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Some of the slides reproduced in this syllabus contain animation in the power point version. This cannot be seen in the printed version.

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Continuing Medical Education

NASPGHAN CME Mission Statement

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

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

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

Physicians

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

AMA PRA Statement

NASPGHAN designates this 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

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

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

PART 2 MOC
THE AMERICAN BOARD of PEDIATRICS

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.

Postgraduate Course
Thursday, October 17

Sheraton Ballroom, Level 4

Course Directors: Jennifer Strople MD and Maria Oliva-Hemker MD

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

NASPGHAN POST-GRAD 2019

Foreign Body Management Update

David Brumbaugh, MD

Children's Hospital Colorado

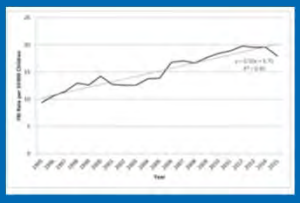
No Disclosures

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.

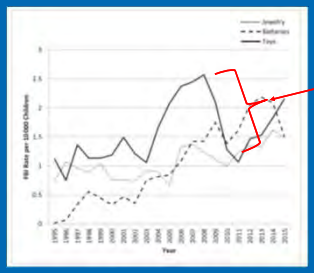


Orsagh-Yentil, D et al. *Pediatrics*. 2019.

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.**

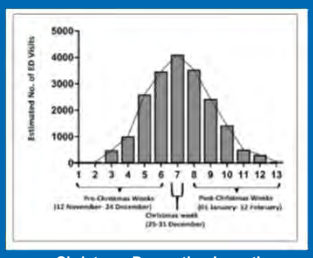
Orsagh-Yentil, D et al. *Pediatrics*. 2019.



Consumer Product Safety improvement Act
- Mandated screw closure for batteries.
- Banned small toys representing choke hazards

Orsagh-Yentil, D et al. *Pediatrics*. 2019.

When to Not be On-Call



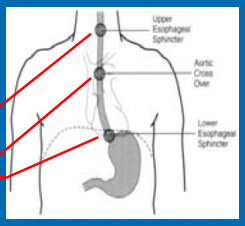
Christmas Decoration Ingestions

Reeves et al. *Clinical Pediatrics*.2019.

Anatomy of Esophageal FB

Key Anatomic Locations For Impaction

- 60%: UES
- 10%: Aortic Arch
- 30%: LES



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

Miller RS et al. *Int J Pediatr Otorhinolaryngol*. 2004.

Timing of Endoscopic Intervention

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

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

Grasping Forceps

Multi-Prong Forceps

Coin Grasper

Rubber-Tipped Forceps

Polyp Snare

Roth Net

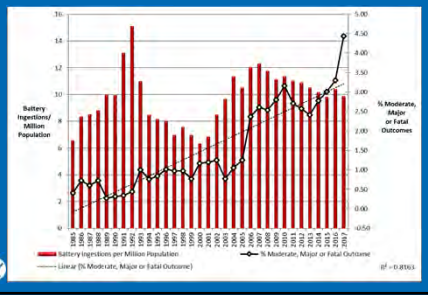
Wire Basket

Foreign Body Hood

Endoscopy Caps

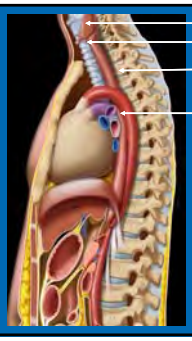
Overtube

Button Batteries



Source:
National Capital Poison Center
www.poison.org

Button Batteries – Structures at Risk



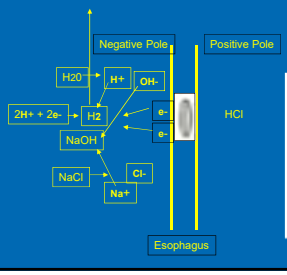
Vocal Cord Paralysis
Tracheo-Esophageal Fistula
Discitis
Aorto-esophageal fistula
Esophageal perforation
Esophageal stricture
Pneumothorax

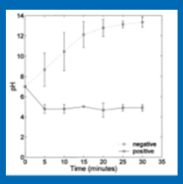
Source: Personal files

Button Battery Management – Murky Areas

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

Mechanism of Battery Injury



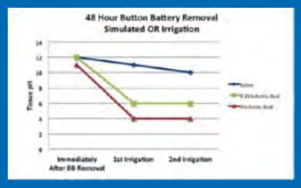


Geddes LA et al. *J Clin Monit* 2004.

Mitigation Strategies

Jatana KR et al. *Laryngoscope*. 2016.

Mitigation Strategies

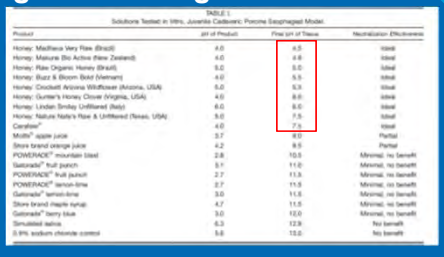


Jatana KR et al. *Laryngoscope*. 2016.

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

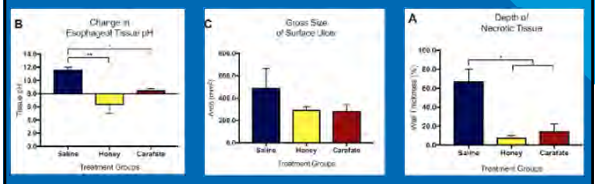
Jatana KR et al. *Laryngoscope*. 2019.

Mitigation Strategies



Anfang RR et al. *Laryngoscope*. 2018.

Mitigation Strategies



Live piglet model – Button Battery in place x 60 mins

Anfang RR et al. *Laryngoscope*. 2018.

Our Expert

https://i.pinimg.com/originals/b1/c9/99/b1c999a1b3a893949849 1ce1cf989dc3.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?

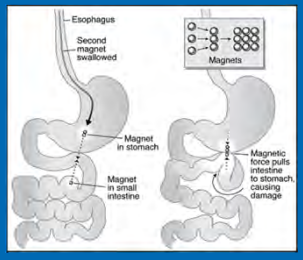
Source: Personal Files

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**

https://www.texaschildrens.org/blog/2012/08/small-magnets-causing-serious-injuries-death-children

Rare Earth Magnets

Consumer Product Safety Commission Intervention

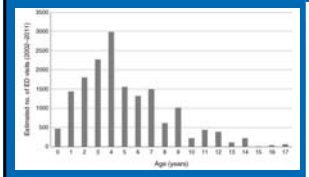


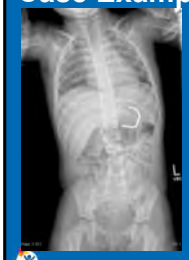
FIGURE 1. National estimated number of pediatric magnet ingestion emergency department visits in the United States from 2002 to 2015.

Abbas M et al. *JPGN.* 2013.
Reeves PT et al. *JPGN.* 2018.

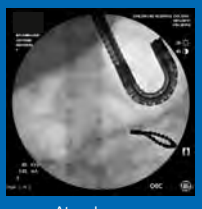
Rare Earth Magnets - Approach

- 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.

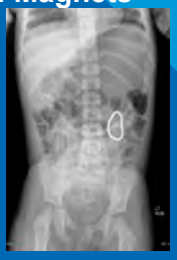
Case Example – Rare Earth Magnets



At presentation



At endoscopy

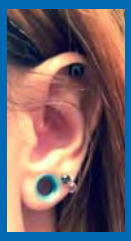


Next day

Case Example – Rare Earth Magnets

Small Bowel Enteroscopy with Magnet Removal

An Emerging Hazard



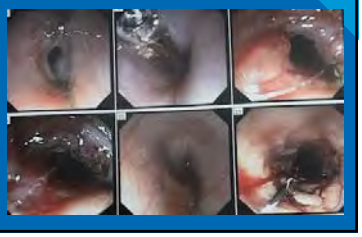
https://www.pinterest.com/pin/440086194817808305/

https://www.soscene.com/large-lip-silicone-ear-gauges/

Gauge Earrings

9 month old with recurrent croup-like presentation.

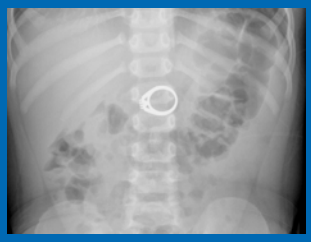
- Repeat x-rays did not show a radio-opaque FB



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, serial x-rays 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)

Epidemiology

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

Banc-Husu et al. JPGN. 2016.

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

Thomson et al. J Peds Surg. 2016.

How about available training?

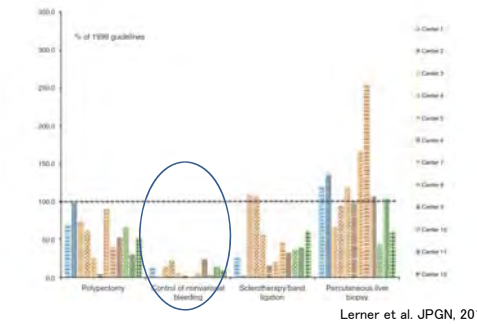
Challenges in Meeting Fellowship Procedural Guidelines in Pediatric Therapeutic Endoscopy and Liver Biopsy

Diana G. Lerner, MD,[1] Li, MD,[1] Petar Mamula, MD,[2] Douglas S. Fishman, MD,[3] Robert Kramer, MD,[4] Liver Gastroenterology Khalil El-Chammas, MD,[5] Scott P. Pentiuk, MD,[6] Robert Rothbaum, MD,[7] Bhaskar Gurram, MD,[8] Riad M. Rahhal, MD,[9] Praveen S. Goday, MD,[10] and Bernadette Viola, MD[11]

- 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?



Lerner et al. JPGN, 2014.

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

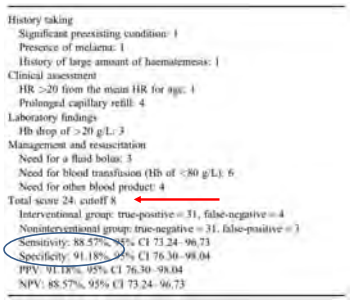
How does one predict who will need an endoscopy?

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

Thomson et al. JPGN, 2015.

Sheffield scoring system


History taking
Significant preexisting condition: 1
Presence of melaena: 1
History of large amount of haematemesis: 1
Clinical assessment
HR >20 from the mean HR for age: 1
Prolonged capillary refill: 4
Laboratory findings
Hb drop of >20 g/L: 3
Management and resuscitation
Need for a fluid bolus: 3
Need for blood transfusion (Hb of <80 g/L): 6
Need for other blood product: 4
Total score 24: cutoff 8
Interventional group: true-positive = 31, false-negative = 4
Noninterventional group: true-negative = 31, false-positive = 3
Sensitivity: 88.57%, 95% CI 73.24–96.73
Specificity: 91.18%, 95% CI 76.30–98.04
PPV: 91.18%, 95% CI 76.30–98.04
NPV: 88.57%, 95% CI 73.24–96.73

Thomson et al. JPGN, 2015.

Who will need therapy during endoscopy?

Forrest classification

Forrest Classification		
Stage	**Characteristics**	**Re-bleeding**
Ia	Spurting Bleed	60 - 100 %
Ib	Oozing Bleed	50%
IIa	Non-Bleeding Visible Vessel	40 - 50 %
IIb	Adherent Clot	20 - 30 %
IIc	Flat Spot in ulcer crater	7 - 10 %
III	Clean Base Ulcer	3 -5 %

Alzoubaidi et al. BMJ, 2018.

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

Injection therapy (video)

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

Gralnek et al. Endoscopy, 2016.

Thermal Therapy- Coaptive Coagulation (video)

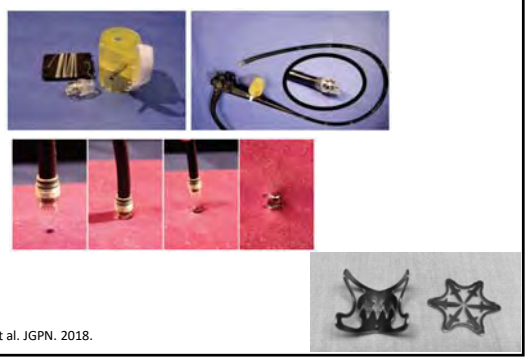
Hemoclips
Active bleeding (video)

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)



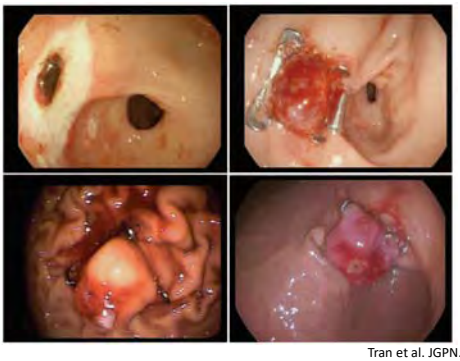
Tran et al. JGPN. 2018.

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.

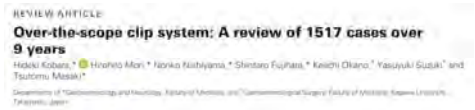
OTSC



Tran et al. JGPN. 2018.

OTSC (video)

OTSC


REVIEW ARTICLE

Over-the-scope clip system: A review of 1517 cases over 9 years

Hideki Kobara,* Hirohito Mori,* Noriko Nishiyama,* Shintaro Fujihara,* Keiichi Okano,† Yasuyuki Suzuki‡ and Tsutomu Masaki*

- Literature search between 2010 and 2018 with 1,517 cases identified
- 559 cases for bleeding with 85% clinical success rate

Kobara et al. J Gastro Hepatol, 2019.

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

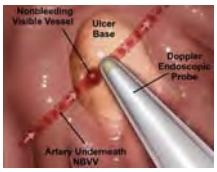
Polysaccharide hemostatic powder

- 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



Jensen et al. Gastro, 2017.

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)

Jensen et al. Gastro, 2017.

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 (Adenoca)
- 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

SEER-NCI 2017

CRC Screening
2016 USPSTF Recommendations

Test	Interval if negative
Stool-based tests	
1. Fecal Immunochemical test (FIT)	Annual
2. FIT-Stool DNA	1 or 3 years
Structural Exam of Colon	
1. Colonoscopy	10 years
2. Flexible Sigmoidoscopy (FS)	5 years
	10 years if combined with FIT
3. CT colonography (CTC)	5 years

* United States Preventive Services Task Force

JSPSTF 2016, JAMA 2016

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

JSPSTF 2016, JAMA 2016

CRC Screening Modalities

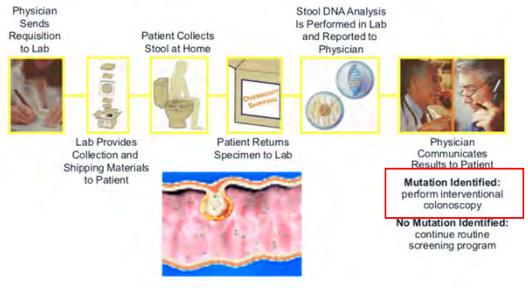
- Colonoscopy
- FOBT
- Fecal Immunochemical Testing (FIT): measures hemoglobin in the stool
  - Suggested q yr
  - Data suggests reduction in mortality from CRC (dependent of f/u)
  - Pooled sensitivity: 79%, Specificity: 94%
- Multitarget stool DNA tests (Cologuard)
  - Suggested q 3yrs
  - Comprehensive 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:

TEST	Sensitivity	Specificity
FIT	74%	95%
MT-sDNA	92%	85%

Imperiale TF et al., NEJM 2014

Lee JK et al., Ann Intern Med 2014

Novel CRC Screening Tools



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. (2004-13)
  - 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

Clarke WT et al, WJG 2019

IBD and Surveillance

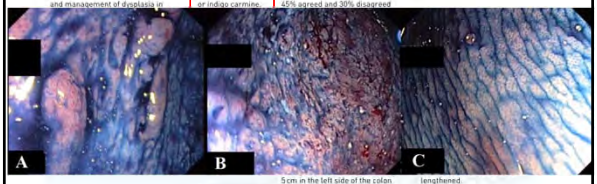
Table 1 Societal recommendations for colorectal cancer surveillance

Society	Surveillance intervals		
ACG (UC) 2019[24]	**Every 1-3 yr** UC of any extent beyond the rectum **Adjust intervals** Based on previous colonoscopies and combined risk factors: Duration of disease, younger age at diagnosis, greater extent of inflammation, first-degree relative with CRC		**Every year** PSC
AGA 2010[25]	**Every 1-2 yr** Extensive or left sided colitis **Every 1-3 yr** After two negative exams	**More frequent surveillance** Ongoing endoscopic or histologic inflammation or History CRC in first degree relative or Anatomic abnormality (*i.e.*, foreshortened colon, stricture or inflammatory pseudopolyps	**Every year** PSC
ASGE 2015[26]	**Beyond every 3 yr** Endoscopically and histologically normal on two or more surveillance colonoscopies	**Every 1-3 yr** Average risk	**Every year** PSC or Active inflammation or History of dysplasia or History CRC in first degree relative or Anatomic abnormality i.e., stricture, multiple pseudopolyps

Clarke WT et al, WJG 2019

IBD and Endoscopic Surveillance Techniques

ASGE & AGA – SCENIC international consensus statement on surveillance and management of dysplasia in	Chromoendoscopy with methylene blue or indigo carmine	No consensus regarding random biopsies 45% agreed and 30% disagreed	N/A



	5 cm in the left side of the colon	lengthened.
If chromoendoscopy is not available or if the yield of chromoendoscopy is reduced	Random biopsies plus targeted biopsies of any suspicious appearing lesions	

Clarke WT et al, WJG 2019

Hereditary Cancers
Bridging Pediatric to Adult GI Care

Common Hereditary Cancer Syndromes, Features and Associated Genes

BREAST CANCER SYNDROMES	CANCERS/FEATURES	GENE(S)
Hereditary Breast and Ovarian Cancer	Breast, ovarian, male breast, prostate, melanoma, pancreatic	*BRCA1, BRCA2*
Cowden Syndrome	Breast, thyroid, uterine, colon, renal	*PTEN*
Li-Fraumeni Syndrome	Breast, sarcoma, brain, adrenal cortical	*Tp53*
Diffuse Gastric Cancer	Lobular breast, diffuse gastric	*CDH1*
COLON CANCER SYNDROMES	**CANCERS/FEATURES**	**GENE(S)**
Lynch Syndrome	Colon, uterine, ovarian, gastric, ureter, kidney, hepatobiliary, duodenal	*MLH1, MSH2, MSH6, PMS2,EPCAM*
Familial Adenomatous Polyposis	Colon, >100 polyps, thyroid	*APC*
Attenuated Familial Adenomatous Polyposis	Colon, 10-100 polyps	*APC*
MYH-Associated Polyposis	Colon, up to 500 polyps	*MUTYH*
Juvenile Polyposis	Colon, hamartomatous polyps	*SMAD4, BMPR1A*
Juvenile Polyposis/Hereditary Hemorrhagic Telangectasia	Colon, hamartomatous polyps, HHT symptoms	*SMAD4*
Peutz-Jeghers Syndrome	Colon, testicular, breast, uterine	*STK11*

Polyposis and Cancer Risk

Hamartomatous	Peutz–Jeghers syndrome (PJS)	*STK11/LKB1*	80 % – 94 %	1 in 250 000	**1** ≥ 2 histologically confirmed Peutz–Jeghers polyps **2** any number of Peutz–Jeghers polyps in an individual with a positive family history of PJS **3** presence of characteristic mucocutaneous pigmentations in an individual with a positive family history of PJS **4** any number of Peutz–Jeghers polyps in an individual with characteristic mucocutaneous pigmentation	15 % – 57 %	[7 – 9, 27]
	Juvenile polyposis syndrome (JPS)	*SMAD4, BMPR1A*	40 % – 60 %	1 – 1.6 in 100 000	**1** ≥ 5 juvenile polyps are present in the colon/rectum or in other parts of the gastrointestinal tract **2** any number of juvenile polyps in a patient with one or more relatives affected with JPS	39 % – 68 %	[10 – 13]
Serrated	Serrated polyposis syndrome (SPS)	No germline mutation identified	NA	31 – 80 in 10 000 in FIT screening 42 in 10 000 in colonoscopy screening	**1** ≥ 5 serrated polyps proximal to the sigmoid with ≥ 2 being > 10 mm **2** > 20 serrated polyps of any size distributed throughout the colon	15 % – 30 %	[14 – 22]

FIT, fecal immunochemical test; NA, not applicable.

Polyposis and Endoscopic Surveillance

► **Table 2** Summary table of colonoscopy surveillance statements.

Polyposis syndrome	Starting age	Surveillance interval	Treatment indication
(Attenuated) familial adenomatous polyposis	12–14 years	Every 1–2 years	Pre- and post-colectomy: remove all polyps > 5 mm
MUTYH-associated polyposis	18 years	Every 1–2 years	Pre- and post-colectomy: remove all polyps > 5 mm
Peutz–Jeghers syndrome	Baseline: 8 years Routine: 18 years	Baseline: if polyps found, every 1–3 years Routine: every 1–3 years	Elective polypectomy
Juvenile polyposis syndrome	12–15 years	Every 1–3 years	Elective polypectomy for polyps > 10 mm
Serrated polyposis syndrome	NA	1 year: after ≥ 1 advanced polyp or ≥ 5 non-advanced clinically relevant polyps 2 years: after no advanced polyps or < 5 non-advanced clinically relevant polyps	Clearing/surveillance phase: remove all polyps ≥ 5 mm and all polyps of any size with optical suspicion of dysplasia

NA, not applicable.

Van Leerdam M et. Al, Endoscopy 2019

Evolution of Barrett's

Squamous esophagus

Chronic inflammation

Barrett's metaplasia

Low-grade dysplasia

High-grade dysplasia

Invasive Adenocarcinoma

Injury
Acid & bile reflux
nitrous oxide

Genetics
Gender, race,
? other factors (cox-2)

Accumulate Genetic Changes

ACG/FGS Annual Spring Symposium

Current Standards for Barrett's Diagnostics

Visible BE on EGD — Where does screening fit?

HD/WLE — Optical Chromo? NBI/BLI/FICE

Targeted sampling of Visible lesions — What is a visible lesion?

Seattle Protocol Sampling — Does this really make sense?

Pathology Interpretation — How can we overcome IOV?

Diagnosis — Should we feel confident in this?

Dysplastic BE → EET

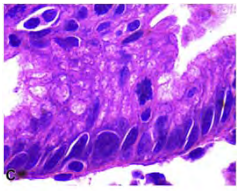
NDBE → Surveillance — Can we risk stratify and eradicate? When can we stop?

Imaging and Barrett's Esophagus

- Surface Imaging
  - HD-WLE
  - Chromoendoscopy
  - Virtual Chromoendoscopy (NBI, FICE, iScan)
  - Magnification Endoscopy (Zoom, Near focus)
  - Endocytoscopy (methylene blue, crystal violet)
  - Autofluorescence Imaging (AFI)
- Subsurface Imaging
  - EUS
  - Confocal Endomicroscopy
  - Optical Coherence Tomography
  - Molecular Markers (WATS^{3D})

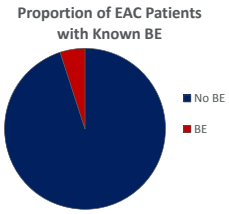
Beyond Seattle Protocol
The Next Generation of Tissue Sampling in BE

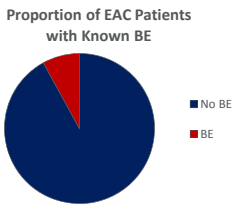
- RCT of 16 centers of 160 patients to WATS then biopsy vs. Biopsy then WATS
- The addition of WATS to biopsy sampling yielded an additional 23 cases of HGD/EAC (14% increase)
- Of these 23, biopsies showed NDBE (n=11), LGD or IFD (n=12)
- Mean time of WATS procedure 4.5 min



Vennalaganti P et al., GIE 2018

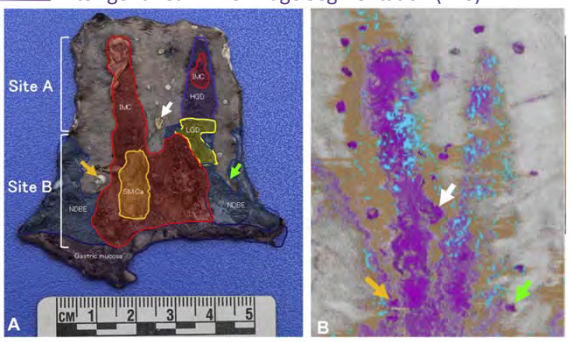
You cannot cure a disease we cannot find…





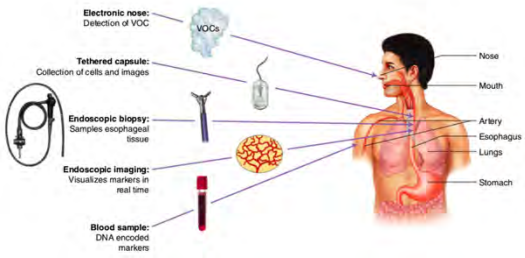
Dulai GS, Gastroenterology 2002.
Cooper GS, GIE, 2009.
Bhatt SK, Gut, 2015.

VLE (The beginnings of AI)
Intelligent Real-Time Image Segmentation (IRIS)



Katada C et al, VideoGIE 2019

Barrett's Screening



Konda V and Souza R, Digestive Dis and Sci 2018

Pancreatic Cancer

- Risk factors
  - Smoking
  - Diabetes
  - Chronic Pancreatitis
  - Hereditary pancreatic cancer syndromes
  - Familial pancreatic cancer (FPC)

Gangi A et al, Pancreas 2018

Pancreatic Cancer Screening
Risk of Susceptibility Genes

High-risk patient population	Mutation	Risk for developing PDAC
Hereditary breast and ovarian cancer	BRCA1 BRCA2 PALB2	HR 2.55 (95% CI, 1.03-5.31)[14] HR 2.13-4.1[10,13,14] Increased[17]
Peutz-Jeghers syndrome	STK11	SIR 132 (95% CI, 44-261)[24]
Ataxia telangiectasia	ATM	RR 2.41 (95% CI, 0.34-1.71)[8]
Familial atypical multiple mole and melanoma syndrome	CDKN2A	SIR 13-38[31]
Lynch syndrome	MLH1 MSH2 MSH6 PMS2	HR 7.5 (95% CI, 2.4-23.0)[43] HR 10.9 (95% CI, 5.5-21.9)[43] NA NA
Hereditary pancreatitis	PRSS1 SPINK1	SIR 53 (95% CI, 23-105)[34]

Lo, W et al., J Surg Onc 2019

Pancreas Screening Studies

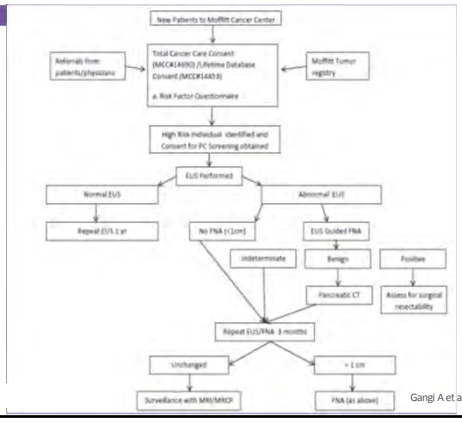
- 12 studies from 2002-12
- Diagnostic yield -precancerous changes or pancreatic cancer range from 1.3%-43%
  - Largest US study was the CAPS 3 study that enrolled 225 high-risk patients – CT/MRI/EUS
    - 84 cysts ,3 Neuroendocrine tumors and 5 with dilated PD in 91 patients (42%)
    - No adenocarcinomas
    - 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

Who to screen*	When to screen	How to screen
Familial pancreatic cancer[a]	Start 10 y before youngest PDAC patient was diagnosed	Endoscopic ultrasound (EUS) MRCP
Genetic predisposition syndromes include: • Hereditary breast and ovarian cancer • Peutz-Jeghers syndrome • Ataxia telangiectasia • Familial atypical multiple mole and melanoma syndrome • Lynch syndrome	Start at age 30	• Normal pancreas → annual surveillance • Nonsuspicious cyst → q6-12 months • Solid lesions → q3 months • Main pancreatic duct stricture → q3 months Worrisome features present[b] → q3 months Stop screening based on medical status, life expectancy
Hereditary pancreatitis	Start at age 40	
Known mutation carriers with 1+ affected first-degree relatives	Start at age 45-50	

Lo, W et al., J Surg Onc 2019

High-Risk Pancreas Screening program



Gangi A et al, Pancreas 2018

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

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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

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

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

The Banana Babies

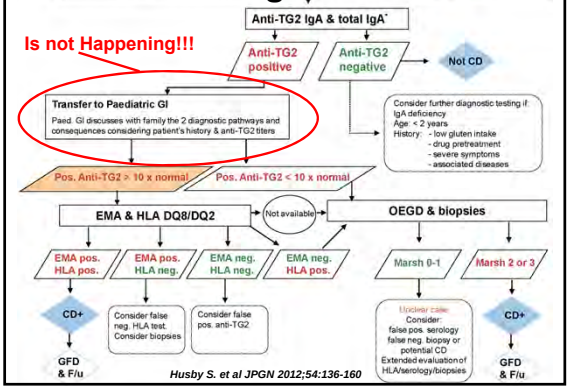
WK Dicke, 1905 - 1962

1st case of CD at UMB: 1938

Celiac Disease as a Unique Model of Autoimmunity

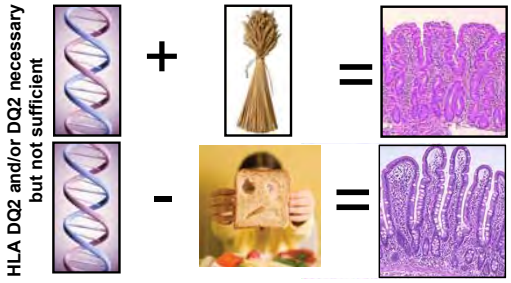
- **The only autoimmune disease in which specific MHC class II HLA (DQ2 and/or DQ8) are present in >95% of patients;**
- **The auto-antigen (tissue Transglutaminase) is known;**
- **The environmental trigger (gluten) is known;**
- **Elimination of the environmental trigger leads to a complete resolution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

Revised Diagnostic Criteria



Husby S. et al JPGN 2012;54:136-160

Paradigm Of Celiac Disease Pathogenesis And Management



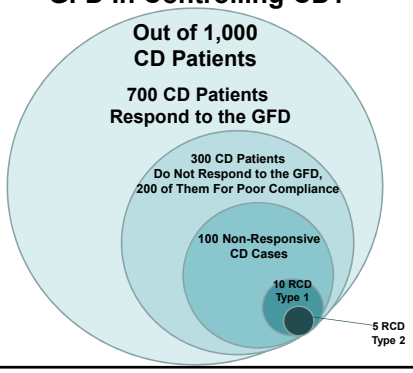
Necessary and Sufficient

Current Management: Follow Up

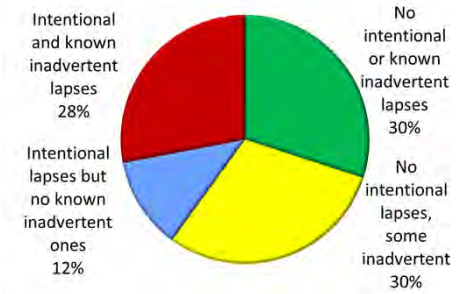
- Follow up 6 months after diagnosis to check:
  - Symptoms;
  - Serology (not validated for monitoring but recommended by current guidelines);
  - Compliance/difficulties with the implementation of the GFD;
  - Check for Hep B Ab;
  - Check thyroid function (T4 and TSH);
  - If problems, follow up in 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?



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



Reported intentional and inadvertent gluten consumption (n=269)

Hall NJ, et al Survey Appetite 68:56-62, 2013

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

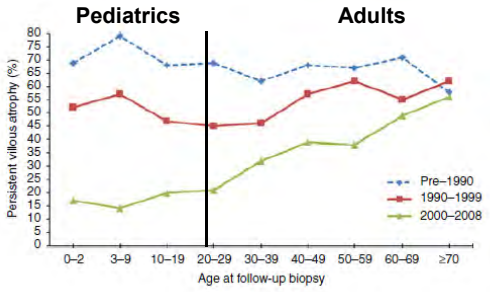
- **Birthday parties**
- **School lunch**
- **Sleepovers**
- **Peer pressure**
- **Lack of appreciation for long term consequences for specific behavior;**
- **Transitioning to college lifestyle**

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

Bannister, *AM J Gastro*, 2014.
Vecsei, *BMC Gastro*, 2014.
Ghazzawi, *JPGN*, 2014.
Leonard, *JPGN*, 2017.
Rubio-Tapa, *AM J Gastro*, 2010
Lebowohl, *APāT*, 2013
Mahadev, *APāT*,2017

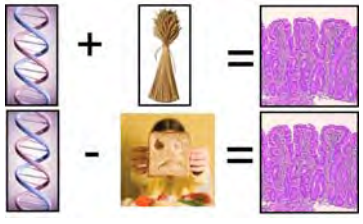
Age and Persistent Villous Atrophy



Aliment Pharmacol Ther. 2014;39:488-95.

Factors Not Correlated with Persistent Villous Atrophy:

- **Adults:**
  - Symptoms
  - Celiac Serology
- **Children**
  - Symptoms
  - Celiac Serology



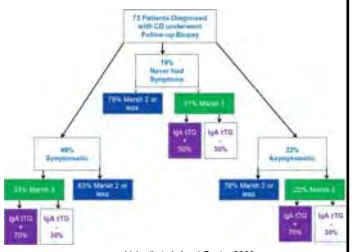
Troncone, *JPGN*, 1995
Vahedi, *Am J Gastro*, 2003
Mahadev, *APāT*, 2017
Leonard, *JPGN*, 2017
Silvester, *Gastro*, 2017

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



Vehadi et al. Am J Gastro 2003.
Hopper et al. Clin Gastroenterol Hepatol 2008
Leonard et al, *JPGN*, 2017

Serology Tests Are Accurate At Diagnosis But Not Follow-Up

Table 1. Serum Tests for the Diagnosis of Celiac Disease.[a]

Test	Sensitivity (Range)	Specificity (Range)	Comments
	percent		
IgA anti-tTG antibodies	>95.0 (73.9–100)	>95.0 (77.8–100)	Recommended as first-level screening test

TABLE 3. Test performance of immunoglobulin A tissue transglutaminase in predicting marsh 3 histology at repeat biopsy

Group	N	Se	Sp	PPV	NPV	Accuracy
Overall	71	0.43	0.68	0.25	0.83	0.63

Fasano et al, *NEJM*, 2012
Leonard et al, *JPGN*, 2017

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 

Lebowohl, *APT*, 2013
Mahadev, *APT*, 2017

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*

McGowan, *Pediatrics*, 2009.
Troncone, *JPGN*, 1995
Vahedi, *Am J Gastro*, 2003
Mahadev, *AP&T*, 2017
Leonard, *JPGN*, 2017
Silvester, *Gastro*, 2017

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

Choung, *Gastro*, 2017
Canavan, *AP&T*.2011
Godfrey, *Gastro*, 2010.
Lebwohl, *Ann Intern Med*, 2013.
Rubio-Tapa, *Am J Gastro*, 2009.
Cosnes, *Clin Gastro & Hep*, 2008.
Rubio-Tapa, *Clin Gastro & Hep*, 2011

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.

McGowan, *Pediatrics*, 2009.

Controversy and Mucosal Recovery #3: Why Diagnose Persistent Villous Atrophy If There Are No Treatment Options?

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

Currently Available Treatment Options

- Gluten Contamination Elimination Diet
- Budesonide

Possible Future Treatment Options

- Polymeric Binder
- Enzymes
- Zonulin Inhibitor
- Induction of Tolerance

Shah, *Am J Gastro*, 2014.
Branchi, *Digestion*, 2016.
Tomal, *Minerva Gastro*, 2016.
Hollon, *BMC Gastro*, 2013.
Castillo, Elsevier,2016.

Alternative/Integrative Approaches To The Gluten Free Diet

Prevention

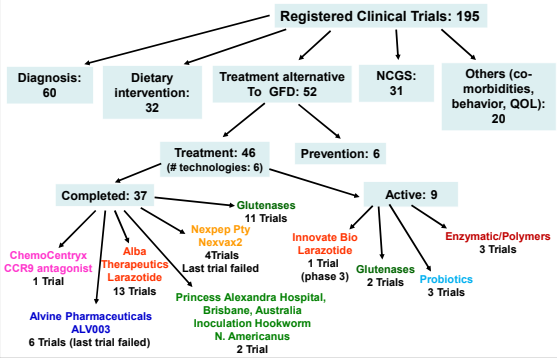
- **Primary Prevention** (Microbiome Modification)

Alternative Treatments

- **Development of genetically modified grains**
- **Inhibitors of tissue transglutaminase**
- **Cytokines and/or cytokine receptors inhibitors**
- **Detoxification 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)



Primary Prevention

Celiac **D**isease **G**enomic **E**nvironmental **M**icrobiome and **M**etabolomic Study

www.CDGEMM.org

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 confermatory 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

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NIH DK048373
NIH DK104344
NIH U19AI082655

Thrasher Research Fund

Mead Johnson Nutrition

Nutrition Obesity Research Center at Harvard

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 :

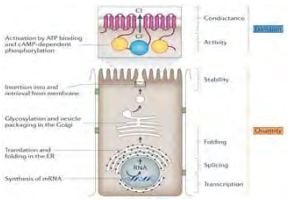
- Describe the state of Cystic Fibrosis (CF) disease in 2019
- Diagnose and manage Exocrine Pancreatic Insufficiency in patients with CF
- Understand the spectrum of liver disease in CF
- Recognize other common gastrointestinal manifestations of CF including Gastroesophageal Reflux (GERD), Distal Intestinal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

Genetic of Cystic Fibrosis

- Autosomal Recessive
- Located on chromosome 7

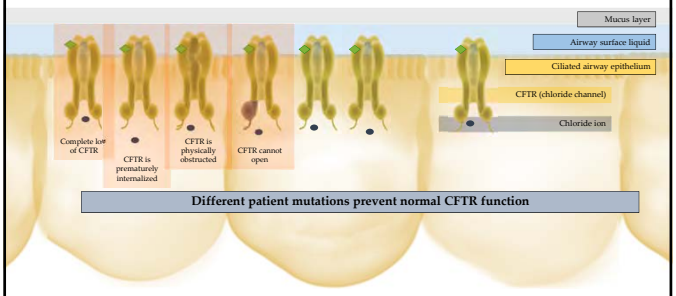
Affected populations	Risk of CF Mutation	Risk of child with CF
Caucasian	1 in 25	1 in 2,500
Ashkenazi Jewish	1 in 29	1 in 3,364
Hispanic	1 in 46	1 in 9,600
African-American	1 in 65	1 in 15,300
Asian e.g. Indonesian, Indian etc.	1 in 90	1 in 32,000

Cystic Fibrosis Transmembrane Regulator (CFTR)



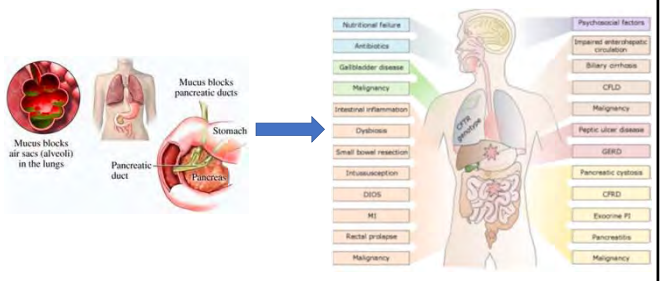
Nat Rev Genet 2015; 16:45-56

Loss of CFTR Function



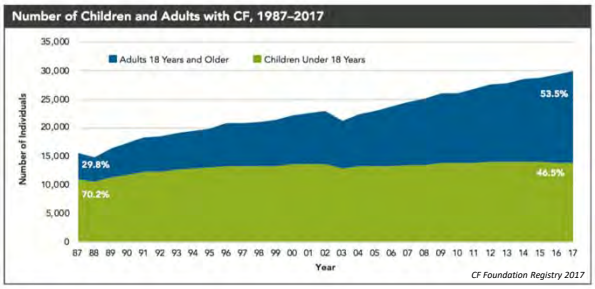
Courtesy of George Solomon MD at University of Alabama

Classic Clinical GI Manifestations of CF

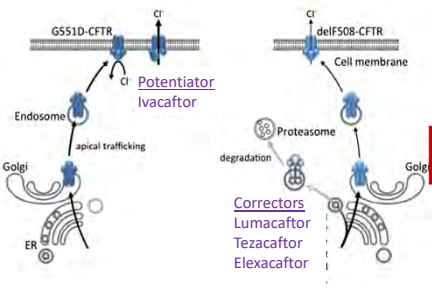


PLOS ONE. 2017;12(5): e0174463.

The Evolution of CF Care and Survival



Modulators



Ivacaftor – gating mutations

Ivacaftor + Lumacaftor = F508x2

Ivacaftor + Tezacaftor =
F508 x2
F508 heterozygotes

Ivacafator + Tezacaftor + Elexacaftor =
F508 x2
F508 + minimal function

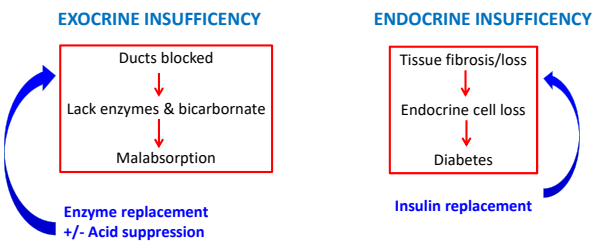
Highly Effective Modulator Treatment

Frontiers in Pharm. 2019; 10(215):1-21.

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 (CFF, Johns Hopkins, Sick Kids)

Pancreatic Insufficiency



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 from porcine pancreas (pancrealipase)
  - 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

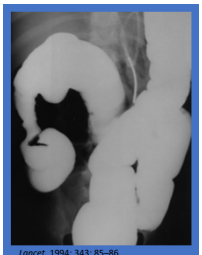
All enzymes were required to be FDA approved between 2009-2012

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

CFF Consensus Guidelines for PERT Dosing

Lipase units/kg/meal	Lipase units/kg/g of fat eaten
<4 years of age: 1000-2500 lipase units/kg/meal ½ for snack	Infants on breast milk or formula: 2000-4000 lipase units/120 ml
>4 years of age: 500-2500 lipase units/kg/meal ½ for snack	Beyond infancy: 500-4000 lipase units/g of fat

Adapted from CF Foundation Census Guidelines 1995.



Lancet. 1994; 343: 85–86.

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

Do Modulators Eliminate Need For PERT?

CAUTION

- 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.
  - Rosenfeld 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

Rule of thumb: Check FE before stopping PERT

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

J Pediatr 2018;201:229-37.e4.
Ital J Pediatr 2017;43(1).
Lancet Respir Med 2018;6(7):545-53.

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
Stellate cell activation
Steatosis

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

JCF. 2017;16: S50-61. and Liver Disease in Pediatrics, 4th edition.

The New Kids on the Block for Diagnosis of CFLD

BIOCHEMICAL MARKERS

- Asparate Aminotransferase-to-Platelet Ratio Index (APRI) Hepatology 2015;62:1576 – 83.
- Persistently elevated GGT JPGN. 2015;61: 113–8.
- Decreasing platelet count
- Investigational: microRNAs and biomarkers of intestinal bile salt absorption JPGN 2015;60:247 – 54. and JCF 2015;14:169 – 77.

IMAGING

- Heterogeneous increased liver echogenicity at ultrasound JCF. 2008;7:215 – 21. and J Pediatr. 2015;167(4):862–868.e2.
- Fibroscan JPGN. 2017;64(4):505-511.
- Liver Elastography
  - Ultrasound
  - Magnetic Resonance

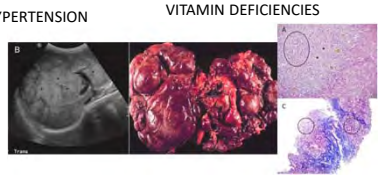
Complications of CFLD

PORTAL HYPERTENSION

WORSE FAT-SOLUBLE VITAMIN DEFICIENCIES

HYPERSPLENISM (THROMBOCYTOPENIA)

DECLINE IN LUNG FUNCTION



SPLENOMEGALY

MALNUTRITION

VARCIES – GI BLEEDING

PORTOPULMONARY HYPERTENSION

ASCITES

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 transjuglar 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

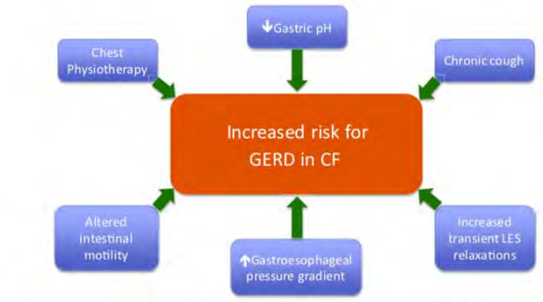
- Liver enzymes are evaluated at baseline
- Every 3 months for the 1st
- Then annually

SPECIAL CIRCUMSTANCE

- Use with caution in patients with pre-existing liver disease, especially cirrhosis
- Stop if ALT >5 times ULN (use lower ALT if bilirubin is also elevated)
- Use caution to resume use of drug – consider starting ½ 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

Vertex modulator package inserts for ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor

GERD

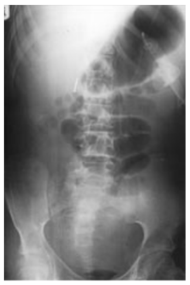


Pediatr Clin N Am. 2016;63:679–698.

Diagnostic Considerations & Treatment Options

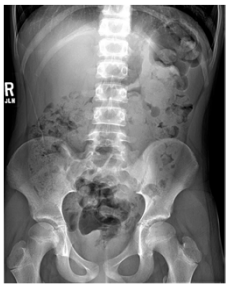
- Clinical symptoms vs pulmonary exacerbations due to presence of Enteric flora on CF culture
- Acidity
  - Empiric Treatment vs pH probe or impedance study
  - Histamine blockers, Proton pump inhibitors
- Motility
  - Gastric emptying scan
  - Azithromycin (often drug of choice due to Pseudomonas treatment), Erythromycin, Metoclopramide, Bethanechol
- Surgical options
  - Reserved for medical management failure: Nissen fundoplication

DIOS



Gut 2002;51:285–286.

Constipation



Management of DIOS

For partial obstruction:

- Polyethylene glycol – clean out
- Gastrografin
  - *Hyperosmolar solution via enema refluxing into terminal ileum (TI)
  - *Surgical consult
  - *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
- Intussception
- Crohn's disease
- Adhesions
- Volvulus
- Fibrosing colonopathy
- **Malignancy**
- *Anastomotic stricture (previous history of meconium ileus or DIOS surgery)*

JCF. 2011;10(2):S24-8.

Management of Constipation

- Adequate PERT
- Hydration
- Stool softners
  - Juice
  - Polyeythelene 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

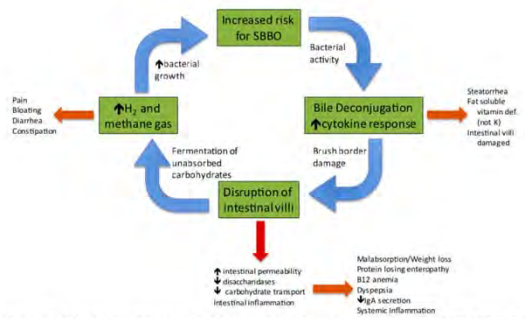
- F508 x2 or severe functional mutation
- Male
- >30 years of age
- Lung transplantation

Other contributing factors

- Inflammatory
  - Intestinal microbiome
  - Disease influence
  - Antibiotic influence
- Non-inflammatory
  - Inestinal 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?

JCF. 2017;16:S40-9.

SBBO



Pediatr Clin N Am. 2016; 63:679–698.

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-trimethroprim
- Amoxicillin/clavulanate

Pediatr Clin N Am. 2016;63:679–698.

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 *Thorax* 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

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Children's Hospital of Los Angeles
10/17/2019

Disclosure

- Rebiotix: Medical Scientific Advisory
- NIH

Objective

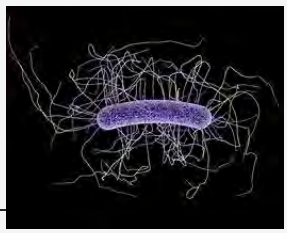
- Update on clostridium difficile epidemiology
- Update on the management of clostridium difficile infections
- Update on the role of fecal microbial transplant and its safety

Outline

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

Introduction: Epidemiology

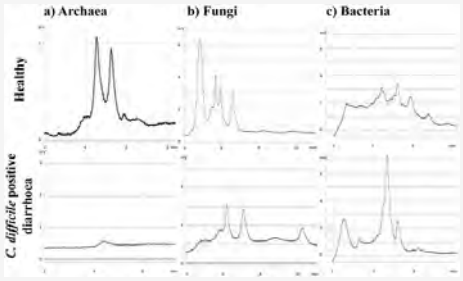
Spore-forming Gram-positive anaerobe



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

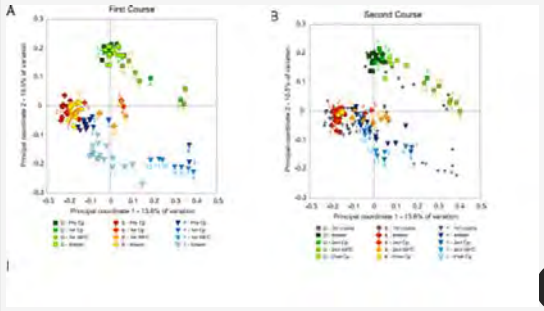
Gut Microbial changes in Clostridium Difficile



Skraban J et al: (2013) Gut Microbiota Patterns Associated with Colonization of Different Clostridium difficile Ribotypes. PLoS ONE 8(2): e58005. doi:10.1371

PLOS | ONE

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



Dethlefsen L , and Relman D A PNAS 2011;108:4554-4561

Epidemiology

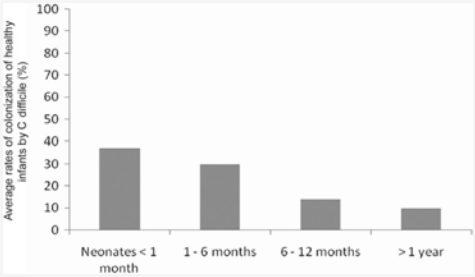
- A large multicenter study of hospitalized patients at 22 children's hospitals in the US
- near doubling in the incidence of *C. difficile* infection (CDI) between 2001 and 2006.
- Although classically identified as a healthcare-associated infection, 70-80% of pediatric cases of CDI identified as community-associated.
- https://www.ncbi.nlm.nih.gov/pubmed/24590748

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.

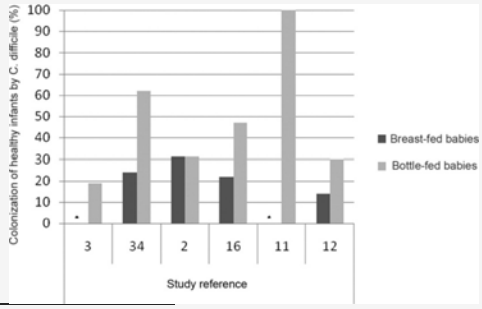
Best EL, J Hosp infection 2012

Colonization in infants

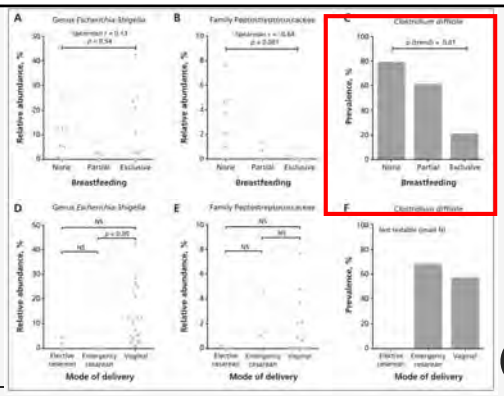


Jangi S, JPGN 2010

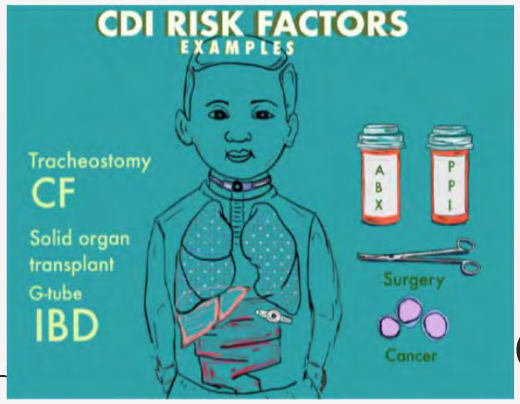
Colonization in infants



Jangi S, JPGN 2010



Child Study-Canada



NASPGHAN Clinical report, JPGN

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

- Toxogenic 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/BI/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.

IDSA April 2018

Testing

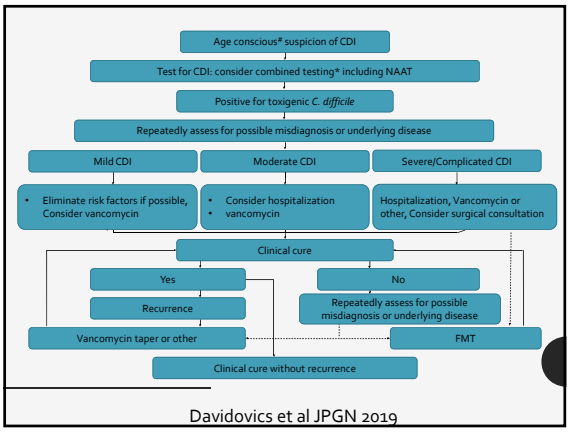
- Recommend only in symptomatic (>3BM)
- IDSA suggest one strategy to optimize toxin assay sensitivity: a two-step method: Glutamate Dehydrogenase (GDH; highly sensitive for *C. difficile* but does not distinguish toxigenic from non-toxigenic *C. difficile*), and if positive, follow-up testing with either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

IDSA April 2018

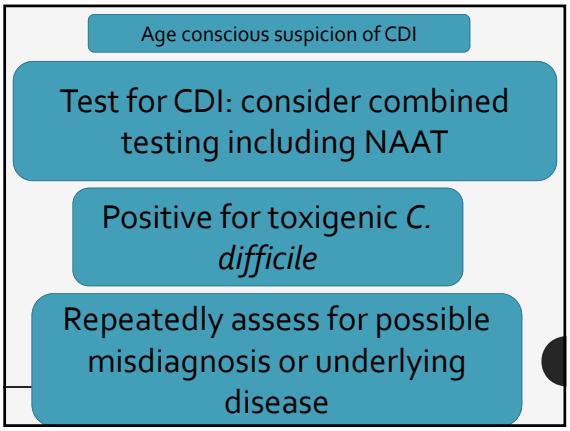
Testing

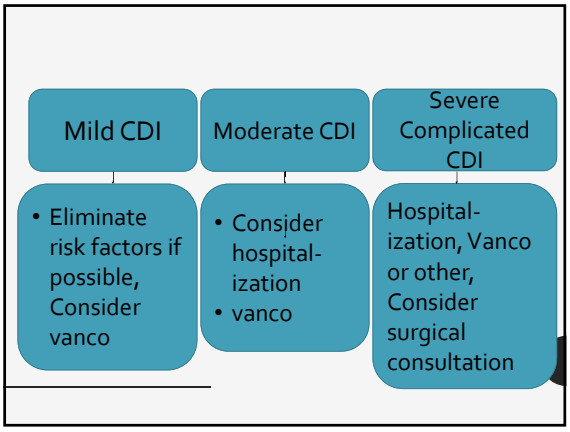
Test	Sens	Availability	Detection
NAAT	High	Available	Toxin gene detection
GDH	High	Available	Detection of common antigens toxigenic and non-toxigenic
EIA toxin A/B	Low	Available	Detection of free toxin
CCCNA or TC	High	Limited availability	Detection of free toxin and culture of a toxigenic *C. difficile* strain, respectively

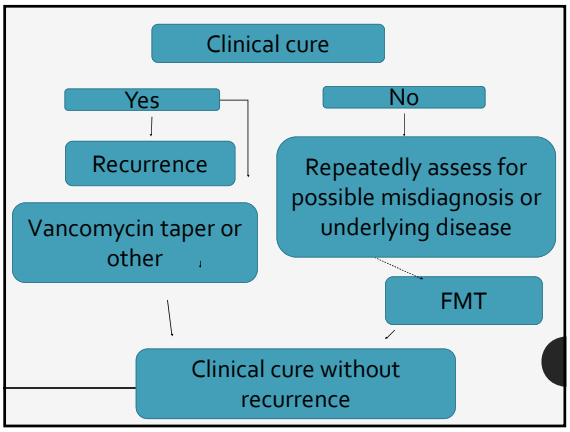
IDSA April 2018



Davidovics et al JPGN 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)*.

IDSA April 2018

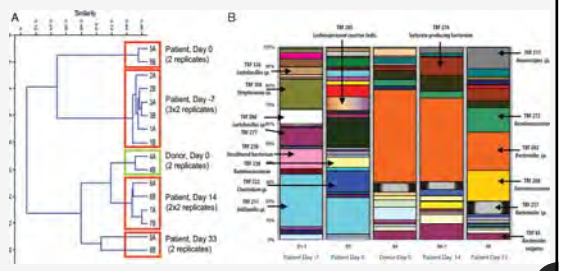
Recurrent CDI treatment (IDSA)

- 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)*.

IDSA April 2018

FMT

Clostridium Difficile



Khoruts et al. Journal of Clinical Gastroenterology. 44(5):354-360, May/June 2010.

Demographics	N=373[1]
Age, years	10.0 (3.0, 15.0)
Female sex	186 (49.9%)
Race	
White	332 (89.0%)
Black	15 (4.0%)
Asian	7 (1.9%)
American Indian	1 (0.3%)
Unknown	21 (5.6%)
Comorbidities	
Inflammatory Bowel Disease	120 (32.2%)
Crohn's disease	51 (13.7%)
Ulcerative colitis	63 (16.9%)
Indeterminate	6 (1.6%)
Presence of feeding tube	72 (19.3%)
Gastroesophageal reflux disease	36 (9.7%)
Short gut syndrome	10 (2.7%)
History of solid organ transplant	9 (2.4%)
Solid tumor malignancy	8 (2.1%)
History of stem cell transplant	6 (1.6%)
Hematologic malignancy	5 (1.3%)

Characteristics of children and young adults undergoing fecal microbiota transplantation (FMT) for *Clostridium difficile* infection. Nicholson et al. CGH J 2019

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]

Predictors[2]	Odds ratio (95% CI)	*P value*
Fresh (vs. frozen) donor stool	2.60 (1.37, 4.96)	0.004
Delivery by colonoscopy (vs. other)	3.34 (1.22, 4.48)	0.01
Feeding tube (vs. no feeding tube)	0.49 (0.25, 0.97)	0.04
No. of CDI episodes prior to FMT	0.83 (0.72, 0.96)	0.01

Nicholson et al. Clin Gastroenterol Hepatol. 2019 Apr 19: S1542-3565(19)30427-6

Characteristic	Overall (n = 137)	Non-RCDI (n = 113)	RCDI (n = 24)	*P* Value
Antibiotic use after last FMT	61/137 (45%)	43/113 (38%)	18/24 (75%)	.0009
Antibiotic after FMT				
Cephalosporin	18/61 (30%)	9/34 (21%)	9/9 (50%)	.03
Clindamycin	7/61 (11%)	6/43 (14%)	1/18 (6%)	.66
Fluoroquinolone	25/61 (41%)	15/43 (35%)	10/18 (56%)	.16
Penicillin	13/61 (21%)	9/34 (21%)	4/18 (30%)	1.00
Probiotic use after last FMT	61/137 (45%)	46/113 (41%)	15/24 (62%)	.05
Surgery	41/130 (32%)	29/108 (27%)	12/22 (55%)	.01
Hospitalization	54/131 (41%)	36/108 (33%)	18/23 (78%)	<.0001
New symptom/diagnosis	45/134 (34%)	38/73 (34%)	7/16 (30%)	.81
Improved symptoms/diagnosis	15/135 (11%)	13/111 (11%)	2/24 (8%)	1.00
Weight change, in pounds	5 (−5, 10)	5 (−3, 10)	0 (−9, 8)	.18

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 ›

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 ›

FDA safety warning

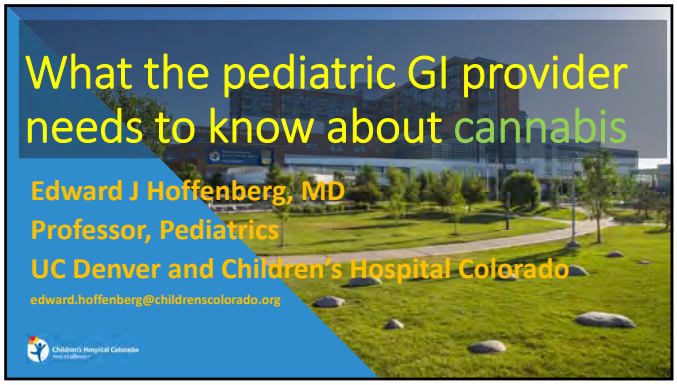
FMT donor stool testing must include MDRO testing should at minimum include extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, vancomycinresistant enterococci (VRE), carbapenem-resistant Enterobacteriaceae (CRE), and methicillin-resistant Staphylococcus aureus (MRSA).

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

What the pediatric GI provider needs to know about cannabis



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Disclosures

CDPHE grant on the benefits of marijuana for adolescents and young adults with IBD

COLORADO
Department of Public Health & Environment

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

Huestis MA Chem Biodivers 2007,4,1770

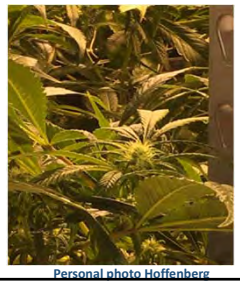
What is in MJ?

Buds, leaves, stems

> 100 known active ingredients

Including chemicals that activate CB1 and CB2 receptors

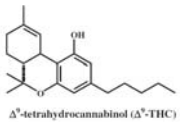
Many other unknown functions



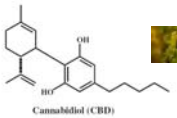
Personal photo Hoffenberg

DE GRUYTER

Mechanism: Cannabis – the Israeli perspective — 183



Δ^9-tetrahydrocannabinol (Δ^9-THC)



Cannabidiol (CBD)

Phytocannabinoids

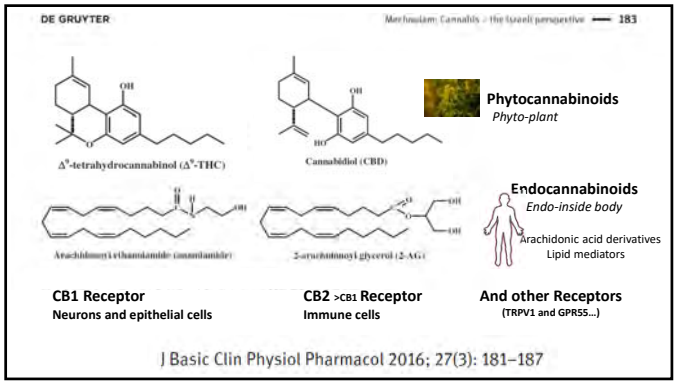
Phyto-plant

(Personal photo Hoffenberg)

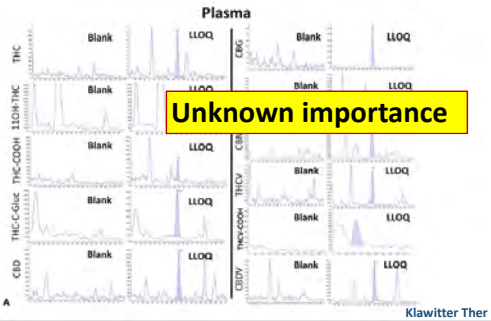
CB1 Receptor
Neurons and epithelial cells

CB2 >CB1 **Receptor**
Immune cells

J Basic Clin Physiol Pharmacol 2016; 27(3): 181–187

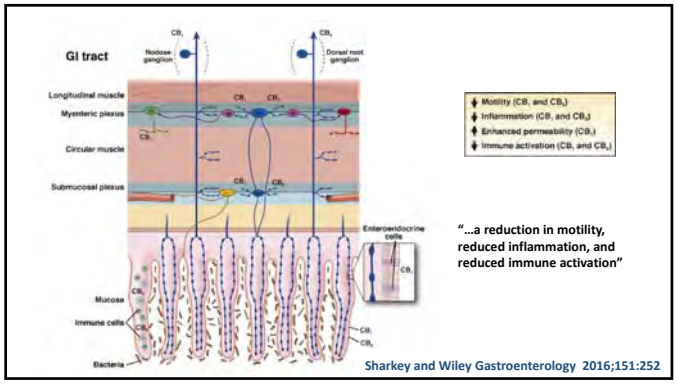


An Atmospheric Pressure Chemical Ionization MS/MS Assay Using Online Extraction for the Analysis of 11 Cannabinoids and Metabolites in Human Plasma and Urine



Unknown importance

Klawitter Ther Drug Monit 2017;39:556



"…a reduction in motility, reduced inflammation, and reduced immune activation"

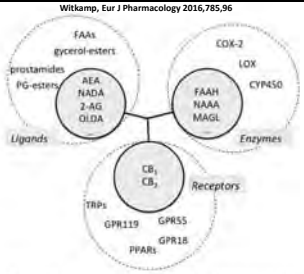
Sharkey and Wiley Gastroenterology 2016;151:252

Fine tune metabolic, physiologic processes
Potential benefit in chronic diseases

CB2R Q63R variant is a risk for celiac and IBD

Rossi Pharmacol Res 2012;66: 88– 94
Strisciuglio J Clin Gastroenterol 2018;52:e37-43

Witkamp, Eur J Pharmacology 2016,785,96



An expanding set of interactions between cannabinoid receptors, ligands, and enzymes

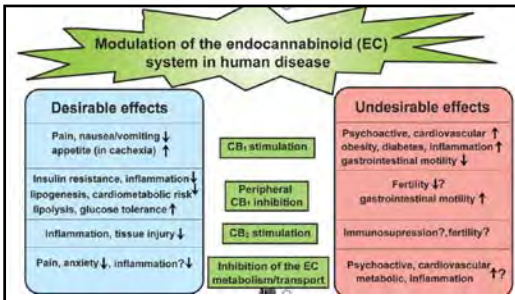


Fig. 1. Cannabinoid therapeutics: finding the right balance.

Pacher and Kunos, FEBS Journal, 2013,280,1918

Additional potential therapeutic areas

GVHD
Autism
Inflammation
Obesity/ metabolic syndrome
Diabetes
Cardiovascular
Liver
Cancer

What are cannabinoids effective for?

There are 3 FDA approved products

Marinol-capsule
epocrates

Syndros – liquid
Syndros.com

Cesamet
cvs.com

- Synthetic THC (Dronabinol, Nabilone)
  - Nausea and vomiting from cancer chemotherapy
  - Anorexia with weight loss from AIDS

Epidiolex
gwpharm.com

- CBD (plant based enriched in cannabidiol)
  - Severe childhood Seizures (Lennox Gastaut and Dravet syndromes)

Does not work through known cannabinoid receptors

Nabiximol (Sativex)

Cannabis.net

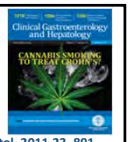
Oromucosal spray
- 1:1 CBD: THC + other cannabinoids + non cannabinoids
- 100 ul spray contains 2.5mg CBD and 2.7mg THC

Approved outside the US for spasticity associated with multiple sclerosis

canada.ca

europa.eu

Cannabis for IBD



- Pediatric data: efficacy data absent
- Adult data:
  - 3 observational studies, about 300 subjects
    - Reports of symptom relief — Lal, Eur J Gastroenterol Hepatol, 2011,23, 891; Ravikoff IBD, 2013, 19, 2809
    - Use > 6m associated with surgery — Storr IBD, 2014, 20, 472-80.
  - 1 trial of cannabis for Crohns: — Cannabis Induces a Clinical Response in Patients With Crohn's Disease: A Prospective Placebo-Controlled Study — Naftali CGH, 2013, 11,1276
    - ↑ appetite, ↓ pain, but no ↓ in inflammation measures.
  - 1 trial of CBD for UC: — Irving, IBD, 24,4, 714, 2018
    - less adherent and did not meet endpoint
  - 1 abstract of cannabis for UC — Naftali, DDW 2018
    - improved endoscopy score

TABLE 1. SUMMARY OF STUDIES ON MEDICINAL CANNABIS USE IN IBD

Year/Author[ref]	Country	Study Design	Cannabis Type	Patients	IBD Diagnosis	Outcomes
2011/Naftali[38]	Israel	Retrospective	[illegible] oral spray	84	CD	Subjective improvement in symptoms
2012/Lahat[42]	Israel	Observational cohort	Inhaled (3 inhalations as needed for pain)	13	11 CD, 2 UC	Improvements in health perception, ability to work, social activities, emotional stress,
2017/Naftali[39]	Israel	RCT	Oral	10 treatment, 10 placebo	CD	Improvement in CDAI (not significant)
2018/Irving	*UK*	*RCT*	*Oral CBD-rich*		*UC*	*AE in Tx group; no difference shown*
2018/Naftali	*Israel*	*RCT*	*Inhale cigarette bid*		*UC*	*Mayo score improved*

1-3 joints/d 0.5-3.5mg THC est

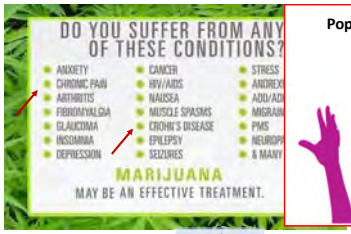
10mg CBD bid

~300 mg CBD

23 mg THC

Inflamm Bowel Dis • Volume 25, Number 3, March 2019

Limited data on potential benefits of cannabis for IBD



legalchemstore.com

Popular demand, not evidence-based

boazpartners.com

Norml.org
Procon.org

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

So what about our patients with IBD?

Personal photo Hoffenberg

Prevalence and Patterns of Marijuana Use in Young Adults With Inflammatory Bowel Disease

Phatak, Pashankar, JPGN, 2017,64,261

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

Marijuana Use by Adolescents and Young Adults with Inflammatory Bowel Disease

Hoffenberg, J Pediatr 2018;199:99

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

Marijuana Use by Adolescents and Young Adults with Inflammatory Bowel Disease

Hoffenberg, J Pediatr 2018;199:99

N = 30

- Self-administered multiple routes:

Products/routes of use	
Smoking	25 (83%)
Ingested as edible	15 (50%)
Dab	12 (40%)
Vape	9 (30%)
Oil	5 (17%)
Other	1 (3%)

Marijuana Use by Adolescents and Young Adults with Inflammatory Bowel Disease

Hoffenberg, J Pediatr 2018;199:99

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

Cannabis Oil Use by Adolescents and Young Adults With Inflammatory Bowel Disease
Hoffenberg, JPGN 2019;68: 348–352

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

Summary of Pediatric IBD Users

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

Perceive safety and some benefit → that is hard to measure

Variety of dosing strategies and amounts

IBD ~10%+ use ~daily **USA: ~ 3% daily use**

~15% past 30 day use

Healthy Kids Colorado Survey (HKCS)
Youth Risk Behavior Surveillance System (YRBSS)
Monitoring the Future 2018 8-10-12th graders

CBS.com

Freeworldmaps.net

Cloud9hemp.com

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

PDF
http://www.nap.edu/24625

amazon.com

valleyrecovery.com/addiction-consequences

Consequences of adolescent use

Impairments in

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

Cannabis Use Disorder DSM 5

DSM-5 SUD Diagnosis Reference Guide

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
Using despite physical or psychological **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	305.20 (F12.10)
✓Moderate	4-5 symptoms	304.30 (F12.20)
✓Severe	6+ symptoms	304.30 (F12.20)

The cannabis withdrawal syndrome: current insights, Bonnet, Preuss, Substance Abuse and Rehabilitation 2017,8,9

Cannabis withdrawal syndrome

Criteria (≥ 3 within 1 wk abrupt stop)

- Irritable
- Nervous/anxious
- Sleep diffic
- ↓ appetite
- Depressed mood
- Physical symptoms:
  - Abdominal pain (± Nausea/vomiting)
  - Shaking/tremors
  - Sweating
  - Fever
  - Chills
  - Headache

"Just Quit" may not work

GI Differential

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

The cannabis withdrawal syndrome: current insights, Bonnet, Preuss, Substance Abuse and Rehabilitation 2017,8,9

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

Cannabis hyperemesis syndrome

Freedomleaf.com

Diagnostic characteristic	GRADE rating
Severe cyclic vomiting usually accompanied by abdominal pain	Low
Symptom onset preceded by at least weekly cannabis use	Low
Temporary relief of symptoms with hot bathing	Low
Resolution of symptoms with cannabis cessation	Low
Supportive features: male gender, cannabis use onset in teenage years, symptom onset in third decade of life	Low

Sorensen Cannabinoid Hyperemesis Syndrome:
Diagnosis, Pathophysiology, and Treatment—a Systematic Review J. Med. Toxicol. (2017) 13:71–87

Cannabis hyperemesis syndrome

Freedomleaf.com

Diagnostic char	GRADE rating
Severe cyclic vo	Low
Symptom onset	Low
Temporary relief	Low
Resolution of sy	Low
Supportive featu years, sympto	Low

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

Sorensen Cannabinoid Hyperemesis Syndrome:
Diagnosis, Pathophysiology, and Treatment—a Systematic Review J. Med. Toxicol. (2017) 13:71–87

Cannabis Hyperemesis Treatment

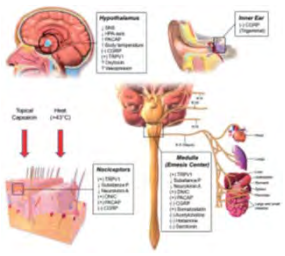
Low Quality of Evidence for any treatment

- Abstinence
- Dopamine antagonists
- Avoidance of opiates

Walgreens.com

- 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

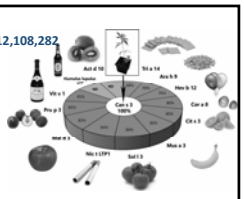
May work by counterbalancing effects of CB1, mechanism unclear

Richards et al Clinical Toxicology, 2018;56:15-24,

Cannabis sativa allergy: looking through the fog Allergy, 2016,72,201

Hypersensitivity reactions to marijuana Ann All Asthma & Immunol, 2012,108,282

Cannabis Allergy



Nationaljewish.org

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
Crossreact with other lipid transfer proteins LTPs
peach, tomato, latex

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

Ocampo and Rans, Ann Allergy Asthma Immunol 2015, 114, 187

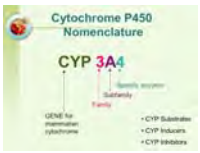
Cannabis Food Allergy (edibles)

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



slideplayer.com

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)

POLITICS · DENVER POLITICS

THE DENVER POST

Denver first in U.S. to decriminalize psychedelic mushrooms

Psilocybin possession would remain illegal but would become police's "lowest law-enforcement priority"

A woman harvests magic mushrooms in a grow room at the Procare farm in Hazerswoude, central Netherlands, Friday Aug. 3, 2007. Procare is the Netherlands' largest grower of hallucinatory mushrooms, supplying more than half the market, a legal business in The Netherlands as long as they are sold fresh. (AP Photo/Peter Dejong)

Diagnosing Children with Functional Abdominal Pain in 2019: How Much Testing is Enough?

Carlo Di Lorenzo, M.D
Twitter: @carlodilorenzo1

Nationwide Children's | The Ohio State University College of Medicine

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

Lane MM et al. Pediatrics 2009; 123: 758

- 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

A Million Dollar Workup for Abdominal Pain. Is It Worth It?

Dhroove G, Chogle A, Saps M. J Pediatr Gastroenterol Nutr. 2010;51:579-83

122 consecutive children with pain predominant FGID. Everyone had some test
34% 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

Kathleb Graham, Jaime Belkind-Gerson, Anil Darbari, and John T. Boyle

JPGN 2019;68: 806–810

NGM conditions	Very comfortable, %	Somewhat comfortable, %	Somewhat uncomfortable, %	Very uncomfortable, %
Functional disorders				
Aerophagia/gaseous abdominal distension	5	50	45	0
Functional dyspepsia	28.8	60	11.3	0
Rumination syndrome	16.3	61.3	20	2.5
Cyclic vomiting syndrome	30	52.5	16.3	1.3
Functional nausea/vomiting	22.5	44	20	2.5
Irritable bowel syndrome	37.5	48	10	1.3
Functional constipation	78.8	18.8	1.3	1.3
Functional diarrhea	40	42.5	15	2.5

Can Rome help?

Adolescent committee

Rome Criteria: Functional abdominal pain

Gastroenterology 2016;150:1456–1468

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 (eg, 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

Gastroenterology 2016;150:1456–1468

Diagnostic Criteria for Functional

How does this help the clinician?

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

Confession

I have had patients complaining to me that I missed:

- "Chronic appendicitis"
- C
- M
- "
- 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."

Hematochezia +
Anemia +
Weight loss

94% sensitivity to predict Crohn's disease

El-Chammas K, et al. J Pediatr 2013;162:783-7.

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

J Gen Intern Med. 2019 Jan;34(1):36-40

ORIGINAL RESEARCH

Eliciting the Patient's Agenda- Secondary Analysis of Recorded Clinical Encounters

Nayikky Singh Ospina, MD, MSc[1,2], Kari A. Phillips, MD[3], Rene Rodriguez-Gutierrez, MD, MSc[2,4,5]

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)

carefully to them contributes to patient-centered care. Yet, clinicians often fail to elicit the patient's agenda and, when they do, they interrupt the patient's discourse.

OBJECTIVE: We aimed to describe the extent to which patients' concerns are elicited across different clinical settings and how shared decision-making tools impact agenda elicitation.

DESIGN AND PARTICIPANTS: We performed a secondary analysis of a random sample of 112 clinical encounters recorded during trials testing the efficacy of shared

agenda; when they do, they interrupt patients sooner than previously reported. Physicians in specialty care elicited the patient's agenda less often compared to physicians in primary care. Failure to elicit the patient's agenda reduces the chance that clinicians will orient the priorities of a clinical encounter toward specific aspects that matter to each patient.

KEY WORDS: agenda setting; patient-centered care; patient-physician communication.

Communication study

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

Kelli J. Swayden [a], Karen K. Anderson [b], Lynne M. Connelly [c], Jennifer S. Moran [d], Joan K. McMahon [a], Paul M. Arnold [b,*]

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Patient Educ Couns. 2012;86:166-71.

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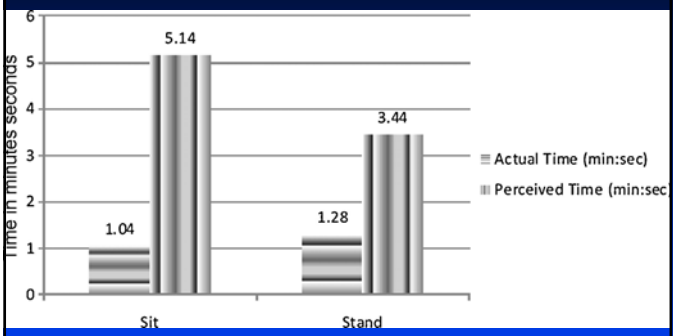
Physician behavior
Patient satisfaction
Patient care outcomes
Quality improvement

ABSTRACT

Objective: Patients commonly perceive that a provider has spent more time at their bedside when the provider sits rather than stands. This study provides empirical evidence for this perception.
Methods: We conducted a prospective, randomized, controlled study with 120 adult post-operative inpatients admitted for elective spine surgery. The actual lengths of the interactions were compared to patients' estimations of the time of those interactions.
Results: Patients perceived the provider as present at their bedside longer when he sat, even though the actual time the physician spent at the bedside did not change significantly whether he sat or stood. Patients with whom the physician sat reported a more positive interaction and a better understanding of their condition.
Conclusion: Simply sitting instead of standing at a patient's bedside can have a significant impact on patient satisfaction, patient compliance, and provider–patient rapport, all of which are known factors in decreased litigation, decreased lengths of stay, decreased costs, and improved clinical outcomes.
Practice implications: Any healthcare provider may have a positive effect on doctor–patient interaction by sitting as opposed to standing during a hospital follow-up visit.

Sitting vs standing



Swayden KJ, et al. Patient Educ Couns 2012;86:166-71.

Let's do some tests!

How can you tell it is functional?

Negative screening tests!

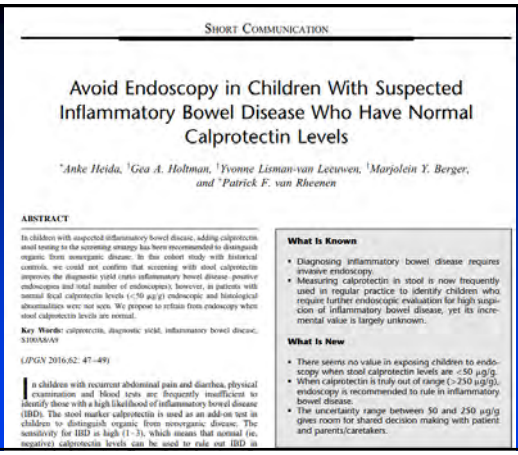
- CBC plus differential
  - Hb/MCV/eosinophilia
- ESR/CRP
- Celiac testing
- Chem profile
  - BUN/Cr/TP,A/LFT's
- Stool
  - heme test, O&P, fecal leukocytes, culture, H. Pylori Ag, calprotectin

What about KUB (constipation!) abdominal US, pH studies, EGD, UGI, HIDA scans, CT, and on and on and on….

Making a prompt diagnosis

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!



SHORT COMMUNICATION

Avoid Endoscopy in Children With Suspected Inflammatory Bowel Disease Who Have Normal Calprotectin Levels

Anke Heida, †Gea A. Holtman, †Yvonne Lisman-van Leeuwen, †Marjolein Y. Berger, and ‡Patrick F. van Rheenen

ABSTRACT

In children with suspected inflammatory bowel disease, adding calprotectin stool testing to the screening strategy has been recommended to distinguish organic from nonorganic disease. In this cohort study with historical controls, we could not confirm that screening with stool calprotectin improves the diagnostic yield (ratio inflammatory bowel disease–positive endoscopies and total number of endoscopies); however, in patients with normal fecal calprotectin levels (<50 μg/g) endoscopic and histological abnormalities were not seen. We propose to refrain from endoscopy when stool calprotectin levels are normal.

Key Words: calprotectin, diagnostic yield, inflammatory bowel disease, S100A8/A9

(*JPGN* 2016;62: 47–49)

In children with recurrent abdominal pain and diarrhea, physical examination and blood tests are frequently insufficient to identify those with a high likelihood of inflammatory bowel disease (IBD). The stool marker calprotectin is used as an add-on test in children to distinguish organic from nonorganic disease. The sensitivity for IBD is high (1–3), which means that normal (ie, negative) calprotectin levels can be used to rule out IBD in

What Is Known

- Diagnosing inflammatory bowel disease requires invasive endoscopy.
- Measuring calprotectin in stool is now frequently used in regular practice to identify children who require further endoscopic evaluation for high suspicion of inflammatory bowel disease, yet its incremental value is largely unknown.

What Is New

- There seems no value in exposing children to endoscopy when stool calprotectin levels are <50 μg/g.
- When calprotectin is truly out of range (>250 μg/g), endoscopy is recommended to rule in inflammatory bowel disease.
- The uncertainty range between 50 and 250 μg/g gives room for shared decision making with patient and parents/caretakers.

Original Investigation

Increased Prevalence of Celiac Disease Among Pediatric Patients With Irritable Bowel Syndrome

A 6-Year Prospective Cohort Study

Fernanda Cristofori, MD; Claudia Fontana, MD; Annamaria Magistà, MD; Teresa Capriati, MD; Flavia Indrio, MD; Stefania Castellaneta, MD; Luciano Cavallo, MD; Ruggiero Francavilla, MD, PhD

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

pISSN: 2234-8646 eISSN: 2234-8840
https://doi.org/10.5223/pghn.2018.21.4.264
Pediatr Gastroenterol Hepatol Nutr 2018 October 21(4):264-270

Original Article **PGHN**

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

Ivana Trivić* and Iva Hojsak*,†,‡

*Referral Centre for Pediatric Gastroenterology and Nutrition, Children's Hospital Zagreb, †School of Medicine, University of Zagreb, Zagreb, ‡School of Medicine, University J.J. Strossmayer of Osijek, Osijek, Croatia

Variable	Hazard ratio	95% confidence inverval
Sex (male as a reference)	1.628	0.912-2.908
Age at diagnosis	1.018	0.946-1.096
Functional diagnosis from the beginning	2.163	1.029-4.544

Binary logistic regression; corrected for diagnosis.

Endoscopy?

Ordering tests is like picking your nose

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

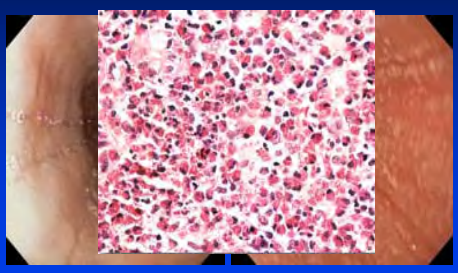
Making a diagnosis has side effects!

Endoscopy to reassure?

Bonilla S, Wang D, Saps M. Clin Pediatr (Phila). 2011;50:396-401

- 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



Clinical Study

Eosinophilic Esophagitis in Children and Adolescents with Abdominal Pain: Comparison with EoE-Dysphagia and Functional Abdominal Pain

Thirumazhisai Gunasekaran,[1] Gautham Prabhakar,[2] Alan Schwartz,[1] Kiranmai Gorla,[2] Sandeep Gupta,[4] and James Berman[3]

[1]*Advocate Children's Hospital, University of Illinois and Loyola Medical Center, 1775 Dempster Street, Park Ridge, IL 60068, USA*
[2]*Advocate Children's Hospital, 1775 Dempster Street, Park Ridge, IL 60068, USA*
[3]*University of Illinois, Chicago, IL 60607, USA*
[4]*University of Indiana, Indianapolis, IN 46202, USA*
[5]*Advocate Children's Hospital and Loyola Medical Center, 1775 Dempster Street, Park Ridge, IL 60068, USA*

Table 3: Symptom score change, dysphagia for EoE-D and abdominal pain for EoE-AP and FAP, baseline versus follow-up.

	EoE-D	EoE-AP	FAP	EoE-D versus EoE-AP (p)	EoE-AP versus FAP (p)
Total, number (%)	64	63	61		
Improved	55 (85.9)	19 (30.2)	49 (80.3)	<0.001	<0.001
Not improved	9 (14.1)	44 (69.8)	12 (19.7)		

EoE-D: baseline mean score = 1.5; sd = 0.69. Follow-up mean score = 0.6; sd = 0.53.
Mean difference is −0.89, which is significant ($p < 0.001$) by paired t-test.
EoE-AP group: baseline mean score = 1.2; sd = 0.43. Follow-up mean score = 1.4; sd = 0.77.
Mean difference is 0.29, which is not significant ($p = 0.25$) by paired t-test.

count fell from 38.5/34.6 (peak and mean) to 31.2/30.4 (p 0.70) and from 43.6/40.8 to 25.2/22.8 ($p < 0.001$), respectively. FAP-N patients had similar symptom improvement like EoE-D. *Cluster Analysis.* EoE-AP and FAP-N were similar in clinical features and response to treatment, but EoE-D was distinctly different from EoE-AP and FAP-N. *Conclusion.* Our study demonstrates that EoE-AP and EoE-D have different histology and outcomes. In addition, EoE-AP has clinical features similar to the FAP-N group.

The incidental H. Pylori

Spee LA, et al. Pediatrics 2010;125:e651-69

- **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?

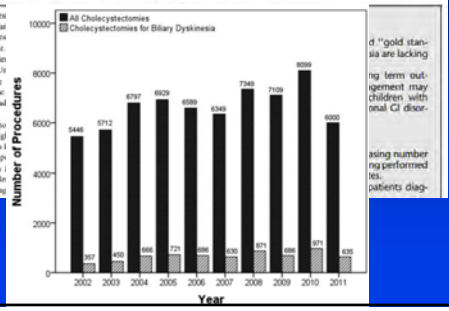
- **Biliary dyskinesia: "My aunt had exactly the same symptoms and a cholecystectomy cured her".**
- **Chronic appendicitis: Many case series in the surgical literature**
- **Abdominal wall pain: Elicit the Carnett sign**
- **Median arcuate ligament syndrome (MALS): Abdominal angina, MR angiography confirms it, rare in children**

Trends of Cholecystectomies for Presumed Biliary Dyskinesia in Children in the United States

*Sravan R. Matta, *Katja Kovacic, †Ke Yan, †Pippa Simpson, and *Manu R. Sood

JPGN 2018;66: 808–810

ABSTRACT



Gallbladder Ejection Fraction Is Unrelated to Gallbladder Pathology in Children and Adolescents

*Patrick M. Jones, †‖Marc B. Rosenman, *Marian D. Pfefferkorn, §Frederick J. Rescorla, and *†‖William E. Bennett Jr

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

Methods: We obtained records from all patients of 21 years and younger who underwent hepatic iminodiacetic acid (HIDA) testing within the Indiana Network for Patient Care from 2004 to 2013. GBEF results were obtained from radiology reports using data mining techniques. Age, sex, race, and insurance status were obtained for each patient. Any gallbladder pathology obtained subsequent to an HIDA scan was also obtained and parsed for mention of cholecystitis, cholelithiasis, or cholesterolosis. We performed

for gallbladder ejection fraction values >35%.
- Gallbladder ejection fraction did not correlate with underlying microscopic gallbladder pathology.
- This should cast some doubt on the importance of gallbladder ejection fraction when managing these difficult patients.

Abdominal wall pain

The Carnett's sign

http://doctorsgates.blogspot.com/2011/06/significance-of-carnetts-sign.html

Abdominal Wall Pain or Irritable Bowel Syndrome: Validation of a Pediatric Questionnaire

*Murid Siawash, †Tijmen van Assen, ‡Walther Tjon a Ten, *Loes Janssen, ‡Ernst van Heurn, *Rudi Roumen, and *Marc Scheltinga

J Pediatr Gastroenterol Nutr 2019 Sep;69:e65-e69

ABSTRACT

Objectives: A questionnaire study demonstrated that some adult patients who were diagnosed with irritable bowel syndrome (IBS) were in fact having an abdominal wall pain syndrome, such as anterior cutaneous nerve entrapment syndrome (ACNES). The aim of the present study was to investigate whether a pediatric version of this questionnaire could distinguish abdominal wall pain syndromes in children from chronic abdominal pain (CAP).

Methods: An 18-item questionnaire was tested in 3 groups of children with CAP: group 1, children who underwent surgery for ACNES (n = 42); group 2, children who were found to have ACNES after an outpatient analysis (n = 57); and group 3, children diagnosed with IBS (n = 53). Qualities including internal consistency (Cronbach α), cut-off points and a ROC-curve were calculated using standard statistical analysis.

Results: Questionnaire response rates in the three populations of CAP children ranged from 69% to 92%. When comparing ACNES and IBS groups, 17 of 18 questions were discriminative ($P < 0.01$, Cronbach α 0.74).

What Is Known

- Children with chronic abdominal pain are frequently diagnosed with irritable bowel syndrome.
- Up to 12% of children with irritable bowel syndrome may suffer from anterior cutaneous nerve entrapment syndrome.

What Is New

- A 17-item questionnaire can distinguish anterior cutaneous nerve entrapment syndrome from irritable bowel syndrome in pediatric populations with chronic abdominal pain.

Median Arcuate Ligament Syndrome (MALS)

Mak GZ, et al. J Pediatr Surg. 2013;48:2261-70

- 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


The End

Achalasia
2019

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

NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

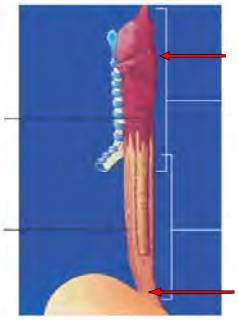
Financial disclosures: PJ Kahrilas 2019

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



18-22 cm long

Upper esophageal sphincter

Striated

Circular

Longitudinal

Smooth

Lower esophageal sphincter

EAP #2 v2/20/10 PJK

Neurogastroenterology & Motility

Neurogastroenterol Motil (2015) **27**, 160–174 doi: 10.1111/nmo.12477

The Chicago Classification of esophageal motility disorders, v3.0

P. J. KAHRILAS, A. J. BREDENOORD, M. FOX, C. P. GYAWALI, S. ROMAN, A. J. P. M. SMOUT, J. E. PANDOLFINO & INTERNATIONAL HIGH RESOLUTION MANOMETRY WORKING GROUP*

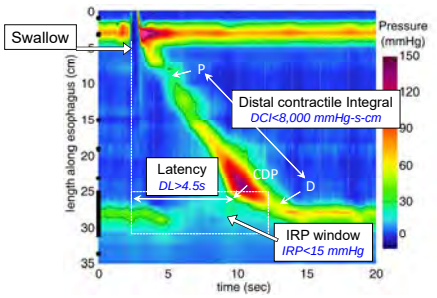
Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

EMD #68 v5/6/15 PJK

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

Normal Esophageal Motility

Pressure topography plot with key metrics



EPT #35 v7/10/13 PJK

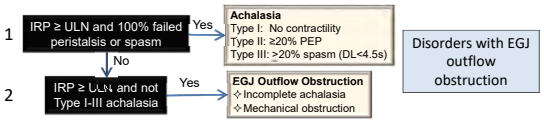
Interpreting Clinical EPT Studies

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

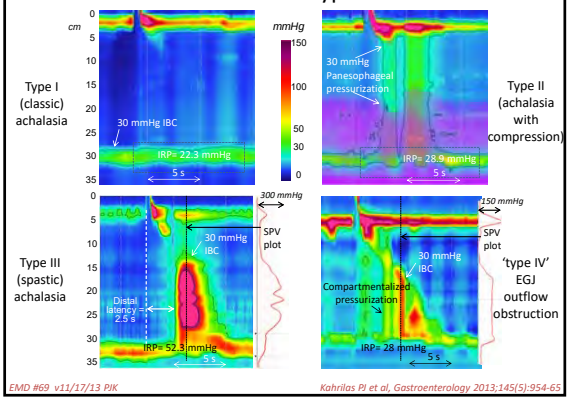
The Chicago Classification v3.0

Hierarchical analysis



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

Achalasia Subtypes



Kahrilas PJ et al, Gastroenterology 2013;145(5):954-65

Previously reported achalasia incidence and prevalence

City/Region	Time period	Incidence rate	Prevalence rate	Case inclusion
Korea[16]	2007–2011	0.39	6.29	ICD-10 code K22.0
Veneto, Italy[6]	2001–2005	1.59	Not reported	ICD-9-CM code 530.0 of hospital discharge data
Alberta, Canada[7]	1995–2008	1.63	10.82	ICD-9-CM code 530.0 and CCP procedure codes 54.92A (endoscopic balloon dilatation) and 54.6 (surgical esophagomyotomy)
Leicester, UK[17]	1986–2005	0.89	Not reported	Hospital discharge data; South Asian population only
Iceland[5]	1952–2002	0.55	8.7	ICD codes 530.0 and K22.0 Records were reviewed to excluded miscoded cases
Singapore[2]	1989–1996	0.3	1.8	Prospective study, identified new patients referred to motility laboratory of a single hospital
Edinburgh, UK[18]	1986–1991	0.8	Not reported	Prospective study, identified new patients referred for esophageal manometry at a single hospital
Zimbabwe[1]	1974–1983	0.03	Not reported	Review of hospital case notes and operation reports of all black patients with achalasia at 3 hospitals
Oxford, UK[19]	1974–1983	0.9 male/0.9 female	9.99	Computer-based records of hospital discharges
Scotland[19]	1974–1983	1.1 male/1.2 female	11.2	Computer-based records of hospital discharges
Nottingham, UK[20]	1966–1983	0.5	8.0	Computer-based classification of hospital discharges
Virginia, United States[3]	1975–1978	0.6	Not reported	Questionnaire surveying physicians in Virginia
Israel[8]	1973–1978	0.8	7.9–12.6	Screening all regional hospitals and departments of gastroenterology for a diagnosis of achalasia
Cardiff, UK[21]	1926–1977	0.4	Not reported	Records review of all resident patients in Cardiff
Rochester, United States[4]	1935–1964	0.6	Not reported	Records review of all resident patients in Rochester

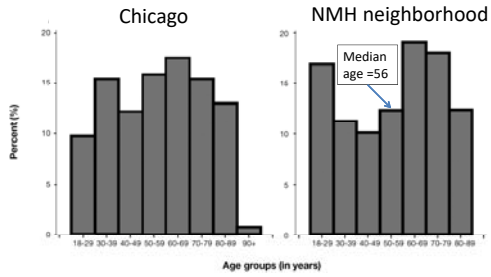
NOTE. Rates are per 100,000 persons per year.
CCP, Canadian Classification of Procedures; ICD, International Classification of Diseases.

EMD #90v1/16/17 PJK — Samo S, et al. Clin Gastroenterol and Hepatol 2017;15:366–373

Achalasia epidemiology in Chicago since the widespread use of HRM

EMD #86 v1/12/17 PJK — Samo S, et al. Clin Gastroenterol and Hepatol 2017;15:366–373

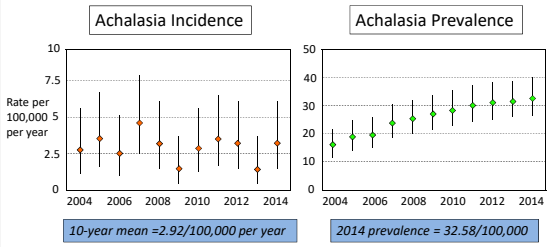
Age distribution of incident achalasia cases



EMD #87 v1/16/17 PJK — Samo S, et al. Clin Gastroenterol and Hepatol 2017;15:366–373

Estimated prevalence of achalasia in the era of HRM

Based on the assumption that we manage all cases!

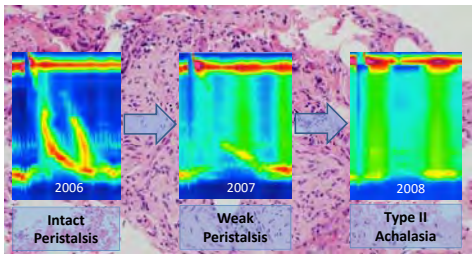


EMD #91 v1/18/17 PJK

Samo S, et al. Clin Gastroenterol and Hepatol 2017;15:366–373

Evolution of achalasia over a 2-year period,

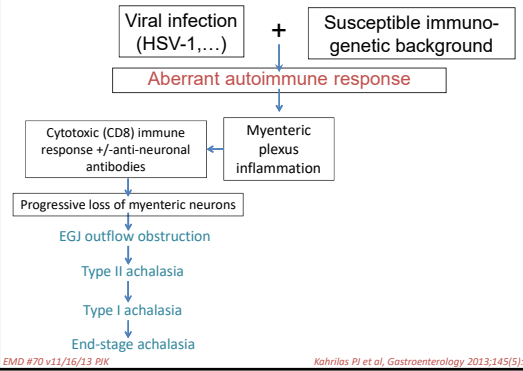
Myenteric plexus inflammation at LES



Finally treated with laparoscopic Heller myotomy

EMD #60 v5/6/15 PJK

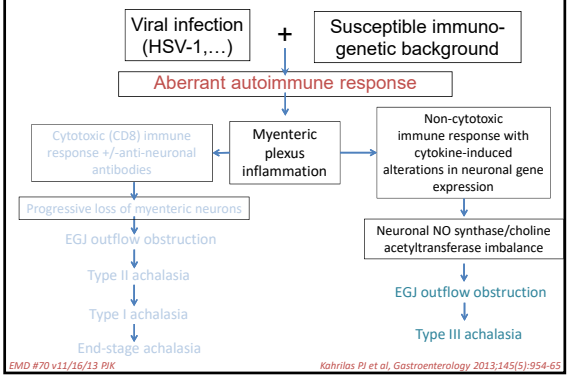
Proposed scheme of achalasia pathogenesis



EMD #70 v11/16/13 PJK

Kahrilas PJ et al, Gastroenterology 2013;145(5):954-65

Proposed scheme of achalasia pathogenesis



EMD #70 v11/16/13 PJK

Kahrilas PJ et al, Gastroenterology 2013;145(5):954-65

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

EMD #12 v4/4/11 PJK

Clinical scoring system for achalasia (Eckardt score)

Table 1 | Clinical scoring system for achalasia (Eckardt score)

Score	Symptom			
	Weight loss (kg)	Dysphagia	Retrosternal pain	Regurgitation
0	None	None	None	None
1	<5	Occasional	Occasional	Occasional
2	5–10	Daily	Daily	Daily
3	>10	Each meal	Each meal	Each meal

nature REVIEWS GASTROENTEROLOGY & HEPATOLOGY

EMD #82 v8/27/19 PJK

Eckardt, A. J. et al. Nat Rev Gastroenterol Hepatol doi:10.1038/nrgastro.2011.68

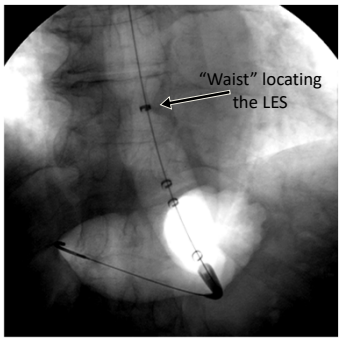
Pneumatic Dilators used for Treating Achalasia

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

EMD #8 v2/20/10 PJK

Microvasive™ Pneumatic Dilation

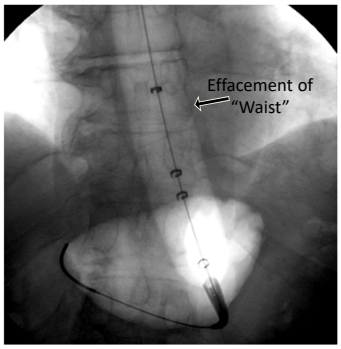
35 mm dilator



EMD #9b v2/20/10 PJK

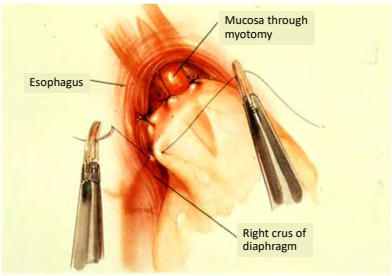
Microvasive™ Pneumatic Dilation

35 mm dilator



EMD #9c v2/20/10 PJK

Laparoscopic Heller Myotomy with Dor Fundoplication



Peters & DeMeester
Minimally Invasive Surgery of the Foregut 1994

EMD #10 v2/20/10 PJK

Success rates of pneumatic dilation and laparoscopic Heller myotomy

The European Achalasia Trial, 2 year results

	Heller myotomy *(n=106)*	Pneumatic dilation *(n=95)*
Successful, ES<3 (%)	90%	86%
Eckardt score	1.1 ± 0.1	1.3 ± 0.1
LES pressure (mmHg)	14 ± 1	12 ± 1
Timed barium swallow (cm)	3.4 ± 0.6	4.8 ± 0.7

- *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*

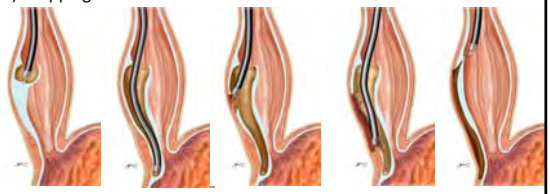
Boeckxstaens GE, et al. NEJM 2011:364:1807-1816

EMD #43 v1/25/13 PJK

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

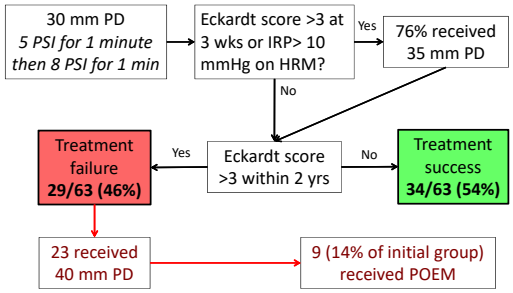


Courtesy of H. Inoue

EMD #35f v4/2/14 PJK

Pneumatic dilation outcome in the POEMA trial

RCT comparing PD to POEM in 1° achalasia



EMD #100 v6/21/19 PJK

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

Wide variability in PD efficacy among trials

Tradeoffs of risk, benefit, and willingness for repetition

	European RCT *LHM vs PD*	POEMA RCT *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%

Which is acceptable in your practice??

EMD #106 v1/16/19 PJK

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

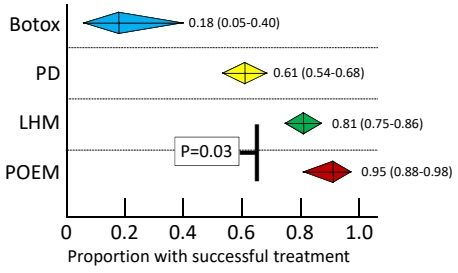
- Studies utilizing Botox, pneumatic dilation, LHM,POEM
- Patients grouped according to Chicago classification
- 20 studies (1575 patients) included

EMD #127 v4/24/19 PJK

Andolfi C & Fiscichella PM. Br J Surg 2019;106:332

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

Type I achalasia totals (random effects)

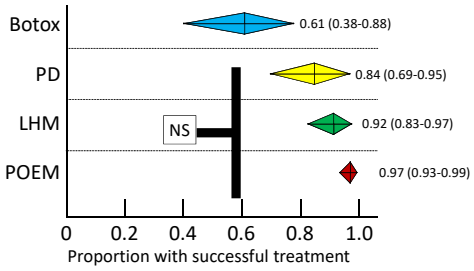


EMD #128 v4/24/19 PJK

Andolfi C & Fiscichella PM. Br J Surg 2019;106:332

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

Type II achalasia totals (random effects)

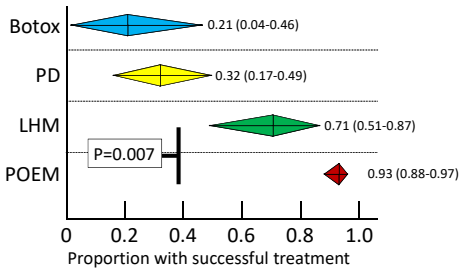


EMD #129 v4/24/19 PJK

Andolfi C & Fiscichella PM. Br J Surg 2019;106:332

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

Type III achalasia totals (random effects)



EMD #130 v4/24/19 PJK

Andolfi C & Fiscichella PM. Br J Surg 2019;106:332

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

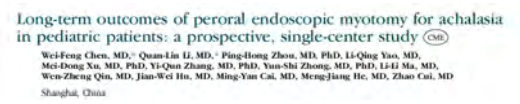
Commentary

- 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)*

EMD #131 v4/24/19 PJK *Andolfi C & Fiscichella PM. Br J Surg 2019;106:332*

POEM in pediatrics

Limited data: case reports and one uncontrolled series


Long-term outcomes of peroral endoscopic myotomy for achalasia in pediatric patients: a prospective, single-center study

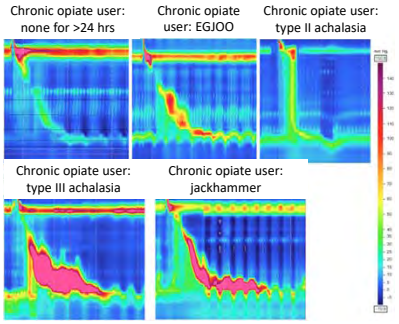
Wei-Feng Chen, MD,* Quan-Lin Li, MD,* Ping-Hong Zhou, MD, PhD, Li-Qing Yao, MD, Mei-Dong Xu, MD, PhD, Yi-Qun Zhang, MD, PhD, Yun-Shi Zhong, MD, PhD, Li-Li Ma, MD, Wen-Zheng Qin, MD, Jian-Wei Hu, MD, Ming-Yan Cai, MD, Meng-Jiang He, MD, Zhao Cui, MD

Shanghai, China

- 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

EMD #136 v8/28/19 PJK *Chen W-F, et al. Gastrointest Endosc 2015;81:91*

Opioid-Induced Esophageal Dysfunction



CCI #34 v7/21/10 PJK *Ratuapli SK, et al. Am J Gastroenterol 2015;110:979*

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*

Columbia University College of Physicians and Surgeons

NewYork-Presbyterian Kids Morgan Stanley Children's Hospital

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

COLUMBIA | Columbia University Children's Health

Columbia University Medical Center

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) of 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?

Classification	Distal esophageal acid exposure	Symptom correlation	Symptom response to PPI
Erosive esophagitis	Increased	(+)	Good
Barrett's esophagus	Increased	(+)	Good
NERD			
Acid reflux related	Increased	(+)	Good
Weakly acid related	Not increased	(+)	Moderate*
Nonacid related	Not increased	(+)	Poor*
Functional heartburn	Not increased	(−)	Poor

*Not well investigated.

Hershcovici T, et al. J Neurogastroenterol Motil 2010 Jan; 16(1): 8–21
Mahoney LB, et al. J Pediatr. 2017 Oct;189:86-91

PH-IMPEDANCE MONITORING (PH-MII)

- **Pediatric Indications:**
- Differentiate NERD, hypersensitive esophagus and functional heartburn 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)

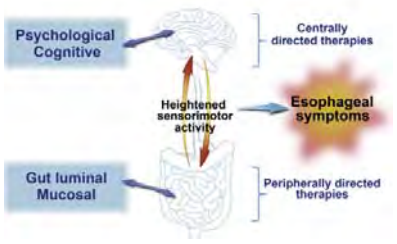
Rosen, R. J Pediatr Gastroenterol Nutr. 2018 Mar;66(3):516-554

PATHOPHYSIOLOGY OF NERD

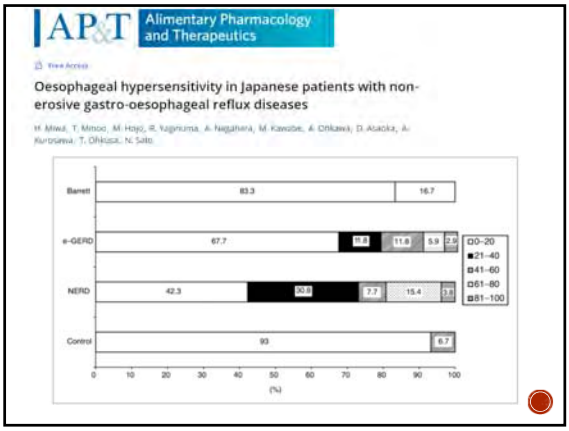
- Peripheral factors (luminal, mucosal, and sensory afferents) as well as central (psychological, stress, sleep, etc.)
- ?Role of microscopic esophagitis
- Proximal esophageal migration of a reflux event (acidic, weakly and nonacidic) has been shown to be an important predictor of symptom generation in NERD
- Higher prevalence of FGID—IBS, FD

Neurogastroenterol Motil. 2009;21:253-258
Gastroenterology, vol. 118, supplement 2, 2000, abstract A481

ROLE OF BRAIN-GUT-AXIS (BGA) IN MEDIATING ESOPHAGEAL SYMPTOMS IN NON-EROSIVE PHENOTYPES



Aziz Q, et al. Gastroenterology 2016;150:1368–1379



POPULATION BASED ADULT STUDIES LOOKING AT PROGRESSION OF NERD TO EROSIVE ESOPHAGITIS

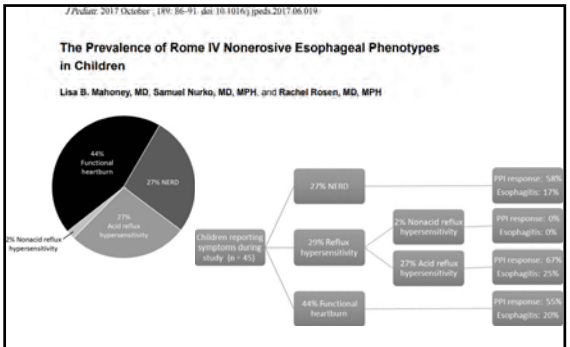
Study	N	Follow-up	Progression
Labenz[32]	3,894	2 years	25.5%
Sontag[35]	2,306	7.6 years	0%
Bardhan[36]	12,374	24 years	4.4%

Herschcovici T, et al. J Neurogastroenterol Motil. 2010 Jan; 16(1): 8–21

NON-EROSIVE ESOPHAGEAL PHENOTYPES (ROME IV)

- **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

SOCIETY PAPER

Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

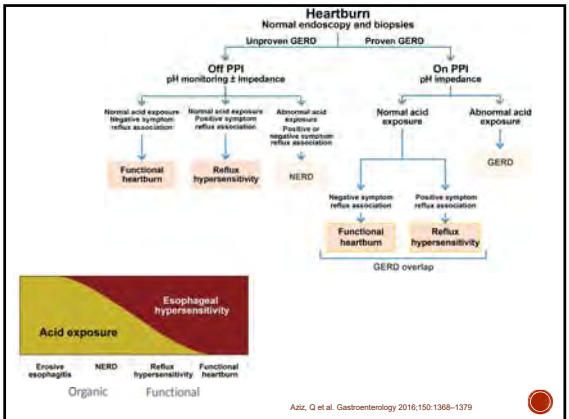
Rosen, R et al. J Pediatr Gastroenterol Nutr. 2018 Mar;66(3):516-554

ENDOSCOPY: ON OR OFF ACID SUPPRESSION?

- 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 GERD, 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

J Pediatr 1980;96:798–803
Rosen, R. J Pediatr Gastroenterol Nutr. 2018 Mar;66(3):516-554



Aziz, Q et al. Gastroenterology 2016;150:1368–1379

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

Study population	PPI symptomatic response pooled rate (95% CI)	Placebo symptomatic response pooled rate (95% CI)	Therapeutic gain – difference (95% CI)
NERD (n = 1854)	36.7 (34.1–39.3)	9.5 (7.1–11.9)	27.2 (25.9–35.3)
ET (n = 705)	15.5 (11.5–19.5)	7.5 (2.5–12.5)	48.0 (24.6–93.8)

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

Dean BB, et al. Clin Gastroenterol Hepatol 2004 Aug;2(8):656-64
Herschkovici T, et al. J Neurogastroenterol Motil. 2010 Jan; 16(1): 8–21

CYP2C19 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 **poor metabolizers (two mutant alleles)**

ID	Allele[1]	Genotype/activity	Phenotype
A	*1/*1	WT/two active alleles	NM
B	*1/*9	Heterozygous WT/one active and one inactive allele	IM
C	*2/*2 or *9/*9	Homozygous inactive/two inactive alleles	PM
D	*1/*17	Heterozygous WT/one active and one increased activity allele	EM
E	*17/*17	Homozygous for increased activity/two alleles	UM

[1]*2, *3, *4, *5 refer to loss-of-function alleles; allele *17 refers to any one of the loss-of-function alleles.
EM: Extensive metabolizer; IM: Intermediate metabolizer; NM: Normal metabolizer; PM: Poor metabolizer; UM: Ultra-rapid metabolizer; WT: Wild type

Pharmacogenomics. 2014 Aug;15(11):1405-16

RECOMMENDATIONS FOR PROTON PUMP INHIBITOR DOSING BASED ON *CYP2C19* HAPLOTYPE AND METABOLIZER PHENOTYPE

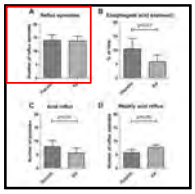
Metabolizer phenotype	Allele	Recommended percentage change in manufacturers' dosing guidelines
NM	*1/*1	No change
PM	*1/LOF or LOF/LOF	60% reduction
EM	*1/*17	50% increase
UM	*17/*17	100% increase

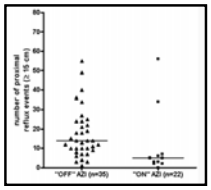
EM: Extensive metabolizer; LOF: Loss-of-function; NM: Normal metabolizer; PM: Poor metabolizer; UM: Ultra-rapid metabolizer

Moving towards personalizing medicine

Pharmacogenomics. 2014 Aug;15(11):1405-16

AZITHROMYCIN AND ITS EFFECTS ON REFLUX





Rohof WO, et al. Gut. 2012 Dec;61(12):1670-7
Mertens V, et al. Dig Dis Sci 2009 May;54(5):972-9

MEDICAL MANAGEMENT: NOT FDA APPROVED

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

Esophageal disorder	Medication Class	Dose
Functional chest pain	Imipramine TCA	25–50 mg[a]
	Sertraline SSRI	50–200 mg[a]
	Venlafaxine SNRI	75 mg
Hypersensitive esophagus	Citalopram SSRI	20 mg
Refractory GERD	Fluoxetine SSRI	20 mg
Globus	Amitriptyline TCA	25 mg

[a]GERD, gastroesophageal reflux disease; SNRI, serotonin-norepinephrin reuptake inhibitors.
[a]Escalating dose.

Maradey-Romero C, et al Clin Gastroenterol Hepatol. 2015 Feb;13(2):260-2

TREATMENT OF FUNCTIONAL ESOPHAGEAL DISORDERS

Complex and Integrated

Lifestyle and Education
- Describing the pathophysiology
- Relaxation Techniques

Behavioral Techniques
- Cognitive Behavioral Therapy
- Hypnosis

Medications
- Acid suppression
- Neuromodulators

Cognitive Behavioral Therapy
- Patients build insights into the relationship between situations, thoughts, behaviors, emotions and symptoms.
- Patients learn to catch and change unhelpful thinking, engage in relaxation exercises and change behaviors [avoidance, isolation].

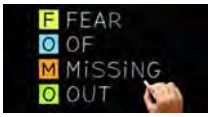
Gut Directed Hypnosis
- Deep physical relaxation and deep mental concentration
- Alters focus of attention, changes meaning about sensations arising from the gut and encourages body to restore itself to a healthier state
- Shown to produce cognitive change and improve pain tolerance
- Modifies physiological arousal and hypersensitivity over long-term
- Initially performed in a doctors office but can eventually be self-guided
- The most scientifically supported non-drug treatment for Functional GI disorders

Aziz Q, et al. Gastroenterology 2016;150:1368–1379

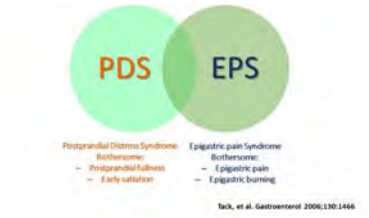
CASE

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, emesis, 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



Hyams J, et al. Gastroenterology 2016;150:1456–1468

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

Hyams J, et al. Gastroenterology 2016;150:1456–1468

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

Prevalence of Pediatric Functional Gastrointestinal Disorders Utilizing the Rome IV Criteria

Samantha G. Robin, BS[1], Catherine Keller, BS[1,3], Russell Zwaniger, MD[2], Paul E. Hyman, MD[1], Samuel Nurko, MD, MPH[1], Miguel Saps, MD[1], Carlo Di Lorenzo, MD[1], Robert J. Shulman, MD[1], Jeffrey S. Hyams, MD[1], Olafur Palsson, PsyD[1], and Miranda A. L. van Tilburg, PhD[1,3]

Table III. Functional GI disorder prevalence in children greater than 4 years old according to Rome III and Rome IV criteria

Diagnoses	Rome IV, N (%)	Rome III*
Functional constipation	135 (14.10%)	122 (12.90%)
Functional dyspepsia – postprandial distress syndrome†	69 (7.20%)	–
Functional dyspepsia – epigastric pain syndrome†	4 (0.40%)	–
Functional dyspepsia – unspecified†	N/A	2 (0.20%)
IBS	49 (5.10%)	27 (2.80%)
FAP NOS	30 (3.1%)	FAP 2 (0.3%) FAPS 8 (0.8%)
Aerophagia	25 (2.60%)	41 (4.30%)
Cyclic vomiting syndrome	19 (2.00%)	10 (1.10%)
Functional vomiting	13 (1.40%)	–
Abdominal migraine	11 (1.10%)	87 (9.20%)
Functional nausea	5 (0.50%)	–
Nonretentive fecal incontinence	2 (0.20%)	17 (1.80%)
Rumination	0 (0%)	0.00%
Any functional GI disorder	25.00%	23.10%

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

Hyams J, et al. Gastroenterology 2016;150:1456–1468

EVALUATION

- Role of EGD is unclear
  - presence of alarm features

Table 2. Potential Alarm Features in Children With Chronic Abdominal Pain*

Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease
Persistent right upper or right lower quadrant pain
Dysphagia
Odynophagia
Persistent vomiting
Gastrointestinal blood loss
Nocturnal diarrhea
Arthritis
Perirectal disease
Involuntary weight loss
Deceleration of linear growth
Delayed puberty
Unexplained fever

Hyams J, et al. Gastroenterology 2016;150:1456–1468

TREATMENT OF FD

- **Lack of good studies in pediatrics**
- **No FDA approved agents**
- PPIs vs. H2RA
- Psychotropics
- Cyproheptadine
- 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[1]
- Patients with *dysmotility* symptoms are less likely to improve with PPI therapy[1]
  - Case control studies suggest nausea[2] and bloating/IBS symptoms[3,4] are negative predictors of PPI response

[1]Talley APT 1998;12:1055
[2]Meineche-Schmidt Am J Gastro 2000;95:2777
[3]Bolling-Sternevald Aliment Pharmacol Ther 2003;18:117
[4]Meineche-Schmidt Aliment Pharmacol Ther 2011;33:41

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

Pamela D. Browne ✉ Sjoerd C. J. Nagelkerke, Farid S. van Etten-Jamaludin, Marc A. Benninga & Merit M. Tabbers

no evidence to support the use of pharmacological drugs to treat FD in children

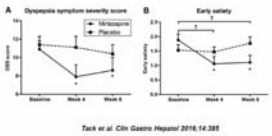
PSYCHOTROPICS FOR FD: A SYSTEMIC REVIEW AND META ANALYSIS IN ADULTS

- 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 0.91)
  - NNT=6; 95% 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 NNH=21

Ford, et al. Gut 2017;66:411

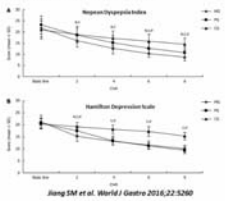
MIRTAZAPINE FOR ADULT FD

- 34 FD pts with weight loss but no depression
- Mirtazapine 15 mg or placebo x 8 weeks
  - H_1, α_2, 5-HT_{2C}, 5-HT_3 antagonist with antidepressant properties



Tack et al. Clin Gastro Hepatol 2016;14:385

- 60 FD pts with depression & weight loss
- Mirtazapine 30 mg, paroxetine 20 mg or conventional therapy x 8 weeks



Jiang SM et al. World J Gastro 2016;22:5260

Neurogastroenterology & Motility

ORIGINAL ARTICLE

Rikkunshito simultaneously improves dyspepsia correlated with anxiety in patients with functional dyspepsia: A randomized clinical trial (the DREAM study)

BMJ Open **Gut-directed hypnotherapy versus standard medical treatment for nausea in children with functional nausea or functional dyspepsia: protocol of a multicentre randomised trial**

Pamela D Browne,[1,2] Bibiche den Hollander,[1] Esther M Speksnijder,[1] Herbert M van Wering,[3] Walther Tjon a Ten,[3] Elvira K George,[4] Michael Groeneweg,[5] Nanja Bevers,[5] Margaretha M S Vessies,[1] Maartje M van den Berg,[6] Joery Goede,[6] Sarah T A Teklenburg-Roord,[1,2] Carla Frankenhuis,[1] Marc A Benninga,[1] Arine M Vlieger[1,7]

CONCLUSIONS

- 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 then in patients with erosive esophagitis
  - role of neuromodulators, prokinetics
- FD is a prevalent and heterogeneous functional GI disorder in children
- When treating FD, its 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
  - multidisciplinary approach

THANK YOU

jk3065@cumc.columbia.edu

The Role of Diet in Managing Irritable Bowel Syndrome

Robert J. Shulman, MD
Professor of Pediatrics

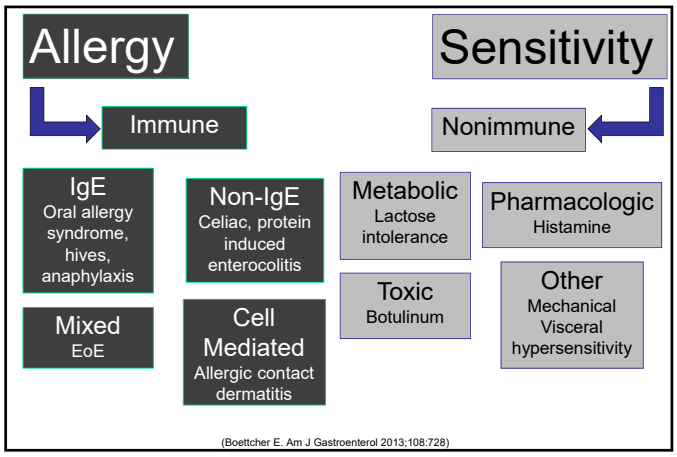
Disclosure

- 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



(Boettcher E. Am J Gastroenterol 2013;108:728)

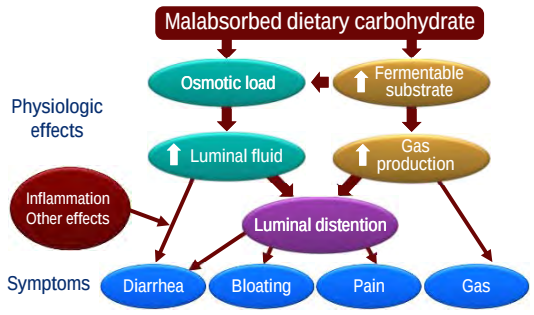
Non-Immune (?) Mechanisms

Dietary FODMAPs

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

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

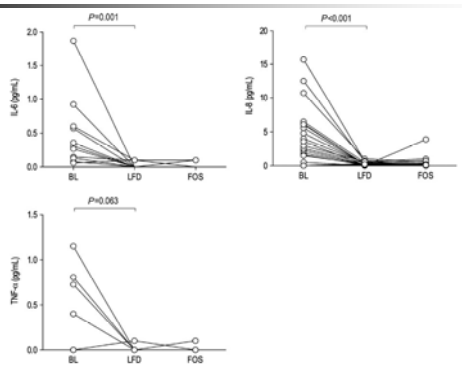
FODMAPs – Traditional Thinking



(Barrett JS. Pract Gastroenterol 2007;31:51)

FODMAPs and Inflammation / Visceral Hypersensitivity

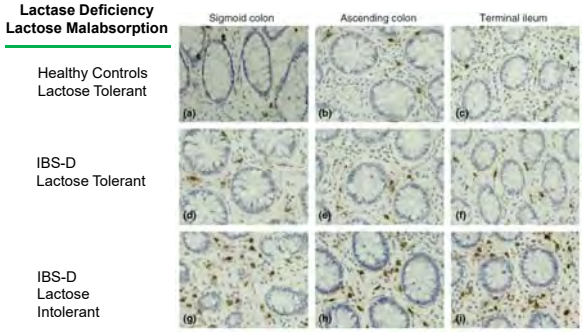
FODMAPs and Inflammation



(Hustoft TN. Neurogastroenterol Motil 2017;29:e12969)

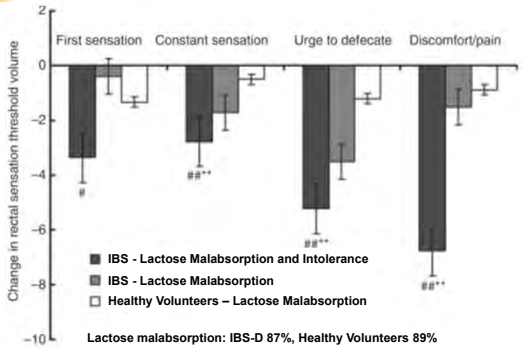
FODMAPs and Inflammation

Lactase Deficiency
Lactose Malabsorption



(Yang Y. Aliment Pharmacol Ther 2014;39:302)

FODMAPs and Visceral Hypersensitivity



Lactose malabsorption: IBS-D 87%, Healthy Volunteers 89%

(Yang Y. Aliment Pharmacol Ther 2014;39:302)

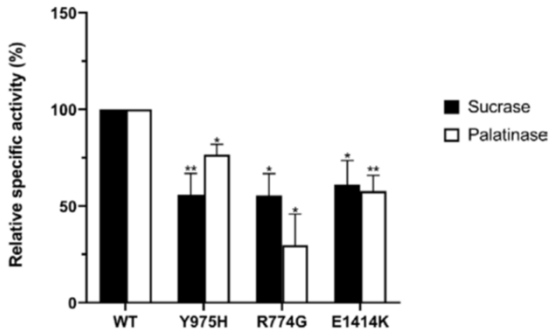
Sucrase-Isomaltase Pathogenic Variants in IBS

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%)

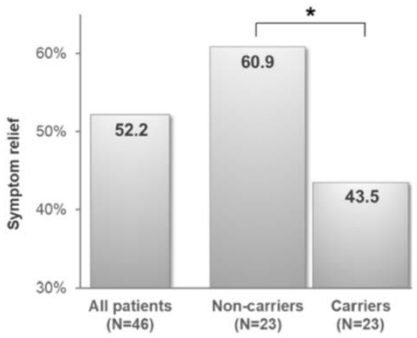
(Henström M. Gut 2018;67:263)
(Bonfiglio F. Gastroenterology 2018;155:168)
(Garcia-Etxebarria K. Clin Gastroenterol Hepatol 2018;16:1673)

Sucrase-Isomaltase Variants



(Husein DM, Naim HY. Gut 2019;Epub)

S-I Variants and Response to Low FODMAP Diet



(Zheng T. Gut 2019;Epub)

Immune (Allergy)
IgE/IgG
Non-IgE

IgE / IgG Food Allergies

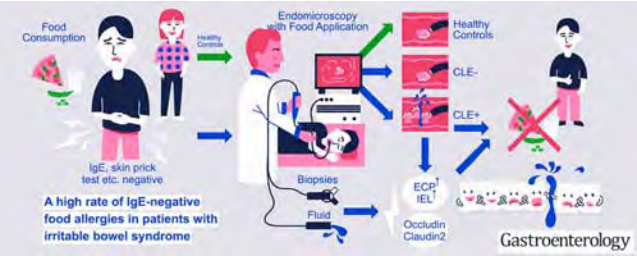
- Overall incidence/prevalence in US
  - 12% by self report
  - ~3% self report plus testing

(Burks AW. Pediatrics 2011;128:955)
(Sicherer SH. Pediatrics 2017;140:e20170194)

- In IBS: range 4%-25%
  - Wheat, milk, nuts, eggs

(Fritscher-Ravens A. Gastroenterology 2019;157:109)
(Ismail FW. Acta Gastro-Enterolog Belgica 2018;81:253)
(Petitpierre M. Ann Allerg 1985;54:538
(Carroccio A. Clin Gastroenterol Hepatol 2011;9:965)
(Carroccio A. Clin Gastroenterol Hepatol 2010;8:254)
(Bentley SJ. Lancet 1988;2:295)
(Farah DA. Gut 1985;26:164)

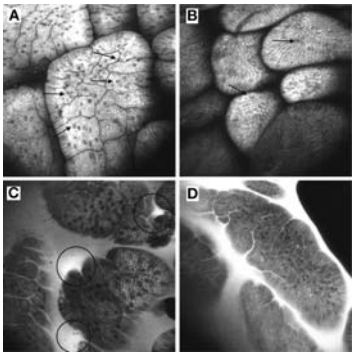
Non-IgE Atypical Food Allergies



CLE = Confocal laser endomicroscopy

(Fritscher-Ravens A. Gastroenterology 2019;157:109)

Non-IgE Atypical Food Allergies



A IBS patient – increased lymphocytes

B Control – Barrett's esophagus

C Positive reaction – increased lymphocytes, mucosal breaks, extravasation

D Positive reaction – further extravasation

(Fritscher-Ravens A. Gastroenterology 2019;157:109)

Non-IgE Atypical Food Allergies

- 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)

(Fritscher-Ravens A. Gastroenterology 2019;157:109)

Diets Used to Manage IBS

Low FODMAP Diet

Low FODMAP – Meta-Analyses

- 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;45:1506)

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;42:418)

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)

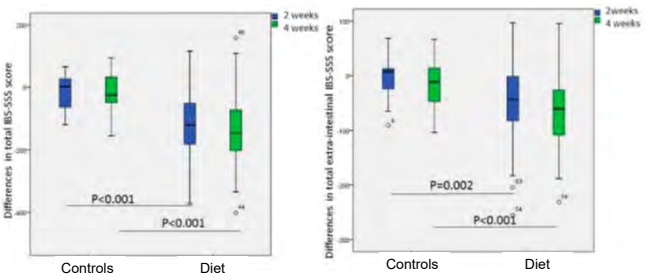
(Laatikainen R. Aliment Pharmacol Ther 2016;44:460)
(Hustoft TN. Neurogastroenterol Motil 2017;29:e12969)
(Shepherd SJ. Clin Gastroenterol Hepatol 2008;6:765)
(Chumpitazi BP. Clin Gastroenterol Hepatol 2018;16:219)

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;11:1662)

Reduced Sucrose/Starch Diet in IBS



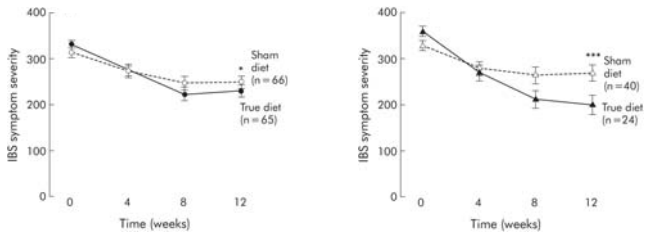
Urinary urgency, tiredness, muscle/joint pain, headache

(Nilholm C. Nutrients 2019;11:1662)

Allergy Elimination Diet

IgG–based Food Allergies

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



(Atkinson W Gut 2004;53:1459)

Milk/Wheat IgE Allergy in IBS

4-wk run-in, allergen specific serum IgE

114/166 (69%) improved on Elimination Diet

Double blind placebo controlled challenge

64/114 (56%) Positive

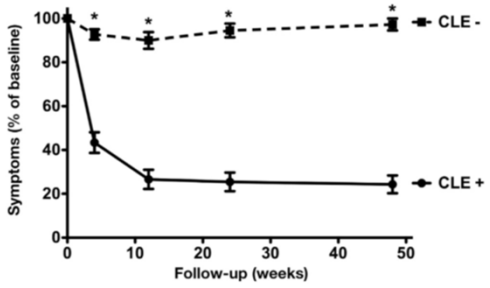
50/114 (44%) Negative

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

(Carroccio A. Clin Gastroenterol Hepatol 2011;9:965)
(Carroccio A. Clin Gastroenterol Hepatol 2010;8:254)

Non-IgE Atypical Food Allergies

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



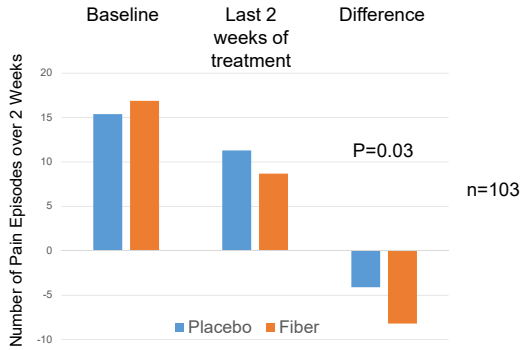
(Fritscher-Ravens A. Gastroenterology 2014;147:1012)

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;27:1002)
- Global assessment of symptoms improved with psyllium (n=7) (NNT=7) (Moayyedi P. Am J Gastroenterol 2014;109:1367)
- Global assessment of symptoms improved with psyllium (n=12) (Chouinard LE. Can J Diet Prac Res 2011;72:e107)
- Global assessment of symptoms improved with soluble fiber (n=9) (Bijkerk CJ. Aliment Pharmacol Ther 2004;19:245)
- 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



(Shulman RJ. Clin Gastroenterol Hepatol 2017;15:712)

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)

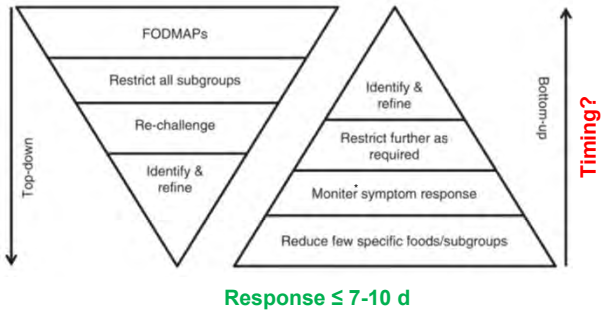
(McKenzie YA. J Hum Nutr Diet 2016;29:549)
(Moayyedi P. J Can Assoc Gastroenterol 2019;2:6)

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



Response ≤ 7-10 d

* British spelling

(Wang XJ. Aliment Pharmacol Ther 2019;Epub)
(Halmos EP. J Gastroenterol Hepatol 2017;32(Supp 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, MSPH
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

EMORY-CHILDREN'S CENTER

Disclosures

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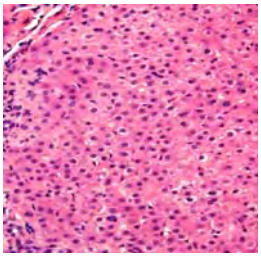
• NIH • Nutrition Science Foundation (NuSI) • Mason Foundation • Resonance Health • AMRA • Siemens • Perspectum • Immuron • Labcorp • Gemphire • Target Pharmasolutions • Shire	• AMRA • Target Pharmasolutions	• Allergan • Axcella Health • Shire • Boehringer Ingelheim • Bristol Myers Squibb • Immuron • Intercept • Novo Nordisk

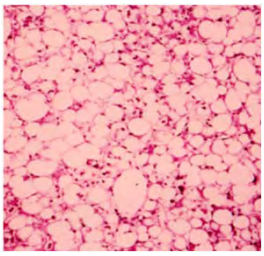
Learning Objectives

Understand	current concepts in pathogenesis
Update	on diagnostic tools for NAFLD
Discuss	clinical management of pediatric NAFLD

Nonalcoholic Fatty Liver



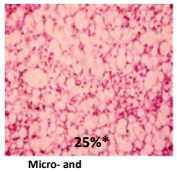
Healthy Liver



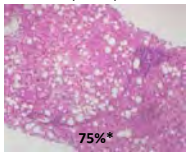
NAFLD = ≥5% steatosis

Range of NAFLD in Children

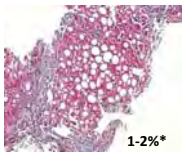
"Simple" Steatosis/Non-NASH → **N**on **A**lcoholic **S**teatohepatitis (NASH) → Cirrhosis



Micro- and macrovesicular fat



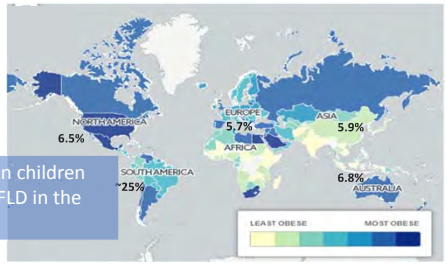
Inflammation, hepatocyte ballooning, steatosis



Bridging fibrosis and NASH

*Prevalence data from NIH NASH CRN and Target NASH Cohorts

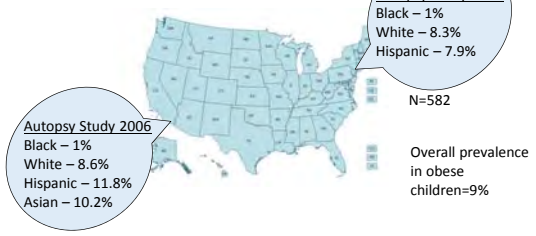
Pediatric NAFLD Across Regions of the World



~7 million children with NAFLD in the U.S.

CIA World Fact book – Digital Traveler (Figure by Oliver Smith, March 2017)
Anderson et al, PLOS One, 2015. Welsh et al, J Ped 2013

Prevalence Differences by Ethnicity & Race



Autopsy Study 2018
Black – 1%
White – 8.3%
Hispanic – 7.9%

N=582

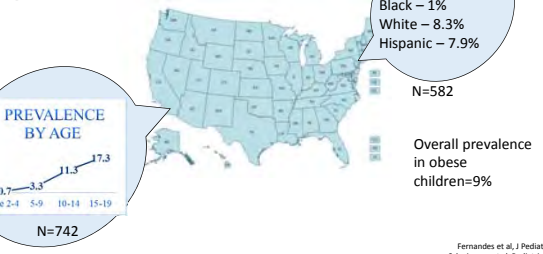
Autopsy Study 2006
Black – 1%
White – 8.6%
Hispanic – 11.8%
Asian – 10.2%

N=742

Overall prevalence in obese children=9%

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

Prevalence Differences by Ethnicity & Race &Age



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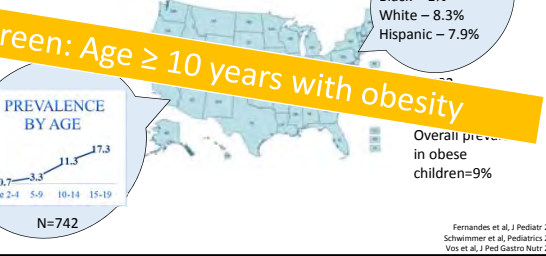


Autopsy Study 2018
Black – 1%
White – 8.3%
Hispanic – 7.9%

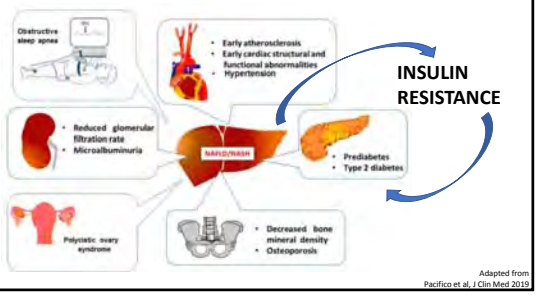
Screen: Age ≥ 10 years with obesity

N=742

Overall prev…
in obese children=9%

Fernandes et al, J Pediatr 2018
Schwimmer et al, Pediatrics 2006
Vos et al, J Ped Gastro Nutr 2016

Not Just a Liver Disease….



Adapted from
Pacifico et al, J Clin Med 2019

Similar BMI but Variable "Endophenotype"

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

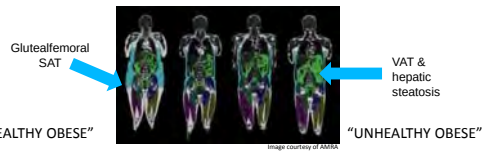
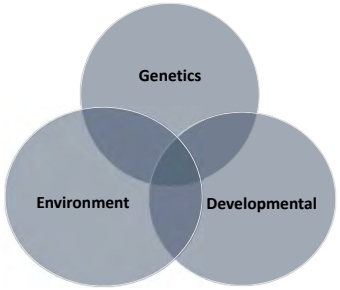


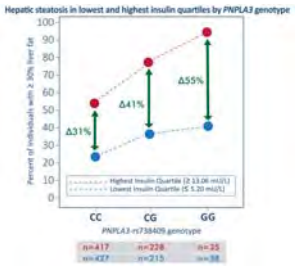
Image courtesy of AMRA

SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue
Caprio S, et al. Gastroenterology 2017;152:1638–46
Lotta L, et al. Nature Genetics 2016; 49: 17-29

What Causes NAFLD?



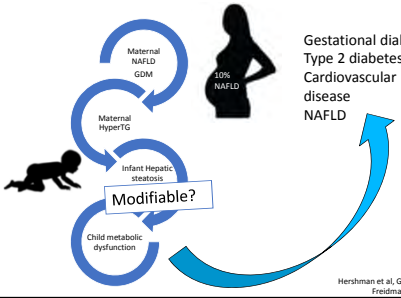
Genetics of NAFLD – Interactions with Insulin & BMI



- PNPLA3 rs738409-G –common polymorphism associated with NAFLD
- PNPLA3 – encodes adiponutrin, an enzyme found on lipid droplets that may decrease stored TG
- High BMI[1], High Insulin[2] plus homozygous (GG) increases risk of NAFLD

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

Developmental Factors



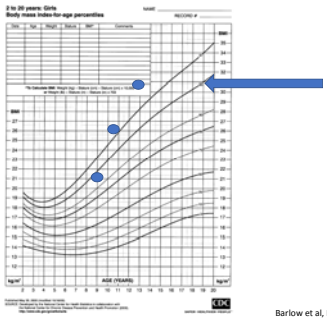
Gestational diabetes
Type 2 diabetes
Cardiovascular disease
NAFLD

Hershman et al, Gasto & Hep 2019
Freidman, 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



Barlow et al, Pediatrics 2007
Vos et al, J Ped Gastro Nutr 2017

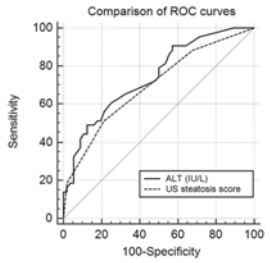
Screening: What is a "Normal" ALT

95th % in normal weight, healthy child:

- **26 U/L for boys**
- **23 U/L for girls**

Schwimmer et al, Gastro 2010

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



Draijer et al, Eur J Ped 2019

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

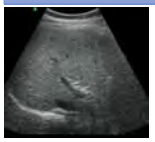
Photo curtesy of CHOA

Typical Pathway to Diagnosis of NAFLD

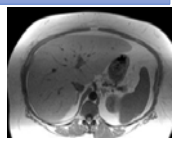
1. Clinical exclusion of medications & alcohol
2. Serologic exclusion of other chronic liver diseases
3. Confirmation of presence of fat in the liver
4. Assessment of severity of disease (NASH, fibrosis)

Imaging

For fat:



Ultrasound
Avg cost $390
Imprecise



MRI
$400 - ~$5000
Highly precise
Tip: Limited MR, no contrast

For fibrosis:

- Acoustic radiation force impulse (ARFI)
- Transient elastography
- MR elastography

Summary: Available, but not yet ready for clinical prime-time

U/S: https://radiopaedia.org/cases/fatty-liver-grade-i-1
MRI image: Curtesy of Diego Martin, MD
https://health.costhelper.com/abdominal-ultrasounds.html
GU et al, Eur Radiol 2019

Differential Diagnosis of Pediatric Hepatic Steatosis

TABLE 3. Differential diagnosis for pediatric hepatic steatosis

Genetic/metabolic disorders	Medications	Dietary causes	Infections
Nonalcoholic fatty liver disease	Amiodarone	Protein-energy malnutrition (Kwashiorkor)	Hepatitis C (genotype 3)
Fatty acid oxidation and mitochondrial disorders	Corticosteroids	Alcohol abuse	
Citrin deficiency	Methotrexate	Rapid surgical weight loss	
Wilson disease	Certain antipsychotics	Parenteral nutrition	
Uncontrolled diabetes	Certain antidepressants		
Lipodystrophies	HAART		
Lysosomal acid lipase deficiency	Valproic acid		
Familial combined hyperlipidemia			
Abeta-hypobetalipoproteinemia			

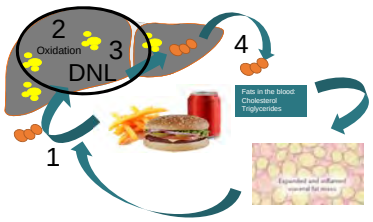
Always consider other diagnoses for “fatty liver.”

When is a Liver Biopsy Helpful?

- When the diagnosis is unclear
  - Screening tests for other liver diseases are positive
  - U/s 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 ped NAFLD has >250, consider other conditions
- When the ALT goes up despite lifestyle changes

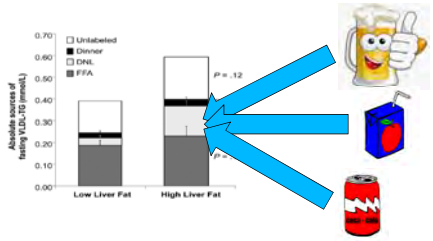
Treatment Considerations for NAFLD

The Liver and Lipid Regulation



DNL, de novo lipogenesis.
Vos et al, Curr Opin Lipid 2014
Lambert JE, et al. Gastroenterology. 2014;146:726–35

NAFLD = Increased DNL



DNL, de novo lipogenesis; FFA, fatty acid; NAFLD, non-alcoholic fatty liver; TG, triglycerides; VLDL, very-low-density lipoprotein.
1. Lambert JE, et al. Gastroenterology. 2014;146:726–35; 2. Fabbrini et al, Gastro 2016.

Sugar Consumption – Still too High

JAMA | Preliminary Communication

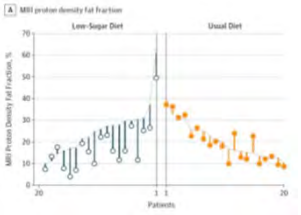
Effect of a Low Fre… on Nonalcoholic Fatty Liver Disease: A Randomized Clin…

Jeffrey B. Schwimmer, MD; Patricia Ugalde-N… Maria Cordero; Kathryn E. Harlow, MD; Adina Alazraki, MD; … lebecca Cleeton, MPH; Cynthia Knott, RDN; Juna Konomi, PhD; Mic… MD; Albert Hernandez; Ahlia Sekkarie, MPH; Cou…

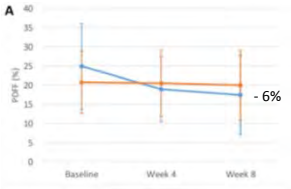
Figure 1. Consort Flow Diagram of Dietary Treatment Study Participants

Study Funded by Nutrition Science Initiative

Primary Outcome: Liver fat improved



Individual data



Adjusted means

8 week study

Schwimmer, Vos et al, JAMA 2019

What About Drugs?

Failed in Clinical Trials

- Vitamin E
- Metformin
- Cysteamine bitartrate (anti-oxidant)
- Gemcabene (PPAR)

Under Investigation Now*

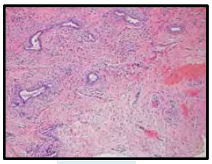
- Losartan (ARB)
- Tomato products
- Omega 3s
- Anti-LPS Milk Supplement (IMM-124)
- AXA1957 (Supplement)
- Bariatric Surgery
- Diets
- Elafibranor

*Active on ClinicalTrials.gov (recruiting)

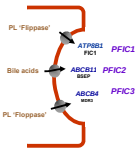
Summary

- 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

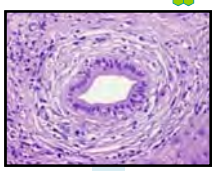
New therapies for chronic cholestatic diseases



Biliary atresia



Genetic cholestasis



PSC

Saul J. Karpen, M.D., Ph.D.

Raymond F. Schinazi Distinguished Biomedical Chair
Professor of Pediatrics
NASPGHAN PG Course
October 17, 2019

Disclosures:

Albireo	Consultant
Intercept	Consultant
LogicBio	Consultant
Mirum	Consultant
Retrophin	Consultant
Spruce Bioscience	Consultant

SJK: 7.29.2019

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:

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

Medical:

a. Cholic acid for BASDs
b. Reduced iv soy lipids for TPNAC
c. **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**

Anti-cholestatic therapies

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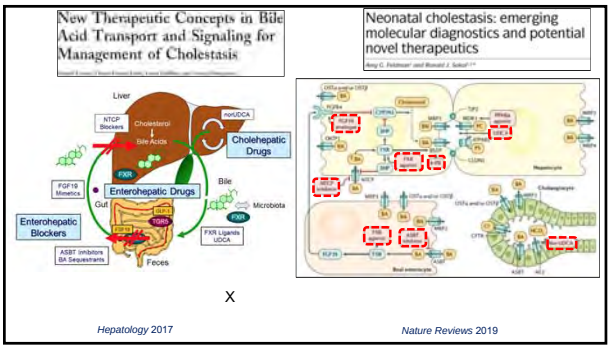
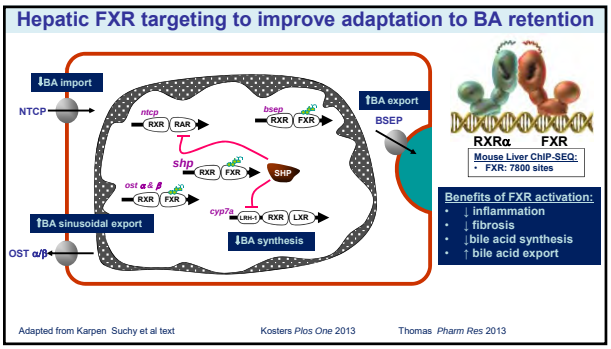
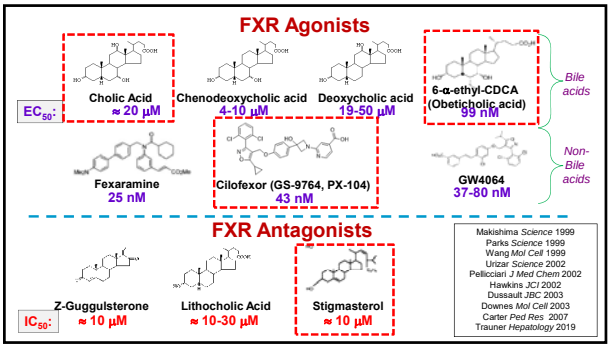
  - ~~**Gene therapy**~~
  - **Steroids/anti-inflammatories**


New Therapeutic Concepts in Bile Acid Transport and Signaling for Management of Cholestasis
Neonatal cholestasis: emerging molecular diagnostics and potential novel therapeutics
Liver
Cholehepatic Drugs
Enterohepatic Drugs
Enterohepatic Blockers
Gut
Bile
Microbiota
Feces
FXR
X
Hepatology 2017
Nature Reviews 2019


Hepatic FXR targeting to improve adaptation to BA retention
↓BA import
NTCP
↑BA export
BSEP
ntcp
bsep
shp
ost α & β
cyp7a
SHP
RXR
RAR
FXR
LRH-1
LXR
↑BA sinusoidal export
OST α/β
↓BA synthesis
RXRα
FXR
Mouse Liver ChIP-SEQ:
FXR: 7800 sites
Benefits of FXR activation:
↓ inflammation
↓ fibrosis
↓bile acid synthesis
↑ bile acid export
Adapted from Karpen Suchy et al text
Kosters Plos One 2013
Thomas Pharm Res 2013


FXR Agonists
EC50:
Cholic Acid
≈ 20 μM
Chenodeoxycholic acid
4-10 μM
Deoxycholic acid
19-50 μM
6-α-ethyl-CDCA (Obeticholic acid)
99 nM
Bile acids
Fexaramine
25 nM
Cilofexor (GS-9764, PX-104)
43 nM
GW4064
37-80 nM
Non-Bile acids
FXR Antagonists
IC50:
Z-Guggulsterone
≈ 10 μM
Lithocholic Acid
≈ 10-30 μM
Stigmasterol
≈ 10 μM
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 activators in 2 adult biliary tract diseases

PBC & PSC

A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis

F. Nevens, P. Andreone, G. Mazzella, S.I. Strasser, C. Bowlus, P. Invernizzi, J.P.H. Drenth, P.J. Pockros, J. Regula, U. Beuers, M. Trauner, D.E. Jones, A. Floreani, S. Hohenester, V. Luketic, M. Shiffman, K.J. van Erpecum, V. Vargas, C. Vincent, G.M. Hirschfield, H. Shah, B. Hansen, K.D. Lindor, H.-U. Marschall, K.V. Kowdley, R. Hooshmand-Rad, T. Marmon, S. Sheeron, R. Pencek, L. MacConell, M. Pruzanski, and D. Shapiro, for the POISE Study Group*

93% Female

56 ±10 y

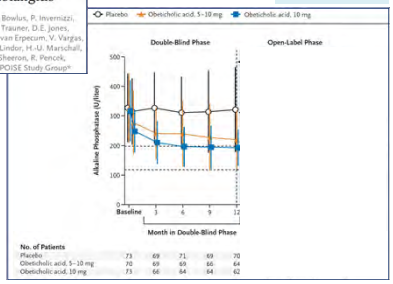
73 ±13 kg
Alk Phos 324 ± 174 U/L
Serum BA 48±68 µM

93% on UDCA
Pruritus Scores tracked

FDA approval May 2016

NEJM 2016: NCT01473524 X

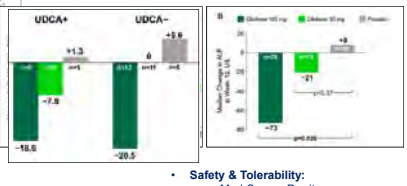
Pruritus: Placebo 38%
5-10 56%
10 68%



The Nonsteroidal Farnesoid X Receptor Agonist Cilofexor (GS-9674) Improves Markers of Cholestasis and Liver Injury in Patients With Primary Sclerosing Cholangitis

PSC: Cilofexor x 12w → reduced AP

Cilofexor 100 mg (n = 22)	Cilofexor 30 mg (n = 20)	Placebo (n = 10)



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**

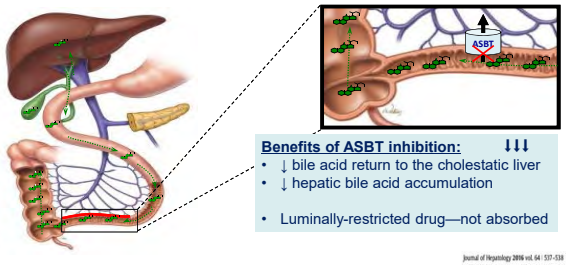
- **Safety & Tolerability:**
  - Mod-Severe Pruritus:
    - 100 mg 14%
    - 30 mg 20%
    - Placebo 40%

Clinicaltrials.gov: NCT02943460 *HEPATOLOGY* 2019

X

ASBT inhibitors in cholangiopathies – Good for mice, good for men?

Raoul Poupon*

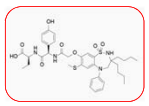


Benefits of ASBT inhibition: ↓↓↓

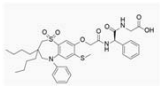
- ↓ bile acid return to the cholestatic liver
- ↓ hepatic bile acid accumulation
- Luminally-restricted drug—not absorbed

Journal of Hepatology 2016 vol. 64 | 517–538

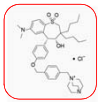
ASBT (IBAT) inhibitors in clinical trials



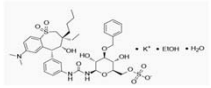
Odevixibat;A4250



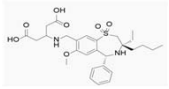
Elobixibat; A3309



Maralixibat



Volixibat



GSK2330672

Clinical trials.gov

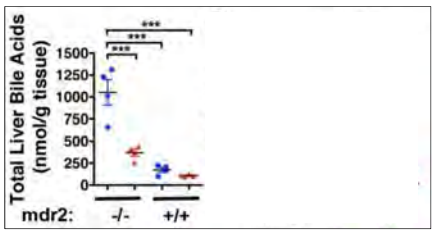
Diseases:
Alagille Syndrome
PFIC1
PFIC2
Biliary Atresia

PBC
PSC

NASH

Constipation

ASBT inhibition → reductions of both liver & serum BA levels

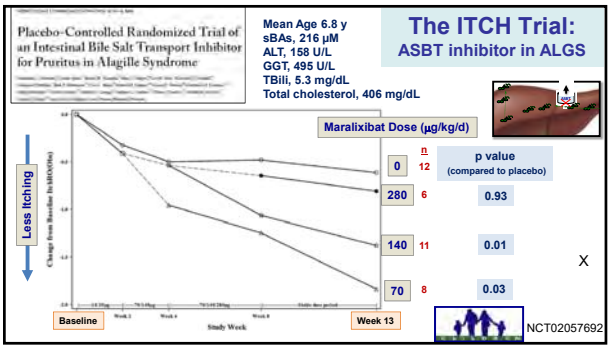


● Chow

▲ ASBTi (sc-435)

PFIC3 mouse model
2 weeks of Rx

Miethke et al *HEPATOLOGY* 2016



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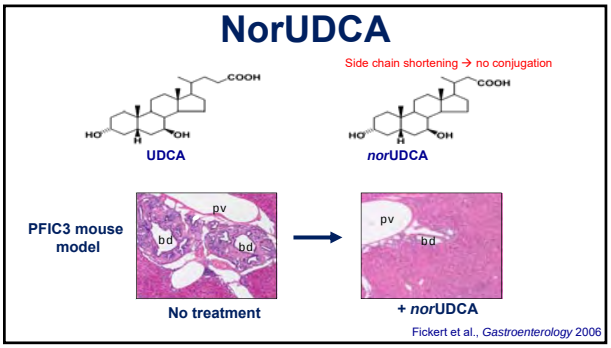

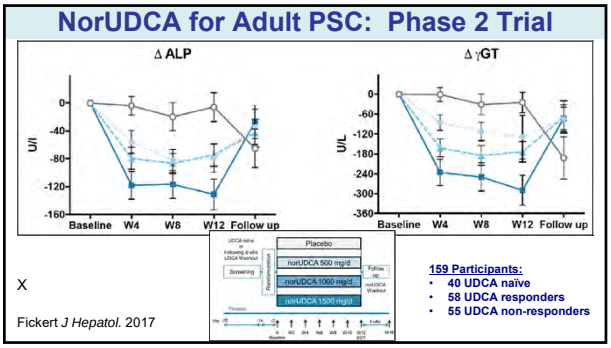

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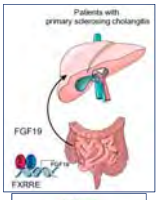
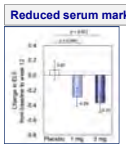
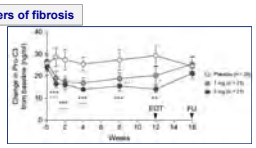
Fickert *J Hepatol.* 2017

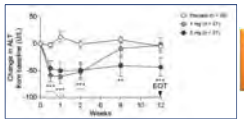
PSC: FGF19 analogue → Less Fibrogenesis



Reduced serum markers of fibrosis







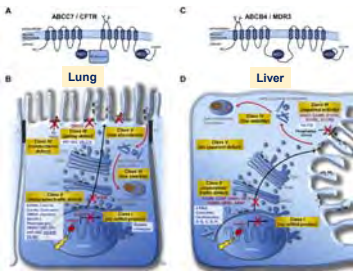
NGM282
- No change in Alk Phos
- Reduced BA synthesis
- Reduced Fibrogenesis markers

X

Hirschfield J Hep 2019

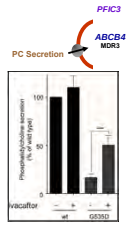
Chaperones & Correctors

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



Vauthier *Biochem Pharm* 2017

- Potentiators
- Stabilizers
- Correctors



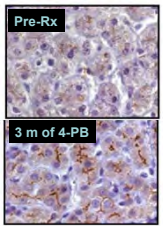
Delaunay *Hepatology* 2016

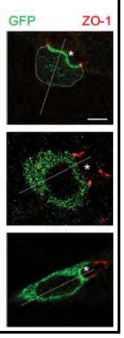
Successful mutation-specific chaperone therapy with 4-phenylbutyrate in a child with progressive familial intrahepatic cholestasis type 2

Emmanuel Gonzales[1,2], Brigitte Grosse[3], Doris Cassio[3], Anne Davit-Spraul[3], Monique Fabre[4], Emmanuel Jacquemin[1,2,*]

10 yo F homozy. *ABCB11*^{T1210P}
Failed UDCA, RIF, Diversion

	Pre	1 y
Pruritus	10 →	3
ALT	125 →	19
BA	493 →	237
Tbili	200 →	11





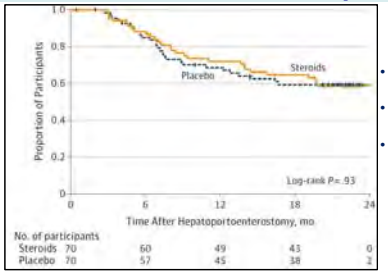
J Hepatol. 2012;57:695–698.

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

SNL

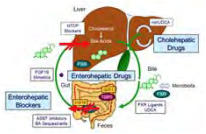


- No benefit from steroids
- Earlier time to SAE's
- Impaired growth

Bezerra JA, et al. (2014). *JAMA*, 311(17), 1750–9. ChiLDReN NCT00294684

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

26

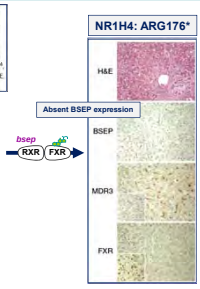
FXR Deficiency → Neonatal Cholestasis/Liver Failure

Mutations in the nuclear bile acid receptor FXR cause progressive familial intrahepatic cholestasis

Natalia Gomez-Ospina[1+], Carol J. Potter[2+], Rui Xiao[3,4,+], Kandamurugu Manickam[2], Mi-Sun Kim[3], Kang Ho Kim[3], Benjamin L. Shneider[5], Jennifer L. Picarsic[6], Theodora A. Jacobson[2], Jing Zhang[4], Weimin He[4], Pengfei Liu[4], A.S. Khnsely[7,], Milton J. Finegold[8], Donna M. Muzny[9], Eric Boerwinkle[9], James R. Lupski[4], Sharon E. Plon[4], Richard A. Gibbs[4,9], Christine M. Eng[4], Yiping Yang[4], Gabriel C. Washington[10], Matthew H. Porteus[10], William E. Berquist[11], Neeraja Kambham[12], Ravinder J. Singh[13], Fan Xia[4], Gregory M. Enns[1] & David D. Moore[3,4]

2 Families:

- **Presentation at birth→6 w of age**
  - ⬆ Direct Bilirubin
  - Coagulopathy
  - Mild ⬆ ALT & AST
  - Low GGT
- **2 died (5 weeks, 8 months)**
- **2 transplanted (4 & 22 months)**



Nature Commun. 2016

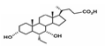
Select anti-cholestatic drugs in clinicaltrials.gov

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

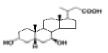
7.31.2019

Bile acid based therapeutics (clinicaltrials.gov)

Glycocholic Acid: BA Synthesis Defect

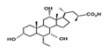


FXR agonists: NASH, PBC, PSC — BA diarrhea, Alcohol, Fibrosis

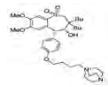


NorUDCA: PSC

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

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

1

Disclosure

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

2

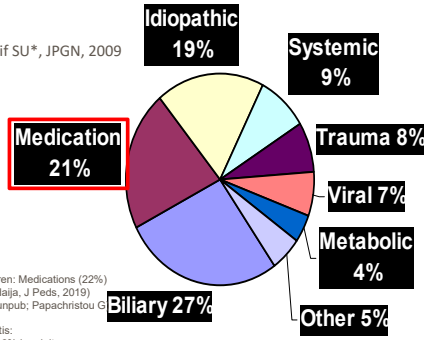
Learning objectives

- 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

Park A*, Latif SU*, JPGN, 2009

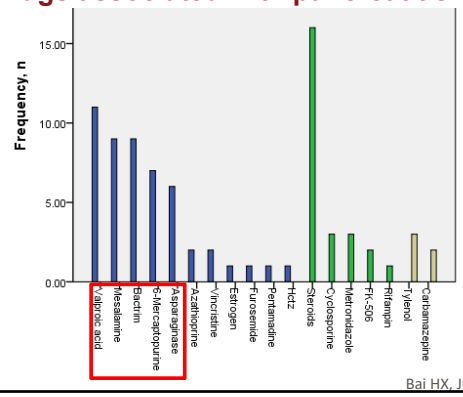


Single AP in children: Medications (22%)
(Maisam Abu-El-Haija, J Peds, 2019)
vs. 2% in adults (unpub; Papachristou G

Chronic pancreatitis:
7% in children vs. 3% in adults
(Schwarzenberg, JPGN, 2019 [INSPPIRE; PI: Aliye UC])

What are the drugs associated with pancreatitis in children?

Drugs associated with pancreatitis in c



Bai HX, JPGN, 2011

Determining whether an association is casual

Category	1. Reasonable temporal sequence	2. Known response pattern	3. Could not be explained by other factors	4. Relieved by stopping the drug	5. Recurred after a repeat challenge
Definite	×	×	×	×	×
Probable	×	×	×	×	
Possible	×	×			

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, hypertriglyceridemia, gallstones, and other drugs

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

Class II drugs
- At least 4 cases in the literature
- Consistent latency (≥75% of cases)

Class III 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

Badalov et al. Clinical Gastroenterology and Hepatology 2007;5:648–661.

Classification of drugs associated with pancreatitis

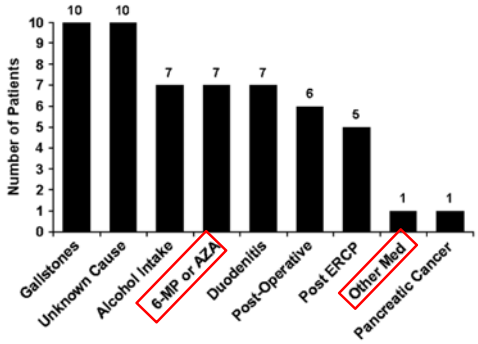
Definite association
- Aminosalicylates (sulfasalazine, mesalamine)
- L-asparaginase
- Azathioprine
- Didanosine
- Estrogen
- Furosemide

Probable association
- Chlorthalidone
- Cyclosporine
- Ethacrynic acid
- FK-506

Possible association
- Acetaminophen
- Amiodarone
- Atenolol
- Carbamazepine
- Chlorpromazine
- Cholestyramine
- Cisplatin
- Contrast media
- Danazol
- Diazoxide
- Diphenoxylate
- Ergotamine
- Pentamidine
- Sulfonamide
- Tetracycline
- Thiazides
- Valproic acid
- Vinca alkaloids
- 6-Mercaptopurine
- HMG-CoA reductase inhibitors
- Metronidazole
- Rifampin
- Steroids

Runzi, Pancreas, 1996
AGA Technical Review, 2007

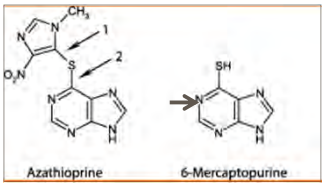
Etiologies for acute pancreatitis in IBD



Moolsintong 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

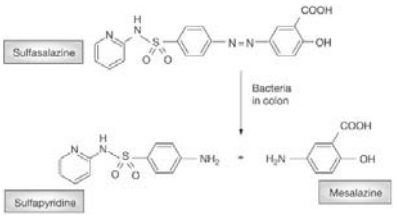
Thiopurine-associated pancreatitis is linked to a class II HLA haplotype

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

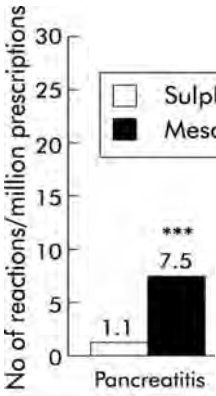
May add to the armamentarium of pharmacogenomics in preventing DAP

Heap, Nat Genetics, 2014

Sulfasalazine-associated pancreatitis



- Initially attributed to the sulfapyridine moiety
  - –Absorbed
  - –Structurally similar to thiazide diuretics



Ransford RA, Gut, 2002

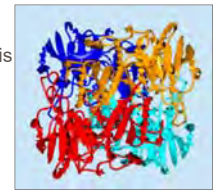
But, 5-ASA users are more likely to develop pancreatitis than sulfasalazine users

5-ASA-associated pancreatitis

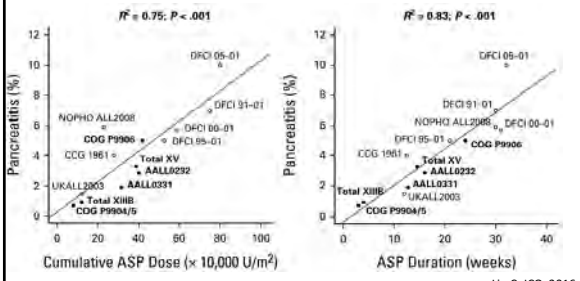
- Pancreatitis within 6 weeks of initiating 5-ASA therapy
- Idiosyncratic
- Improves after the drug is discontinued
- Repeat challenge has resulted in pancreatitis
- Mechanism for pancreatitis unclear
  - –Local effect of 5-ASA on pancreas—pancreatic duct permeability?

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?**



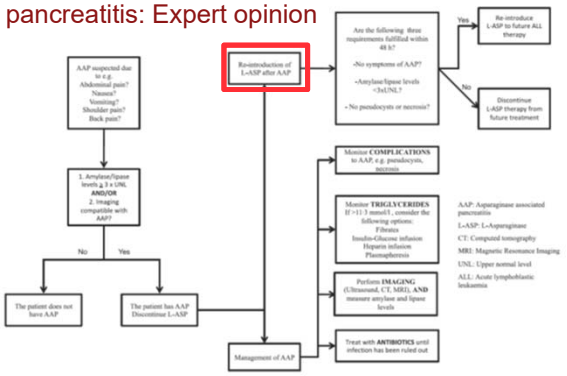
The risk of pancreatitis increases with higher or more prolonged exposure



Liu C, JCO, 2016

- **Dose-dependent risk**

Reintroduction of asparaginase after pancreatitis: Expert opinion

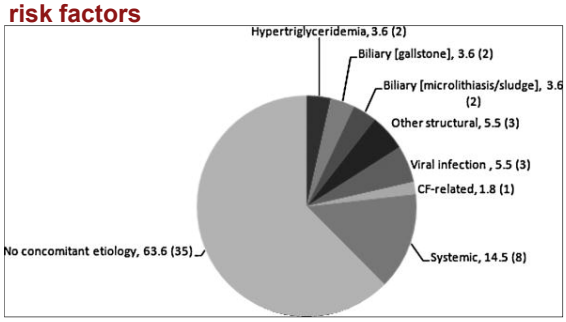


Why do some drugs cause pancreatitis?

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



Bai HX, JPGN, 2011

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

Pediatric Pancreatic Masses: Steroids, Surgery, or Surveillance

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Associate Professor of Pediatrics and Surgery
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Cincinnati, Ohio

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

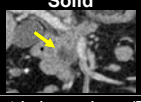
Entity	Pancreatic Neoplasms, %
Ductal adenocarcinoma	85%
Serous cystadenoma	1 – 2%
Mucinous cystic neoplasm	1 – 2%
Intraductal papillary mucinous neoplasm	3 – 5%
Acinar cell carcinoma	1 – 2%
Pancreatoblastoma	< 1%
Pancreatic endocrine neoplasm	3 – 4%
Solid pseudopapillary neoplasm	1 – 2%

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

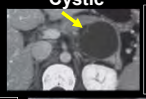
Classification of Pancreatic Neoplasms

- ***Gross configuration***

Solid

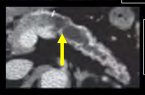


Cystic



True
Serous cystic neoplasm (SCN)
Mucinous cystic neoplasm (MCN)
Degenerative
Solid pseudopapillary tumor

Ductal adenocarcinoma (PDAC)
Acinar cell carcinoma
Pancreatoblastoma (PBL)
Neuroendocrine tumors
Solid pseudopapillary tumor (SPT)



Intraductal
Intraductal papillary mucinous neoplasm (IPMN)

- ***Lines of cellular differentiation***

Cell Line	Functional	Immunophenotype	Neoplasms
Ductal	Mucin production	CA 19-9, CEA, CK19, MUC1	PDAC, SCN, MCN, IPMN
Acinar	Enzyme production	Trypsin, chymotrypsin, lipase	Acinar cell carcinoma, PBL
Endocrine	Peptide hormones	Chromogranin, synaptophysin	Neuroendocrine tumor

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

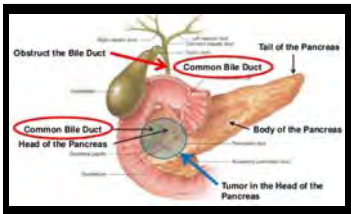
Diagnostic Clues

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

Table 5. Sex Ratio and Location of Pancreatic Neoplasms

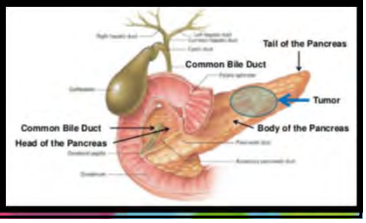
Entity	M:F	Location
Ductal adenocarcinoma	1.3:1	Head > Tail
Serous cystadenoma	1:2.3	Head = Tail
Mucinous cystic neoplasm	1:20	Tail
Intraductal papillary mucinous neoplasm	1.5:1	Head > Tail
Acinar cell carcinoma	3.6:1	Head = Tail
Pancreatoblastoma	1.7:1	Head = Tail
Pancreatic endocrine neoplasm	1:1	Head = Tail
Solid-pseudopapillary neoplasm	1:9	Head = Tail

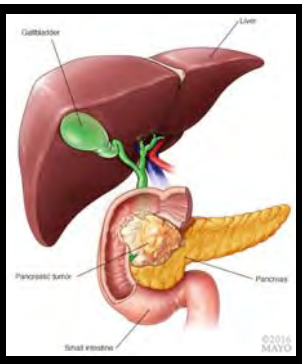
Klimstra et al, *Arch Pathol Lab Med* 2009;133:454-464



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

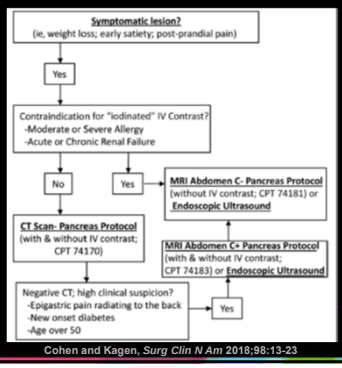
Diagnostic Approach

Table 1
Pancreatic imaging modalities

Modality	Benefits	Downside	Preferred Indications
CT	• Rapid acquisition • Less susceptible to artifacts • High resolution	• Radiation • Need for Iodinated contrast	• Solid tumor staging
TAUS	• Low cost • Accessibility • Noninvasive	• Suboptimal pancreas visualization • User dependent	• Abdominal pain • Follow-up of a known lesion in selected patients
EUS	• High resolution • Sampling ability	• Needs intravenous sedation	• Solid lesions for tissue • Evaluate cystic lesions
MRI	• Characterize lesions based on content • Ability to depict fluid-containing structures	• Air, motion produce artifacts • High cost	• Cystic lesion assessment

Cohen and Kagen, *Surg Clin N Am* 2018;98:13-23

Algorithm for Symptomatic Mass



Cohen and Kagen, *Surg Clin N Am* 2018;98:13-23

EU

- EUS
  asp
  (FN
  – M
    va
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    sa
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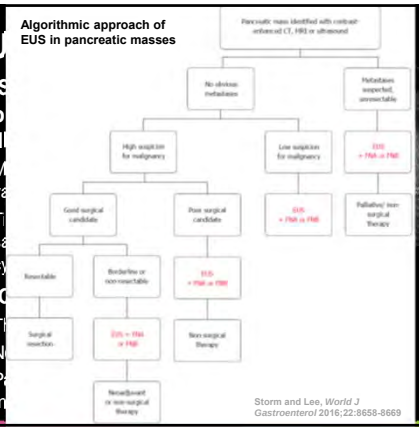
- ERC
  – Th
  – N
  – Pa
    m

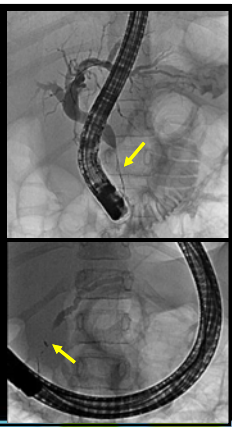
Algorithmic approach of EUS in pancreatic masses



Storm and Lee, *World J Gastroenterol* 2016;22:8658-8669

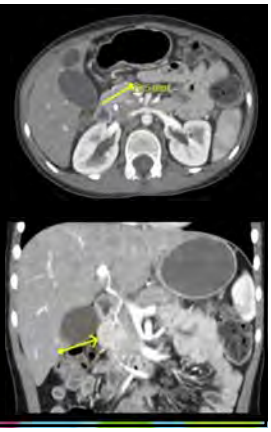
Case

- 8 yo male presented with 3 days of painless jaundice, acholic stools
- Elevated bilirubin and lipase
- MRI/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

Takeshi Ezaki[a] Atsuhiro Masuda[a] Hideyuki Shiomi[a] Takashi Nakagawa[a] Keitaro Sofue[b] Hirochika Toyama[c] Yoh Zen[d] Yuzo Kodama[a]

Case Rep Gastroenterol 2019;13:265–270

Autoimmune pancreatitis masquerading as carcinoma head of pancreas: A case report and review of literature

Meenu Gill[a], Komal Brar[b,c], Rajesh Godara[b], Shilpi Bhargava[a], Bhawna Sachdeva[a], Rajeev Sen[a], Promil Jain[a]

Annals of Medicine and Surgery 45 (2019) 82–85

Solid Pseudo-Papillary Tumor Mimicking as Complicated Pseudocyst

Multimodality Imaging and Pathological Correlation

Clin Nucl Med 2018;43: e368–e371

Sophie Turpin, MD,* Marjorie Perron, MD,† Stéphanie Vairy, MD,‡ Sébastien Bénali, MD,§ and Amélie Damphousse, MD§

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

Cincinnati Children's

International Consensus Diagnostic Criteria for Autoimmune Pancreatitis

Guidelines of the International Association of Pancreatology

Pancreas 2011;40: 352–358

Tooru Shimosegawa, MD, Suresh T. Chari, MD,† Luca Frulloni, MD,‡ Terumi Kamisawa, MD,§ Shigeyuki Kawa, MD,|| Mari Mino-Kenudson, MD,¶ Myung-Hwan Kim, MD,# Günter Klöppel, MD,** Markus M. Lerch, MD,†† Matthias Löhr, MD,‡‡ Kenji Notohara, MD,§§ Kazuichi Okazaki, MD,||| Alexander Schneider, MD,¶¶ and Lizhi Zhang, MD##*

- **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*):**
  - ***H***istopathology
  - ***I***maging: parenchyma (CT/MRI) and PD (ERCP/MRCP)
  - ***S***erology: IgG4, IgG, ANA
  - ***O***ther organ involvement
  - ***R***esponse to steroids

Cincinnati Children's

Autoimmune Pancreatitis in Children: Characteristic Features, Diagnosis, and Management

Scheers et al., *Am J Gastroenterol* 2017;112:1604-1611

- 48 children (systematic literature search, INSPPIRE, CUSL)
- Abdominal pain (91%), obstructive jaundice (42%)
- Positive serology IgG4 in only 22%
- MRCP:
  - Global (30%) or focal (53%) 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***

Recommendations for Diagnosis and Management of Autoimmune Pancreatitis in Childhood: Consensus from INSPPIRE

Scheers et al., *J Pediatr Gastroenterol Nutr* 2018;67:232-236

Statement 8
Histological findings of acute and/or chronic inflammatory cell infiltration around pancreas acini or peri-ductular and/or presence of IgG4-positive plasma cells with or without pancreas fibrosis is suggestive for the diagnosis of P-AIP.
A tissue diagnosis should ideally be obtained prior to initiating therapy. However, barriers exist to recommend routine EUS-guided biopsies for all children (e.g. limited number of EUS-skilled pediatric endoscopists and pediatric pathologists, inadequate biopsy needles). If these barriers cannot be overcome, we suggest that the diagnosis of P-AIP can be made based on the clinical and imaging findings, since the risk for pancreatic cancer in children is extremely low.

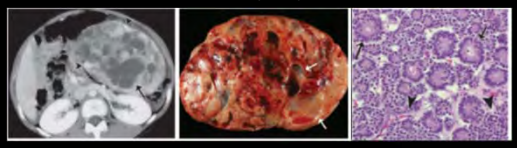
Statement 11
Oral prednisone, 1 to 1.5 mg/kg/day to a maximum of 40–60 mg given in one or 2 divided daily doses for 2–4 weeks is recommended as first line treatment in P-AIP. Prednisone should then be tapered.

Statement 12
Treatment response to corticosteroid therapy should be assessed as a) clinical response within 2 weeks after starting corticosteroid therapy, b) imaging response by imaging such as transabdominal US, MRI/MRCP or EUS about 3 months after starting corticosteroid therapy.

Caution should be maintained in setting of focal pancreatic enlargement or non-regression of mass lesion

Pancreatoblastoma (PBL)

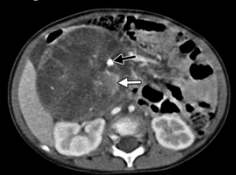
- Most common malignant pancreatic tumor in children
- Affects children < 10 yo (median 4 – 5 yo); male > female
- Arise from embryonic pancreatic acinar cells
- Pain, large palpable mass >>> jaundice, emesis
- Neonatal cases associated with Beckwith-Wiedemann syndrome or Familial Adenomatous Polyposis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



Chung et al, *Radiographics* 2006;26:1211-1238

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)

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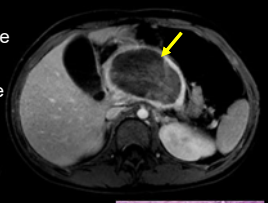
Pancreatoblastoma: A report from the European cooperative study group for paediatric rare tumours (EXPeRT)

EUROPEAN JOURNAL OF CANCER 47 (2011) 2347–2352

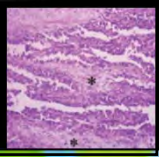
Ewa Bien [a], Jan Godzinski [b], Patrizia Dall'Igna [c], Anne-Sophie Defachelles [d], Teresa Stachowicz-Stencel [a], Daniel Orbach [e], Gianni Bisogno [f], Giovanni Cecchetto [c], Steven Warmann [g], Verena Ellerkamp [g], Bernadette Brennan [h], Anna Balcerska [a], Malgorzata Rapala [b], Ines Brecht [i], Dominik Schneider [i], Andrea Ferrari [k,*]

- 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

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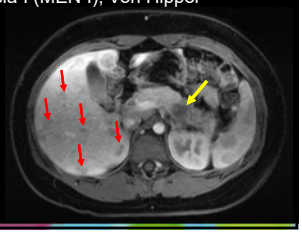
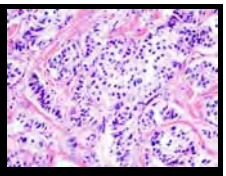
Neuroendocrine Tumors

- 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



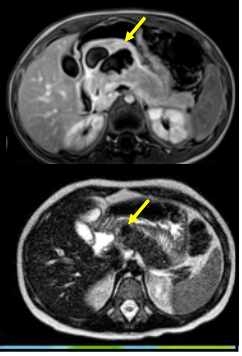
Insulinomas



- 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

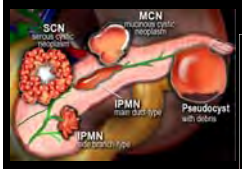
- Lymphoma
  - Non-Hodgkin lymphoma
  - Burkitt's lymphoma
- Primitive neuroectodermal tumors/Ewing's sarcoma
- Lymphangioma
  - Lymphatic malformation
- Hemangioendothelioma
- Dermoid cyst/mature teratoma

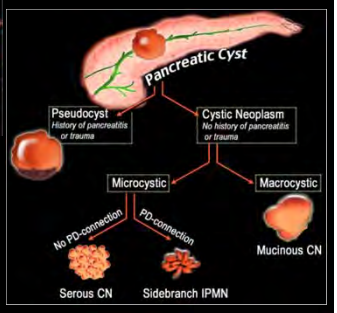


Cystic Lesions

- ***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***

http://www.radiologyassistant.nl/en/p4ec7bb77267de/pancreas-cystic-lesions.html

Solid pseudopapillary and malignant pancreatic tumors in childhood: A systematic review and evidence quality assessment

Konstantinos S. Mylonas[1,2] | Ilias P. Doulamis[3] | Diamantis I. Tsilimigras[3,4] | Dimitrios Nasioudis[3,5] | Dimitrios Schizas[3,4] | Peter T. Masiakos[1] | Cassandra M. Kelleher[1]

Pediatr Blood Cancer. 2018;65:e27114.

- 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

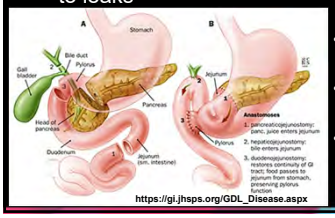
Type of tumor	N (%)
SPT	300 (61%)
PBL	81 (17%)
Exocrine	43 (9%)
Neuroendocrine	40 (8%)
Other	25 (5%)

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

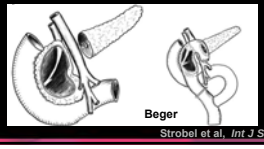


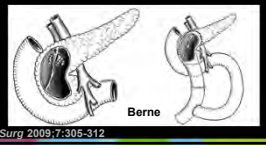
https://gi.jhsps.org/GDL_Disease.aspx

- "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


Beger


Berne

Strobel et al, *Int J Surg* 2009;7:305-312

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

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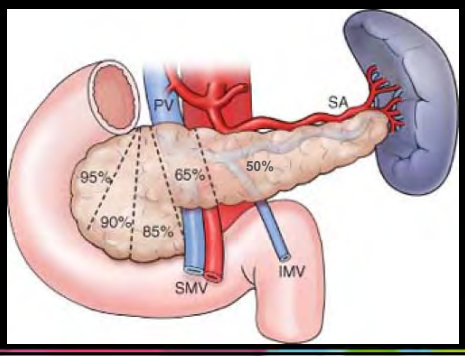
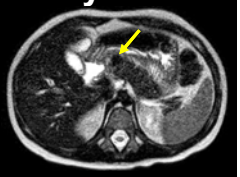
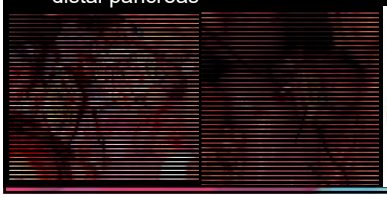
Percentages of Resection



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

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Questions?

CCHMC Pancreas Care Center

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Positioning the New IBD Therapies – Merging Experience with Evidence

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NASPGHAN – North American Society for Pediatric Gastroenterology, Hepatology and Nutrition – October 17, 2019

Disclosures

Consultant and/or Grant Support

- Abbvie
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- Arena Pharmaceuticals
- Biomica
- Boehringer Ingelheim, Ltd.
- Bristol-Myers Squibb
- Celgene Corp/Syneos
- Check-cap
- Dizal Pharmaceuticals
- GalenPharma/Atlantica
- Genentech/Roche
- Gilead Sciences
- Glenmark Pharmaceuticals
- Janssen Pharmaceuticals
- Lilly
- Mahana Therapeutics
- Medtronic
- Narrow River Mgmt
- Pfizer
- Prometheus Laboratories
- Reistone
- Seres Therapeutics
- Shire
- Takeda
- Target PharmaSolutions, Inc.

Board Membership/Other

- ACG Board of Trustees
- Co-Founder, CFO, Cornerstones Health, Inc (non-profit medical education organization)
- GoDuRn, 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!**

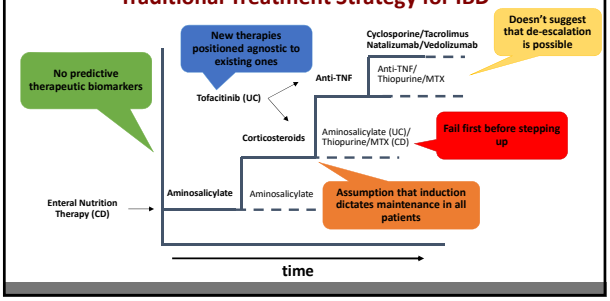
Treatments are Aimed at Observations and Theories (the Not Cause of the Disease)

Immune modification
- 5-ASA (?)
- Steroids
- Thiopurines/methotrexate
- Anti-TNFα therapies
- Anti-integrin therapies
- Anti-IL12/23
- JAK inhibitors

Microbiota manipulation
- Antibiotics
- Prebiotics
- Probiotics
- Fecal transplantation
- Bacterial derived proteins
- Diet

Surgery
- Resection of fibrostenosis
- Resection in fulminant disease

Traditional Treatment Strategy for IBD



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

Peyrin-Biroulet L, et al. *Am J Gastroenterol*. 2015;110:1324-38.

Use Organ-Selective Therapies Before Systemic Therapies

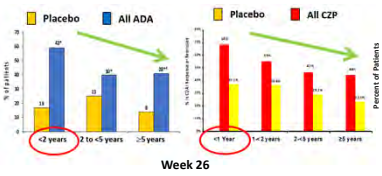
- Topical rectal therapy before systemic therapy in distal colitis
- Budesonide before systemic corticosteroids
- Vedolizumab before systemically active immunosuppressants
  - Older patients
  - Paradoxical IBD in the setting of organ transplantation
- Enteral Therapy in CD (Peds)

Rubin DT, et al. *Am J Gastroenterol*. 2019;114:384-413.

Higher Remission Rates and Lower Loss of Response with Shorter Disease Duration

ADULT

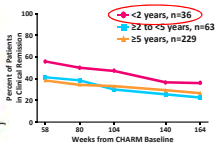
Post-Hoc Analyses of Remission Rates with Adalimumab and Certolizumab Pegol



Week 26

*p=0.02; **p<0.001; all vs placebo
<2 years: PBO n=37, Adalimumab n=56; 2 to <5 years: PBO n=53, Adalimumab n=95; ≥5 years: PBO n=170, Adalimumab n=366

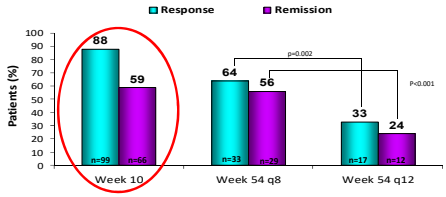
Clinical remission with adalimumab in ADHERE



Schreiber S, et al. *J Crohns Colitis.* 2013;7(3):213-21.
Schreiber S, et al. *Am J Gastroenterol.* 2010;105(7):1574-82.

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

PEDS



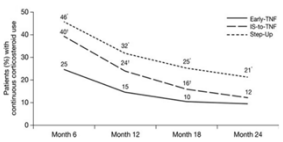
n=112, disease duration ~2 years

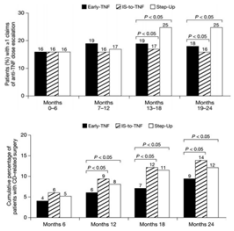
Hyams J, et al. *Gastroenterology.* 2007;132(3):863-73

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

ADULT

- 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")





Rubin DT, et al. *Inflamm Bowel Dis.* 2012;18(12):2225-2231.

Early Anti-TNF Reduces Cost of Crohn's Care

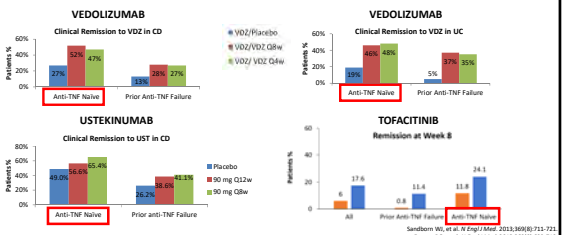
ADULT

	Early Initiation			Late Initiation		
	Mean	Lower end of 95% CI	Upper end of 95% CI	Mean	Lower end of 95% CI	Upper end of 95% CI
Infliximab						
Cost($)	$628,603	$505,698	$765,033	$679,022	$544,734	$829,211
QALYs	12.2	-24.6	39.1	11.5	-23.3	37.7
Net monetary benefit	$16,975	-$1,860,586	$1,328,658	-$103,184	$1,866,584	$1,208,949
Adalimumab						
Cost($)	$472,612	$309,787	$676,268	$516,581	$349,282	$730,350
QALYs	11.9	-23.8	38.8	11.4	-23.9	37.6
Net monetary benefit	$123,388	-$1,663,731	$1,454,085	$52,220	-$1,713,336	$1,345,681

Beilman CL, et al. *Clin Gastroenterol Hepatol.* 2019;17(8):1515-24.

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

ADULT



Sandborn WJ, et al. *N Engl J Med.* 2013;369(8):711-721.
Feagan BG, et al. *N Engl J Med.* 2013;369(8):699-710.
Sandborn W, et al. *Gastroenterology.* 2016;150(4 Suppl 1):S1134-S1135.
Data on file. Pfizer Inc. New York, NY.

Tofacitinib PE and Mortality Interim Report

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

[1]FDA. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-responds-safety-signal-reported-required-postmarketing-trial-xeljanz. Accessed 15 May 2019.
[2]Mease PJ, et al. *Arthritis Rheumatol.* 2017;69(Suppl 10).
[3]EMA. https://www.ema.europa.eu/en/news/restrictions-use-xeljanz-while-ema-reviews-risk-blood-clots-lungs. Accessed 17 May 2019.
[4]FDA. https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and. Accessed 15 August 2019.

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)

	Impact on Pharmacokinetics	Drug Levels (Exposure)
Presence of ADAs	• Decreases serum mAbs • Threefold-increased clearance • Worse clinical outcomes	↓
Concomitant use of IS	• Reduces formation • Increases serum mAbs • Decreases mAb clearance • Better clinical outcomes	↑
High baseline TNF-α	• May decrease mAbs by increasing clearance	↓
Low albumin	• Increases clearance • Worse clinical outcomes	↓
High baseline CRP	• Increases clearance	↓
Body size	• High BMI may increase clearance	↓
Male Sex	• Men have higher clearance	↓

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

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

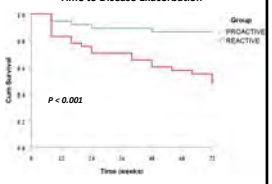
Feuerstein JD, et al. *Gastroenterology*. 2017;153:827-834.

Using TDM with Adalimumab in Pediatric CD (PAILOT)

PEDS

- **PAILOT trial**: peds 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



Assa A, et al. Presented at ECCO 2019. Abstract OP18.

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

ADULT

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

IFX Conc. (% patients)	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	P-values
Week 8	26.3% (<21.3µg/mL)	37.9% (≥21.3-<33µg/mL)	43.9% (≥33-<47.9µg/mL)	43.1% (>47.9µg/mL)	P=0.0504
Week 30	14.6% (<0.11µg/mL)	25.5% (≥0.11-<2.4µg/mL)	59.6% (≥2.4-<6.8µg/mL)	52.1% (>6.8µg/mL)	P<0.0001
Week 54	21.1% (<1.4µg/mL)	55.0% (≥1.4-<3.6µg/mL)	79.0% (≥3.6-<8.1µg/mL)	60.0% (>8.1µg/mL)	P=0.0066

Adedokun OJ, et al. *Gastroenterology*. 2014;146(6):1296-1307.

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

ADULT

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

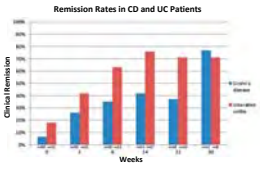
Limitations to VARSITY:
- No dose escalation
- No drug levels
- If on steroids or IMMs, no difference between groups

Sands B, et al. Presented at DDW 2019. Abstract 416a.

Multi-Center Experience of Vedolizumab Effectiveness in Pediatric IBD

PEDS

- **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**



Singh N, et al. *Inflamm Bowel Dis*. 2016;22(9):2121-6.

Escalation of Ustekinumab Dosing is Associated with Recapture of Response

ADULT

- 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)

Treatment: N (%)	Complete Remission N (%)	Response N (%)	No response N (%)
No change: 4 (11)	3 (75)	1 (25)	0 (0)
Q8 to Q4 Weeks: 22 (58)	10 (45)	7 (31)	5 (23)
IV/SQ Reinduction: 7 (18)	1 (14)	2 (29)	4 (57)
+IMM: 3 (8)	0 (0)	1 (33)	2 (67)
Changed out of class: 2 (5)	0 (0)	1 (50)	1 (50)

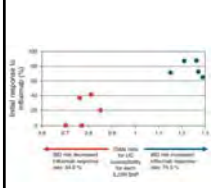
Heron V, et al. Presented at DDW 2019. Abstract Tu1825.

Other Specific Scenarios for Choice of First IBD Therapy

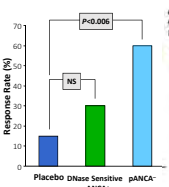
ADULT PEDS

Disease	Modifier	First drug consideration	Reason
CD	Psoriasis	Ustekinumab	On label
IBD	>60 yo	Vedolizumab	Older patients have higher risk of infections
UC	Synovitis Arthritis	Anti-TNF or Tofacitinib	On label
UC	Low albumin	Cyclosporine Tacrolimus Tofacitinib	Small molecules

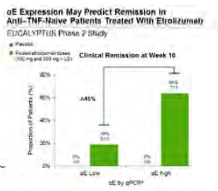
The Ongoing Search for Therapeutic Biomarkers



Schmechel S, et al. *Inflamm Bowel Dis.* 2008;14(2):204-12.



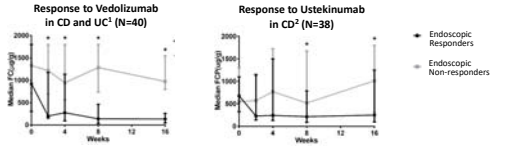
Taylor KD, et al. *Gastroenterology.* 2001;120(6):1347-55.



Vermeire S, et al. *Lancet.* 2014;384(9940):309-18.

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

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

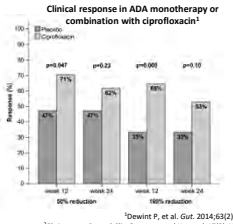


[1]Pauwels RWM, et al. Presented at DDW 2019. Abstract S37.
[2]Pauwels RWM, et al. Presented at DDW 2019. Abstract Mo1887.

Combination of Therapies

ADULT

- **Oral plus rectal 5-ASA**
- **Anti-TNF plus antibiotics for perianal disease[1]**
- **Anti-TNF plus IMM**
- **Calcineurin plus vedolizumab[2,3]**
- **Combination biologics?**
- **Tofacitinib plus vedolizumab?**



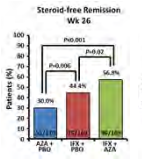
[1]Dewint P, et al. *Gut.* 2014;63(2):292-9.
[2]Christensen B, et al *Clin Gastroenterol Hepatol.* 17(3):486-493.
[3]Pellet G, et al. *Clin Gastroenterol Hepatol.* 17(3):494-501.

Why Might Combination Therapy Be More Effective?

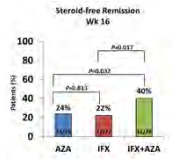
ADULT

- True for both CD (SONIC) and UC (SUCCESS) with infliximab[1,2]
- Multiple mechanisms of disease control
- Reduction in anti-drug antibodies
- Elevation of serum drug levels (greater exposure)

SONIC Trial (CD)[1]



UC SUCCESS Trial[2]



[1]Colombel JF, et al. *N Engl J Med.* 2010;362(15):1383-95.
[2]Panaccione R, et al. *Gastroenterology.* 2014;146(2):392-400.

Combination Therapy is NOT Always Necessary Or Helpful

- SONIC post-hoc: infliximab levels more important than combination therapy[1,2]
- Ustekinumab doesn't benefit from combination therapy[3]
- Vedolizumab doesn't benefit from combination therapy[4-6]
- 5-ASA not helpful when escalating to TNFi[7-8]

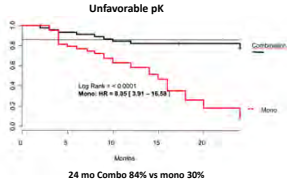
[1]Colombel JF, et al. *N Engl J Med.* 2010;362(15):1383-95.
[2]Colombel JF, et al. *Gastroenterology.* 2017;152(5):537-38.
[3]Sands BE, et al. *Am J Gasteroenterol.* 2018;113:5330.
[4]Colombel JF, et al. *Gastroenterology.* 2015;148(4):5277-8.
[5]Kovlov U, et al. *Inflamm Bowel Dis.* 2017;23:404-408.
[6]Amiot A, et al. *Aliment Pharmacol Ther.* 2017;46:310-321.
[7]Singh S, et al. *Am J Gastroenterol.* 2018;113(8):1197-1205.
[8]Ungaro RC, et al. *Gut.* 2019;68:977-84.

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

ADULT

- 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)

Unfavorable pK



24 mo Combo 84% vs mono 30%

Roblin X, et al. *Inflamm Bowel Dis.* 2018;24(9):2078-85.

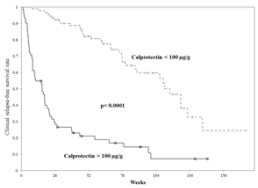
Planning for De-escalation

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

ADULT

- 160 IBD patients (50.6% Male)
- Fcal >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
  - Fcal > 100 µg/g in patients attempting to discontinue steroids was predictive of relapse (n=37; p=0.001)



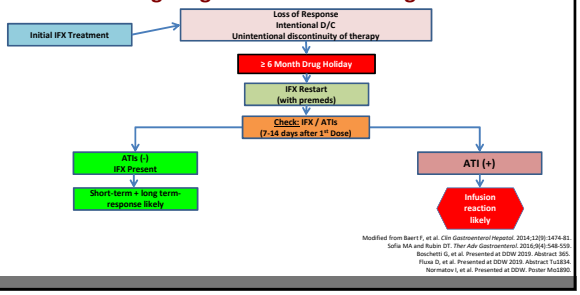
Fcal should be measured 3 months after therapeutic de-escalation and then every 6 months

Buisson A, et al. *J Crohns Colitis.* 2019;13(8):1012-24.

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 that was 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



Modified from Baert F, et al. *Clin Gastroenterol Hepatol*. 2014;12(9):1474-81.
Sofia MA and Rubin DT. *Ther Adv Gastroenterol*. 2016;9(4):548-559.
Boschetti G, et al. Presented at DDW 2019. Abstract 365.
Fluxa D, et al. Presented at DDW 2019. Abstract Tu1834.
Normatov I, et al. Presented at DDW. Poster Mo1890.

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

ADULT | PEDS

- 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 its needed
- Circling backwards is reasonable, but unproven
- Restarting after elective drug holidays

Immunosuppressive therapy in pediatric IBD: can we de-escalate therapy?

Anne M Griffiths, MD, FRCPC
Co-Lead, Inflammatory Bowel Disease Centre
Northbridge Chair in IBD,
SickKids Hospital,
Professor of Pediatrics,
University of Toronto

UNIVERSITY of TORONTO

SickKids | Inflammatory Bowel Disease Centre

1

Disclosures

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

Commercial	Relationship
Janssen, Abbvie, Lilly	Advisory board or other consulting
Abbvie	Speaker fees
Abbvie	Investigator-initiated research support
Takeda, Janssen	Industry-initiated clinical trial participation

2

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**

3

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

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

4

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

- **Stopping anti-TNFs**

Discontinuation of concomitant immunemodulator in patients receiving biologics

Altering regimen to reduce biologic exposure

5

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

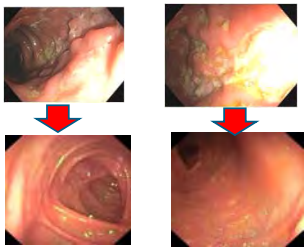
- **Luminal inflammatory Crohn's disease following failure of immunemodulators to achieve steroid-free clinical remission and/or intestinal healing**
- **As first-line therapy for luminal inflammatory Crohn's disease**
- **Perianal fistulizing disease**

- **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**

6

Can we stop anti-TNF therapy? After successful treatment of luminal inflammatory CD?

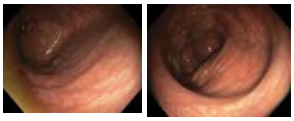
- 11 year old boy presented with endoscopically severe ileocolonic disease
- Treated initially with infliximab induction and maintenance dosing guided by trough levels (5 mg/kg q 6 weekly) in combination with MTX
- Intestinal healing documented at 18 months



7

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
- Endoscopic and histologic remission



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Pediatric framework for discussion of stopping

- Anti-TNF therapy is very frequently used early in pediatric Crohn's disease management without trial of immunemodulators
- 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?

9

Stopping anti-TNFs

What is the concern about stopping?

- Recurrence of active IBD
- **Subsequent lack of efficacy**

What is the worry about continuing?

- **Potential side effects (particularly neoplasia risk)**
- Cost/inconvenience

10 *Beaugerie L, Clin Gastro Hepatol 2019; 17: 370-379

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

11

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

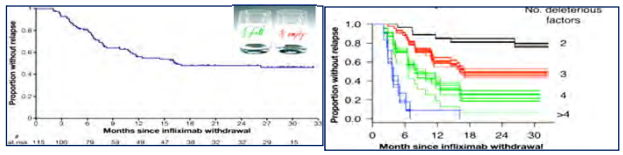
- **In Crohn's disease: The STORI continues: recent longer term follow-up of the original GETAID cohort**
  (Reenaers C et al. Clin Gastro Hepatol 2018;16:234-243)
- **In any IBD:**
  - Systematic review and meta-analysis (2016)
  - More recent observational studies

Gisbert JP, Am J Gastro 2016; 111: 632-647; Casanova, Am J Gastro 2017; 112: 120-131; Molander, Scand J Gastro 2017; 52:284-290

12

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

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



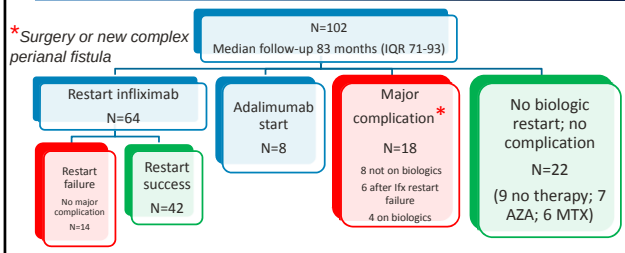
Time to relapse

Risk factors for relapse

Remission regained with re-treatment in 88%

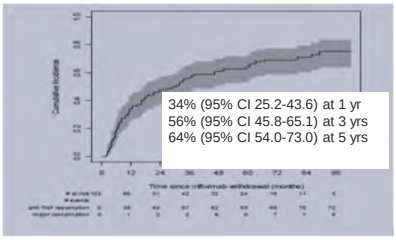
Louis E. et al Gastroenterology 2012: 42: 63-70

The STORI continues: 7 year follow-up



Reenaers C et al. Clin Gastroenterol Hepatol *2018;16:234-243*

Time to resumption of anti-TNF following infliximab discontinuation

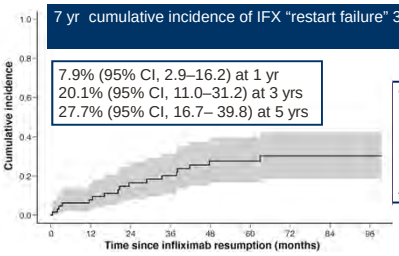


71% restarted anti-TNF (infliximab or adalimumab) after
median 13 months (IQR 6-33 months)

Reenaers C et al. Clin Gastroenterol Hepatol *2018;16:234-243.*

Time to infliximab "restart failure" following resumption (n=64)

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

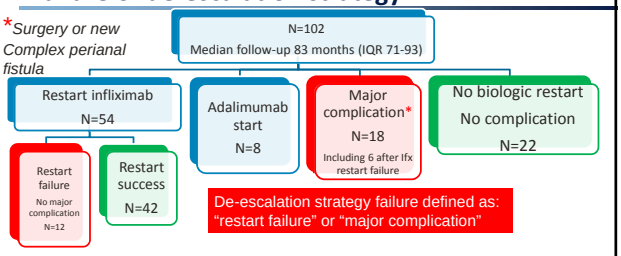


7.9% (95% CI, 2.9–16.2) at 1 yr
20.1% (95% CI, 11.0–31.2) at 3 yrs
27.7% (95% CI, 16.7– 39.8) at 5 yrs

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

16 Reenaers C et al. Clin Gastroenterol Hepatol *2018;16:234-243.*

"Failure of de-escalation strategy"



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

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

17 Reenaers C et al. Clin Gastroenterol Hepatol *2018;16:234-243.*

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

	Total number of patients	Percentage with relapse	Follow-up (months)
Crohn's Disease	912	44% 95% CI (36-51%)	6-125
Ulcerative Colitis	266	38% 95% CI (23-52%)	6-24

Gisbert JP et al. Am J Gastroenterol. 2016;111:632-647

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Increasing risk of relapse over time (Crohn's Disease)

Total number of patients	Follow-up	Percentage with relapse
126	6 months	38% 95% CI (13-63%)
813	12-24 months	40% 95% CI (33-48%)
288	>25 months (28-125 months)	49% 95% CI (31-68%)

Gisbert JP et al. Am J Gastroenterol. 2016;111:632-647

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Risk of relapse in those with prior clinical vs endoscopic remission

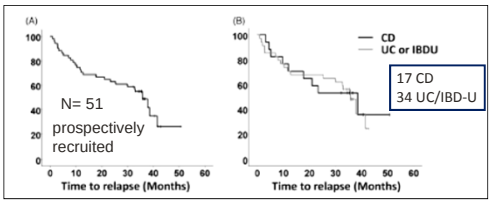
	Clinical Remission	Endoscopic Remission
Relapse by 6months	61%	18%
Relapse within first year	42% 95% CI (32-52%) n=448	26% 95% CI (15-37%) n=57
After first year, by 24 months	42% 95% CI (25-58%) n=231	44% 95% CI (31-58%) n=52

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

Gisbert JP et al. Am J Gastroenterol. 2016;111:632-647

20

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



60% relapse after median follow-up 36 months

21

Molander P et al. Scandinavian Journal of Gastroenterology, 2017 52: 284-290

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 immunemodulator

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%

22 Casanova et al. Am J Gastroenterol. 2017;112(1):120-131

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

- **Luminal inflammatory Crohn's disease following failure of immunemodulators 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**

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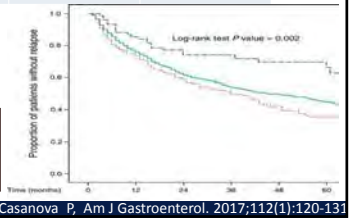
Small subset treated with "top-down" anti-TNF

	Top-down (n=24)	Elective (n=400)	Adverse events (n=36)
Anti-TNF duration	4 months	21 months	14 months
IFX induction only	44% (30)	4% (30)	7% (12)

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

Factors	HR	95% CI	P value
Maintenance of IMMs after discontinuation	0.70	0.57–0.88	0.002
Older age at discontinuation	0.99	0.98–0.99	<0.0001
Elective discontinuation (vs. discontinuation for top-down strategy)	1.82	1.19–2.79	0.006
Discontinuation because of adverse events (vs. discontinuation as part of a top-down strategy)	1.95	1.22–3.12	0.005

IMM, immunomodulator; TNF, tumor necrosis factor.



24 Casanova P, Am J Gastroenterol. 2017;112(1):120-131

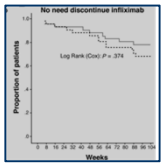
Outline: De-escalation of biologic therapy (anti-TNFs)

Stopping biologics

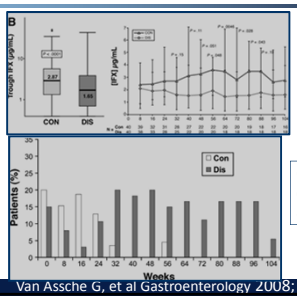
- **Lesser degrees of de-escalation**
  - Discontinuation of concomitant immunemodulator in patients receiving biologics
  - Altering regimen (guided by therapeutic drug monitoring) to reduce (avoid unnecessarily high) biologic exposure

25

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



Similar durability of clinical response



Lower infliximab trough levels following discontinuation

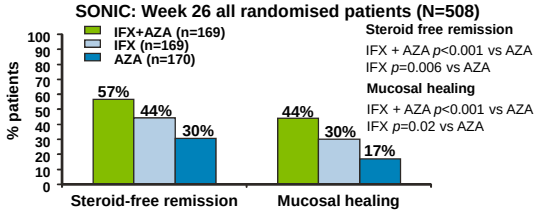
Greater prevalence of undetectable drug at trough

26

Van Assche G, et al Gastroenterology 2008; 134: 1861-1868

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

Infliximab combination therapy has a small treatment benefit compared with monotherapy



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

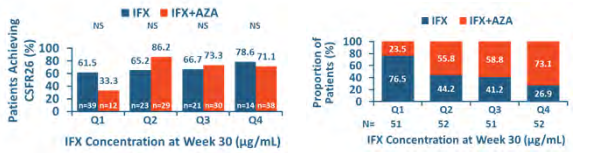
IFX p=0.02 vs AZA

27

Colombel J, *et al. N Engl J Med* 2010;362:1383

Likelihood of clinical remission according to drug level concentration at trough (patients grouped according to quartiles of drug level)

SONIC



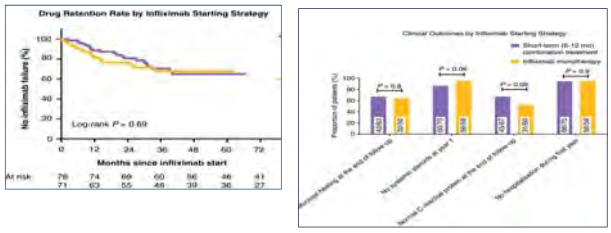
Q1: <0.84 µg/mL Q2: 0.84 µg/mL to <2.36 µg/mL Q3: 2.36 µg/mL to <5.02 µg/mL Q4: ≥5.02 µg/mL

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

Colombel JF, et al. Clin Gastro Hepatol 2018

28

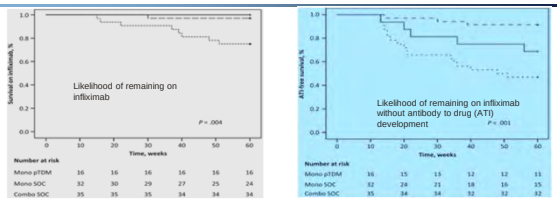
Optimised infliximab monotherapy versus combination therapy



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

29

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

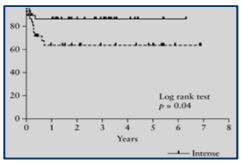


Solid line = personalized monotherapy n=16
Dotted line = standard monotherapy n= 32
Dashed line = combination therapy n= 35

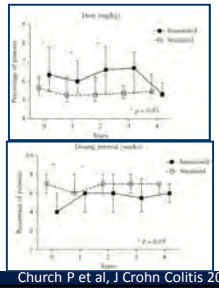
Lega S et al. Inflamm Bowel Dis 2019; 25: 134-141

30

Intensified infliximab reduces colectomy rates in acute severe steroid-refractory pediatric UC: subsequent de-escalation



Colectomy-free survival (intensified versus standard Induction dosing)



Per kg dose reduction

and/or

Interval lengthening

Church P et al, J Crohn Colitis 2019; 13: 982-989

31

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 immunemodulator is continued
- Experience with stopping anti-TNF when administered as **first** therapy (without prior failure of immunemodulator) is, however, very limited, despite the increasing prevalence of such patients in pediatric practice
- Re-treatment with anti-TNF is usually (in ~70-80%) successful
- Lesser degrees of de-escalation (e.g. stopping concomitant immunemodulator) are more successful and can be guided by therapeutic drug monitoring (TDM)

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FUTURE DIRECTIONS

- Proactive TDM is opening an era of individualized therapy with potential to ascertain and maintain optimal target levels and avoid over-exposur**e**
- 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)

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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
- Eosinophilic/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

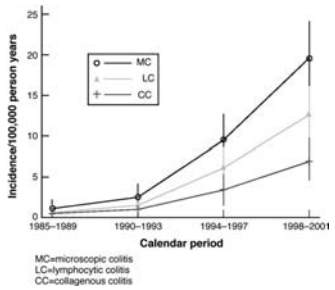
IBD	Microscopic Colitis
Females ~ Males	Females >> Males
Young adults and children	Ages 50-60
Bloody diarrhea	Watery diarrhea
Urgency	Urgency and incontinence
Weight loss	Little/no weight loss
Endoscopic inflammation	Visually normal endoscopy

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

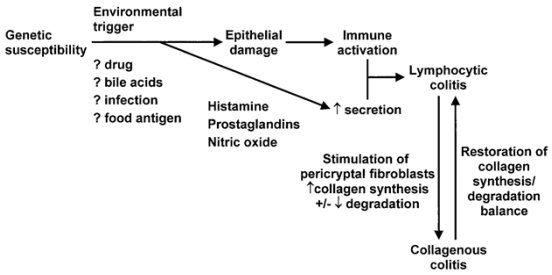
Pardi DS. Am J Gastroenterol 2017
Munch A and Langner C. Clin Gastroenterol and Hep 2015

Microscopic Colitis is on the Rise



Pardi D and Kelly C. Gastroenterol. 2011

Pathogenesis of Microscopic Colitis



Pardi D et al. Am J Gastroenterol 2002

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

Morgan DM. et al. Clin Gastroenterol and Hepatol. 2019

Drugs That Trigger MC

Low Likelihood	Intermediate Likelihood	High Likelihood
Cimetedine	Carbamazepine	Acarbose
Gold Salts	**Celecoxib**	Aspirin
Piascledine	Duloxetine	Clozapine
	Fluvastatin	Entocapone
	Flutamide	Flavonoid
	Oxetorone	**Lansoprazole**
	Madopar	**Es/omeprazole**
	Paroxetine	**NSAIDs**
	Simvistatin	**Ranitidine**
	Stevelo	Sertraline
		Ticlopidine

Munch A. et al. J Crohn's and Colitis. 2012

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

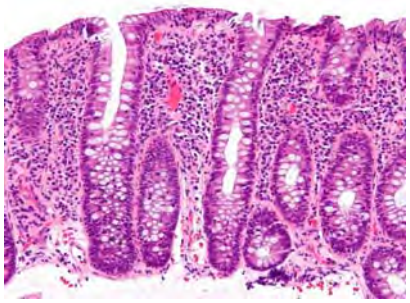
Watery Diarrhea Syndromes

Histology Is the Key to Diagnosis

Percent (%)	Normal	IBD	Lymphocytic Colitis	Collagenous Colitis
Intraepithelial lymphocytes	4.6	4.4	**24.6**	**21.2**
Intraepithelial eosinophils	<0.1	0.8	**1.3**	**4.8**
Intraepithelial neutrophils	0.4	**1.4**	0.3	0.2
Crypt distortion	0.3	**1.9**	0.8	0.5
Sub-epithelial collagen	0	0	0	**100**
Epithelial flattening	7.3	8.2	**35.2**	**35.4**
Epithelial loss	10	6	4.7	**20**

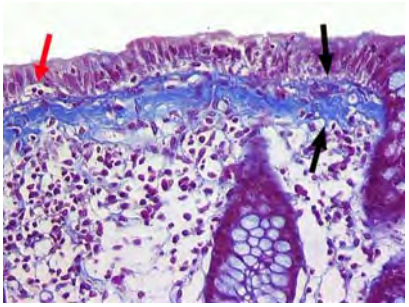
Lazenby A. et al. Human Pathology. 1989

Lymphocytic Colitis



https://www.webpathology.com/image.asp?case=1038&n=14

Collagenous Colitis



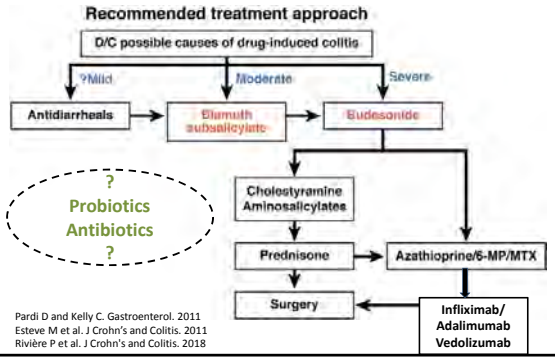
https://www.webpathology.com/image.asp?case=1038&n=8

Collagenous Colitis in Children

	Pediatric-Onset	Adult-Onset
Symptoms	Abdominal pain Iron deficiency anemia	Abdominal pain Voluminous non-bloody diarrhea Malabsorption Protein-losing enteropathy
Histology	Collagen in stomach	Collagen throughout GI tract Increased inflammation
First Pediatric Case	Dick Colletti & Thomas Trainer 1989	Dick Colletti et al. 1998

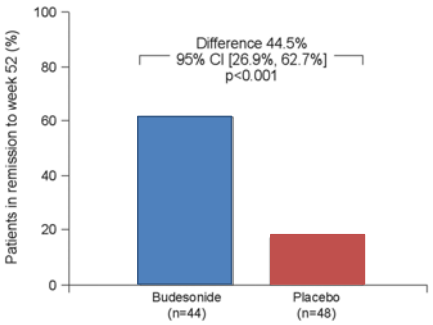
Matta J et al. JPGN 2018

Management of Microscopic Colitis



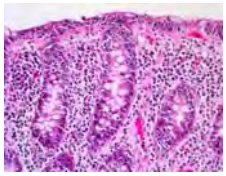
Pardi D and Kelly C. Gastroenterol. 2011
Esteve M et al. J Crohn's and Colitis. 2011
Rivière P et al. J Crohn's and Colitis. 2018

Budesonide Treatment for MC



Münch A et al. Gut 2016

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


"THE GIRL WITH COLITIS GOES BY."
WRONG. THAT'S "THE GIRL WITH KALEIDOSCOPE EYES".
I THOUGHT THE BEATLES HAD A THING FOR INFLAMED COLONS.

Eosinophilic Inflammation Beyond the Esophagus

Edaire Cheng, MD

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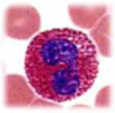
UT Southwestern
Medical Center

Disclosures

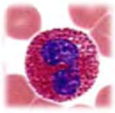
- Consultant – Guide Point Global

Eosinophils Beyond the Esophagus: Outline

- Definition and Diagnosis
- Epidemiology and Demographics
- Clinical Presentation
- Diagnostic Approach
- Management Approach



Eosinophilic Gastrointestinal Diseases (EGIDs)



EGIDs are a group of immune-mediated diseases characterized by gastrointestinal eosinophilia accompanied with gastrointestinal symptoms.

Dellon et al. Clin Gastroenterol Hepatol 2014;
Mansour et al. Clin Gastroenterol Hepatol 2017;
Liacouras et al. J Allergy Clin Immunol 2011.

Eosinophilic Gastrointestinal Disorders (EGIDs)

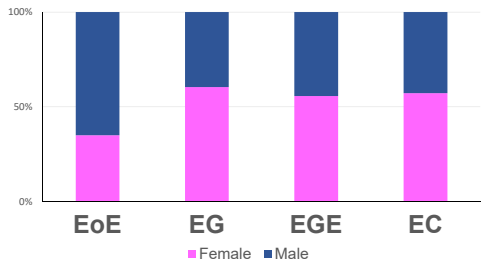
- Eosinophilic Esophagitis (EoE)
- Eosinophilic Gastritis (EG)
- Eosinophilic Gastroenteritis (EGE)
- Eosinophilic Enteritis (EEnt)
- Eosinophilic Colitis (EC)

EGID Epidemiology

EGID	Prevalence (per 100,000)
EoE	57
EG	6.3
EGE	5.1 - 8.4
EC	2.1 – 3.3

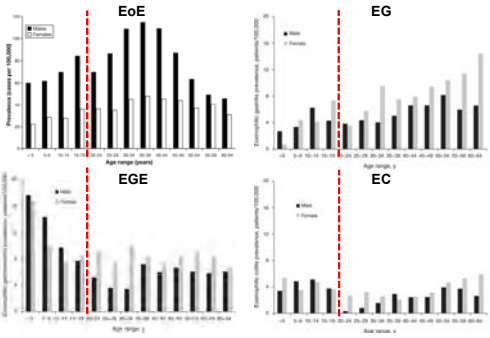
Jensen et al. J Pediatr Gastroenterol Nutr 2016.
Mansoor et al. Clin Gastroenterol Hepatol 2017.

EGID Demographics: Gender



Dellon et al. Clin Gastroenterol Hepatol 2014.
Jensen et al. J Pediatr Gastroenterol Nutr 2016.
Mansoor et al. Clin Gastroenterol Hepatol 2017.
Pesek et al. Am J Gastroenterol 2019.

EGID Demographics: Age

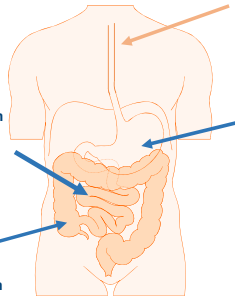


Dellon et al. Clin Gastroenterol Hepatol 2014.
Jensen et al. J Pediatr Gastroenterol Nutr 2016.

EGID Diagnosis

- **Clinical Features**
  - Gastrointestinal symptoms
- **Histological Features**
  - Eosinophil-predominant gastrointestinal inflammation
  - Exclude other intestinal eosinophilia

EGID Clinical Presentation Depends on Location



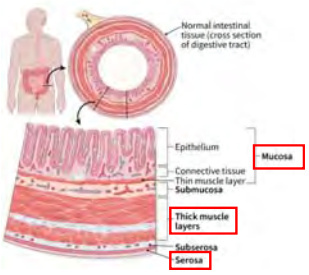
Esophagus
- Dysphagia
- Odynophagia
- Food impaction
- Heartburn
- Vomiting

Small Intestine
- Abdominal pain
- Nausea
- Vomiting
- Diarrhea
- Obstruction

Stomach
- Abdominal pain
- Nausea
- Early Satiety
- Loss of Appetite
- Vomiting
- Bloating
- Diarrhea

Colon
- Diarrhea
- Blood in stool
- Abdominal pain

EGID Clinical Presentation Depends on Depth



- **Mucosal Disease**
  - Abdominal pain
  - Vomiting
  - Diarrhea
  - Anorexia
  - Weight loss
  - Failure to Thrive
  - Protein Losing Enteropathy (edema and anemia)
- **Muscular Disease**
  - Obstruction
- **Serosal Disease**
  - Ascites

Klein et al. Medicine 1970.
Talley et al. Gut 1990.
Chehade et al. J Pediatr Gastroenterol Nutr 2006.
Ko et al. Am J Gastroenterol 2014.

EGID Diagnostic Workup

Other Clinical History That Raises Your Suspicion

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%)

Talley et al. Gut 1990.
Chang et al. Clin Gastroenterol Hepatol 2010.
Ko et al . Am J Gastroenterol 2014.
Jensen et al. J Pediatr Gastroenterol Nutr 2016.
Mansoor et al. Clin Gastroenterol Hepatol 2017.

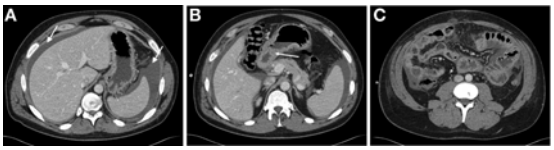
EGID Diagnostic Workup

Other Clinical/Laboratory Findings That Raises Your Suspicion

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

EGID Diagnostic Workup

Other Radiological Findings That Raises Your Suspicion



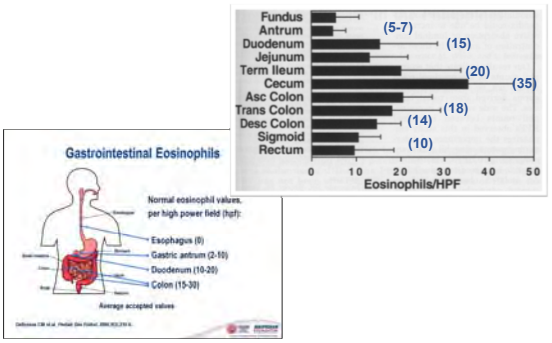
Ascites | **Gastric Mural Thickening** | **Small Bowel Mural Thickening**

Chang et al. Clin Gastroenterol Hepatol 2010.

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?



Lowichik, Weinberg. Mod Path 1996.
DeBrosse et al. Pediatr Dev Pathol 2006

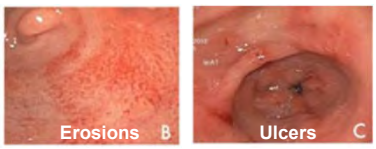
What is an Abnormal Number of Eosinophils?

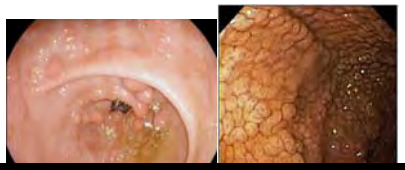
- Greater than two times the normal (rule of thumb)
- Stomach
  - ≥30 eosinophils/HPF
- Duodenum
  - >52 eosinophils/HPF
- Ileum
  - >56 eosinophils/HPF
- Colon
  - Right colon: >100 eosinophils/HPF
  - Transverse and descending colon: >84 eosinophils/HPF
  - Rectosigmoid colon: >64 eosinophils/HPF
- Note any altered eosinophil distribution and epithelial changes

Collins. Gastroenterol Clin North Am 2014.

Eosinophilic Gastritis: Endoscopic Features

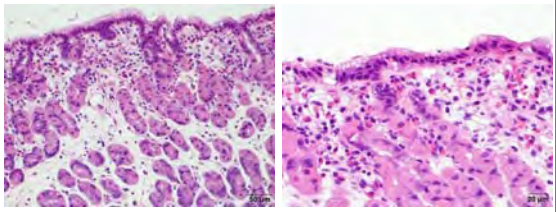
- Erythema
- Edema
- Ulcerations
- Erosions
- Nodules
- Polyps
- Normal





Mucosa can appear normal.

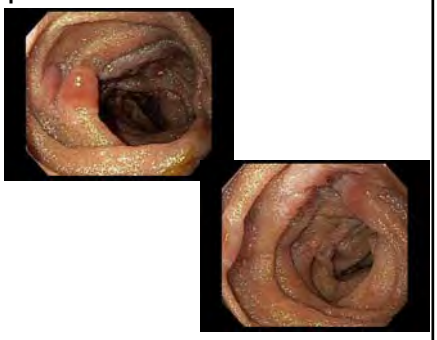
Eosinophilic Gastritis: Histologic Features



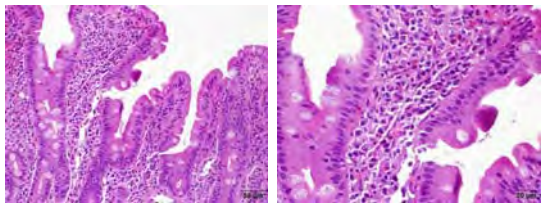
The disease is patchy!

Eosinophilic Enteritis/Gastroenteritis: Endoscopic Features

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

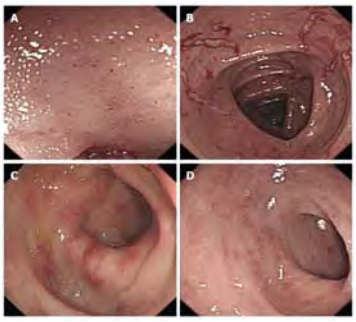


Eosinophilic Enteritis/Gastroenteritis: Histologic Features



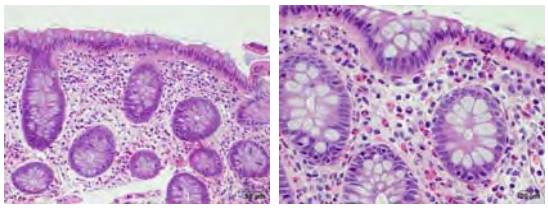
Eosinophilic Colitis: Endoscopic Features

- Erythema
- Edema
- Polyps
- Ulcerations
- Normal



Abassa et al. World J Gastroenterol 2017.

Eosinophilic Colitis: Histologic Features



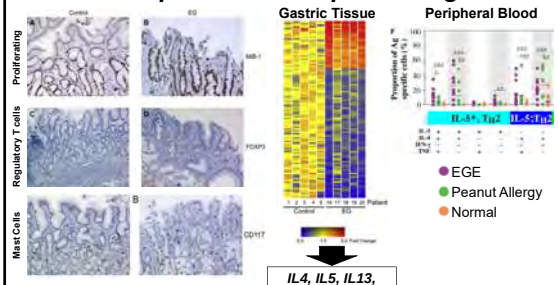
EGID Diagnostic Workup

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?

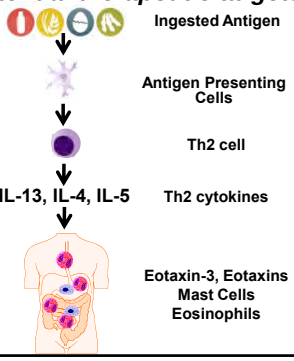


IL4, IL5, IL13, IL17, CCL26, mast cell-specific transcripts

Prussin et al. J Allergy Clin Immunol 2009.
Foster et al. Clin Mol Allergy 2011.
Caldwell et al. J allergy Clin Immunol 2014.

EGID Pathogenesis

What are potential therapeutic targets?



Prussin et al. J Allergy Clin Immunol 2009.
Foster et al. Clin Mol Allergy 2011.
Caldwell et al. J allergy Clin Immunol 2014.

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”

Pineton de Chambrun et al. Clin Gastroenterol Hepatol 2011.
Reed et al. Dig Liv Dis 2015.

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”

Lucendo et al. J Pediatr Gastroenterol Nutr 2015.

EGID Management

- **Other therapies**
  - Cromolyn (mast cell stabilizer)
    - Symptomatic relief
      - *Moots et al. Gut 1988.*
      - *Talley et al. Gut 1990.*
      - *Di Gioacchino et al. Allergy 1990.*
      - *Ko et al. Am J Gastroenterol 2014.*
  - Montelukast
    - Symptomatic relief
      - *Neustrom et al. J Allergy Clin Immunol 1999.*
      - *Friesen et al. J Pediatr Gastroenterol Nutr 2004.*
  - Omalizumab (anti-IgE)
    - Not effective
      - *Foster et al. Clin Mol Allergy 2011.*
  - Vedolizumab (anti-α4β7)
    - Effective in series of steroid-refractory cases (3/4 patients)
      - *Grandinetti et al. Dig Dis Sci 2019.*

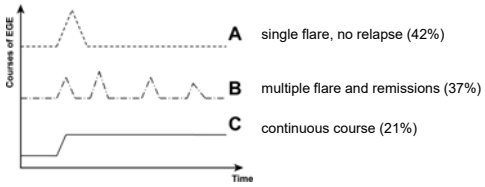
EGID Future

- **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)**

http://investor.allakos.com/news-releases/

  - Elemental diet in adults with EGE (NCT 03320369)
  - Benralizumab (anti-IL5R) in teens/adults with EG (NCT 03473977)
  - Dupilumab (anti-IL4R) in adults with EG (NCT 03678545)

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