>
<td>Imipramine TCA</td>
<td>25-50 mg</td>
</tr>
<tr>
<td></td>
<td>Sertraline SSRI</td>
<td>50-100 mg</td>
</tr>
<tr>
<td>Hyperensive esophagus</td>
<td>Omeprazole SR</td>
<td>20 mg</td>
</tr>
<tr>
<td>Refractory GORD</td>
<td>Fluoxetine SSRI</td>
<td>20 mg</td>
</tr>
<tr>
<td>Reflux</td>
<td>Antidepressant TCA</td>
<td>15 mg</td>
</tr>
</tbody>
</table>

*Atypical anticholinergic reflux disease (AHRD), unexplained non-erosive reflux disease (NERD).
*Nonspecific reflux.

TREATMENT OF FUNCTIONAL ESOPHAGEAL DISORDERS

Lifestyle and Dietary Modifications
- Avoid spicy, greasy, or acidic foods
- Eat smaller, more frequent meals
- Avoid smoking and alcohol
- Sleep with head elevated

Cognitive Behavioral Therapy
- Helps patients understand the relationship between stress, anxiety, and symptoms
- Focuses on identifying and changing unhelpful thoughts, emotions, and behaviors

Medications
- Acid suppression
- Neuromodulation
- Proton pump inhibitors
- Antidepressants

References:
15 y.o. F presenting with long standing history of abdominal pain (upper abdomen), early satiety and bloating mostly around meal time. She denies weight loss, anemia, fever, nighttime symptoms. She endorses intermittent nausea. Pt is well appearing on physical examination with slight tenderness over epigastrium.

- Next Steps?
- Is further testing necessary? FOMO?
- Diagnosis!

FUNCTIONAL DYSPEPSIA: ROME IV

FUNCTIONAL NAUSEA

Must include all of the following fulfilled for the last 2 months:
1. Bothersome nausea as the predominant symptom, occurring at least twice per week, and generally not related to meals
2. Not consistently associated with vomiting
3. After appropriate evaluation, the nausea cannot be fully explained by another medical condition
PATHOPHYSIOLOGY OF FD

- Heterogeneous disorder
  - Gastric motor function (impaired accommodation, slow gastric emptying), visceral hypersensitivity due to central or peripheral sensitization (lower sensory thresholds to balloon distention of the proximal stomach), low-grade inflammation, and genetic predisposition play a role

- There is no evidence in children that Helicobacter pylori causes dyspeptic symptoms in the absence of duodenal ulcer

- Overlap with anxiety, depression, other FGIDs

EVALUATION

- Role of EGD is unclear
  - Presence of alarm features

<table>
<thead>
<tr>
<th>Alarm Features</th>
<th>Presence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of inflammatory bowel disease</td>
<td>12%</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>12%</td>
</tr>
<tr>
<td>Intractable diarrhea</td>
<td>12%</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>12%</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>12%</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>12%</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>12%</td>
</tr>
<tr>
<td>Mechanical bowel obstruction</td>
<td>12%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>12%</td>
</tr>
<tr>
<td>Recent weight loss</td>
<td>12%</td>
</tr>
<tr>
<td>Marked weight loss</td>
<td>12%</td>
</tr>
<tr>
<td>Persistent weight loss</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea &gt; 200 g/day</td>
<td>12%</td>
</tr>
<tr>
<td>Dilated polyps</td>
<td>12%</td>
</tr>
<tr>
<td>Unusual stools</td>
<td>12%</td>
</tr>
</tbody>
</table>
Lack of good studies in pediatrics
No FDA approved agents
PPIS vs. H2RA
Psychotropics
Cyclosporine
Prokinetics
Gastric electric stimulation
Herbal preparations (Iberogast, Rikkunshito)
Complimentary alternative medicine

Consider symptoms specific subgroups: PDS and EPS

Which factors predict response to PPI therapy in FD

- Patients with reflux symptoms more likely to respond to PPI therapy
- Patients with dysmotility symptoms are less likely to improve with PPI therapy
- Case control studies suggest nausea and bloating/IBS symptoms are negative predictors of PPI response

Pharmacological treatments for functional nausea and functional dyspepsia in children: a systematic review

no evidence to support the use of pharmacological drugs to treat FD in children
**Psychotropics for FD: A Systemic Review and Meta Analysis in Adults**

- 13 RCTs (1241 patients) included
- Ten trials were at low risk of bias.

**Main Results:**
- RR of FD symptoms not improving with psychotropic vs placebo = 0.78 (95% CI: 0.68 to 0.89)
- NNT=4; 55% CI 4 to 16
- Benefits limited to antipsychotics and TCAs.
- When only studies that excluded individuals with mood disorders considered, there was no benefit.
- Adverse events and AEs leading to withdrawal significantly more common NNT=21

---

**Mirtazapine for Adult FD**

- 36 FD patients with weight loss but no depression
- Mirtazapine 15mg vs placebo 0-12 weeks
- H. Pylori, H. pylori, H. pylori, associated with antidepressant properties

---

**Nanogastroenterology & Motility**

Rikkunshito simultaneously improves dyspepsia correlated with anxiety in patients with functional dyspepsia: A randomized clinical trial (the DREAM study)
Non-erosive reflux disorder should be considered in children with typical reflux symptoms, normal EGD and increased reflux burden on pH-impedance monitoring. NERD is a heterogeneous disorder with BGA and proximal reflux likely playing an important role in mediating esophageal symptoms. Although PPIs remain first line therapy for patients with NERD, the overall response rate is less than in patients with erosive esophagitis. The role of neuromodulators, prokinetics, FD is a prevalent and heterogeneous functional GI disorder in children. When treating FD, it's best to consider the Rome IV symptom specific subgroups: PDS and EPS. Hypnotherapy may be a promising and safe treatment option for children with FD. A multidisciplinary approach.

CONCLUSIONS

THANK YOU

Thats all Folks!

jk3065@cumc.columbia.edu
The Role of Diet in Managing Irritable Bowel Syndrome

Robert J. Shulman, MD
Professor of Pediatrics

Disclosure

- I have the following financial relationships to disclose:
  - Rome Foundation (potential royalties)
  - No products or services produced by these companies are relevant to my presentation

Outline

- How might diet exacerbate symptoms in IBS
  - Non-Immune mechanisms
    - FODMAPs
    - Sucrase-isomaltase deficiency
  - Immune mechanisms
    - IgE, IgG
    - Non-IgE
- Review of diets for treatment of IBS
- Suggestions for clinical management
How Might Diet Be An Issue

Non-Immune (?) Mechanisms
### Dietary FODMAPs

<table>
<thead>
<tr>
<th>Fermentable Group</th>
<th>FODMAP Subgroup</th>
<th>Food Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligosaccharides</td>
<td>Fructans Galacto-oligosaccharides</td>
<td>Onion, garlic, wheat, rye, artichoke, banana</td>
</tr>
<tr>
<td>Disaccharides</td>
<td>Lactose (Sucrose)</td>
<td>Milk Multiple</td>
</tr>
<tr>
<td>Monosaccharides</td>
<td>Fructose</td>
<td>Apple, pear</td>
</tr>
<tr>
<td>Polyols</td>
<td>Sorbitol Mannitol</td>
<td>Sugar-free foods, plums, mushrooms</td>
</tr>
</tbody>
</table>

(Wang XJ. Aliment Pharmacol Ther 2019;Epub)  
(Roberfroid MB. J Nutr 2007;137:2493S)

### FODMAPs – Traditional Thinking

- Physiologic effects
  - Malabsorbed dietary carbohydrate
  - Osmotic load
  - Fermentable substrate
  - Luminal fluid
  - Gas production
- Physiological effects
  - Luminal distention
  - Inflammation
  - Other effects
- Symptoms
  - Diarrhea
  - Bloating
  - Pain
  - Gas

(Barnet JS. Post Gastroenterol 2007;21(S1))

### FODMAPs and Inflammation / Visceral Hypersensitivity
FODMAPs and Inflammation

Hustoft TN. Neurogastroenterol Motil 2017;29:e12969

Yang Y. Aliment Pharmacol Ther 2014;39:302

Healthy Controls
Lactose Tolerant
IBS-D
Lactose Tolerant
Lactose Intolerant

Lactose Deficiency
Lactose Malabsorption

Healthy Controls
Lactose Tolerant

IBS-D
Lactose Tolerant
Lactose Intolerant

FODMAPs and Visceral Hypersensitivity

Yang Y. Aliment Pharmacol Ther 2014;39:302

Lactose malabsorption: IBS-D 87%, Healthy Volunteers 89%
Sucrase-Isomaltase Pathogenic Variants in IBS

Sucrase-Isomaltase Deficiency

- Traditionally thought to be a rare condition (0.1%)
- Genetic studies – increased prevalence of potentially pathogenic sucrase-isomaltase variants in IBS (~4%)

Sucrase-Isomaltase Variants

[Graph showing relative specific activity]
S-I Variants and Response to Low FODMAP Diet

Immune (Allergy)
IgE/IgG
Non-IgE

IgE / IgG Food Allergies

- Overall incidence/prevalence in US
  - 12% by self report
  - ~3% self report plus testing
    
- In IBS: range 4%-25%
  - Wheat, milk, nuts, eggs
Non-IgE Atypical Food Allergies

CLE = Confocal laser endomicroscopy

A IBS patient – increased lymphocytes
B Control – Barrett’s esophagus
C Positive reaction – increased lymphocytes, mucosal breaks, extravasation
D Positive reaction – further extravasation

76/108 (70%) IBS patients CLE+
Wheat 61%, yeast 20%, soy 7%, egg white 4% - 12% reacted to two
70% of patients/1st degree relatives had increased prevalence of atopy (inhaled)
Diets Used to Manage IBS

Low FODMAP Diet

- Decrease in symptom severity / improved quality of life (QoL); n=9 (Schumann D. Nutrition 2018:45:24)
- Reduced global symptoms; n=7 (Dionne J. Am J Gastroenterol 2018:113:1290)
- Decrease in symptom severity; n=6 (Altobelli E. Nutrients 2017:9)
- Decrease in symptom severity / improved quality of life (QoL); n=6 (Marsh A. Eur J Nutr 2016; epub)
- Improvement in symptom scores; n=10 (Varjú P. PLoS One 2017:12:e0182942)
- Too much bias (blinding and choice of control group; n=9 (Krogsgaard LR. Aliment Pharmacol Ther 2017:45:1507))
Double Blind Low FODMAP Trials

- Adults with IBS
  - Regular diet then low FODMAP or National Institute for Health and Care Excellence (NICE) guidelines (4 wk each) (n=84)*
  - Children with IBS
    - Low FODMAP diet then low vs high FODMAP diet – crossover (3 d – 5 d – 3 d) (n=33)

* Not entirely clear it was double blind

- (Eswaran SL. Am J Gastroenterol 2016;111:1824)
- (Chumpitazi BP. Aliment Pharmacol Ther 2015;42:419)

Double Blind FODMAP Challenges

- Adults with IBS
  - Regular diet then high vs low FODMAP rye bread – crossover (4 wk each) (n=73)
  - Low FODMAP diet then fructooligosaccharides vs maltodextrin (placebo) – crossover (10 d – 3 wk – 10 d) (n=20)
  - Low FODMAP diet then fructans vs fructose vs fructans(fructose vs glucose – crossover (2 wk and ≥7d washout) (n=23)
- Children with IBS
  - Low FODMAP diet then fructans vs maltodextrin – crossover (3 d – 10 d – 3 d) (n=23)

- (Laatikainen R. Aliment Pharmacol Ther 2016;44:460)
- (Hustoft TN. Neurogastroenterol Motil 2017;29:e12969)
- (Shepherd SJ. Clin Gastroenterol Hepatol 2008;6:765)
- (Chumpitazi BP. Clin Gastroenterol Hepatol 2018;16:219)

Reduced Sucrose/Starch Diet in IBS

- Adults with IBS (n=105)
  - Randomized, open 4-wk trial
    - Sucrose/starch reduced diet
    - Regular diet
  - Primary outcome ≥ 50 point reduction in IBS symptom severity score (IBS-SSS)

- (Nilholm C. Nutrients 2019;11:1962)
Reduced Sucrose/Starch Diet in IBS

- Controls
- Diet

Dietary interventions: 2 weeks

Urinary urgency, tiredness, muscle/joint pain, headache

(Blathin C. Nutrients 2019;11:1082)

Allergy Elimination Diet

- Tested for IgG Ab to 29 food antigens
- Double blind randomization to real or sham exclusion diet

IgG–based Food Allergies

- Allergy Testing
- Randomization to real or sham exclusion diet

(Atkinson W Gut 2004;53:1459)
Milk/Wheat IgE Allergy in IBS

114/166 (69%) improved on Elimination Diet

50/114 (44%) Negative

64/114 (56%) Positive

77% Cow milk, wheat proteins
14% Cow milk proteins
9% Wheat proteins

Double blind placebo controlled challenge

Fritscher-Ravens A. Gastroenterology 2014;147:1012

Non-IgE Atypical Food Allergies

In prior study, CLE+ went on exclusion diet and CLE-
continued usual diet

Fiber Supplementation
Dietary Fiber for Adults with IBS

- Global assessment of symptoms improved with soluble fiber (n=9) (NNT=6)  
  (Nagarajan N. Eur J Gastroenterol Hepatol 2015;27:1032)
- Global assessment of symptoms improved with psyllium (n=7) (NNT=7)  
  (Moayyedi P. Am J Gastroenterol 2014;109:1307)
- Global assessment of symptoms improved with psyllium (n=12)  
  (Chouinard LE. Can J Diet Pract Res 2011;72:e107)
- Global assessment of symptoms improved with soluble fiber (n=9)  
- Global assessment of symptoms improved in IBS-C with various types of fiber (n=4)  
  (Rao SSC. Aliment Pharmacol Ther 2015;41:1256)

Psyllium Fiber in Childhood IBS

![Graph showing the difference in number of pain episodes over 2 weeks between placebo and fiber treatment. P=0.03, n=103.](image)

(Sheehan RJ. Curr Gastroenterol Rep 2017;19:39)

Suggestions for IBS Dietary Management
Suggestions

- Diet history
- Lactose-free diet trial (7 days)
- Decrease in fatty foods (limited data)
- Increase dietary fiber intake (potential role for psyllium)
  - Some types appear to worsen symptoms (bran)

(McKenzie YA. J Hum Nutr Diet. 2016;29:549)
(Moayyedi P. J Can Assoc Gastroenterol. 2019;2:6)

Suggestions

- 4(?)-food diet elimination
  - Wheat
  - Milk
  - Eggs
  - Soy
- Sucrose / starch elimination
- Top down vs bottom up low FODMAP trial supervised by dietitian

(Groetch M. J Allergy Clin Immunol Pract. 2017;5:312)
(Wang XJ. Aliment Pharmacol Ther. 2019;Epub)

Suggestions

Timing?

Response ≤ 7-10 d

* British spelling

(Halmos EP. J Gastroenterol Hepatol. 2017;32(Suppl 1):69)
(Helvo EJ. J Gastroenterol Hepatol. 2017;32(Suppl 1):69)
Summary

- Evidence FODMAPs can engender symptoms (multiple mechanisms)
- Efficacy of low FODMAP diet less clear
- Sucrase deficiency a potential confounder
- Fiber supplementation may be of benefit (psyllium)
- Food allergy (various mechanisms) should be considered
New News in NAFLD

Miriam B. Vos, MD, MPH
Professor, Department of Pediatrics, School of Medicine
Co-Director, Center for Clinical and Translational Research, Emory Children's Pediatric Institute
Director, Pediatric Fatty Liver Program, Children's Healthcare of Atlanta
Director of Graduate Studies, Nutrition and Health Science Program
Laney Graduate School, Emory University

Disclosures

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- Bioness Foundation
- Siemens
- Novartis
- Texas Children's Hospital
- Genentech
- Target Pharmaceuticals
- Shire

Advisor Boards:
- ABIM
- Target Pharmaceuticals

Consultant:
- Alnylam
- Australian Health
- Shire
- Shire/Genentech
- Becton Dickinson
- Intercept
- Novo Nordisk

Learning Objectives

Understand: Current concepts in pathogenesis
Update: Diagnostic tools for NAFLD
Discuss: Clinical management of pediatric NAFLD
Nonalcoholic Fatty Liver

Range of NAFLD in Children

Pediatric NAFLD Across Regions of the World
Prevalence Differences by Ethnicity & Race

Autopsy Study 2018
Black – 1%
White – 8.3%
Hispanic – 7.9%
Overall prevalence in obese children=9%
N=582

Fernandes et al., J Pediatr 2018
Schwimmer et al., Pediatrics 2006

Overall prevalence in obese children=9%
Not Just a Liver Disease....

Similar BMI but Variable “Endophenotype”

- Presence of hepatic steatosis = strongest predictor of metabolic abnormalities long-term

What Causes NAFLD?
Genetics of NAFLD – Interactions with Insulin & BMI

- PNPLA3 rs738409-G – common polymorphism associated with NAFLD
- PNPLA3 – encodes adiponutrin, an enzyme found on lipid droplets that may decrease stored TG.
- High BMI¹, High Insulin² plus homozygous (GG) increases risk of NAFLD

¹Stenger et al, Nat Genet 2017
²Barata et al, Hep Comm 2019

Developmental Factors

- Gestational diabetes
- Type 2 diabetes
- Cardiovascular disease
- NAFLD

Modifiable factors:
- Maternal GDM
- Maternal hyperinsulinemia
- Urban residence
- Pharmacologic exposure

Modifiable? 10% NAFLD

Maternal NAFLD

GDM

Hershman et al, Gasto & Hep 2019
Friedman, Diabetes 2018

Advances in NAFLD Diagnosis
Who to screen?

- All obese children age ≥ 10 years (every other year)
- Overweight children with risk factors
  - Type II diabetes
  - Hispanic
  - Family history
  - Pituitary disorders (GH)
  - Right-sided abdominal pain

Screening: What is a “Normal” ALT

95th % in normal weight, healthy child:
- 26 U/L for boys
- 23 U/L for girls

ALT and Ultrasound have Similar (low) Sensitivity and Specificity for Screening
Typical Clinical Presentation

- Acanthosis nigricans
- Mild hepatomegaly
- Abdominal obesity (or generalized)
- ALT = 83 U/L
- AST = 55 U/L
- TG = 235
- HDL = 35

Clinical ultrasound:
- Echogenic
- Otherwise normal

Typical Clinical Presentation

Typical Pathway to Diagnosis of NAFLD

1. Clinical exclusion of medications & alcohol
2. Serologic exclusion of other chronic liver diseases
3. Confirmation of presence of fat in the liver
4. Assessment of severity of disease (NASH, fibrosis)

Imaging

<table>
<thead>
<tr>
<th>For fat:</th>
<th>For fibrosis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound Avg cost $390 Imprecise</td>
<td>• Acoustic radiation force impulse (ARFI)</td>
</tr>
<tr>
<td>MRI $600 – $5000 Highly precise Tip: Limited MR, no contrast</td>
<td>• Transient elastography</td>
</tr>
<tr>
<td></td>
<td>• MR elastography</td>
</tr>
</tbody>
</table>

Summary: Available, but not yet ready for clinical prime-time
Differential Diagnosis of Pediatric Hepatic Steatosis

Table 1: Differential diagnosis for pediatric hepatic steatosis

<table>
<thead>
<tr>
<th>Diagnosis/condition</th>
<th>Medication</th>
<th>Diet</th>
<th>Exercise</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td></td>
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<tr>
<td>Cystic fibrosis</td>
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<tr>
<td>Iron overload</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Wilson's disease</td>
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<tr>
<td>Hemochromatosis</td>
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<tr>
<td>Fatty liver disease</td>
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<tr>
<td>Alcohol consumption</td>
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<tr>
<td>Obesity</td>
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<td></td>
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<tr>
<td>Congenital disorders</td>
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<tr>
<td>Metabolic syndrome</td>
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</tbody>
</table>

Always consider other diagnoses for “fatty liver.”

When is a Liver Biopsy Helpful?

- When the diagnosis is unclear
  - Screening tests for other liver diseases are positive
  - Ultrasound or MRI does not show hepatic steatosis
- When fibrosis is suspected
  - By imaging
    - By a long history of significantly elevated ALT (>70-80 U/L)
  - When medications are being considered
    - Research study medications
    - Diabetes medications
    - Acne medications
- When the ALT is very high (>250 U/L)
  - Less than 15% of pediatric NAFLD has >250, consider other conditions
  - When the ALT goes up despite lifestyle changes

Treatment Considerations for NAFLD
The Liver and Lipid Regulation

NAFLD = Increased DNL

Sugar Consumption – Still too High
Primary Outcome: Liver fat improved

- 6%

Individual data 8 week study Adjusted means

What About Drugs?

Failed in Clinical Trials
- Vitamin E
- Metformin
- Cysteamine bitartrate (antioxidant)
- Gemcabene (PPAR)

Under Investigation Now*
- Losartan (ARB)
- Tomato products
- Omega 3s
- Anti-LPS Milk Supplement (IMM-124)
- AX412957 (Supplement)
- Bariatric Surgery
- Diets
- Elafibraror

*Active on ClinicalTrials.gov (recruiting)
Summary

• NAFLD is part of a systemic lipid disorder and strongly associated with insulin resistance
• Diagnosis - focus on ruling out other liver diseases and establishing severity
• Evidence supports beneficial treatment response to a low sugar diet (short-term)
• Many studies are underway for more effective therapies
• Long term focus includes extrahepatic components and avoidance of other diseases
New therapies for chronic cholestatic diseases

- ATP8B1
- FIC1
- ABCB11
- BSEP
- ABCB4
- MDR3
- Bile acids
- PL 'Flippase'
- PL 'Floppase'
- PFIC2
- PFIC3
- PFIC1
- Biliary atresia
- PSC
- Genetic cholestasis

Disclosures:
- Albireo Consultant
- Intercept Consultant
- LogicBio Consultant
- Mirum Consultant
- Retrophin Consultant
- Spruce Bioscience Consultant

Learning Objectives
1. Know the array of new agents that target bile acid based hepatotoxicity of cholestatic diseases
2. Understand the approach to therapy for genetic forms of cholestatic diseases based upon specific genes and variants—chaperones and potentiators
3. Know the current status of the field regarding treatments for biliary atresia
Effective anti-cholestatic therapies: 2019

Surgical:
- Kasai PE for biliary atresia: ~50% to 2y, ~25% to 18y
- Choledochal cyst excision: very effective
- Liver transplantation: ~90% effective for 10 years

Medical:
- Cholic acid for BASDs
- Reduced iv soy lipids for TPNAC
- Nothing else → opportunity for new science

Anti-cholestatic therapies

- **Bile acid based targets in cholestasis**
  - FXR activators
  - ASBT & NTCP inhibitors
  - Bile acids: Cholic acid (CA), UDCA & NorUDCA(*)
  - FGF19 analogue

- **Non-bile acid based therapeutics**
  - Antifibrotics (inc. PPAR modulators)
  - Gene-specific "correctors"
  - Gene therapy
  - Steroids/anti-inflammatories
Hepatic FXR targeting to improve adaptation to BA retention

Benefits of FXR activation:
- ↓ inflammation
- ↓ fibrosis
- ↓ bile acid synthesis
- ↑ bile acid export

Cholic Acid
Chenodeoxycholic acid
Lithocholic Acid
Z-Guggulsterone
FXR Agonists

EC50: 4-10 μM
IC50: 37-80 nM

FXR Antagonists

GW4064
Deoxycholic acid
19-50 μM
6-α-ethyl-CDCA (Obeticholic acid)
99 nM

Makishima Science 1999
Parks Science 1999
Wang Mol Cell 1999
Urizar Science 2002
Pellicciari J Med Chem 2002
Hawkins JCI 2002
Dussault JBC 2003
Downes Mol Cell 2003
Carter Ped Res 2007
Trauner Hepatology 2019

FXR: 7800 sites

Benefits of FXR activation:
- ↓ inflammation
- ↓ fibrosis
- ↓ bile acid synthesis
- ↑ bile acid export

FXR: 7800 sites

Adapted from Karpen Suchy et al text Kosters Plos One 2013 Thomas Pharm Res 2013
FXR activators in 2 adult biliary tract diseases
PBC & PSC

A Placebo-Controlled Trial of Orelbozol: Acid in Primary Biliary Cholangitis

Patient characteristics:
- Age: 43 (58% M)
- IBD: 60%
- MRCP: 60% Panbiliary
- UDCA: 46%
- AP: 348 U/L
- GGT: 423 U/L
- T Bili: 0.7 mg/dL
- Total serum BAs: 5 µM

Safety & Tolerability:
- Mod-Severe Pruritus:
  - 100 mg: 14%
  - 30 mg: 20%
  - Placebo: 40%

PSC: Cilofexor x 12w → reduced AP

FDA approval May 2016
Benefits of ASBT inhibition:

1. ↓ bile acid return to the cholestatic liver
2. ↓ hepatic bile acid accumulation
3. Luminally-restricted drug—not absorbed

ASBT (IBAT) inhibitors in clinical trials

Clinical trials.gov

Diseases:
- Alagille Syndrome
- PFIC1
- PFIC2
- Biliary Atresia
- PBC
- PSC
- NASH
- Constipation

ASBT inhibition → reductions of both liver & serum BA levels

ASBTi (sc-435)

PFIC3 mouse model
2 weeks of Rx
The ITCH Trial: ASBT inhibitor in ALGS

NorUDCA

NorUDCA for Adult PSC: Phase 2 Trial

159 Participants:
- 40 UDCA naive
- 58 UDCA responders
- 55 UDCA non-responders
PSC: FGF19 analogue → Less Fibrogenesis

NGM282
• No change in Alk Phos
• Reduced BA synthesis
• Reduced Fibrogenesis markers

Hirschfield J Hep 2019

Chaperones & Correctors

Lessons from the CF world → drugs to increase mutant protein function

• Potentiators
• Stabilizers
• Correctors

Vauthier Biochem Pharm 2017

Delaunay Hepatology 2016
Biliary Atresia

- ~40% of cholestatic neonates
- Principal indication for pediatric liver transplantation (LT)
- Incidence of ~1:12,000 US births (1:5,000 in Taiwan)
- ~50% avoid LT during infancy → Survival with Native Liver (SNL)

BA: No role for steroids post-Kasai PE

- No benefit from steroids
- Earlier time to SAE's
- Impaired growth

Summary: Cholestasis & New Therapeutics

- **Cholestasis**: New era in diagnostics & therapeutics
  - Paucity of validated clinical outcome biomarkers
  - Therapeutic Goal: Reduce intrahepatic bile acid accretion
    - Bile acids & FXR activity
    - ASBT inhibitors
    - FGF19 analogues
    - Chaperones & correctors

- **Biliary atresia**
  - No role for steroids
  - New opportunities for bile acid and non-bile acid therapies

Supplementary slides, not for presentation

**FXR Deficiency → Neonatal Cholestasis/Liver Failure**

- Mutations in the nuclear bile acid receptor FXR cause progressive familial intrahepatic cholestasis
- NR1H4: ARG176*
- Absent BSEP expression
- bsep
- RXR FXR

2 Families:
- Presentation at birth–36 w of age
  - ↑ Direct Bilirubin
  - Coagulopathy
  - Mild ↑ ALT & AST
  - Low GGT
- 2 died (5 weeks, 8 months)
- 2 transplanted (4 & 22 months)
### Select anti-cholestatic drugs in clinicaltrials.gov

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>Diseases with relevance for Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>FXR activator</td>
<td>Obeticholic acid</td>
<td>PSC, BA</td>
</tr>
<tr>
<td></td>
<td>Cilofexor</td>
<td>PSC</td>
</tr>
<tr>
<td>ASBT inhibitor</td>
<td>Odevixibat</td>
<td>PFIC's, ALGS, BA</td>
</tr>
<tr>
<td></td>
<td>Maralixibat</td>
<td>PFIC's, ALGS</td>
</tr>
<tr>
<td>FGF19 analogue</td>
<td>NGM282</td>
<td>NASH, PSC</td>
</tr>
<tr>
<td>NTCP inhibitor</td>
<td>Myrcludex</td>
<td>HBV</td>
</tr>
<tr>
<td>Bile Acid</td>
<td>NorUDCA</td>
<td>PSC, NASH</td>
</tr>
<tr>
<td></td>
<td>UDCA</td>
<td>Many</td>
</tr>
<tr>
<td>Anti-oxidant</td>
<td>NAC</td>
<td>BA</td>
</tr>
</tbody>
</table>

### Bile acid based therapeutics (clinicaltrials.gov)

**Glycocholic Acid:** BA Synthesis Defect

**FXR agonists:**
- NASH
- PBC
- BA diarrhea
- Alcohol
- Fibrosis

**NorUDCA:**
- PSC

**TGR5 agonists:**
- Satiety
- Constipation

**ASBT inhibitors:**
- Pruritus in cholestasis (ALGS, PFIC's)
- IBS-C
- PSC

**BA Sequestrant:** Colesevelam
- Diabetes
- NASH
- Obesity
Diagnosing drug-induced pancreatitis
Sohail Z Husain, MD

Disclosure

I have equity in PrevCon and serve on its Scientific Advisory Board

Learning objectives

• Recognize the burden of drug-induced pancreatitis in children and the commonly associated drugs

• Evaluate the causality assessments for drug-induced pancreatitis

• Review management guidelines for drug-induced pancreatitis in children
How common is drug-induced pancreatitis in children?

Medications are the second most common risk factor for acute pancreatitis in children

What are the drugs associated with pancreatitis in children?
Drugs associated with pancreatitis in children

Determining whether an association is casual

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Definite</td>
<td>×</td>
<td>×</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Probable</td>
<td>×</td>
<td>×</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Possible</td>
<td>×</td>
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</tbody>
</table>

Karch and Lasagna, Adverse drug reactions, JAMA, 1975

- Over 20 causality assessments (ALDEN, Liverpool, Naranjo)
- Opportunity to establish optimal causality assessments for drug-induced pancreatitis

Factors to consider in drug-induced pancreatitis

- Causality
- Classification of drugs according to risk for pancreatitis
- Characteristics of the drug association
- Latency (time to pancreatitis onset from drug ingestion)
- Idiosyncratic versus dose-dependent reaction
- Re-introduction of the drug
- Fertile ground for pharmacovigilance
- Example of the Drug-induced Liver Injury Network (DILIN) – Livertox database
- Future for drug-associated pancreatitis pharmacovigilance – DiPIN – Pancreastox
Classifications of drug-induced pancreatitis

Class Ia drugs
At least 1 case report with positive rechallenge, excluding all other causes, such as alcohol, hyperglycemia, gallstones, and other drugs.

Class Ib drugs
At least 1 case report with positive rechallenge; however, other causes, such as alcohol, hyperglycemia, gallstones, and other drugs not ruled out.

Class IIa drugs
At least 4 cases in the literature
Consistent latency (≤75% of cases)

Class IIb drugs
At least 2 cases in the literature
No consistent latency among cases
No rechallenge

Class IV drugs
Drugs not fitting into the earlier described classes, single case report published in medical literature, without rechallenge.


Classification of drugs associated with pancreatitis

Definite association
- Antimycobacterials (rifampin, isoniazid)
- L-asparaginase
- Allopurinol
- Diltiazem
- Digoxin
- Cobicistat

Probable association
- Omeprazole
- Carbamazepine
- Disulfiram
- Methotrexate
- Steroids

Possible association
- Azathioprine
- Amsacrine
- Atovaquone
- Carbon tetrachloride
- Omeprazole
- Chlorpromazine
- Citrate
- Contrast media
- Dexamethasone
- Diphenylhydantoin
- Digoxin

Runzi. Pancreas, 1996
AGA Technical Review, 2007

Etiologies for acute pancreatitis in IBD

Moolintong P. IBD, 2005
The thiopurines: azathioprine or 6-mercaptopurine

- 8-fold risk of pancreatitis
- Frequency—4-6%
- Idiosyncratic
- Onset of pancreatitis within 3 weeks of starting medication

Srinath A, IBD, 2016

Thiopurine-associated pancreatitis is linked to a class II HLA haplotype

- Heterozygotes - 9% risk of pancreatitis with thiopurines
- Homozygotes - 17% risk

May add to the armamentarium of pharmacogenomics in preventing DAP

Heap, Nat Genetics, 2014

Sulfasalazine-associated pancreatitis

- Initially attributed to the sulfapyridine moiety
  -- Absorbed
  -- Structurally similar to thiazide diuretics
5-ASA-associated pancreatitis

- Pancreatitis within 6 weeks of initiating 5-ASA therapy
- Idiosyncratic
- Improves after the drug is discontinued
- Repeat challenge has resulted in pancreatitis
- Mechanism for pancreatitis unclear
  - Local effect of 5-ASA on pancreas—pancreatic duct permeability?

Asparaginase-associated pancreatitis

- Crucial chemotherapeutic for acute lymphoblastic leukemia (ALL)
  - Transformed survival from 10% (1960s) to 90+% (2000s)
- Pancreatitis in 5-10% of users
- One third develop severe pancreatitis
- One quarter develop pseudocysts
- Most develop pancreatitis
  - Within 10 weeks
  - And 5-7 doses
- Why?
The risk of pancreatitis increases with higher or more prolonged exposure

Reintroduction of asparaginase after pancreatitis: Expert opinion

Why do some drugs cause pancreatitis?

Why do only some patients develop pancreatitis with exposure to a particular drug?

How can we identify patients who are at risk before they receive the drug and thus prevent pancreatitis, or provide a rescue therapy?
One third of children with drug-associated pancreatitis have concomitant etiologies, or risk factors.

Future for a personalized approach to drug-induced pancreatitis

Input
- History
- Anthropometric data
- Genomics
- Transcriptomics (plus ncRNA)
- Metabolomics

Output
- What drugs to
  - Avoid
  - Use judiciously
  - Employ prophylaxis

Summary of drug-induced pancreatitis
- Drugs are a major risk factor for pancreatitis in children
- Determining causality is an important challenge
  - Helpful to know the temporal relationship and known pattern responses
- Decision to discontinue drug exposure and later re-introduction
- Need for
  - Characterizing the types and classes of drugs associated with pancreatitis
  - Determining the optimal causality assessments
  - Pharmacovigilance
Disclosures

• In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

Objectives

• Recognize the presentation of pancreatic masses in children.
• Understand the workup and evaluation of pediatric pancreatic masses.
• Recognize the different etiologies and outcomes of pancreatic masses in children.
General Concepts

- Pancreatic tumors are rare in children
- Less than 0.2% of cancer-related deaths
- Histologic spectrum differs from adults
- Better clinical outcomes than adults

Klimstra et al., Arch Pathol Lab Med 2009;133:454-464

<table>
<thead>
<tr>
<th>Entity</th>
<th>Pancreatic Neoplasms, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal adenocarcinoma</td>
<td>85%</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>1 – 2%</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm</td>
<td>1 – 2%</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm</td>
<td>3 – 9%</td>
</tr>
<tr>
<td>Acinar cell carcinoma</td>
<td>1 – 2%</td>
</tr>
<tr>
<td>Pancreatoblastoma</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Pancreatic endocrine neoplasm</td>
<td>3 – 4%</td>
</tr>
<tr>
<td>Solid pseudopapillary neoplasm</td>
<td>1 – 2%</td>
</tr>
</tbody>
</table>

Klimstra et al., Arch Pathol Lab Med 2009;133:454-464

Classification of Pancreatic Neoplasms

- **Gross configuration**
  - Solid
  - Cystic

- **Lines of cellular differentiation**
  - Ductal adenocarcinoma (PDAC)
  - Acinar cell carcinoma
  - Pancreatoblastoma (PBL)
  - Neuroendocrine tumors
  - Solid pseudopapillary tumor (SPT)

- True Serous cystic neoplasm (SCN)
- Mucinous cystic neoplasm (MCN)
- Degenerative Solid pseudopapillary tumor
- Intraductal papillary mucinous neoplasm (IPMN)

Klimstra et al., Arch Pathol Lab Med 2009;133:454-464

Diagnostic Clues

- Variable presentation depending on type of tumor and location
- Clinical features that help to distinguish type of tumor:
  - Age
  - Sex
  - Location
  - Symptoms

Klimstra et al., Arch Pathol Lab Med 2009;133:454-464
Tumor in head of pancreas more likely to present with jaundice

Tumor in body or tail is more likely to present with pain or weight loss

Tumor in head of pancreas may cause duodenal obstruction

Clinical Presentation

- Palpable mass, abdominal distension
- Epigastric abdominal pain, radiation to back
- Weight loss, anorexia, nausea, emesis
- Fatigue, lethargy
- Early satiety (gastric/duodenal compression)
- Jaundice (biliary obstruction)
- New-onset diabetes
- Pancreatitis
- Asymptomatic incidental lesions
  - Solid lesion more worrisome than cystic
  - PDAC, neuroendocrine, SPT, lymphoma, metastases
**Diagnostic Approach**

<table>
<thead>
<tr>
<th>Table 1 Pancreatic imaging modalities</th>
</tr>
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<tbody>
<tr>
<td>Modality</td>
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<tr>
<td>CT</td>
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<td>EUS</td>
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<td>MRI</td>
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**Algorithm for Symptomatic Mass**

Algorithmic approach of EUS in pancreatic masses

Case
• 8 yo male presented with 3 days of painless jaundice, acholic stools
• Elevated bilirubin and lipase
• MR/MRCP: dilated biliary system and mildly dilated pancreatic duct to head, homogeneous increased T2 signal in pancreatic head
• ERCP: biliary and PD strictures, biliary stent placed
• Biliary cytology negative
• 4-week steroid treatment then taper for presumed autoimmune pancreatitis (IgG4 normal)

Case
• Interval CT scan at 3 mos: discrete, well-circumscribed, hyperenhancing head mass, 1.6 cm x 3.0 cm x 2.5 cm
• EUS: 2.6 cm x 2.0 cm hypoechoic lesion in pancreatic head
• FNA/B: atypical cells, suspicious for neoplasm
• OR for possible Whipple
  – No discrete pancreatic mass
  – Pancreas firm with fibrotic areas
  – Biopsies: fibrosis, periductal lymphoplasmacytic infiltrate, negative for neoplasia

Masquerades and Mimicking
Type 1 Autoimmune Pancreatitis with Imaging Appearance Similar to That of Malignant Cystic Tumor

Solid Pseudo-Papillary Tumor Mimicking as Complicated Pseudocyst
Multimodality Imaging and Pathological Correlation

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Diagnostic Challenge: Autoimmune Pancreatitis (AIP) vs Neoplasm?

- AIP may present as diffuse pancreatic enlargement or as pancreatic mass, or both
- AIP is often accompanied by obstructive jaundice
- AIP can cause cystic lesions in pancreas
  - Pseudocysts
  - Retention cysts (PD stenosis)
- Neoplastic cystic lesions can coexist with AIP
  - Intraductal papillary mucinous neoplasm
- Difficult to distinguish non-neoplastic from neoplastic cysts
- Clinical courses, management, prognosis of AIP vs neoplasm differ markedly

Types:
- Type 1: lymphoplasmacytic sclerosing pancreatitis (LPSP), IgG4-related systemic disease, elevated IgG4 levels, other organ involvement
- Type 2: idiopathic duct-centric pancreatitis (IDCP), pancreas-specific disorder, IgG4 levels not elevated, 30% assoc w/IBD

Cardinal features of AIP (HISORt):
- Histopathology
- Imaging: parenchyma (CT/MRI) and PD (ERCP/MRCP)
- Serology: IgG4, IgG, ANA
- Other organ involvement
- Response to steroids

- 48 children (systematic literature search, INSPIRE, CUSL)
- Abdominal pain (91%), obstructive jaundice (42%)
- Positive serology IgG4 in only 22%
- MRCP:
  - Global (29%) or focal (63%) enlargement
  - Main PD irregularity (64%), CBD stricture (55%)
  - Capsule-like rim / "halo sign" (16%)
- Histology: 72% combination of lymphoplasmacytic infiltration, fibrosis, granulocytic epithelial lesions
- Steroid response 93%; 8 improved without treatment

**Clinical symptoms + imaging findings can be highly suggestive of AIP in children**

- AIP in children more commonly follows Type 2 presentation or may be distinct disease pattern
Caution should be maintained in setting of focal pancreatic enlargement or non-regression of mass lesion.

Pancreatoblastoma (PBL)
- Most common malignant pancreatic tumor in children
- Affects children < 10 yo (median 4 – 5 yo); male > female
- Arise from embryonic pancreatic acinar cells
- Pain, large palpable mass >>> jaundice, emesis
- Neonatal cases associated with Beckwith-Wiedemann syndrome or Familial Adenomatous Polyposis
- Elevated alpha-fetoprotein (AFP) in up to 70 – 80%

Pancreatoblastoma
- CT or MRI to characterize:
  - Size, extent
  - Location (2/3 in head)
  - Metastatic disease
  - Resectability
- 35 – 50% present with metastases (liver, LNs, lung, brain)
- Complete surgical excision is most important prognostic factor, at diagnosis or after chemotherapy
- Biopsy performed if unresectable (vascular invasion)
- Chemotherapy: cisplatin, doxorubicin (PLADO)
Pancreatoblastoma: A report from the European cooperative study group for paediatric rare tumours (EXPERT)

- 20 patients, 2000 – 2009
- Median age 4 yrs, male 65%
- Size: <5 cm 15%, 5 – 10 cm 35%, >10 cm 50%
- Distant metastases 45%
- 85% underwent resection
- 73% chemo response rate in 18 pts (90%)
- 35% received XRT
- 5 yr EFS = 58.8%, OS = 79.4%
- Outcome influenced by feasibility of complete resection
  – 5 yr EFS: R0 resection 75% vs other 29% (p = 0.01)

Solid Pseudopapillary Tumor (SPT)

- 2 – 3% of all pancreatic tumors
- Young females, 2nd – 3rd decade
- Abdominal pain or incidental
- Predominantly acinar, can have ductal/endocrine components
- Unclear cellular origin
- No specific tumor markers
- Slow-growing, indolent
- Low-grade malignant potential (7 – 16%)
- May become cystic due to necrosis
- Complete surgical resection offers only cure
- Avoid enucleation or biopsy
- Recurrence 10%, 10 yr survival > 95%

Carcinoma

- Pancreatic ductal adenocarcinoma (PDAC)
  – 85% of pancreatic neoplasms
  – Extremely rare in children
  – Many cases in literature were likely SPT or PBL misidentified
- Acinar cell carcinoma
  – Extremely rare in children, but more common than PDAC
- Surgery remains mainstay
- No pediatric recommendations for management due to sparse literature
Neuroendocrine Tumors

- 1–2% of all pancreatic tumors
- Adenomas are benign, carcinomas metastasize
- Children > 10 yo; more common in middle age
- May or may not be hormonally active
- Multiple Endocrine Neoplasia I (MEN I), Von Hippel-Lindau, tuberous sclerosis

Types:
- Insulinoma (47%)
- Gastrinoma (30%)
- Glucagonoma
- VIPoma
- Somatostatinoma
- Non-functioning

Insulinomas

- Usually benign, 6% malignant
- 90% are solitary
- 10% associated with MEN I
- Symptoms typical of hypoglycemia
- Low plasma glucose, high insulin, high C-peptide
- Localization: MRI +/- EUS → PET-CT → intra-arterial calcium-stimulated venous sampling, transhepatic selective portal venous sampling
- Intraoperative: 98% are palpable, ultrasound is useful for small lesions
- Enucleation as parenchyma-preserving approach
- Long-term survival for non-malignant disease = 90%

Non-Epithelial Tumors

- Lymphoma
  - Non-Hodgkin lymphoma
  - Burkitt’s lymphoma
- Primitive neuroectodermal tumors/Ewing’s sarcoma
- Lymphangioma
  - Lymphatic malformation
- Hemangioendothelioma
- Dermoid cyst/mature teratoma
Cystic Lesions

- Cystic collection should never be labeled as “pseudocyst” in absence of clinical history of pancreatitis
- Types of cystic lesions:
  - Pseudocyst
  - Non-neoplastic cysts
    - True cyst
    - Retention cyst
    - Mucinous non-neoplastic cyst
    - Lymphoepithelial cyst
  - Cystic neoplasms

Cystic Neoplasms

- Varied malignant potential
- Imaging cannot distinguish benign vs malignant
- Symptomatic or any nodular/solid component or main PD dilation > 10 mm should be considered malignant

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>SPT</td>
<td>300 (61%)</td>
</tr>
<tr>
<td>PBL</td>
<td>81 (17%)</td>
</tr>
<tr>
<td>Exocrine</td>
<td>43 (9%)</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>40 (8%)</td>
</tr>
<tr>
<td>Other</td>
<td>25 (5%)</td>
</tr>
</tbody>
</table>

Systematic review, 32 studies, 489 pts
- Whipple 48%, distal pancreatectomy 24%
- Adjuvant chemo (76%), XRT (34%) in PBL
- Mortality was highest in exocrine tumors (50%)
- 99% of SPT patients survived
- PBL had overall survival 63% and highest recurrence rate (15%) within mean 24 mos
Approach to Resection

- Tumor location determines approach
  - Head of pancreas
  - Pancreatic body/tail
- Radical resections are the gold standard for malignant pancreatic tumors in children
  - Significant endocrine and exocrine impairment
- For benign, low-grade tumors, borderline tumors, parenchyma-sparing approach may be justified
  - Duodenum-preserving pancreatic head resection
  - Central pancreatectomy
  - Enucleation

Pancreaticoduodenectomy
“Whipple procedure”

- Complete resection of pancreatic head
- Bile duct, duodenum resected/reconstructed
- Low mortality (0 – 5%), high morbidity (40%) due to leaks
  - “Standard” Whipple or pylorus-preserving
  - 3 anastomoses: pancreatic, biliary, GI
  - Endocrine, exocrine dysfunction in up to 50%

Duodenum-preserving Pancreatic Head Resection (DPPHR)

- Parenchymal preservation, preservation of bile duct and GI continuity
- Reconstruction with Roux-en-Y jejunal limb
- Low mortality (0 – 3%), morbidity 20 – 32%
- Preserves function with less exocrine and endocrine insufficiency versus Whipple
Distal Pancreatectomy
- Considered if mass limited to body/tail
- Resection of pancreas to left of portal vein (50%)
- Low risk of complications, especially if spleen preserved

Percentages of Resection

Central Pancreatectomy
- Mass limited to pancreatic neck (overlying portal vein) or proximal body
- Roux-en-Y jejunal limb reconstruction of remnant distal pancreas
Conclusions

- Pancreatic tumors are rare in children, but have better prognosis than in adults
- SPT and PBL are most common epithelial pancreatic tumors in children
- Insulinoma is most common pancreatic neuroendocrine tumor
- Differentiation between AIP and pancreatic tumor may be very challenging and EUS can play a role
- Malignant tumors require radical resection with Whipple procedure or distal pancreatectomy
- Parenchyma-sparing may be justified for benign or low-grade tumors to preserve endocrine and exocrine function

Questions?

CCHMC Pancreas Care Center
Positioning the New IBD Therapies – Merging Experience with Evidence

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The Joseph B. Kirsner Professor of Medicine
Chief, Section of Gastroenterology, Hepatology and Nutrition
University of Chicago

Disclosures

Consultant and/or Grant Support
- Abilene
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- Cymatix
- Danaher
- DiaSorin
- Genentech/Roche
- Glenmark Pharmaceuticals
- GlaxoSmithKline
- Janssen Pharmaceutical Companies of Merck
- Macorich
- Medtronic
- Merck
- Mylan
- Novartis
- Pfizer
- Prometheus Laboratories
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- Shire
- Takeda
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- Sabin, LLC, Co-Founder

Learning Objectives

• Choose therapies based on prognosis and confirm effectiveness
• Identify targets of treatment that are individualized based on patient symptoms and objective measures of disease activity
• Understand risks and benefits of considering de-escalation and restart protocols in management
Where Do We Want To Be?
“Just Right” Use of Therapy for IBD

1. The right efficacy: safety
   - disease control
   - no adverse events
2. The right dose
   - not too little
   - not too much (?)
3. The right time
   - not too early
   - not too late
4. The right interval
   - no breakthrough between doses
5. The right duration
   - not too short
   - not too long (?)
6. The right cost!

Treatments are Aimed at Observations and Theories (the Not Cause of the Disease)

<table>
<thead>
<tr>
<th>Immune modification</th>
<th>Microbiota manipulation</th>
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</thead>
<tbody>
<tr>
<td>S-ASA (?), Steroids, Thiopurines/methotrexate, Anti-TNFα therapies, Anti-integrin therapies, Anti-IL12/23, JAK inhibitors</td>
<td>Antibiotics, Prebiotics, Probiotics, Fecal transplantation, Bacterial derived proteins, Diet</td>
</tr>
</tbody>
</table>

Surgery
- Resection of fibrostenosis
- Resection in fulminant disease

Traditional Treatment Strategy for IBD

- Aminosalicylate
- Corticosteroids
- Anti-TNF
- Aminosalicylate (UC)/Thiopurine/MTX (CD)
- Cyclosporine/Tacrolimus
- Natalizumab/Vedolizumab
- Tofacitinib (UC)
- Enteral Nutrition Therapy (CD)

No predictive therapeutic biomarkers

Time

Doesn’t suggest that de-escalation is possible.
What to Use First?

- We don’t really know yet
- Disease and patient issues
- Activity versus Severity
- Efficacy: Safety
- First drug works best

ACTIVITY: how sick the patient is NOW
SEVERITY: includes elements of PROGNOSIS

Treat to Target

1. Initial treatment
2. Assessment of target
3. Adjustment of treatment
4. Assessment of target
5. Target reached: continue monitoring

Treat to Target

Use Organ-Selective Therapies Before Systemic Therapies

- Topical rectal therapy before systemic therapy in distal colitis
- Budesonide before systemic corticosteroids
- Vedolizumab before systemically active immunosuppressants
  - Older patients
  - Paradoxical IBD in the setting of organ transplantation
- Enteral Therapy in CD (Peds)
Higher Remission Rates and Lower Loss of Response with Shorter Disease Duration

- Post hoc analysis of remission rates with Adalimumab and Certolizumab Pegol

Clinical remission with adalimumab in ADHERE

Weeks from CHARM Baseline

<table>
<thead>
<tr>
<th>Percent of Patients in Clinical Remission</th>
<th>Weeks</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

58 80 104 140 164

- <2 years, n=36
- ≥2 to <5 years, n=63
- ≥5 years, n=229

Post‐Hoc Analyses of Remission Rates with Adalimumab and Certolizumab Pegol

Week 26

Infliximab for Moderate to Severe Crohn's Disease in Children with Shorter Disease Duration (REACH)

- Patients (%)
  - Week 1: 15
  - Week 54 q8: 24
  - Week 54 q12: 24

- n=99
- n=66
- n=29
- n=33
- n=17
- n=12

- Week 10
- Week 54
- q8
- q12

- p=0.002
- P<0.001


“Real World” Earlier Anti-TNF in Crohn’s Has Better Outcomes

- Claims data assessment
- >3700 patients all who received anti-TNF at some point
- Three groups: "Step-up," IMM to anti-TNF, early TNF ("top-down")


- "Real World" Earlier Anti-TNF in Crohn’s Has Better Outcomes

- Claims data assessment
- >3700 patients all who received anti-TNF at some point
- Three groups: "Step-up," IMM to anti-TNF, early TNF ("top-down")
Early Anti-TNF Reduces Cost of Crohn’s Care

<table>
<thead>
<tr>
<th></th>
<th>Early Initiation</th>
<th>Late Initiation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean Lower end of 95% CI</td>
<td>Mean Lower end of 95% CI</td>
</tr>
<tr>
<td>Infliximab</td>
<td>$628,603 $505,698 $765,033</td>
<td>$679,022 $544,734 $829,211</td>
</tr>
<tr>
<td>QALYs</td>
<td>12.2 -24.6 39.1 11.5 -23.3 37.7</td>
<td></td>
</tr>
<tr>
<td>Net monetary benefit</td>
<td>$16,975 $1,860,586 $1,328,658 $103,184</td>
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Adalimumab
<table>
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<tr>
<th></th>
<th>Early Initiation</th>
<th>Late Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Lower end of 95% CI</td>
<td>Mean Lower end of 95% CI</td>
</tr>
<tr>
<td>Cost($)</td>
<td>$472,612 $309,787 $676,268</td>
<td>$516,581 $349,282 $730,350</td>
</tr>
<tr>
<td>QALYs</td>
<td>11.9 -23.8 38.8 11.4 -23.9 37.6</td>
<td></td>
</tr>
<tr>
<td>Net monetary benefit</td>
<td>$123,388 $1,663,731 $1,454,085 $52,220</td>
<td></td>
</tr>
</tbody>
</table>

Anti-TNF Naïve Patients Do Better with Other Classes of Therapy

Anti-TNF Naïve Prior Anti-TNF Failure

<table>
<thead>
<tr>
<th>Patients %</th>
<th>Clinical Remission to VDZ in UC</th>
<th>Clinical Remission to VDZ in CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF Naïve</td>
<td>27%</td>
<td>49.0%</td>
</tr>
<tr>
<td>Prior Anti-TNF Failure</td>
<td>13%</td>
<td>26.2%</td>
</tr>
</tbody>
</table>

Anti-TNF Naïve Prior anti-TNF Failure

<table>
<thead>
<tr>
<th>Patients %</th>
<th>Clinical Remission to UST in CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF Naïve</td>
<td>90 mg Q12w 90 mg Q8w</td>
</tr>
<tr>
<td>Placebo</td>
<td>90 mg Q12w 90 mg Q8w</td>
</tr>
</tbody>
</table>

Tofacitinib PE and Mortality Interim Report

- Phase 4 RA study
- ≥1 cardiovascular risk factors
- ↑ in PE/mortality
- Only at 10 mg BID
- Mechanism unclear
- Not seen in any Phase 2 or Phase 3 trials
- Recent EMA advice
- Label change; tofacitinib after anti-TNF

Optimizing Treatment

- Can the patient afford what you’ve prescribed? Will they get the therapy?
- Combine therapies:
  - Anti-TNF with IMMs
  - Anti-TNF with antibiotics in perianal disease
- Judicious use of therapeutic drug monitoring
  - Know who is at high risk for disease progression or complications
  - Know who is at high risk for rapid clearance
  - Consider post-loading drug levels (IFX week 8, ADA week 4)

Factors Affecting the Pharmacokinetics of Monoclonal Antibodies (Mostly Anti-TNF)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Impact on Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of ADAs</td>
<td>Decreases serum mAbs, Threefold-increased clearance, Worse clinical outcomes</td>
</tr>
<tr>
<td>Concomitant use of IS</td>
<td>Reduces formation, Increases serum mAbs, Decreases mtb clearance, Better clinical outcomes</td>
</tr>
<tr>
<td>High baseline TNF-α</td>
<td>May decrease mAbs by increasing clearance</td>
</tr>
<tr>
<td>Low albumin</td>
<td>Increases clearance, Worse clinical outcomes</td>
</tr>
<tr>
<td>High baseline CRP</td>
<td>Increases clearance</td>
</tr>
<tr>
<td>Body size</td>
<td>High BMI may increase clearance</td>
</tr>
<tr>
<td>Male Sex</td>
<td>Men have higher clearance</td>
</tr>
</tbody>
</table>

AGA Clinical Guidelines for TDM in IBD

- The AGA suggests reactive TDM to guide treatment changes in adults with active IBD treated with anti-TNF
- The AGA makes no recommendation regarding the use of proactive TDM
- The AGA suggests routine TPMT testing to guide thiopurine dosing in adult patients with IBD being started on thiopurines
- The AGA suggests reactive thiopurine metabolite monitoring to guide treatment changes in adults with active IBD
- The AGA suggests against routine thiopurine metabolite monitoring in adult patients with quiescent IBD
Using TDM with Adalimumab in Pediatric CD (PAILOT)

- PAILOT trial: pediatric CD adalimumab-level-based optimization treatment multi-center, non-blinded trial
- N=80, randomized to proactive (n=39) or reactive (n=41) therapeutic drug monitoring of ADA
- Primary endpoint: sustained corticosteroid-free clinical remission (PCDAI<10) from week 8 to week 72
- Proactive trough measurements + tight control based on clinical indices (CRP, fecal calprotectin) were superior to reactive trough measurements + tight control

Kaplan-Meyer Curve Representing Time to Disease Exacerbation

Proportion of Patients Achieving Clinical Remission by Serum IFX Concentration: ACT 1 and 2

- At weeks 8, 30 and 54, the proportion of patients achieving clinical remission increased with increasing quartiles of IFX concentrations.

Randomized, Controlled Trial of Vedolizumab vs Adalimumab in Patients with Active UC (VARSITY)

N=769, VDZ (n=383) or ADA (n=386)

Limitations to VARSITY:
- No dose escalation
- No drug levels
- If on steroids or IMM, no difference between groups
Multi-Center Experience of Vedolizumab Effectiveness in Pediatric IBD

- Retrospective review
- N=52 pediatric patients with IBD, 90% of whom had failed ≥1 anti-TNF agent
- 80% of anti-TNF naïve patients were in remission at week 14 and 100% in remission at week 22
- Anti-TNF naïve patients achieved remission at higher rates than anti-TNF exposed patients at week 22


Escalation of Ustekinumab Dosing is Associated with Recapture of Response

- Prospective study, n=35 CD patients with partial response or secondary LOR to UST
- Optimization in CD patients with LOR → recapture of response in 69% of patients
- Mean [UST] was higher at baseline and post-treatment in those achieving complete remission
- Baseline fcal lower in pts who achieved complete remission vs. those who did not (414 vs. 993 μg/g, P=0.03)


Other Specific Scenarios for Choice of First IBD Therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Modifier</th>
<th>First drug consideration</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>Psoriasis</td>
<td>Ustekinumab</td>
<td>On label</td>
</tr>
<tr>
<td>IBD</td>
<td>&gt;60 yo</td>
<td>Vedolizumab</td>
<td>Older patients have higher risk of infections</td>
</tr>
<tr>
<td>UC</td>
<td>Synovitis</td>
<td>Anti-TNF or Tofacitinib</td>
<td>On label</td>
</tr>
<tr>
<td>UC</td>
<td>Low albumin</td>
<td>Tacrolimus Tofacitinib</td>
<td>Small molecules</td>
</tr>
</tbody>
</table>
**The Ongoing Search for Therapeutic Biomarkers**

![Graph showing biomarker trend](image)

**Fecal Calprotectin (FC) Predicts Endoscopic Response to Therapy with VDZ and UST**

- FC levels decreased as early as week 2 in responders
- FC < 250 μg/g at week 8 predicts endoscopic response at week 16

![Graph showing endoscopic response](image)

**Combination of Therapies**

- Oral plus rectal 5-ASA
- Anti-TNF plus antibiotics for perianal disease
- Anti-TNF plus IMM
- Calcineurin plus vedolizumab
- Combination biologics?
- Tofacitinib plus vedolizumab

![Graph showing clinical response](image)
Why Might Combination Therapy Be More Effective?

- True for both CD (SONIC) and UC (SUCCESS) with infliximab1,2
- Multiple mechanisms of disease control
- Reduction in anti-drug antibodies
- Elevation of serum drug levels (greater exposure)


Combination Therapy is NOT Always Necessary Or Helpful

- SONIC post-hoc: infliximab levels more important than combination therapy1,2
- Ustekinumab doesn't benefit from combination therapy3
- Vedolizumab doesn't benefit from combination therapy4-6
- 5-ASA not helpful when escalating to TNFi7-8


Pair Second Anti-TNF with IMM when Switching Anti-TNFs if “Unfavorable pK” of FIRST Anti-TNF

- n=85 (45 CD, 40 UC)
- Two-center, prospective, open-label randomized trial
- Unfavorable pK - undetectable serum concentration of the anti-TNF with high Ab (> 20 ng/mL for IFX or ADA)

Planning for De-escalation

1. Discuss WHY this might be reasonable (Is the patient healthy because of your therapy or in spite of it?)
2. Confirm deep remission (mucosal healing), preferably for >1 year
3. Confirm optimization of drug (make SURE it’s working)
4. De-escalate
5. Have a monitoring strategy (Serial labs, fecal calprotectin, scope)
6. Know your rescue plan (Resume prior therapy or Move on to next strategy)

Fecal Calprotectin as a Tool to Monitor Relapse after Therapeutic De-escalation

- 160 IBD patients (50.6% Male)
- Fecal Calprotectin >100 μg/g predicts clinical relapse after de-escalation
- Current use of steroids (HR=1.67 [1.00-2.79]; p<0.0001) a risk factor for relapse
  - Fecal Calprotectin >100 μg/g in patients attempting to discontinue steroids was predictive of relapse (HR=1.67 [1.00-2.69])


Fecal should be measured 3 months after therapeutic de-escalation and then every 6 months

Circling Backwards

- Can you go back to a therapy that had worked and stopped working?
- Theoretically, if the inflammatory pathway related to the mechanism of treatment is reactivated, YES.
- If prior loss of response was due to anti-drug antibodies, NO.
- After surgery, probably YES. Did they just need surgery anyway, and was that the reason for the lack of response to therapy? Or did they progress right through the prior therapy? (then NO)
Chicago Algorithm for Restarting IFX

Summary: Positioning the New IBD Therapies – Merging Experience with Evidence

- Your first therapy will work best
- Consider co-morbidities
- Combination therapies make sense for some scenarios (and not just anti-TNF+IMM!) 
- Optimize
- Thoughtful choice of second therapy and understanding why it's needed
- Circling backwards is reasonable, but unproven
- Restarting after elective drug holidays
Immunosuppressive therapy in pediatric IBD: can we de-escalate therapy?

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Disclosures
In the past 12 months, I have had the following relevant financial relationships:

<table>
<thead>
<tr>
<th>Commercial</th>
<th>Relationship</th>
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<td>Janssen, Abbvie, Lilly</td>
<td>Advisory board or other consulting</td>
</tr>
<tr>
<td>Abbvie</td>
<td>Speaker fees</td>
</tr>
<tr>
<td>Abbvie</td>
<td>Investigator-initiated research support</td>
</tr>
<tr>
<td>Takeda, Janssen</td>
<td>Industry-initiated clinical trial participation</td>
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Learning Objectives:
As a result of the talk, the audience will be able to:

- Advise families concerning likelihood of (and factors predictive of) successful discontinuation of biologic therapies
- Utilize therapeutic drug monitoring to plan de-escalation of combination therapy with biologics
- Initiate and utilize biologic therapies in a way most likely to allow long-term effectiveness while balancing risks
Outline: De-escalation of biologic therapy (focus on anti-TNFs)

- Stopping anti-TNFs
- Lesser degrees of de-escalation
  - Discontinuation of concomitant immunomodulator in patients receiving anti-TNFs
  - Altering regimen (guided by therapeutic drug monitoring) to reduce (avoid unnecessarily high) anti-TNF exposure

Outline: De-escalation of biologic therapy (anti-TNFs)

- Stopping anti-TNFs
  - Discontinuation of concomitant immunomodulator in patients receiving biologics
  - Altering regimen to reduce biologic exposure

Stopping in whom?: heterogeneity of patients successfully treated with anti-TNFs

- Luminal inflammatory Crohn’s disease following failure of immunomodulators to achieve steroid-free clinical remission and/or intestinal healing
- As first-line therapy for luminal inflammatory Crohn’s disease
- Perianal fistulizing disease
- As rescue therapy for steroid-refractory ulcerative colitis (often first presentation)
- Steroid-dependent ulcerative colitis despite optimized 5-ASA
- Steroid-dependent ulcerative colitis despite optimized 5-ASA and thiopurines
Can we stop anti-TNF therapy? After successful treatment of luminal inflammatory CD?

- 11 year old boy presented with endoscopically severe ileocolonic disease
- Treated initially with infliximab induction and maintenance dosing guided by trough levels (5 mg/kg q 6 weekly) in combination with MTX
- Intestinal healing documented at 18 months

Can we stop anti-TNF therapy? After successful treatment of steroid-refractory UC?

- 12 year old boy presented to ER with 3-4 weeks of bloody diarrhea, cultures negative
- Failure of symptom resolution over ~ 5 days of IV steroids; therefore infliximab added
- 18 months of steroid-free continuous clinical remission

Pediatric framework for discussion of stopping

- Anti-TNF therapy is very frequently used early in pediatric Crohn’s disease management without trial of immunomodulators
- Infliximab is used as customary rescue therapy in pediatric patients with acute onset steroid-refractory extensive/pancolitis
- When outcomes in such patients are excellent, should there be an attempt at de-escalation?
**Stopping anti-TNFs**

<table>
<thead>
<tr>
<th>What is the concern about stopping?</th>
<th>What is the worry about continuing?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence of active IBD</td>
<td>Potential side effects (particularly neoplasia risk)</td>
</tr>
<tr>
<td>Subsequent lack of efficacy</td>
<td>Cost/inconvenience</td>
</tr>
</tbody>
</table>


**Data to be considered in discussion of stopping**

- Data concerning outcomes following cessation of anti-TNF therapy
  - in Crohn's disease
  - in ulcerative colitis

- Data concerning risks (particularly neoplasia) with long-term therapy
  - versus risks with other potentially effective maintenance strategies
  - In Crohn's disease
  - In ulcerative colitis

**Data concerning outcomes following de-escalation of anti-TNF therapy... in adults with IBD**

- In Crohn's disease: The STORI continues: recent longer term follow-up of the original GETAID cohort

- In any IBD:
  - Systematic review and meta-analysis (2016)
  - More recent observational studies

STORI trial: Infliximab discontinuation in Crohn’s disease patients in stable remission on combined therapy with immunomodulators

115 adults with Crohn’s disease receiving combination therapy Infliximab >/= 1 year; >/= 6 months sustained clinical remission

Remission regained with re-treatment in 88%

The STORI continues: 7 year follow-up

*N surgery or new complex perianal fistula

Time to resumption of anti-TNF following infliximab discontinuation

71% restarted anti-TNF (infliximab or adalimumab) after median 13 months (IQR 6-33 months)
Time to infliximab "restart failure" following resumption (n=64)

7 yr cumulative incidence of IFX "restart failure" 30.1% (95%CI: 19-43%)

7.9% (95% CI, 2.9–16.2) at 1 yr
20.1% (95% CI, 11.0–31.2) at 3 yrs
27.7% (95% CI, 16.7–39.8) at 5 yrs

"Restart failure" = Cessation due to Non-response/loss of response Infusion reactions Adverse event

---

"Failure of de-escalation strategy"

N=102
Median follow-up 83 months (IQR 71-99)

Restart infliximab N=54

Adalimumab start N=8

Major complication* N=18
Including 6 after IFX restart failure

No biologic restart N=22

Restart failure due to major complication N=13

Restart success N=42

De-escalation strategy failure defined as: "restart failure" or "major complication"

"70.2% (95%CI:60-80) had not experienced de-escalation strategy failure"

---

Risk of Relapse after discontinuing anti-TNF therapy: systematic review and meta-analysis of 27 studies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total number of patients</th>
<th>Percentage with relapse</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn's Disease</td>
<td>912</td>
<td>44% 95% CI (36-51%)</td>
<td>6-125</td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
<td>266</td>
<td>38% 95% CI (23-52%)</td>
<td>6-24</td>
</tr>
</tbody>
</table>

### Increasing risk of relapse over time (Crohn’s Disease)

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>Follow up</th>
<th>Percentage with relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>126</td>
<td>6 months</td>
<td>38% 95% CI (13-63%)</td>
</tr>
<tr>
<td>813</td>
<td>12-24 months</td>
<td>40% 95% CI (33-48%)</td>
</tr>
<tr>
<td>288</td>
<td>&gt;25 months (28–125 months)</td>
<td>49% 95% CI (31-68%)</td>
</tr>
</tbody>
</table>


### Risk of relapse in those with prior clinical vs endoscopic remission

<table>
<thead>
<tr>
<th></th>
<th>Clinical Remission</th>
<th>Endoscopic Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse by 6 months</td>
<td>61%</td>
<td>18%</td>
</tr>
<tr>
<td>Relapse within first year</td>
<td>42% 95% CI (32-52%) (n=448)</td>
<td>26% 95% CI (15-37%) (n=57)</td>
</tr>
<tr>
<td>After first year, by 24 months</td>
<td>42% 95% CI (25-58%) (n=231)</td>
<td>44% 95% CI (31-58%) (n=52)</td>
</tr>
</tbody>
</table>

Retreatment with the same anti-TNF induced remission in 80% (68-91%)


### Time to relapse after stopping anti-TNF therapy in UC and CD patients in deep remission (clinical + endoscopic + calprotectin <100)

- CD: 17
- UC: 34

60% relapse after median follow-up 36 months

Anti-TNF discontinuation: large retrospective multicenter Spanish study

- N=1055 (69% CD; 31% UC) in clinical remission; 74% infliximab, 26% adalimumab
- Anti-TNF therapy discontinued: elective decision (75%), onset of adverse events (18%) or remission after ‘top-down’ therapy (7%)
- 68% treated with immunomodulator

Cumulative incidence of relapse
24% 1yr; 38% at 2yrs, 56% at 5yrs
310/467 (69%) retreated with same anti-TNF
Same anti-TNF induced remission in 75%

Stopping in whom?: Are “our” patients represented by these studies

- Luminal inflammatory Crohn’s disease following failure of immunomodulators to achieve steroid-free clinical remission and/or intestinal healing
- As first-line therapy for luminal inflammatory Crohn’s disease
- Perianal fistulizing disease
- As rescue therapy for steroid-refractory ulcerative colitis (often first presentation)
- Steroid-dependent ulcerative colitis despite optimized 5-ASA
- Steroid-dependent ulcerative colitis despite optimized 5-ASA and thiopurines

Small subset treated with “top-down” anti-TNF

<table>
<thead>
<tr>
<th></th>
<th>Top-down (n=24)</th>
<th>Soluble (n=400)</th>
<th>Adverse events (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF duration</td>
<td>6 months</td>
<td>24 months</td>
<td>14 months</td>
</tr>
<tr>
<td>IFX induction only</td>
<td>44% (10)</td>
<td>9% (30)</td>
<td>7% (6)</td>
</tr>
</tbody>
</table>

Table 3: Factors associated with the risk of relapse after discontinuation of anti-TNF therapy in the multivariate analysis.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male vs. female</td>
<td>1.02</td>
<td>(0.99, 1.05)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.04</td>
<td>(1.00, 1.09)</td>
</tr>
<tr>
<td>Calprotectin &gt; 150 μg/g (vs. &lt; 150 μg/g)</td>
<td>1.63</td>
<td>(1.19-2.25)</td>
</tr>
<tr>
<td>Anti-TNF treatment duration &gt; 30 months</td>
<td>1.13</td>
<td>(1.03, 1.25)</td>
</tr>
<tr>
<td>Anti-TNF treatment</td>
<td>7.95</td>
<td>(2.21, 2.51)</td>
</tr>
</tbody>
</table>

Casanova P, Am J Gastroenterol. 2017;112(1):120-131
Outline: De-escalation of biologic therapy (anti-TNFs)

Stopping biologics

- Lesser degrees of de-escalation
  - Discontinuation of concomitant immunemodulator in patients receiving biologics
  - Altering regimen (guided by therapeutic drug monitoring) to reduce (avoid unnecessarily high) biologic exposure

Continuation versus discontinuation of thiopurine after 6 months combination therapy with infliximab: randomized controlled trial

Similar durability of clinical response

Greater prevalence of undetectable drug at trough

Do we need to use combination therapy in the first place?

Infliximab combination therapy has a small treatment benefit compared with monotherapy

SONIC: Week 26 all randomised patients (N=508)

- Steroid-free remission
  - IFX + AZA p<0.001 vs AZA
  - IFX p=0.006 vs AZA

- Mucosal healing
  - IFX + AZA p<0.001 vs AZA
  - IFX p=0.02 vs AZA
Likelihood of clinical remission according to drug level concentration at trough (patients grouped according to quartiles of drug level)

Q1: <0.84 μg/mL  Q2: 0.84 μg/mL to <2.36 μg/mL  Q3: 2.36 μg/mL to <5.02 μg/mL  Q4: ≥5.02 μg/mL

Benefit of combination therapy on steroid-free clinical remission primarily due to AZA’s influence on pharmacokinetics of infliximab

Optimised infliximab monotherapy versus combination therapy

Drobne D, Aliment Pharm Therapeutics 2019; 49: 880-889

Infliximab monotherapy with pro-active therapeutic drug monitoring (at week 10) versus combination therapy (retrospective analysis)

Solid line = personalized monotherapy  n=16
Dotted line = standard monotherapy  n=32
Dashed line = combination therapy  n=35

Lega S et al. Inflamm Bowel Dis 2010; 25: 134-141
**SUMMARY**

- In observational studies, stopping successful anti-TNF in patients with IBD (CD and UC) is usually (~75%) associated with subsequent relapse and re-treatment even if immunomodulator is continued.
- Experience with stopping anti-TNF when administered as first therapy (without prior failure of immunomodulator) is, however, very limited, despite the increasing prevalence of such patients in pediatric practice.
- Re-treatment with anti-TNF is usually (~70-80%) successful.
- Lesser degrees of de-escalation (e.g., stopping concomitant immunomodulator) are more successful and can be guided by therapeutic drug monitoring (TDM).

**FUTURE DIRECTIONS**

- Proactive TDM is opening an era of individualized therapy with potential to ascertain and maintain optimal target levels and avoid over-exposure.
- Continued examination of target levels of anti-TNFs and newer biologics according to treatment target (clinical versus endoscopic versus histologic remission) in CD and UC.
- With emerging biologics and small molecules,... evaluation of novel treatment algorithms to induce and maintain deep remission (e.g., de-escalation to agents with lower potential for long-term systemic unwanted effects).
When it is not IBD...Rare forms of Intestinal Inflammation

Stacy A. Kahn, MD
Boston Children’s Hospital
Inflammatory Bowel Disease Center
October 17, 2019

Disclosures

• AbbVie: consultant, research collaboration
• OpenBiome: research collaborator
• Grant support:
  – Cures Within Reach
  – NIH 1R24AI118629-01A1 (PI: Wu)

Objectives

• Learn to recognize and diagnose intestinal inflammation not due to IBD.
• Understand the natural history of a variety of rare forms of intestinal inflammation.
• Learn how to treat rare forms of intestinal inflammation.
Not all we see is IBD...

- Microscopic colitis
- Lymphocytic colitis
- Collagenous colitis
- Diversion colitis
- Bechet’s Disease
- Primary Immunodeficiency Diseases (PID)
  - Chronic Granulomatous Disease (CGD)
- Graft-Versus Host Disease
- Solitary rectal ulcer
- Eosinophil/allergic colitis
- Hirschsprung’s enterocolitis
- Neutropenic colitis (typhlitis)
- NSAID-induced colitis
- Radiation Colitis
- Ischemic colitis
- Medication-induced Colitis
- Check-point inhibitor colitis

Case Presentation

- 15 yo girl presents with diffuse abdominal pain for the last few months
- Intermittent diarrhea up to 4-5 x per day and urgency, but no visible blood or mucus
- She has had no weight loss
- She denies fevers, oral ulcers, joint pain, or rashes and ROS was otherwise negative
- FH: maternal aunt with Crohn’s disease

Work-Up

- All labs including CRP, ESR and celiac serologies are negative.
- Stool calprotectin 230 (mildly elevated)
- EGD and colonoscopy are grossly normal
- Your preliminary diagnosis:

  IBS-D
**IBD vs. Microscopic Colitis**

<table>
<thead>
<tr>
<th></th>
<th>IBD</th>
<th>Microscopic Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>Males</td>
<td>Females &gt;&gt; Males</td>
</tr>
<tr>
<td>Young adults and children</td>
<td>Ages 50-60</td>
<td>Watery diarrhea</td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td>Urgency</td>
<td>Urgency and incontinence</td>
</tr>
<tr>
<td>Urgency</td>
<td>Weight loss</td>
<td>Little/no weight loss</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Endoscopic inflammation</td>
<td>Visually normal endoscopy</td>
</tr>
</tbody>
</table>

**Epidemiology of Microscopic Colitis**

- Incidence: 1-25 per 100,000 person-years
- Average age at diagnosis: 65 yrs
- 25% are younger than 45 yrs
- More common in females
- Up to 1/3 of celiac patients have microscopic colitis
- Increased in patients with autoimmune disease

Pardi D. Am J Gastroenterol 2017
Munch A and Langner C. Clin Gastroenterol and Hep 2015

**Microscopic Colitis is on the Rise**

Pardi D and Kelly C. Gastroenterol 2011
Microscopic Colitis is Associated with Intestinal Dysbiosis

- Diversity was significantly higher in active MC compared to healthy controls, functional diarrhea, and MC in remission
- *Haemophilus parainfluenzae* and *Veillonella* species were significantly more abundant in MC than in healthy controls
- *Alistipes putredinis* were less abundant in MC
  - Butyrate-producing
  - ? Anti-inflammatory properties?
  - Depleted in new-onset pediatric IBD

Drugs That Trigger MC

<table>
<thead>
<tr>
<th>Low Likelihood</th>
<th>Intermediate Likelihood</th>
<th>High Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>Carbamazepine</td>
<td>Acarbose</td>
</tr>
<tr>
<td>Gold Salts</td>
<td>Celecoxib</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Piasclodine</td>
<td>Diclofenac</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Entacapone</td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td>Flavonoid</td>
<td></td>
</tr>
<tr>
<td>Oxetorone</td>
<td>Lansoprazole</td>
<td></td>
</tr>
<tr>
<td>Madopar</td>
<td>Esomeprazole</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Ranitidine</td>
<td></td>
</tr>
<tr>
<td>Stevelo</td>
<td>Sertraline</td>
<td></td>
</tr>
<tr>
<td>Ticlopidine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Microscopic Colitis

- **Collagenous Colitis**
  - Increased subepithelial collagenous layer > 10μm
  - Lindström 1976
  - Freeman et al. 1976

- **Lymphocytic Colitis**
  - Increased intraepithelial lymphocytes > 20 IEL/100 epithelial cells
  - Lazenby et al. 1989

- **Incomplete Microscopic Colitis**
  - Does not fulfill histological criteria
  - Münch et al. 2012

### Watery Diarrhea Syndromes

### Histology Is the Key to Diagnosis

<table>
<thead>
<tr>
<th>Percent (%)</th>
<th>Normal</th>
<th>IBD</th>
<th>Lymphocytic Colitis</th>
<th>Collagenous Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraepithelial lymphocytes</td>
<td>4.6</td>
<td>4.4</td>
<td>24.6</td>
<td>21.2</td>
</tr>
<tr>
<td>Intraepithelial eosinophils</td>
<td>&gt;0.1</td>
<td>0.8</td>
<td>1.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Intraepithelial neutrophils</td>
<td>0.4</td>
<td>1.4</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Crypt distortion</td>
<td>0.3</td>
<td>1.9</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Sub epithelial collagen</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Epithelial flattening</td>
<td>7.3</td>
<td>8.2</td>
<td>35.2</td>
<td>35.4</td>
</tr>
<tr>
<td>Epithelial loss</td>
<td>10</td>
<td>6</td>
<td>4.7</td>
<td>20</td>
</tr>
</tbody>
</table>


### Lymphocytic Colitis

[Image: https://www.webpathology.com/image.asp?case=1038&n=14]
Collagenous Colitis

https://www.webpathology.com/image.asp?case=1038&n=8

Collagenous Colitis in Children

<table>
<thead>
<tr>
<th></th>
<th>Pediatric-Onset</th>
<th>Adult-Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Iron deficiency anemia</td>
<td>Voluminous non-bloody diarrhea</td>
</tr>
<tr>
<td>Histology</td>
<td>Collagen in stomach</td>
<td>Collagen throughout GI tract</td>
</tr>
<tr>
<td>First Pediatric</td>
<td>Dick Colletti &amp; Thomas Trainer 1989</td>
<td>Dick Colletti et al. 1998</td>
</tr>
<tr>
<td>Case</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Matta J et al. JPGN 2018

Management of Microscopic Colitis

Probiotics
Antibiotics

Porto D and Kelly L. Gastroenterol. 2011
Esteve M et al. J Crohn's and Colitis. 2011
Barker P et al. J Crohn's and Colitis, 2018
**Budesonide Treatment for MC**

- **Difference**: 64.5% (95% CI [22.9%, 63.9%], p<0.001)

**Case Follow-Up**

- **Histology**:
  - Increased IEL
  - Epithelial flattening/damage
  - No collagen band
- **Diagnosis**: Lymphocytic colitis
- **Started on budesonide 9 mg/d**
- **Sx resolved after a 2 wks**
- **Tx with budesonide for 8 wks, then tapered down to 3 mg/d but sx returned**
- **Dose increased back to 9 mg/d and in remission.**

**Take Home Points**

- Microscopic colitis can cause non-bloody voluminous diarrhea and belly pain in children
- Microscopic colitis may be due to medications and/or associated with autoimmune disease
- Consider MC in patients with celiac disease
- Histopathology is lymphocytic colitis and collagenous colitis is distinct from IBD
- Budesonide is the only evidenced based tx and is the most effect treatment
Thank You

“O.K. Girl... with color. Goes buy.”

Wrong. That’s the girl with a kaleidoscope. Else?

I thought the ruffles looked nice. For padded gloves.
Eosinophilic Inflammation Beyond the Esophagus
Edaire Cheng, MD

Disclosures

• Consultant – Guide Point Global

Eosinophils Beyond the Esophagus:
Outline

• Definition and Diagnosis
• Epidemiology and Demographics
• Clinical Presentation
• Diagnostic Approach
• Management Approach
EGIDs are a group of immune-mediated diseases characterized by gastrointestinal eosinophilia accompanied with gastrointestinal symptoms.

Eosinophilic Gastrointestinal Disorders (EGIDs)
- Eosinophilic Esophagitis (EoE)
- Eosinophilic Gastritis (EG)
- Eosinophilic Gastroenteritis (EGE)
- Eosinophilic Enteritis (EEnt)
- Eosinophilic Colitis (EC)

EGID Epidemiology

<table>
<thead>
<tr>
<th>EGID</th>
<th>Prevalence (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EoE</td>
<td>57</td>
</tr>
<tr>
<td>EG</td>
<td>6.3</td>
</tr>
<tr>
<td>EGE</td>
<td>5.1 - 8.4</td>
</tr>
<tr>
<td>EC</td>
<td>2.1 – 3.3</td>
</tr>
</tbody>
</table>
EGID Demographics: Gender


EGID Demographics: Age


EGID Diagnosis

- **Clinical Features**
  - Gastrointestinal symptoms

- **Histological Features**
  - Eosinophil-predominant gastrointestinal inflammation
  - Exclude other intestinal eosinophilia
EGID Clinical Presentation Depends on Location

**Esophagus**
- Dysphagia
- Odynophagia
- Heartburn
- Vomiting
- Food impaction
- Abdominal pain
- Nausea
- Vomiting
- Early satiety
- Loss of appetite
- Bloating
- Diarrhea

**Stomach**
- Abdominal pain
- Nausea
- Heartburn
- Vomiting
- Diarrhea
- Bloating
- Loss of appetite
- Vomiting
- Abdominal pain

**Small Intestine**
- Abdominal pain
- Nausea
- Early satiety
- Loss of appetite
- Vomiting
- Diarrhea
- Obstruction

**Colon**
- Diarrhea
- Blood in stool
- Abdominal pain

**Muscular Disease**
- Obstruction

**Serosal Disease**
- Ascites

**Mucosal Disease**
- Abdominal pain
- Nausea
- Anorexia
- Weight loss
- Failure to thrive
- Protein losing enteropathy
- Edema and anemia

**EGID Diagnostic Workup**

*Other Clinical History That Raises Your Suspicions*

**Allergic Conditions (>50%)**
- Allergic Rhinitis (28-34%)
- Sinusitis (29-30%)
- Asthma (15-33%)
- Dermatitis/Eczema (18-32%)
- Food Allergies (18-24%)
- Urticaria (5-7%)
- Drug Allergies (49-53%)
EGIDDiagnostic Workup

Other Clinical/Laboratory Findings That Raises Your Suspicion

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>Laboratory Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Eosinophilia (20-85% of cases)</td>
<td>✓ CBC with differential</td>
</tr>
<tr>
<td>Subset with Protein Losing Enteropathy</td>
<td>✓ Albumin</td>
</tr>
<tr>
<td>• Anemia</td>
<td>✓ Stool α1-antitrypsin</td>
</tr>
<tr>
<td>• Hypoalbuminemia</td>
<td></td>
</tr>
<tr>
<td>• Intestinal protein loss</td>
<td></td>
</tr>
<tr>
<td>Bloody Stools</td>
<td>✓ Fecal occult blood</td>
</tr>
</tbody>
</table>

EGID Diagnostic Workup

Other Radiological Findings That Raises Your Suspicion

- Ascites
- Gastric Mural Thickening
- Small Bowel Mural Thickening


EGID Diagnostic Workup

- Remember!
  - Clinical Features
    - Gastrointestinal symptoms
  - Histological Features
    - Eosinophil-predominant gastrointestinal inflammation

- You’ve Got an Issue, You Need Tissue!
  - Endoscopy
  - Laparoscopy (if you suspect serosal disease)
What is a Normal Number of Eosinophils?

<table>
<thead>
<tr>
<th>Region</th>
<th>Normal Eosinophils/HPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>(5-7)</td>
</tr>
<tr>
<td>Duodenum</td>
<td>(15)</td>
</tr>
<tr>
<td>Terminal Ileum</td>
<td>(20)</td>
</tr>
<tr>
<td>Ascending Colon</td>
<td>(35)</td>
</tr>
<tr>
<td>Descending Colon</td>
<td>(18)</td>
</tr>
<tr>
<td>Rectum</td>
<td>(10)</td>
</tr>
</tbody>
</table>


What is an Abnormal Number of Eosinophils?

- Greater than two times the normal (rule of thumb)
- Stomach: ≥30 eosinophils/HPF
- Duodenum: >52 eosinophils/HPF
- Ileum: >55 eosinophils/HPF
- Colon:
  - Right colon: >100 eosinophils/HPF
  - Transverse and descending colon: >84 eosinophils/HPF
  - Rectosigmoid colon: >64 eosinophils/HPF
- Note any altered eosinophil distribution and epithelial changes


Eosinophilic Gastritis: Endoscopic Features

- Erythema
- Edema
- Ulcerations
- Erosions
- Nodules
- Polyps
- Normal

Mucosa can appear normal.


**Eosinophilic Gastritis: Histologic Features**

*The disease is patchy!*

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**Eosinophilic Enteritis/Gastroenteritis: Endoscopic Features**

- Erythema
- Edema
- Exudates
- Ulcerations
- Erosions
- Nodules
- Normal

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**Eosinophilic Enteritis/Gastroenteritis: Histologic Features**
Eosinophilic Colitis: Endoscopic Features

- Erythema
- Edema
- Polyps
- Ulcerations
- Normal

Eosinophilic Colitis: Histologic Features

EGID Diagnostic Workup
Excluding Other Causes of Intestinal Eosinophilia

- Parasitic Infection
- Menetrier’s Disease
- Inflammatory Bowel Disease
- Celiac Disease
- Connective Tissue Disease
- Neoplasias
- Hypereosinophilic Syndrome
EGID Pathogenesis

What are potential therapeutic targets?

Ingested Antigen

- Antigen Presenting Cells
- Th2 cell
- IL-13, IL-4, IL-5 (Th2 cytokines)
- Eotaxin-3, Eotaxins
- Mast Cells
- Eosinophils

EGID Management

- Steroids
  - Systemic Steroids
    - Prednisone 0.5-1 mg/kg/day (or 20-40mg/day) x 2-4 weeks followed by taper
    - 95% (18/19 EGE patients) "responded"
  - Topical Steroids
    - Budesonide 0.25-9mg/day
      - Open enteric-coated capsule and crush granules and mix with 15ml of water/juice
      - Viscous slurry
      - 61% (22/36 EGE patients) "responded"
EGID Management

• Dietary Therapy
  • Elemental Diet
    • 75% (22/29 EGE patients) "responded"
    • 83% (5/6 EG patients) "responded"
  • Empiric Elimination
    • Milk elimination
      • 63% (10/16 patients) "responded"
    • 6-food elimination/7-food elimination
      • 85% (29/34 EGE or EC patients) "responded"
  • Allergy Test-Directed
    • 100% (4/4 EGE patients) "responded"


• Other therapies
  • Cromolyn (mast cell stabilizer)
    • Symptomatic relief
      • GruppoItalianoPediatria Allergologica.
      • D. Gescher et al. Allergy 1990.
  • Montelukast
    • Symptomatic relief
  • Omalizumab (anti-IgE)
    • Not effective
  • Vedolizumab (anti-α4β7)
    • Effective in series of steroid-refractory cases (3/4 patients)


EGID Future

• Clinical Trials
  • AK002 (anti-Siglec8) in adults with EG and/or EGE
    • Randomized, Double-Blind, Placebo-Controlled Study in Patients with Eosinophilic Gastritis (EG) and/or Eosinophilic Gastroenteritis (EGE)

  • Elemental diet in adults with EGE (NCT 03320399)
  • Benralizumab (anti-IL5R) in teens/adults with EG (NCT 32437977)
  • Dupilumab (anti-IL4R) in adults with EG (NCT 03675545)
EGID Natural History and Monitoring

Monitoring:
- Histopathologic monitoring is needed to document remission
- Abnormal labs improve with remission

Take Home Points

- GI symptoms/presentation correlate to location and depth of disease
- Suspect in patients with allergic disorders and atopy
- Endoscopic features can be normal
  - Biopsy normal areas as well
- Histopathology can be patchy
  - Take multiple biopsies from separate GI segments
- Therapy is limited to diet, topical steroids, or systemic steroids
- Monitoring does require repeat endoscopy/biopsy
  - But improving labs can also help