# WORLD CONGRESS OF PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

OCTOBER 5-8, 2016 • MONTRÉAL • CANADA

*Dedicated to the memory of*

**Dr. Claude Roy**

## Wednesday October 5, 2016

# Postgraduate Course

Place d'Armes / Credit : © Tourisme Montréal, Stéphan Poulin

# Table of Contents

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## Continuing Medical Education

### NASPGHAN CME Mission Statement

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

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

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

### Physicians

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

### AMA PRA Statement

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

**World Congress of Pediatric Gastroenterology, Hepatology and Nutrition**

**Postgraduate Course** October 5, 2016 Palais des Congres Montreal, PQ

8:00 am- 5:00 pm

7:55am – 8:00am Welcome and Introduction

**8:00am – 9:15am MODULE 1 - ENDOSCOPY**

Moderators: Marsha Kay MD and Melanie Greifer MD

Practical advances in pediatric endoscopy: Keeping it real

*Bradley Barth MD, University of Texas Southwestern*

Learning Objectives*:*

1. Improve understanding of pediatric specific factors relating to emerging hemostatic techniques
2. Improve understanding of the role that diagnostic and therapeutic endoscopic ultrasound can play in the care of pediatric patients
3. Discuss the role of the pediatric gastroenterologist and pediatric endoscopist in 2016

Colonoscopy considerations in lower GI emergencies

*Doug Fishman MD, Baylor College of Medicine*

Learning Objectives:

1. Discuss the role of endoscopy in lower GI emergencies
2. Explain peri-procedure considerations in various disease states
3. Outline diagnostic and therapeutic options and techniques in colonoscopy for lower GI emergencies

Endoscopic Interventions in GI motility disorders

*Ajay Kaul MD, Cincinnati Children's Hospital Medical Center*

Learning Objectives:

1. Identify motility disorders of the GI tract that are amenable to endoscopic intervention
2. Discuss specific endoscopic interventions as treatment options for GI motility disorders
3. Discuss outcomes of endoscopic interventions for GI motility disorders

Rapid Fire Q and A

**9:15am – 10:50am MODULE 2 - GI POTPOURRI**

Moderators: Terry Sigman MD and Jennifer Strople MD

New insights into congenital diarrheal disorders

*Martín Martín MD, University of California, Los Angeles*

Learning Objectives:

1. Review the clinical work-up of an infant with congenital diarrhea
2. Outline the diagnostic dietary challenges that can be used to categorize this group of children
3. Discuss the use of whole exome sequencing in evaluating patients with congenital diarrhea

Genotype and phenotype characterization of hereditary polyposis syndromes

*Carol Durno MD, University of Toronto*

Learning Objectives:

1. Understand the current classification of intestinal polyposis
2. Highlight new diagnostic considerations in polyposis syndromes
3. Review the emerging role of immunotherapy in the management of specific polyposis associated colorectal cancers

Interventions for managing obesity in children: Lifestyle, medications and surgery
*Joel Lavine MD, Columbia University*
Learning Objectives:

1. Recognize the need for early identification of children at risk for obesity and recommend institution of sustainable lifestyle interventions
2. Be aware of the pharmacologic targets based on knowledge of energy regulation and feeding behavior, and evolving strategies to intervene
3. Be able to identify adolescents who may benefit from bariatric surgery intervention and be knowledgeable of risk

Intestinal failure: The long and short of the matter
*Valeria Cohran MD, Ann and Robert Lurie Children's Hospital*
Learning Objectives:

1. List the prognostic indicators of achieving enteral autonomy
2. Describe the rationale for the use of prebiotics
3. Discuss the evidence that supports the use of breast milk in patients with short bowel syndrome
4. Define dysbiosis in patients with short bowel syndrome

Rapid Fire Q and A

**10:50am** **Break**

**11:10am – 12:25pm** **MODULE 3 – INFLAMMATORY BOWEL DISEASE**
Moderators: Maria Oliva - Hemker MD and Jennifer Strople MD

Diet in pediatric IBD: Food for thought…
*Sandy Kim MD, Nationwide Children's Hospital*
Learning Objectives:

1. Address how our diet impacts the gastrointestinal tract
2. Review the efficacy of enteral therapy in Crohn's disease
3. Discuss specific defined diets which have been utilized in IBD

Biosimilars in IBD: Lessons from our European colleagues
*Lissy de Ridder MD, Erasmus Hospital, Rotterdam, Netherlands*
Learning Objectives:

1. Learn the difference between a generic and a biosimilar
2. Understand the important driver behind the introduction of anti-TNF biosimilars
3. Know if and when we should we switch to biosimilars or not

The role of objective disease monitoring in IBD
*Anne Griffiths MD, Hospital for Sick Kids*
Learning Objectives:

1. Establish treatment targets in IBD
2. Understand the utility and limitations of serum and fecal inflammatory biomarkers.
3. Utilize and interpret imaging and/or endoscopic findings appropriately

Rapid Fire Q and A

**12:25pm – 1:50pm** **Learning Lunches**

**1:50pm – 3:25pm** **MODULE 4 - LIVER/PANCREAS**

Moderators: Regino Gonzalez-Peralta MD and Melanie Greifer MD

Updates on autoimmune hepatitis and "overlap syndromes"

*Fernando Alvarez MD, University of Montreal*

Learning Objectives:

1. Characterize the clinical, biochemical, and histologic phenotypes of liver autoimmune disorders
2. Understand the differential diagnosis of liver autoimmune diseases
3. Learn the prognosis of patient based on final diagnosis and liver status at onset

Alagille syndrome: What's new?

*Binita Kamath MD, Hospital for Sick Kids*

Learning Objectives:

1. Recognize the broader genotype and phenotype associated with Alagille syndrome
2. Identify a novel method to predict liver disease outcomes in Alagille syndrome
3. Discover a potential novel therapy for pruritus in Alagille syndrome
4. Explore advances in stem-cell based technologies that may shed light on disease mechanisms in Alagille syndrome and other biliary disorders

Steatorrhea: What if it's not cystic fibrosis

*Mark Lowe MD, University of Pittsburgh*

Learning Objectives:

1. Explain the physiology of dietary fat digestion and absorption
2. Recall the differential diagnosis of fat malabsorption
3. Discuss the pros and cons of tests for pancreatic insufficiency

*Bienvenue*: 2016 updates in pediatric acute pancreatitis management

*Maisam Abu-El-Haija MD, Cincinnati Children's Hospital Medical Center*

Learning Objectives:

1. Recognize the impact of acute pancreatitis in pediatrics.
2. Identify background, prevalence & etiologies of pediatric pancreatitis
3. Recognize the advances in management of acute pancreatitis up to the year 2016
4. Recognize and manage severe acute pancreatitis

Rapid Fire Q and A

**3:45pm – 5:00pm** **MODULE 5 - FUNCTIONAL GASTROENTEROLOGY**

Moderators: Deepali Tewari MD and Melanie Greifer MD

The new Rome IV criteria for infants with functional gastrointestinal disorders

*Marc Benninga MD, University of Amsterdam*

Learning Objectives:

1. Learn about the new Rome IV criteria for functional GI disorders in the first 4 years of life
2. Learn about the microbiome in infants with colic
3. Learn about new algorithms to diagnose and treat infants and toddlers with functional GI disorders

Not everything that comes up IS reflux: "Vomiting" in the older child

*Samuel Nurko MD, Boston Children's Hospital*

Learning Objectives:

1. Recognize the differential diagnosis of vomiting in the older child
2. Describe the evaluation of the child with vomiting
3. Understand the treatment of the older child with vomiting

How to make the bowel less irritable: Update on treatment of IBS
*Carlo Di Lorenzo MD, Nationwide Children's Hospital*
Learning Objectives:

1. Become familiar with the central and peripheral pathogenetic mechanisms of IBS
2. Recognize the role of dietary treatment of childhood IBS
3. Understand the value of pharmacological and non-medical treatment of childhood IBS

Rapid Fire Q and A

**LEARNING LUNCHES (separate registration required):**

1. Therapeutic endoscopy - Bradley Barth and Doug Fishman
   Moderator: Marsha Kay
2. Upper GI tract motility disorders - Ajay Kaul and Samuel Nurko
   Moderator: Ritu Walia
3. Challenging Liver Cases – Binita Kamath and Fernando Alvarez
   Moderator: Henry Lin
4. Diet in IBD – Sandra Kim, Lindsey Albenberg and Inez Martincevic
   Moderator: Dinesh Pashankar
5. IBD: Top down/step up – Lissy de Ridder and Anne Griffiths
   Moderator: Maria Oliva Hemker
6. Short gut - Valeria Cohran and Ethan Mezoff
   Moderator: Jyoti Ramakrishna
7. Obesity –Joel Lavine, Jennifer Woo Baidal and Christine Haro
   Moderator: Elizabeth Yu
8. Pancreas – Mark Lowe and Maisam Abu-El-Haija
   Moderator: Deborah Neigut
9. Polyposis – Carol Durno and Shlomi Cohen
   Moderator: Maria Perez
10. Diarrhea – Martín Martín and Natalie Terry
    Moderator: Terry Sigman
11. Functional GI Disorders – Marc Benninga and Carlo Di Lorenzo
    Moderator: Deepali Tewari

children's health Children's Medical Center | UT Southwestern Medical Center

# Practical Advances in Pediatric Endoscopy: Keeping it Real

**Brad Barth, MD, MPH, FASGE**

**October 5, 2016**

## Disclosures

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

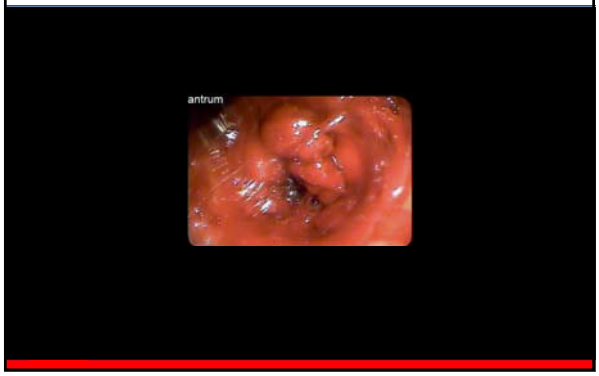
## Objectives

- Improve understanding of pediatric specific factors relating to emerging hemostatic techniques
- Improve understanding of the role that diagnostic and therapeutic endoscopic ultrasound can play in the care of pediatric patients
- Discuss the role of the pediatric gastroenterologist and pediatric endoscopist in 2016

## Content

- Hemostasis
  - Over-the-scope clips
  - Hemospray
- Balloon assisted enteroscopy
- Endoscopic ultrasound
- Cholangioscopy

## Hemostasis



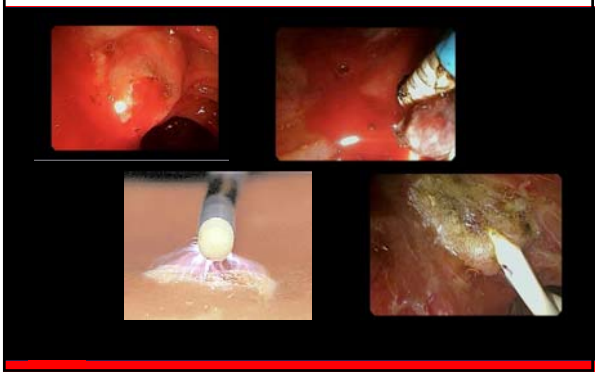

## Hemostasis

**TABLE 3. Stigmata of ulcer hemorrhage and risk of recurrent bleeding without endoscopic therapy**

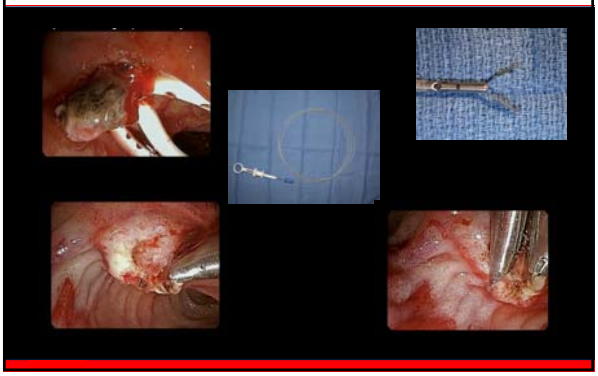
| Stigmata | Risk of recurrent bleeding without therapy |
|---|---|
| Active arterial bleeding (spurting) | Approaches 100% |
| Non-bleeding visible vessel | Up to 50% |
| Non-bleeding adherent clot | 8%-35% |
| Ulcer oozing (without other stigmata) | 10%-27% |
| Flat spots | <8% |
| Clean-based ulcers | <3% |

Standards of Practice Committee. GIE 2012.

## Hemostasis



## Hemostasis



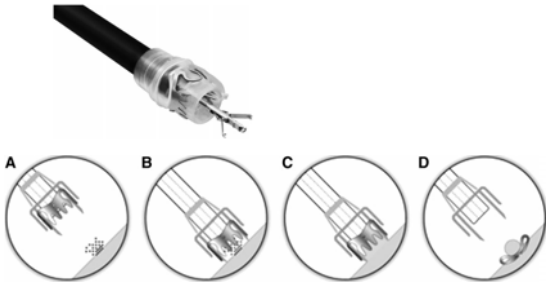
## Hemostasis

So what's new?

## Hemostasis

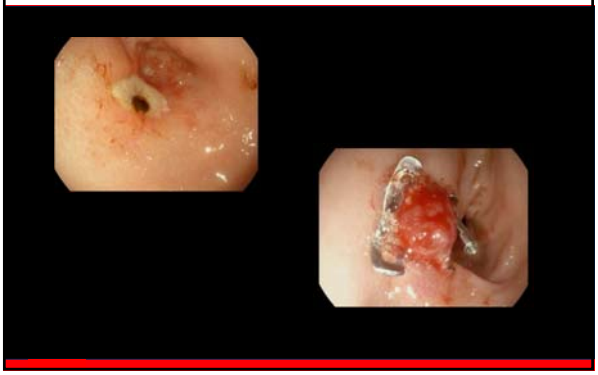
- Over-the-scope clips
  - Easy to use
  - Cover large area
  - Excellent for “en-face” lesions
  - Strong and lasting grasp
  - Requires standard gastroscope (9 mm OD) or larger
  - 3 or 6 mm deep cap
  - Nitinol alloy, MRI “safe”

## Hemostasis

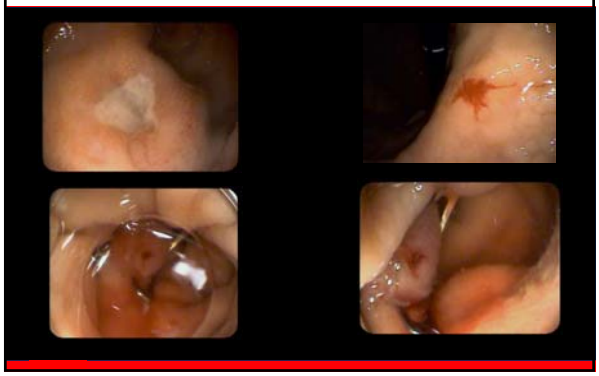



Wright et al. J Lap Surg Tech 2015

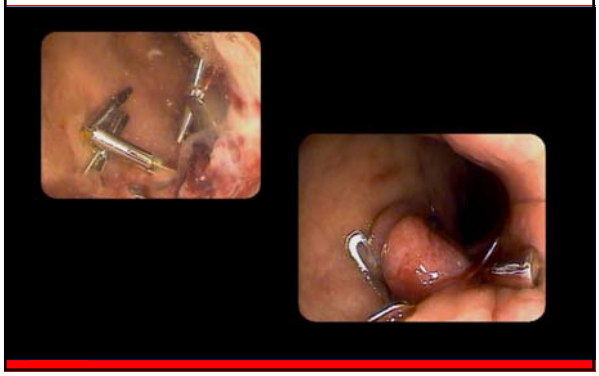
## Hemostasis



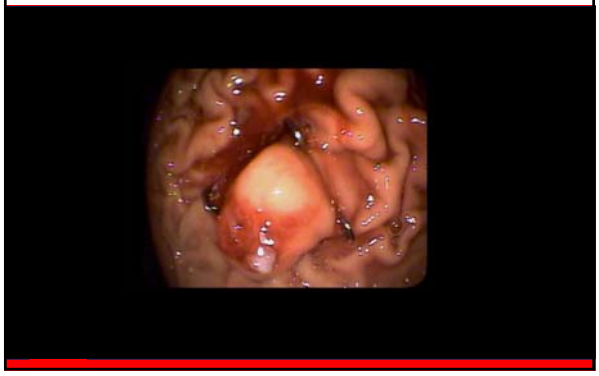
## Hemostasis



## Hemostasis



## Hemostasis

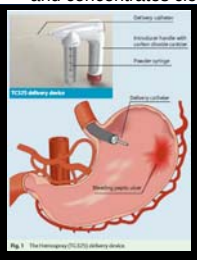


## Hemostasis

What about Hemospray?

## Hemostasis

- Hemostatic spray
  - Inorganic powder that attaches to areas of active bleeding and concentrates clotting factors at bleeding site



Sung, Endoscopy 2011

## Hemostasis

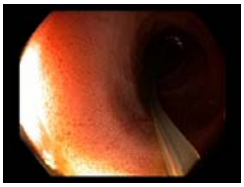
- Hemostatic spray
  - Delivered by 7 F or 10 F catheter
  - Review of published series*
    - Heterogeneous population
    - Technical and clinical “success” 88.5% (207/234)
    - Re-bleeding occurred in 16.2% (38/234)
    - No adverse events

Changela K. Ther Adv Gastro 2015

## Balloon-assisted Enteroscopy

## Balloon-assisted Enteroscopy

- Through-the-Scope Balloon Enteroscopy
  - Requires minimum 3.7 mm channel
  - Short learning curve
  - Does NOT claim to offer complete small bowel exam
  - Extends depth of insertion about 100 cm past Ligament of Treitz, and 100 cm past ileocecal valve

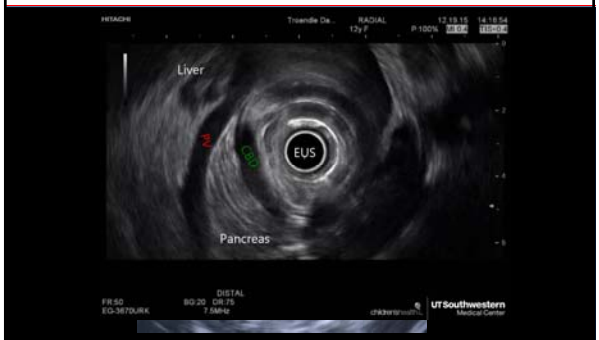


## Endoscopic Ultrasound

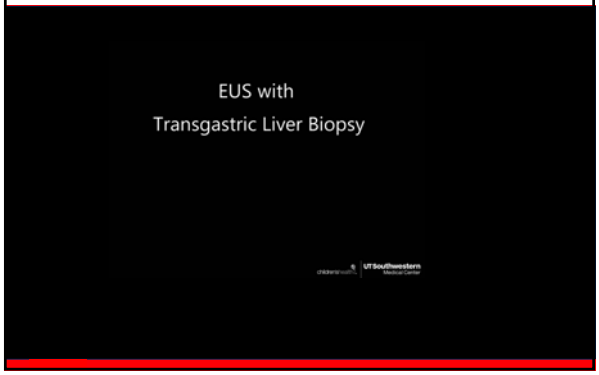
## Endoscopic Ultrasound

- Considered helpful in the evaluation and therapy of:
  - Biliary obstruction/choledocholithiasis
  - Chronic pancreatitis
  - Pancreatic pseudocyst
  - Pancreatic mass (including tissue analysis)
  - Pancreatic trauma
  - Liver disease (including liver biopsy)
  - Mediastinal mass
  - Gastric lesions

## Endoscopic Ultrasound




## Endoscopic Ultrasound



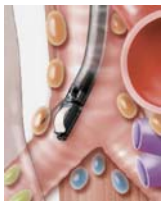
## Endoscopic Ultrasound

EUS

FNA Mediastinal Mass

## Endoscopic Ultrasound

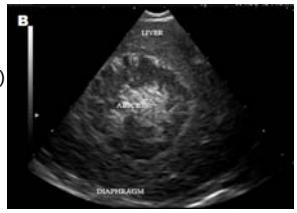
- What about EUS in REALLY small children?
- Endobronchial ultrasound
  - Scope size
    - 7.4 mm insertion diameter
    - 2.0 mm channel
    - 60 cm working length



*Dhooria et al. Pediatr Pulmonol 2016

## Endoscopic Ultrasound

- Endobronchial ultrasound in kids < 4 yo with **GI** disease
  - N = 10
  - Age = 2 months to 4 years
    - Esophageal stricture (3)
    - Pancreatobiliary (4)
    - Abdominal cyst (1)
    - Liver abscess (1)
    - Abdominal lymphadenopathy (1)




*Sharma, Endosc Ultrasound 2013

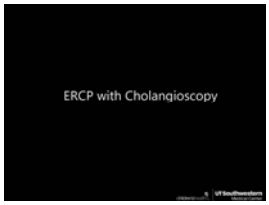
## Cholangioscopy

## Cholangioscopy

- Single use, disposable digital scope
- 10 F outer diameter (3.3 mm)
- Dials for 4-way tip deflection
- Irrigation and suction port
- Forcep 1.0 mm outer diameter, cup has 4.1 mm opening width

## Cholangioscopy

- Indications
  - Biopsy intraductal lesions
  - Lithotripsy
  - Difficult wire access
  - Anything you need to SEE in a duct
  - Anything else you can dream up



## Take Home Points

- Skilled advanced Pediatric Endoscopists are more available than ever before
- Techniques used in adult patients are easily applied to older children
- Techniques applied in adults and older children may be safely adapted in many cases to smaller children and infants ***if we are careful***
- Hemostatic techniques continue to evolve and improve
- New techniques allow us to evaluate and treat lesions in locations not accessible in the past

## Thank you

- Questions?





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# Colonoscopy Related Emergencies:

Je me souviens

Douglas S. Fishman, MD FAAP FASGE
Director GI Endoscopy
Texas Children's Hospital
Associate Professor of Pediatrics

## Disclosures

- Cook Medical; Consultant
- UpToDate; Contributor
- Norgine Pharmaceuticals; Advisory Board
- Pentax Medical; Consultant
- DueNorth Innovations; Unpaid Consultant

## Disclosures

I will discuss technology and tools not FDA approved for use in children

## Goals

- Discuss the role of endoscopy in lower GI emergencies
- Explain peri-procedure considerations in various disease states
- Outline diagnostic and therapeutic options and techniques in colonoscopy for lower GI emergencies

## Clinical considerations

- Obstruction or distention
- Bleeding
- Abnormal imaging
- Related comorbidity
  - GI: Inflammatory bowel disease, Polyposis, post-surgical
  - Heme: Bleeding diasthesis, GVHD or chemotherapy related
  - Systemic: Cystic fibrosis

## Shlemiel and Shlemazel?

- Yiddush terms for two unlucky people
  - Shlemiel: Spills the soup
  - Shlemazel: Always has the soup spilled on him
- Colonoscopy you are asked to assist with:
  - Emergency Department
  - Surgery
  - Radiology
- Colonoscopy adverse events you need to address

## Colonoscopy considerations

- Need for blood products
- Coagulation status
- Acuity/Urgency (Time for bowel prep?)
- Location (ED, OR, ICU)

## Colonoscopy Emergencies-Tools

- "Tackle box" (foreign body and bleeding)
- Large channel endoscopes or double channel endoscopes
- Excellent suction capabilities
- Skilled team
- Best surgeon on "speed dial"

## Equipment

## Emergent Colonoscopy

- Obstruction
  - -Volvulus
  - -Intussusception
  - -Stricture (benign and malignant)
- Bleeding
- Foreign bodies
- Perforation (intraprocedural)

## Volvulus

- Twisting results in obstruction, venous congestion and arterial obstruction
- Common locations are sigmoid colon and cecum
- Endoscopic appearance: Abruptly twisted and closed lumen
- Mortality with gangrene (25-80%)

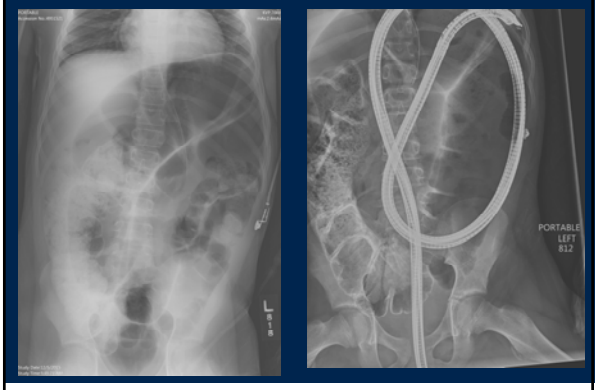
## Endoscopic technique

- Early awareness
- Have surgical backup
- Counter-clockwise torque
- May enter a cavernous area
- Can place a wire (.035 inch) with a rectal tube

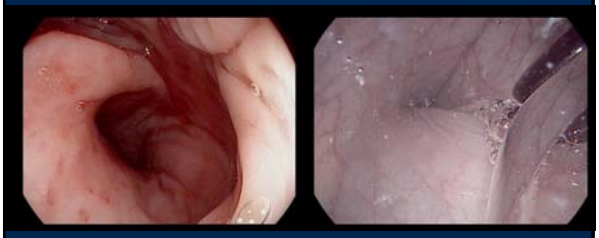
## Endoscopic decompression

- Varied experience in pediatric patients reports (47-92%), recurrence is high
- Largest adult series with 78% success rate of 562 patients
- Emergent surgery with failed attempts, perforation, infarction, or peritonitis
- Cecal volvulus reduction reported but not recommended

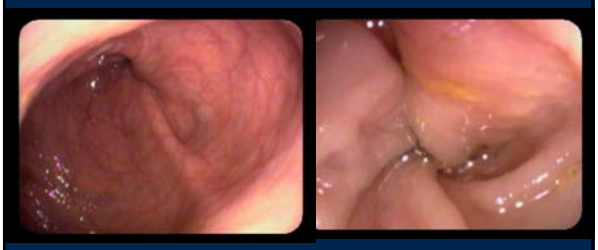
Colinet et al. Eur J Pediatr 2015;
Oren et al. Dis Col Rec 2007



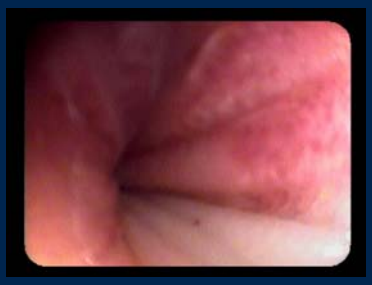

## Endoscopic appearance of volvulus



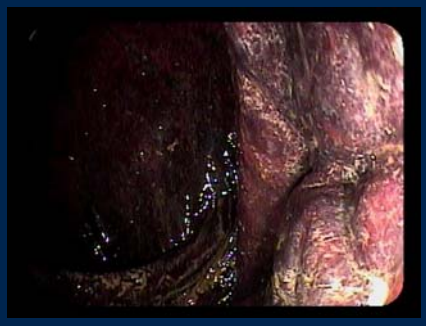
## Endoscopic appearance of volvulus



## Endoscopic appearance of volvulus



## Ischemic bowel from volvulus

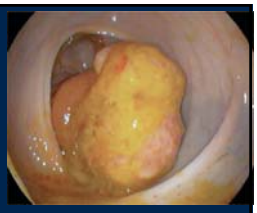


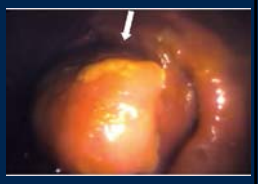
## Intussusception of the Colon

- Meckel's diverticulum
- Appendix
- Polyp (Peutz-Jeghers and Juvenile)
- Other tumors

## Intussusception

- May be ileocolic or colo-colic
- Insufflation be therapeutic
- Caution in polypectomy
- May be able to mark location





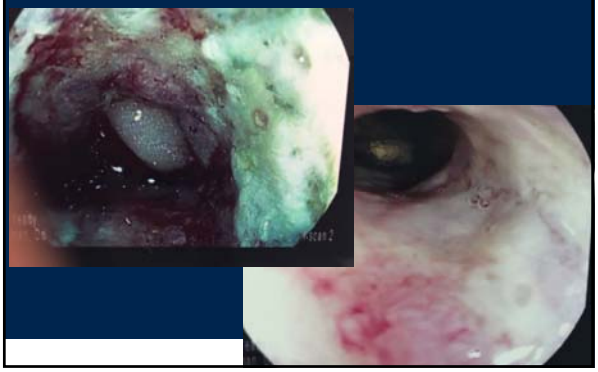
Hollier et al. JPGN2014

## Emergent Stricture Management

- Malignant obstruction rare in children, presents later stages
  - -Limited to case reports
  - -In adults, majority adenocarcinoma
  - -Left-sided most commonly
- Urgent surgery >10% mortality in adults
- Tumor ablation, decompression tubes, self-expanding metal stents (SEMS)

Blumer SL et al. Pediatr Hematol Onc 2012.

## Malignant Obstruction

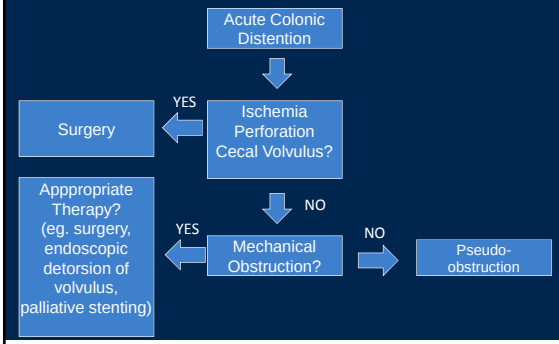


## Emergent Stricture Management

- Benign stricture management in IBD
  - -Symptomatic therapy reported in adults and children
  - -Majority have recurrence
  - -2% complication rate
- Anastomotic stricture
  - -Dilation is effective
  - -Electroincision (needle-knife)

Harrison ME et al. Gastrointest Endosc 2010

## Acute colonic distention algorithm




Harrison ME et al. Gastrointest Endosc 2010

## Emergent Lower GI Bleeding

- Age dependent
- Common causes include:
  - -Infection
  - -Inflammatory bowel disease
  - -Vascular Malformation
  - -Graft versus host disease (GVHD)
  - -Severe upper gastrointestinal bleeding

## Bleeding During Colonoscopy

- PEDS-CORI reported 34 bleeding events in 8841 colonoscopies (.38%)
- Independent risk factor for bleeding related events
  - -Age < 10: Adjusted odds ratio of 3.2 (1.5-.6.8)
  - -Polyps: Adjusted odds ratio of 2.7 (1.0-7.0)
- 8 polypectomies with adverse events
  - -5 were related to bleeding

Thakkar et al. Clin Gastroenterol Hepatol 2008

## Acute LGI Bleeding Management

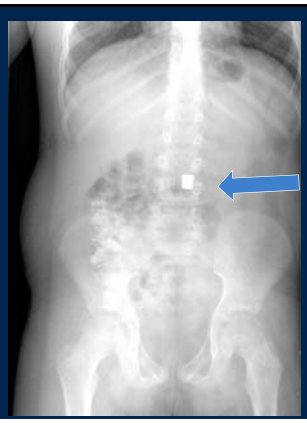
- Assess and treat hemodynamic instability
- If unstable >> Surgery or IR
- Endoscopic assistance can be provided in absence of perforation
- Decide on need for bowel prep
  - -Enemas
  - -Balanced electrolyte solutions (eg. PEG)

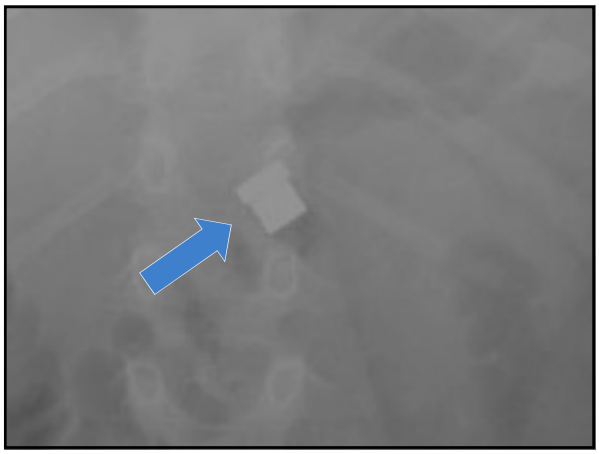
## Acute LGI Bleeding Management

- Suction, Suction, Suction
- C02 insufflation
- Appropriate tools
- Localize and treat based on cause/lesion
  - -APC
  - -Multipolar probe
  - -Hemostatic clips and sprays

## Foreign Body Management

- Ileocecal region most common
- Magnets
- Sharps
- Toothpicks
- Bone





## Drug Packets

- Endoscopic retrieval contraindicated
- 1-3 grams of cocaine is lethal
- Do not rupture packets
- Avoid rectal exams
- Remove surgically

http://i.dailymail.co.uk/i/pix/2010/12/16/article-1339020-0C7FE651000005DC-760_634x457.jpg

## Tricks of the Trade

- Use protective hood

- Consider overtube
- Have double-channel endoscope available
- Have surgical backup

- "When in doubt—Don't"

## Perforation during colonoscopy

- Rates highest in rectosigmoid colon and cecum
- Reported incidence rates from .016% to 6.7%
- Increased with hot biopsy, polypectomy, and endoscopic mucosal resection (EMR)
- Inflammatory bowel disease (up to 1% in adults)
  - -1 UC patient with sigmoid perforation from PEDS-CORI
  - -2 Crohn's patients with colonic perforation from CHOP series

Hsu EK et al. Gastrointest Endosc 2013

## Perforation repair

- Only 20% noted during colonoscopy
- Standard hemostatic clips
- Closure with Over the Scope Clip (OTSC)
- Suturing Device-limited to case reports

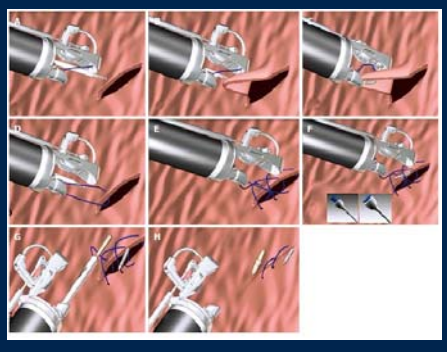
## Perforation repair?

- Effective?
- Feasibility?
- Limited leak and bowel contamination?
- Type of perforation
  - -Small hole
  - -Circular?
  - -Wide open defect?

## Closure of perforation with clips

https://www.youtube.com/watch?v=n_vatHcfE-c

## Endoscopic suturing



Stavropoulos SN et al. World J Gastrointest Endosc 2015.

## Future Areas of Development

- Newer hemostatic devices and agents
- With increasing use of EMR, need for pediatric-friendly suturing devices
- Multicenter and multidisciplinary studies on management of emergent colonoscopic disease

## Conclusion

- Colonoscopy used in a variety of emergent conditions
- A multidisciplinary team approach is encouraged
- Patients with polyps or IBD
  - At risk for needing an emergent colonoscopy
  - Higher risk of an adverse event during colonoscopy

# Endoscopic Interventions in GI Motility Disorders

Ajay Kaul, MD
Professor of Clinical Pediatrics
Director, Neuro-Gastroenterology and
Motility Disorders Program

## Disclosures

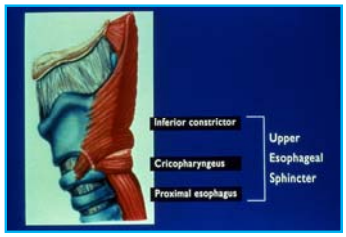
- Laborie: Speaker

## Endoscopic Interventions in Motility Disorders

1. Cricopharyngeal achalasia (CPA)
2. Lower Esophageal Sphincter (LES) Achalasia
3. Gastroparesis

# Cricopharyngeal Achalasia

## Upper Esophageal Sphincter "Complex"




Each muscle contributes differentially, depending on the physiologic state of the sphincter

## Upper Esophageal Sphincter (UES)

- UES pressures are asymmetric (greater in the A-P dimension)
- The high pressure zone has a resting pressure of 50 to 100 mm Hg
- Resting pressures are lower in infancy, the elderly and during sleep
- Reflex increases in UES pressure occur with
  - pharyngeal stimulation
  - esophageal distention
  - esophageal acid infusion
  - emotional stress

## Cricopharyngeal Dysfunction

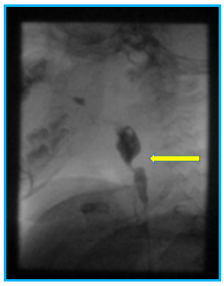
Pathogenesis:

- Failure of neural inhibition of baseline tonic CP contraction
- Weakness of UES muscles
- Decreased compliance of CP muscle

These factors can impact

- Timing of UES relaxation
- Duration of UES relaxation
- Degree of UES relaxation

## Cricopharyngeal Achalasia



Posterior Indentation

## Cricopharyngeal Bar/Achalasia

In pediatrics, commonly occurs as an isolated condition but there is a reported association with Chiari malformation

Consider brain MRI to r/o Chiari malformation in a child with dysphagia who has CP bar on VFSS

Pollack IF et al. Neurosurgery,1992.

## Cricopharyngeal Bar/Achalasia

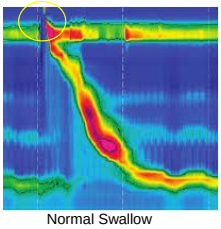
"Bar" frequently detected in asymptomatic individuals

Other etiologies of dysphagia must be excluded before dysphagia can be attributed to a CP bar

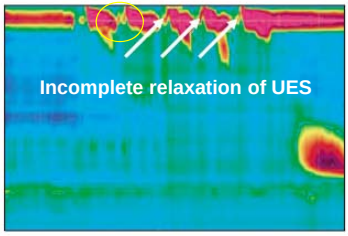
Symptoms:

- Effortful swallowing with both solids and liquids,
- Choking and gagging with swallows
- Food refusal and weight loss
- Aspiration pneumonia

## HREM in Cricopharyngeal Achalasia



Normal Swallow



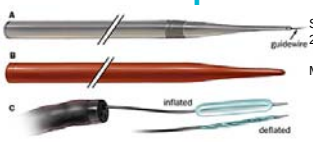

## Endoscopic Treatment of CPA

1. Dilate using wire-guided dilators (Savary-Gilliard) or TTS, CRE endoscopic balloon dilators
2. Endoscopic Botulinum Toxin "A" injection of CP muscle
3. Endoscopic Myotomy: CO2 laser or Needle-Knife cautery

## Cricopharyngeal Dilation

- Performed using either a
  - through-the-scope balloon dilator or
  - bougie dilator (Savary–Gilliard dilator) advanced over an endoscopically positioned guidewire
- Both techniques are safe and effective,
- Some patients required repeat procedures
- Dilatation might be used after trial on PPI and speech therapy and prior to more definitive management
- No pediatric data comparing the two methods

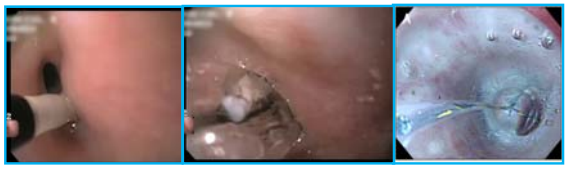
## Endoscopic Balloon Dilation




Savary Dilator (w/ guidewire and fluoroscopy 21-60 Fr

Maloney Dilator


## Endoscopic Balloon Dilation of CPA



Size of CRE balloon depends upon size of patient and tightness of the UES

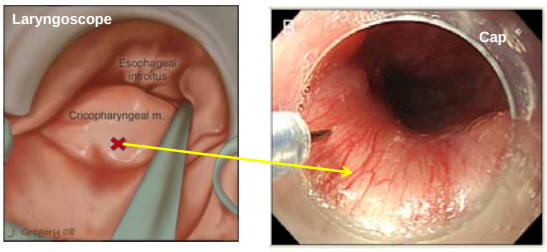
## Endoscopic Balloon Dilation of CPA

1. Before starting to inflate balloon, inform the anesthesiologist as it maybe difficult to ventilate the child due to compression of the airway (membranous trachea) by the distended balloon
2. Make sure the balloon continues to straddle the UES and does not slip during inflation
3. Do not distend excessively or for too long as it may damage the laryngeal structures anteriorly
4. If response to dilation is favorable, may need repeated dilations every few weeks

## Cricopharyngeal Achalasia: Botox 'A' Injection

- Botulinum toxin inhibits release of acetylcholine from presynaptic channels in ganglia of the myenteric plexus and relaxes the muscle
- Dissolve 100 IU of botox (powder) in 2ml diluent and inject 0.5 ml (25 IU of botox) into the cricopharyngeal mound (or ~3 IU/kg)

## Endoscopic Botox Injection

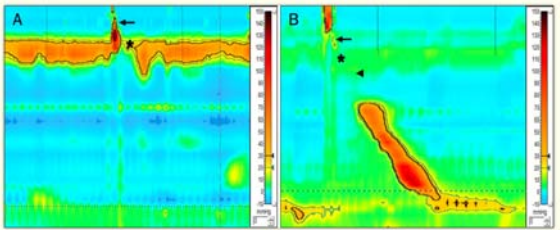




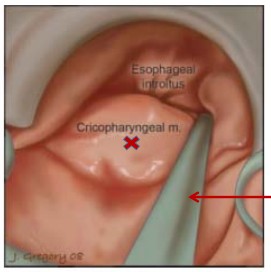


Wear gown, mask and protective goggles when handling botox

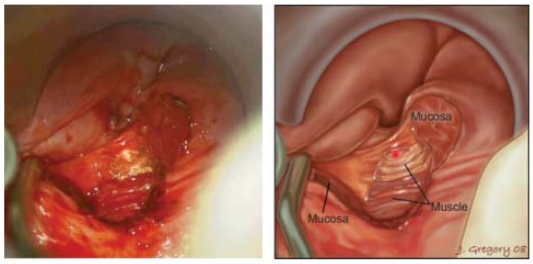
## HREM after Botox Injection of CP



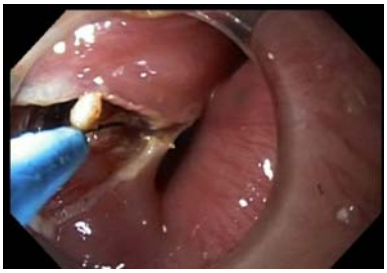

## Endoscopic Myotomy



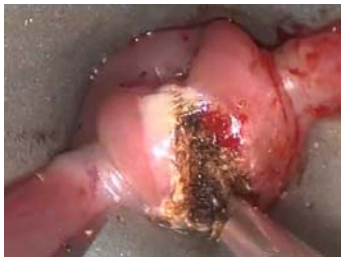

## CP Endoscopic Myotomy



## Minimal Incision, Needle-Knife Endoscopic Cricopharyngeal Myotomy



## Cricopharyngeal Myotomy with the OmniGuide CO2 Laser Fiber System



## Cricopharyngeal Achalasia: Comparing Outcomes

Distribution of Success Rates of BoT Injection, Dilation, and Myotomy.

| | No. of Articles | Range of Success Rates (Crude Average) | No. of Patients (Sum) | No. of Successes (Sum) | Patient-Weighted Average Success Rate |
|---|---|---|---|---|---|
| BoT Injection | 12 | 43%–100% (76%) | 148 | 102 | 69% |
| Dilation | 6 | 58%–100% (81%) | 113 | 83 | 73% |
| Myotomy | 16 | 25%–100% (75%) | 369 | 286 | 78% |

Distribution of Complications of BoT Injection, Dilation, and Myotomy

| | No. of Articles | Range of Complication Rates (Crude Average) | No. of Patients (Sum) | No. of Complications (Sum) | Patient-Weighted Average Complication Rate |
|---|---|---|---|---|---|
| BoT Injection | 12 | 0%–25% (5%) | 148 | 6 | 4% |
| Dilation | 6 | 0%–20% (5%) | 113 | 6 | 5% |
| Myotomy | 16 | 0%–39% (6%) | 369 | 27 | 7% |

Kocdor P et al. The Laryngoscope, 2016.

# LES Achalasia

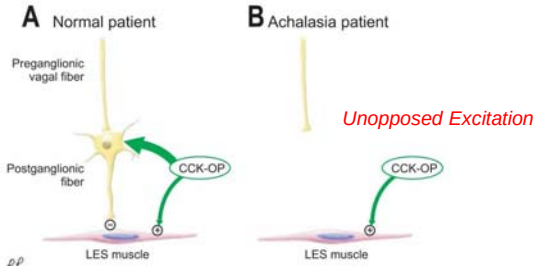
## LES Achalasia

Loss of the inhibitory innervation of the esophagus can be due to either extrinsic or intrinsic causes

Extrinsic causes may include CNS lesions involving the dorsal motor nucleus or the vagal nerve fibers

Intrinsic loss may be due to loss of the inhibitory (nitrenergic) ganglion cells in the myenteric plexus

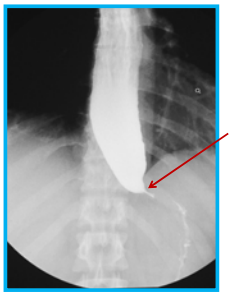
## Achalasia: Pathophysiology



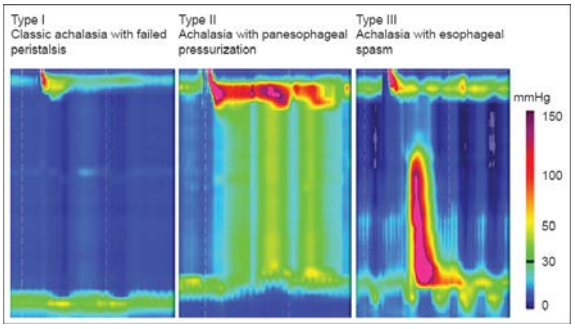
## Achalasia

- Symptoms: Gradual onset of
  - Regurgitation
  - Chest pain
  - Heartburn
  - Globus sensation
  - Hiccups
  - Weight loss
  - Aspiration
- Mostly isolated
- Association with Allgrove's Syndrome (AAA syndrome), Down Syndrome, Congenital Central Hypoventilation Syndrome

## Achalasia: Contrast Study

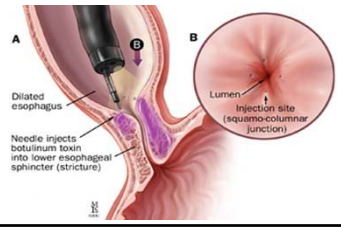



## Achalasia: Subtypes on HREM
## *Chicago Classification*



## Achalasia: Botox Injection

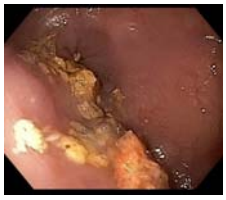
- Dissolve 100 IU of botox in 2ml diluent and inject 0.5 ml (25 IU of botox/0.5 ml) into each of 4 quadrants at or just above the Z-Line (squamo-columnar junction)




## Achalasia: Rigiflex II Pneumatic Dilation

Polyethylene balloon with guidewire

## Achalasia



Rapid sequence induction (RSI) of general anesthesia (succinylcholine)

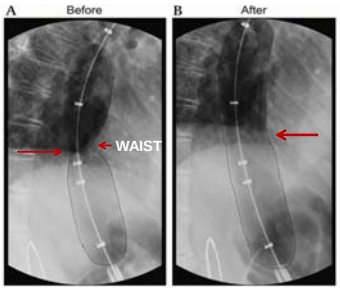
Esophageal toilet/cleaning

Wake up in the endoscopy suite post op to address aspiration

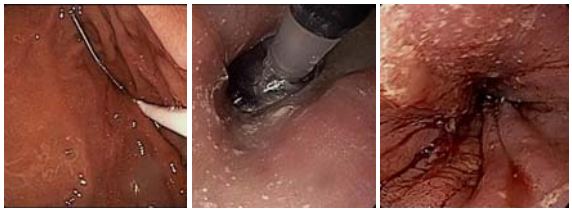
Contrast study post op to r/o perf

Min 6 hour observation prior to D/C

## Achalasia: Pneumatic Dilation




## Achalasia: Pneumatic Dilation



Pass balloon over guidewire

Distend balloon to 7-10 psi pressure

Post dilation tear and bleed

## Achalasia: Pneumatic Dilation

Things to consider:

- balloon size (30, 35, 40cm inflated OD),
- inflation pressures (7-15 psi),
- duration of inflation (0.5 to up to 5 minutes),
- rapid vs gradual dilation, and
- number of dilatations per session (1 to 5)

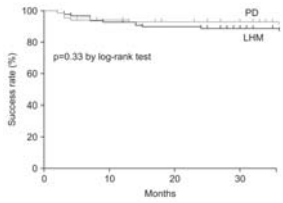
None seem to influence the risk of perforation

Review of 25 published studies:

- Total pneumatic dilations (Rigiflex) =3071
- Perforations = 56 (1.8%)

Lynch KL. et al. Amer J Gastroenterol, 2012

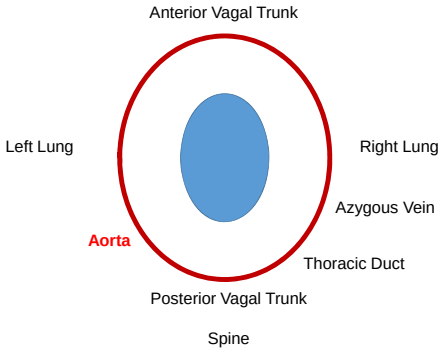
## Achalasia: Pneumatic dilation Vs. Myotomy



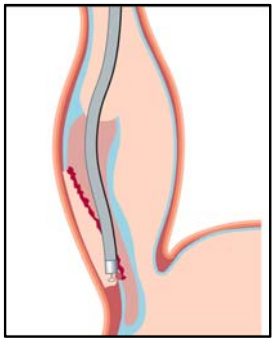

Kaplan-Meier graph showing equivalent success with pneumatic dilation (PD) versus laparoscopic Heller's myotomy (LHM)

Ates F. et al. Gut Liver, 2015

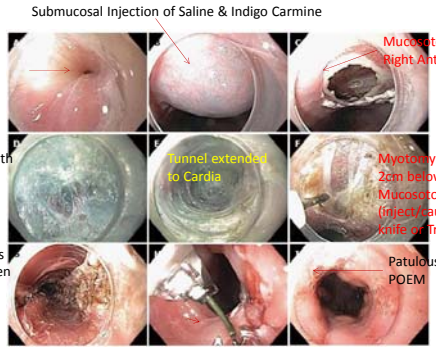
## Achalasia: POEM Landmarks




## Achalasia: POEM

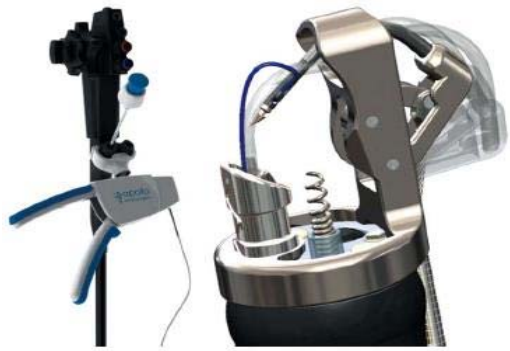


## Achalasia: POEM




Suturing the Mucosotomy Site:
Endoscopic suturing device, endoclips or fibrin glue

## POEM: Endoscopic Suturing Device



## Changes Before and After POEM

HREM: Pressures FLIP: EGJ Distensibility

# Gastroparesis

## Gastroparesis

- A chronic disorder defined by delayed gastric emptying in the absence of mechanical obstruction
- Symptoms: Early satiety, bloating, nausea, vomiting, post prandial pain, weight loss
- Gold standard diagnosis: Gastric emptying time of radiolabeled solids (> 10% of meal after 4 hours is abnormal)

## Gastroparesis: Scintigraphy


4-hour Gastric Emptying Scan picks up more cases of gastroparesis

Chogle A, et al. JPGN, 2013

## Gastroparesis

- Etiologies: Idiopathic (most common), Diabetes mellitus, post viral illness, and postsurgical
- Can be secondary to systemic diseases such as amyloidosis, collagen tissue disorders such as scleroderma, neurological disorders such as myotonic dystrophy
- Symptoms: Nausea, vomiting, post-prandial fullness, early satiety, abdominal discomfort, bloating, anorexia, pain, and weight loss.

Gonzalez et al, 2010, Islam et al, 2008

## Gastroparesis: Classification

**MILD (Grade 1):**

- Symptoms relatively easy to control
- Ability to maintain weight and nutrition on a regular diet or with minor dietary modifications

**COMPENSATED (Grade 2):**

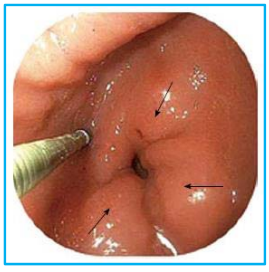
- Moderate symptoms with partial control using pharmacologic agents (antiemetics and prokinetics given at regularly scheduled intervals
- Ability to maintain nutrition with dietary and lifestyle adjustments
- Rare hospital admissions

**GASTRIC FAILURE (Grade 3):**

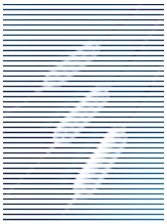
- Refractory symptoms despite medical therapy
- Inability to maintain nutrition orally (enteral feeds and/or TPN)
- Hospitalization for IV hydration, anti-emetics and prokinetics
- Endoscopic and/or surgical intervention

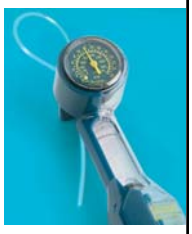
Abell TL et al. Neurogastroenterol Motil, 2006

## Endoscopic Pyloric Botox Injection

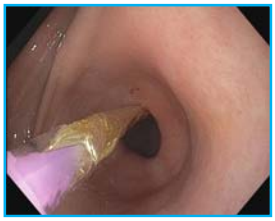


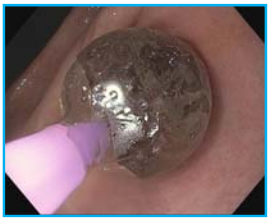
## Endoscopic Pyloric Balloon Dilation

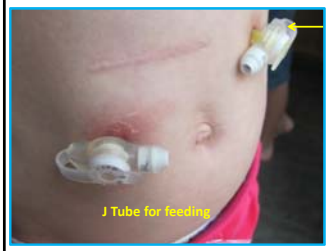


## Pyloric Balloon Dilation





## Endoscopic PEG and PEJ Tubes




G Tube for venting
(skin-level, balloon or non balloon)


GJ Tube

## Gastroparesis: Temporary Gastric Electric Stimulation-GES *(Neuromodulation)*

FDA 2014: Total 89 pediatric (<18 years) implantations

## SUMMARY

For all these innovative and technically demanding techniques:

- learning curve for technical competence
- proper indication and patient selection
- management of (potential) complications and logistics/back-up

- Preliminary results from high-skilled pediatric endoscopy centers have been encouraging

- Long-term data and prospective randomized controlled trials are needed to validate the efficacy and safety of these procedures in children

## New Insights into Congenital Diarrheal Disorders

Martín G. Martín M.D., M.P.P.

Professor of Pediatric Gastroenterology and Nutrition
UCLA School of Medicine, Department of Pediatrics

- I have no financial relationships to disclose

## Overview & Objectives

- Review the clinical work-up of an infant with congenital diarrhea
- Outline the diagnostic dietary challenges that can be used to categorize this group of children.
- Discuss the use of whole exome sequencing in evaluating patients with congenital diarrhea.
- Discuss future prospects of stem cell therapy.

## Diagnostic Odyssey

**CC:** recurrent diarrhea and metabolic acidosis

**HPI:**

- 3 wk MA male, born 17-yo G1; biological father - mother's father's first cousin
- Prenatal Hx – normal; born NSVD, normal APGARS
- 6 days, HCO3 - 8 and anion gap; r/o RTA and treated for r/o sepsis
- Labs - urine organic acids, serum amino acids, acylcarnitine profile, lactate, pyruvate, ammonia levels – normal; CFTR sequencing - normal
- Newborn state metabolic screens X 2 - normal
- Multiple dietary challenges: suggested generalized malabsorption
- Upper and lower endoscopies - H&E/EM and disaccharidase - normal
- D/C home at 3 mo (Elecare) - diagnosis - chronic diarrhea of unknown etiology

## Diagnostic Odyssey

- 5 weeks after D/C - presented in hypovolemic shock with profound metabolic acidosis, $HCO3^-$ 4.1, $Na^+$ 163; loss of 420 grams
- At 6 mo - significant FFT (length <5%; wt 5.1 Kg, Z = -3.75)
- CVC placed, and started on TPN
- Readmitted to local hospitals 8x's, and seen in ER 9x's over 31 mos.
- Subsequently placed into foster care – b/c many admissions were due to inadequate care of CVC line, and due to lack of appropriate outpatient F/U.
- Subsequent multiple problems with CVC occlusions
- Diagnosed with heparin-induced thrombocytopenia
- Multiple deep venous thrombi – deep venous access lost

## Diagnostic Odyssey

- Secondary to thrombotic events, his CVC was removed and a GT placed
- Repeat endoscopy at that time revealed normal H&E, and lactase deficiency
- UGI-SBFT & transit time - normal
- Admitted for pneumonia and respiratory distress
- Exhibit excessive thirst and hyperglycemia (high 100's)
- Hypokalemic and acidotic requiring HCO3 infusions and baking soda enterally
- Evidence of left ventricular dysfunction - Lasix, Enalapril and K+
- Despite these problems he never developed cholestasis.

## Diagnostic Odyssey

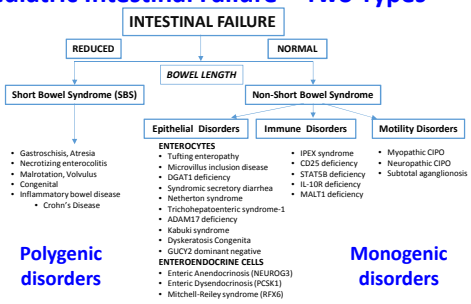
**Questions**:

1) What is this child's primary diagnosis, and how many resources were spent trying to establish it?

2) How do we provide anticipatory guidance without a clear diagnosis?

3) Should he be on the intestinal transplant waiting list?

## Pediatric Intestinal Failure – Two Types




## CONGENITAL ENTEROPATHIES

*Background*

- Background
  - All rare disorders
  - Typically autosomal recessive, few X-linked and autosomal dominant
  - Frequently misdiagnosed
  - High morbidity and mortality; very costly
  - Diarrhea generally starts within the first several weeks of life

## CONGENITAL ENTEROPATHIES

*Diagnostic Approach*

- Approach
  - Diagnostic Dietary Challenges -
    - Accurate assessment of stool volumes (fasting and feeding)
    - Challenge with full calories (bolus preferred over continuous feeds) if possible
    - Assess a range of nutrients (glucose vs. fructose; simple CHOs vs. complex CHOs; CHOs vs. AA vs. fats)
  - UGI - SBFT
  - Intestinal Biopsy -
    - R/O infection
    - EM; H&E & PAS; anti - CD10, EpCAM, Chromogranin A
  - Next Generation Sequencing: Whole Genome and/or Exome Sequencing

## REDUCTION OF INTESTINAL ABSORPTIVE CAPACITY

*Categorization*

- **REDUCED ABSORPTIVE CAPACITY: SECONDARY TO A DECLINE IN SURFACE AREA**

  Reduced…
  - Length of Small Bowel – SBS
  - Villus Length (and/or crypt/villus axis) – e.g., Autoimmune Enteropathies
  - Microvillus Length – e.g., MVID

- **REDUCED ABSORPTIVE CAPACITY: DESPITE NORMAL SURFACE AREA**

  DEFECT IN NUTRIENT AND/OR ELECTROLYTE ASSIMILATION
  - Selective Class of Nutrients or Electrolytes – NOT INTESTINAL FAILURE
    Reduced Digestion – e.g., Amylase; Lactase; Sucrase-Isomalatase
    Reduced Absorption – e.g., Glucose/Galactose; Chloride
  - Broad Class of Nutrients and/or Electrolytes – INTESTINAL FAILURE
    Gut Endocrinopathies

## Innovations in Translational Research

*last five years – and the future*

Whole Exome Sequencing

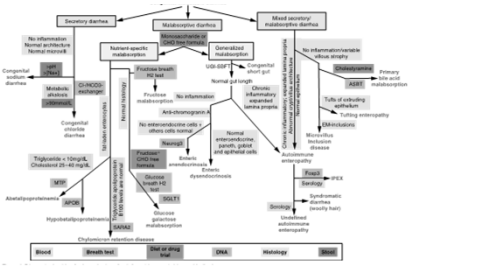

Stem Cell Biology


Gene Editing

**Era of Regenerative Medicine**

## The Old Diagnostic Odyssey

**Congenital Intractable Diarrhea**



M Martin and E Wright, *Congenital Intestinal Transport Defects*

## Whole Exome Sequencing

*Intestinal Failure Genes*

- Human genome 3 billion nucleotides
- Coding region (exons) accounts for 1% genome; 30 million bases
- Human genome – ~23,000 genes
- Coding region accounts for 85% disease causing mutations
- Next-generation sequencing – Illumina Genome Analyzer
- Developed a rich annotation of DNA sequencing variants

Brief Bioinformatics. 2014

## MICROVILLUS INCLUSION DISEASE

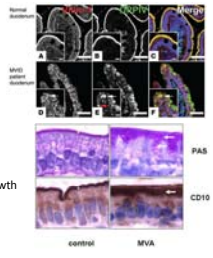
*MYO5B, STX3*

**Key Distinguishing Features:**

- Mixed secretory + malabsorptive diarrhea
- Inclusion bodies (EM, CD10/PAS) – 10% enterocytes
- Absent or reduced microvilli by EM
- Inclusions and reduced microvilli not as apparent in crypt
- Likely predisposed to significant liver disease
- Usually villous atrophy w/ crypt hypoplasia
- Late onset variant – wean TPN when older

**Pathogenesis:**

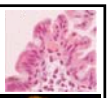
- Regulates enterocyte polarity, apical trafficking, and microvilli growth
- MYO5B - dynamic tether – interacts with RAB8a and RAB11a
- Microvillus growth – requires MYO5b + RAB8a
- Subapical membrane inclusions – loss of MYO5b + RAB11a
- Atypical form associated with STX3 variants




PMID: 24892806, 16800870

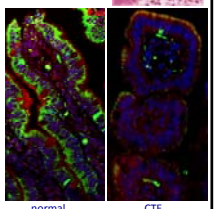
## CONGENITAL TUFTING ENTEROPATHY

*EpCAM*



**Key Distinguishing Features:**

- Mixed secretory + malabsorptive diarrhea
- "Tufted" cells near tip of the villus
- Usually villous atrophy w/ crypt hyperplasia
- Neonatal biopsies may have fewer Tufted cells
- EpCAM staining of epithelium is negative
- Arab (c.498insC) and Mexican (c.491+1G>A) founder variants
- Phenotype severity differs even within family



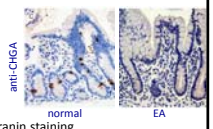

**Pathogenesis:**

- EpCAM regulates composition and function of tight junction
- EpCAM mediates localization and degradation of claudins - 1, 7
- EpCAM null intestine has enhanced permeability and epithelial proliferation

PMID: 18572020, 23486470

## ENTERIC ANENDOCRINOSIS

*NEUROGENIN-3*




**Key Distinguishing Features:**

- Pure malabsorptive diarrhea
- Normal crypt/villus axis – Enterocytes normal
- Absent enteroendocrine (EE) cells assessed by anti-chromogranin staining
- Likely associated with diabetes mellitus beyond 3-5 years of age
- Not associated with other endocrinopathies
- While diarrhea persists indefinitely, most can be weaned off TPN >2 or 3 yo

**Pathogenesis:**

- NEUROG3 is required and sufficient to induce EE cells from intestinal stem cells
- Mutations result in a broad loss of all small and large bowel EE cells
- Disorder suggests that certain undefined hormone(s) augment broad type of nutrient assimilation

PMID: 16855267

## ENTERIC DYSENDOCRINOSIS

*PCSK1*


**Key Distinguishing Features:**

- Autosomal Recessive
- Pure malabsorptive diarrhea
- Normal crypt/villus axis – Enterocytes normal
- Normal appearing enteroendocrine (EE) by CHGA staining
- Age-dependent endocrinopathies
  Adrenal insufficiency, hypothyroidism, central diabetes insipidus, growth hormone deficiency, primary hypogonadism, male predominance
- Severity of diarrhea improves moderately at ~18 months and associated with moderate obesity

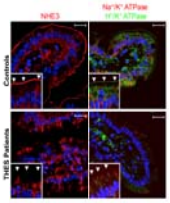
**Pathogenesis:**

- PCSK1 is required for processing prepro-hormones into functional peptides in multiple organs including gut, pancreas, pituitary & hypothalamus.

PMID: 23562752, 24280991

## TRICHOHEPATOENTERIC SYNDROME

*TTC37, SKIV2L*



**Key Distinguishing Features:**

- Mixed secretory + malabsorptive diarrhea
- IUGR
- Brittle – woolly hair - Trichorrhexis invaginata
- Developmental delay; Facial dysmorphism
- Hepatomegaly and Cirrhosis
- Villus atrophy with mixed inflammatory infiltrate
- Immune abnormalities: Low Ab's and Ag-specific skin response
- Diarrhea may improve over time in a small subset of children
- Enlarged platelets on light microscopy

**Pathogenesis:**

- TTC37 & SKIV2L - members of the exosome complex that degrades RNA
- Exosome contains many exoribonucleases that degrades mRNAs from the 3' end.

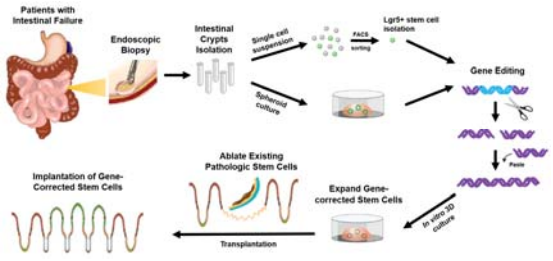
PMID: 20176027, 22444670

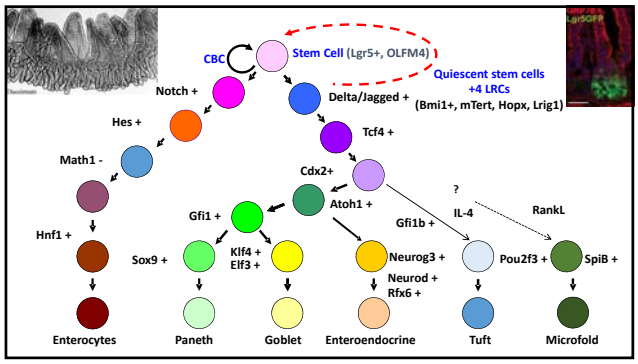
## HONORABLE MENTION

Mitchell Riley Syndrome (MIM 615710) – RFX6
Kabuki Syndrome (MIM 147920) – MLL2
DGAT Deficiency (MIM 615863) – DGAT1
Netherton Syndrome (MIM 256500) – SPINK5
Syndromic Na+ Secretory Diarrhea (MIM 270420) – SPINT2
Primary bile acid diarrhea (MIM 601295) - *SLC10A2*
Congenital lactase deficiency (MIM 603202) - *LCT*
Sucrase-isomaltase deficiency (MIM 609845) - *SI*
Fanconi-Bickel syndrome (MIM 138160) - *GLUT2*
Glucose-galactose malabsorption (MIM 182380) - *SGLT1*
Congenital Chloride Diarrhea (MIM 126650) - *DRA*
X-linked lissencephaly and MR (MIM 300382) - *ARX*
Abetalipoproteinemia (MIM 157147) – *MTTP*
Chylomicron retention disease (MIM 607690) – *SAR1B*
Dyskeratosis Congenita (MIM 613989) – *TERT*
Hypobetalipoproteinemia (MIM 107730) – *ApoB*
Acrodermatitis enteropathica (MIM 607059) – *ZIP4*
Arthrogryposis-Renal dysfunction-Cholestasis syndrome (MIM #208085) - *VPS33B*
Congenital Na+ Diarrhea (MIM #616868) - *NHE3*
IL-10 receptor deficiency (MIM 613148) - *IL10RA*
CD25 deficiency (MIM 606367) - *CD25*
*STAT5B* deficiency (MIM 245590) - *STAT5B*
*STAT1* deficiency (MIM 600555) - *STAT1*
MALT1 deficiency (MIM 615468) – *MALT1*
Neonatal Inflammatory Skin and Bowel Disease (MIM 614328) – *ADAM17*
IPEX Syndrome (MIM 304790) – *FOXP3*
GI Defects and Immunodeficiency Syndrome (MIM #243150) – *TTCF7A*

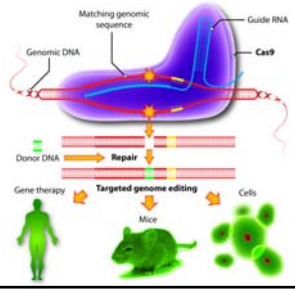
## Intestinal Stem Cell-Based Therapy

***Autologous* Epithelial Stem Cell Transplant**



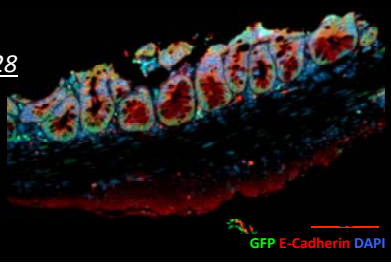


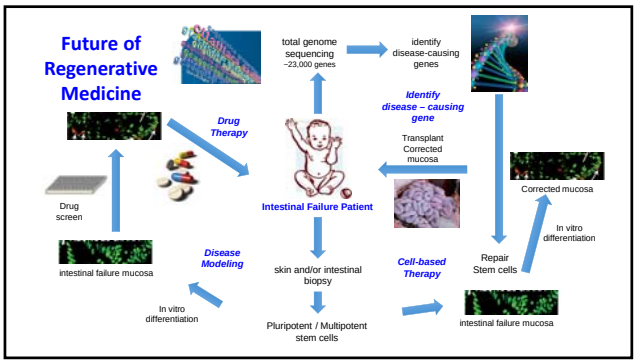

## Gene Editing: CRISPR/Cas9 Technologies




## Intestinal Stem Cell-Based Therapy

Engrafted GFP Spheroids, *Day 28*






## Future Challenges

- Development of a more complete list of genes responsible for the congenital diarrhea phenotype
  - Whole genome sequencing may provide some answers
- Identify modifying genes that alter the severity of the phenotype
- Develop accurate in vitro models that recapitulates the pathophysiology of the disorders
- Use these models to perform high throughput screening of small molecules
- Develop FDA approved methods and reagents to perform autologous gut stem cells therapies.

## Summary

- Next generation sequencing has expedited the diagnostic evaluation of patients with congenital diarrhea.
- Exome sequencing has helped elucidate molecular basis of several novel disorders, and we should anticipate more in the coming years.
- This will provide clinicians with accurate information to give families appropriate anticipatory guidance.
- Stem cell research will allow for a personalized medicine approach to develop novel small molecules and cell-based therapies that may someday provide meaningful treatment options for these patients.

# The Challenge…Genotype and Phenotypic Characterization of Polyposis Syndromes

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Division of Gastroenterology/Hepatology/Nutrition,
Hospital for Sick Children,
University of Toronto, Toronto, Canada

World Congress Pediatric GI, Hepatology, Nutrition
Oct 5, 2016.

SickKids

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University of Toronto

## No Disclosures


## Objectives

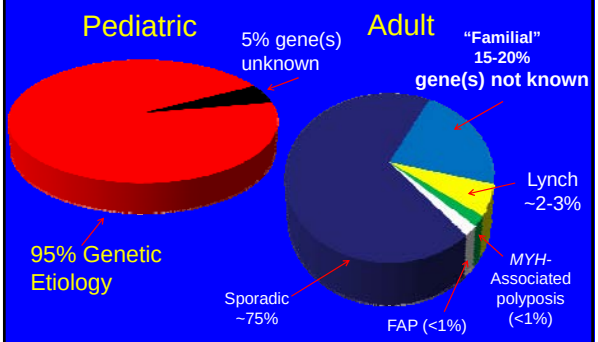
1. Understand the implications of classification of polyposis patients.
2. Highlight novel research in polyposis.
3. Review immunotherapy in polyposis syndromes.

# Inherited Polyposis Syndromes

| Adenomatous polyposes | Gene |
|---|---|
| Lynch syndrome | *MLH1, MSH2, MSH6, PMS2* |
| Biallelic mismatch repair deficiency syndrome | *MLH1, MSH2, MSH6, PMS2* |
| Adenomatous polyposis coli | *APC* |
| *MYH*-associated polyposis | *MYH* |

| Hamartomatous polyposes | Gene |
|---|---|
| Juvenile polyposis syndrome | *SMAD4 or BMPR1A* |
| Peutz Jeghers syndrome | *STK11* |
| Cowden's disease | *PTEN* |

# Colorectal Cancer




*(Jasperson et al. Gastroenterology 2010.)*

# Classification and Reclassification of Polyposis Patients

**Colorectal cancer in two pre-teenage siblings with familial adenomatous polyposis.**

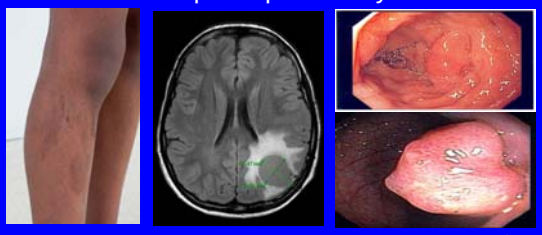
*Jerkic et al. Eur J Pediatr 2005.*

**Turcot's Syndrome: A Diagnostic Consideration in a Child With Primary Adenocarcinoma of the Colon.**

*Tithecott et al. J of Pediatric Surg 1989.*

## Biallelic Mismatch Repair Gene Deficiency Syndrome (BMMRD)

- Biallelic mutations in the MMR genes: *PMS2*, *MSH6*, *MLH1*, *MSH2*
- Novel cancer predisposition syndrome



*C. Durno, A Pollett, S Gallinger. Unifying diagnosis for adenomatous polyps, café-au-lait macules, and a brain mass? Gastroenterology 2013.*

## BMMRD Under Recognized Jordan Cohort (n=42)

- immunohistochemistry in brain tumor and normal tissue
- up to 50% of children with glioblastoma in Jordan may have BMMRD

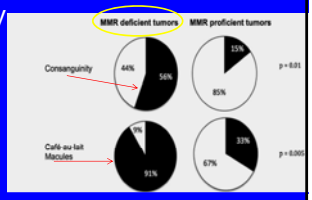
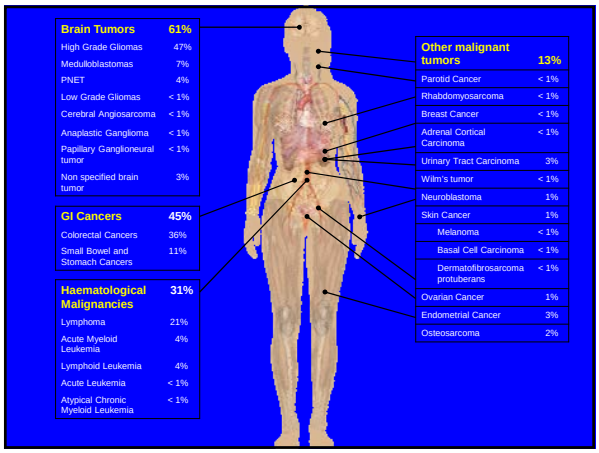



Figure 1. (modified)

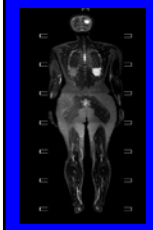
*(Amayiri et al. Inter J Cancer 2016.)*

## Tumor Spectrum expanding…

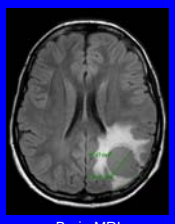



# Surveillance Protocol Impacts Survival

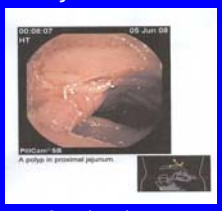
55 tumors detected over 12 years



Body MRI



Brain MRI
anaplastic astrocytoma



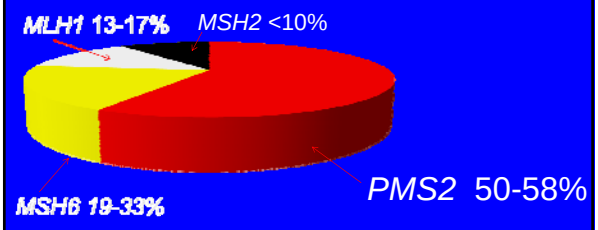
Capsule endoscopy
polyp in proximal jejunum

All patients undergoing GI surveillance are alive at 5 years (1.5 to 12.5 years)

*(Aronson et al. Am J Gastro 2016.)*
*(Durno et al. Eur J of Cancer 2015.)*

# Genotypic Classification

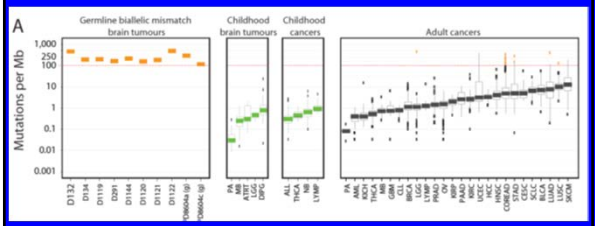
(International n=45, French n=31)




*Durno C et al. International BMMRD Consortium. Eur J of Cancer. 2015.*
*Lavoine N, et al. French cohort. J Med Genet 2015.*

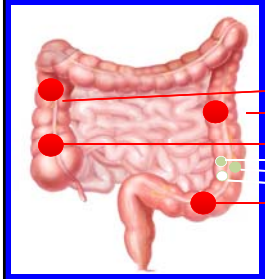
# Research in Polyposis

## BMMRD Cancers Harbor the Highest Mutation Burden Across 7000 Cancers




(*Shlien et al. Nat Genet 2015.*)

## Mutation Load in BMMRD Tumors



**GI cancers are hypermutant**

922 mutations
1164 mutations
6380 mutations
1919 mutations

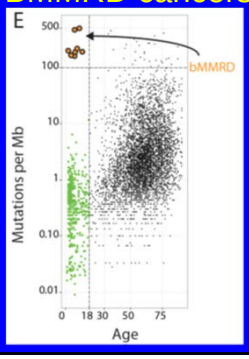
**Polyps low to high grade dysplasia**

39 mutations
21 mutations
57 mutations

- management: resect polyps
- hypermutant cancers require alternative therapies

(*Shlien et al. Nat Genet 2015.*)

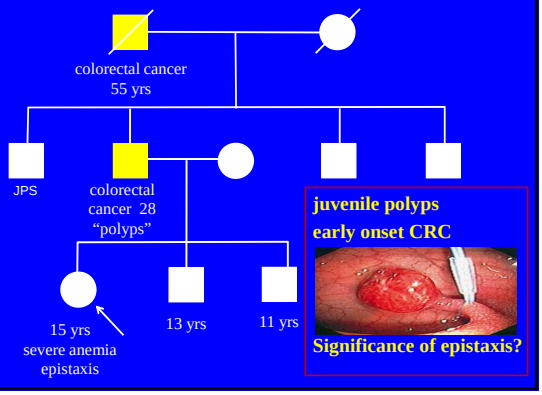
## Can we use this observation to detect BMMRD cancers in children?



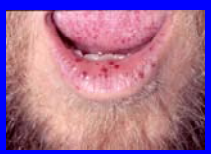

Probability of observing ultra-hypermutation in an age matched non-BMMRD cancer patient is $<10^{-13}$

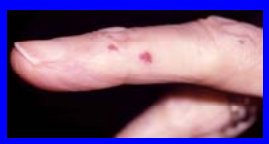
(*Shlien et al. Nat Genet 2015.*)

## Consultation

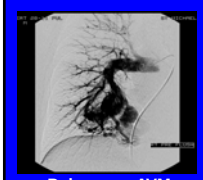



## Hereditary hemorrhagic telangiectasia (HHT)

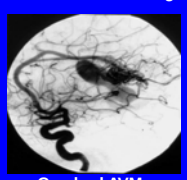




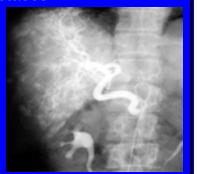
mucosal and skin telangiectases



Pulmonary AVM



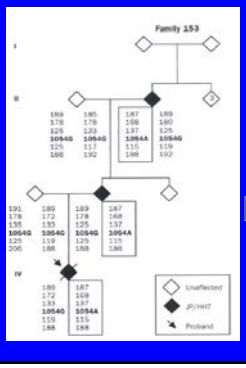
Cerebral AVM



Hepatic AVM

(*Faughnan. J Med Genet 2011.*)

## New syndrome=HHT-JPS

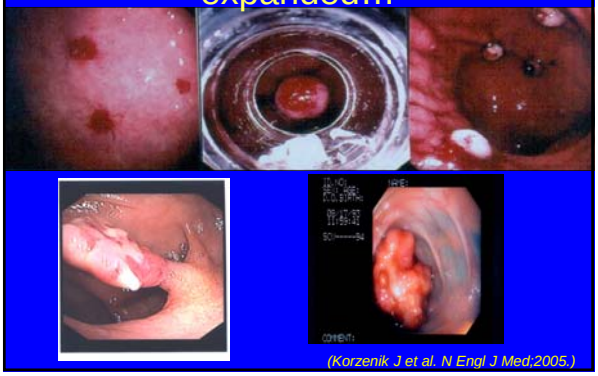



- 7 unrelated kindreds
- segregating both JPS and HHT

All patients had *SMAD4* mutations

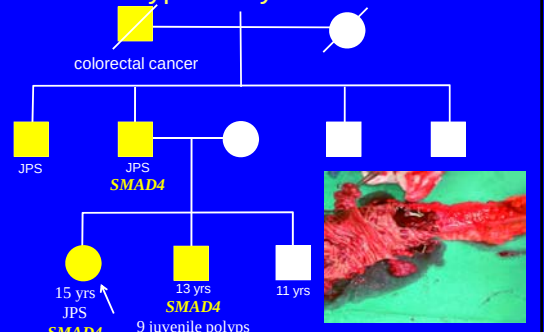
*(Gallione CJ et al. Lancet;2004.)*

## Intestinal phenotype in HHT expanded…



*(Korzenik J et al. N Engl J Med;2005.)*

## Hereditary hemorrhagic telangiectasia-Juvenile Polyposis Syndrome Kindred

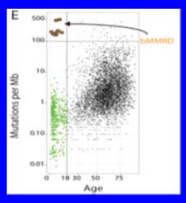



*(Schwenter F, Durno C. J of Gastroenterol 2012.)*
*(Schwenter F, Durno C. J Pediatr Gastroenterol Nutr 2012.)*

# Immunotherapy in Polyposis Syndromes

## Molecular Characterization Immune Checkpoint Blockade

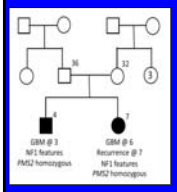

mutational load (**over 100**) is positively correlated with clinical benefit in melanoma, lung and gastrointestinal microsatellite instability high cancers

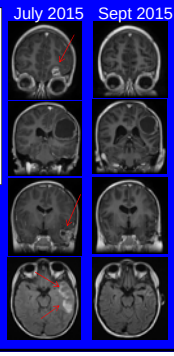



ultra-hypermutant cancers in childhood is highly specific to BMMRD

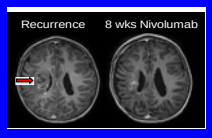
(*Shlien et al. Nat Genet 2015.*)
*(Le DT et al. NEJM 2015.)*
*(Snyder et al. NEJM 2014.)*
*(F. Collins. NIH. 2015)*

## Recurrent Multifocal Glioblastoma Response to Immune Checkpoint Inhibitor






Sibling #2



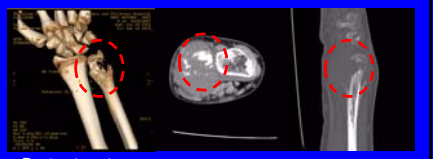

Nivolumab 1-10 mg/kg

*(Bouffet et al. JCO 2016.)*

## Immune checkpoint inhibitors and Recurrent Metastatic Colorectal Cancer

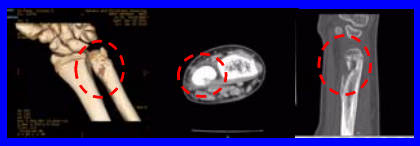
13 year old male

Colorectal cancer with mets to wrist



Pre treatment

Dramatic reduction in soft tissue mass



Post Pembrolizumab

## Conclusions

- Classification of polyposis syndromes impacts screening, surveillance and outcome
- BMMRD tumors have the highest mutation burden
- Novel therapies based on molecular characterization

## The International BMMRD Consortium

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**Sitemen Cancer Center, USA**
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World Congress of
Pediatric GI/Hepatology/Nutrition
Montreal, 2016

# Managing Obesity in Children: Lifestyle, Medications & Surgery


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Chief, Gastroenterology/Hepatology / Nutrition
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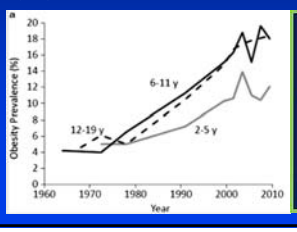
**Joel Lavine, MD, PhD**

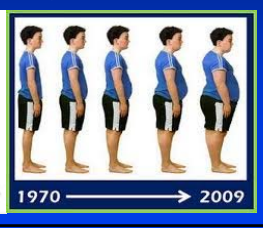
**None related to obesity**

**Consultant for:**
**Alexion, Allergan, Pfizer, Merck, Takeda, Janssen, Humana**

## Learning Objectives

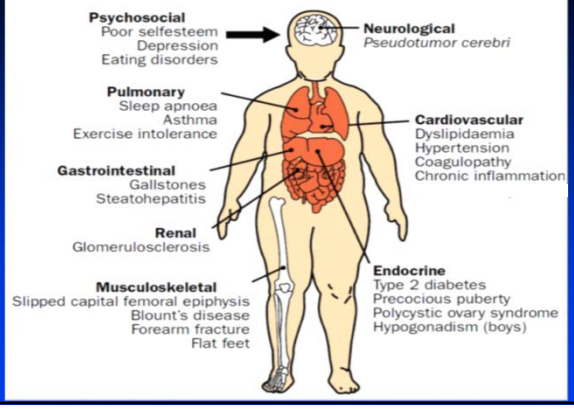
- Recognize the need for early identification of children at risk for obesity and recommend sustainable lifestyle interventions
- Be aware of the pharmacologic targets based on knowledge of energy regulation and feeding behavior, and strategies to intervene
- Be able to identify adolescents who may benefit from bariatric surgery intervention and be knowledgeable of risk




Ogden et al.NCHS Health Stat 2010

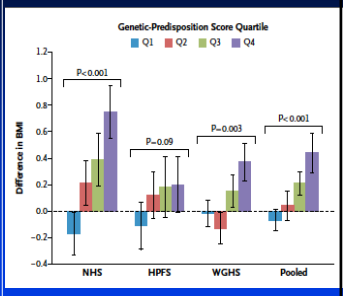
## COMPLICATIONS OF CHILDHOOD OBESITY




## Identification of Children at Risk for Obesity- Infancy

**"Fixed or unmodifiable"**
- Genetic variation

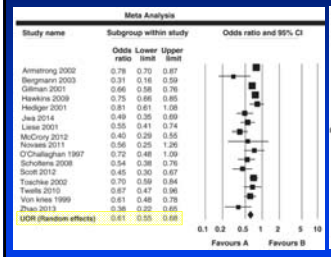
**Possibly Modifiable**
- In utero "epigenetics"
- Low birth weight
- Diet
  - Breast feeding or formula composition
  - Refined sugars, added fats
- Gut microbiome
  - Antibiotic exposure
  - Diet composition
- Familial behavior
  - Portion sizes, feeding cues, activity time

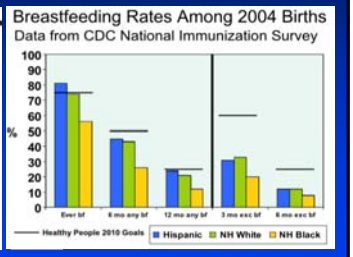



Qi et al. NEJM 2012

## Children at Risk for Obesity- Infancy

**Possibly Modifiable**
- Diet




Yan et al. BMC Public Health. 2014

## Children at Risk for Obesity- Infancy

**Possibly Modifiable**

- **Gut microbiome**
  - **Antibiotic exposure**
  - **Diet composition**

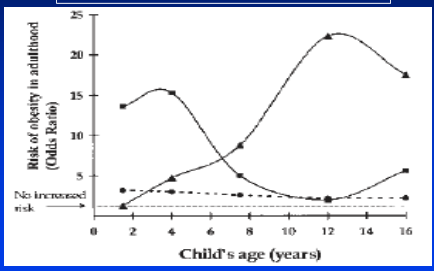
Antibiotics Before Age 2 Years Increases Childhood Obesity Risk

| Exposure | Exposed, n | Obese, n (% of exposed) | Univariable analysis, OR (95% CI) | Adjusted model assessing no. of prescriptions, OR (95% CI) |
|---|---|---|---|---|
| No. of antibiotic prescriptions | | | | |
| 0 (ref) | 6844 | 355 (5.2) | 1.00 | 1.00 |
| 1–2 | 8761 | 492 (5.6) | 1.09 (0.95–1.25) | 1.07 (0.93–1.23) |
| 3–5 | 4481 | 332 (7.4) | 1.46 (1.25–1.71) | 1.41 (1.20–1.65) |
| >5 | 1628 | 127 (7.8) | 1.55 (1.25–1.91) | 1.47 (1.19–1.82) |

Scott et al, Gastroenterology 2016

## Early Childhood Risk for Obesity

- **Parental obesity**
- **Rapid catch-up growth**
- **Family lifestyle**




Hoppin et al., Sem Liv Dis 2004

## Early Childhood Risk for Obesity

- **Parental obesity**
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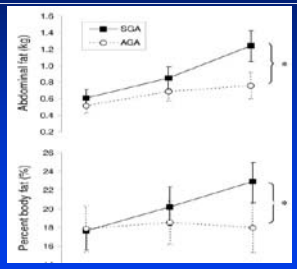



Ibanez et al., J. Clin Endocrin Metabol. 2006: 91

## Early Childhood Risk for Obesity

- Parent(s) obesity
- Rapid catch-up growth
- Family lifestyle (diet/exercise)

**Insufficient activity/play**

- Decreased PE in schools
- Availability of transportation
- Sedentary time/TV/games
- Neighborhood safety
- Latchkey kids


## Risks for Obesity
### Late Childhood and Adolescence

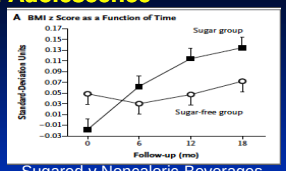
**Late childhood**

- Parent or provider recognition of overweight
- Parental obesity
- Family lifestyle
  - Fast foods and food shopping
  - Sports participation

**Adolescence**

- School lunches
- Food choices
  - High fat/refined sugars

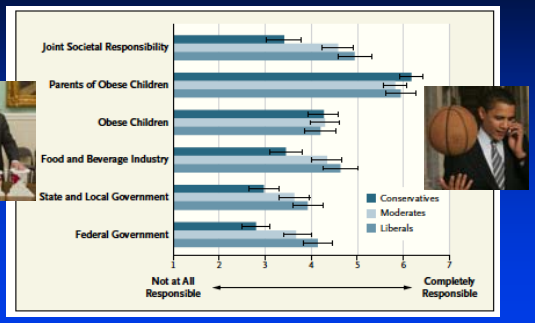
deRuyter et al, NEJM. 2012
Cohen D. NEJM. 2012




Sugared v Noncaloric Beverages

Impulse Marketing

## Attributions of Responsibility for Addressing Childhood Obesity According to Political Ideology






Barry CL et al, NEJM. 2012

## How Governments (Could) Regulate "Fat"


- Portion size of sweetened beverages
- Banning *trans*-fats
- Posting of calories on labels/restaurants
- Taxation of sugar/fat foods
- Removal of impulse marketing
- Banning sugared beverages from schools
- Mandatory institution of physical activity in schools
- City zoning policy
- Eliminate food deserts
- Food stamp exclusions


Portion sizes

## Approved Pharmaceuticals for Treatment of Obesity

| Generic Drug (Proprietary Name[s]) Dose Frequency/d) | Mechanism of Action | Wholesale Price/mo, $[a] | 1-y Weight Change Relative to Placebo, Mean (95% CI), kg[b] | Common Adverse Effects |
|---|---|---|---|---|
| Short-term approval[c] | | | | |
| Phentermine 15-37.5 mg (Adipex-P, Fastin, Oby-Cap, Ionamin, Others; 1×)[d] | Noradrenergic causing appetite suppression | 6-45 | Not included | Insomnia, elevation in heart rate, dry mouth, taste alterations, dizziness, tremors, headache, diarrhea, constipation, vomiting, gastrointestinal distress, anxiety, and restlessness[e] |
| Diethylpropion 25 mg or 75 mg, SR (Tenuate, Tenuate Dospan, Tepanil; low dose, 3×; SR dose, 1×)[d] | Noradrenergic causing appetite suppression | 47-120 | Not included | Same as phentermine[e] |
| Phendimetrazine 17.5-70 mg or 105 mg, SR (Bontril; lower doses, 2-3×; SR dose, 1×)[f] | Noradrenergic causing appetite suppression | 6-20 | Not included | Same as phentermine[e] |
| Benzphetamine 25-50 mg (Didrex; 1-3×)[f] | Noradrenergic causing appetite suppression | 20-50 | Not included | Same as phentermine[e] |
| Long-term approval[c] | | | | |
| Orlistat 60 mg (Alli) or 120 mg (Xenical; 3× within 1 h of a fat-containing meal)[g] | Lipase inhibitor causing excretion of approximately 30% of ingested triglycerides in stool | 60 mg, 45<br>120 mg, 207 | 60 mg, −2.5 kg (−1.5 to −3.5)<br>120 mg, −3.4 kg (−3.2 to −3.6) | Oily spotting, flatus with discharge, fecal urgency, fatty oily stool, increased defecation, fecal incontinence[h] |
| Lorcaserin 10 mg (Belviq; 2×)[d] | Highly selective serotonergic 5-HT2C receptor agonist causing appetite suppression | 240 | −3.2 kg (−2.7 to −3.8) | Headache, dizziness, fatigue, nausea, dry mouth, cough, and constipation; and in patients with type 2 diabetes, back pain, cough, and hypoglycemia[h] |
| Phentermine plus topiramate-ER (Qsymia; 3.75 mg/23 mg for 2 weeks, increased to 7.5 mg/46 mg, escalating to a max of 15 mg/92 mg; 1×)[d] | Noradrenergic + GABA-receptor activator, kainite /AMPA glutamate receptor inhibitor causing appetite suppression | 140-195 | 7.5 mg/46 mg, −6.7 kg (−5.9 to −7.5)<br>15 mg/92 mg, −8.9 kg (−8.3 to −9.4) | Paresthesias dizziness, taste alterations, insomnia, constipation, dry mouth, elevation in heart rate, memory or cognitive changes[h] |

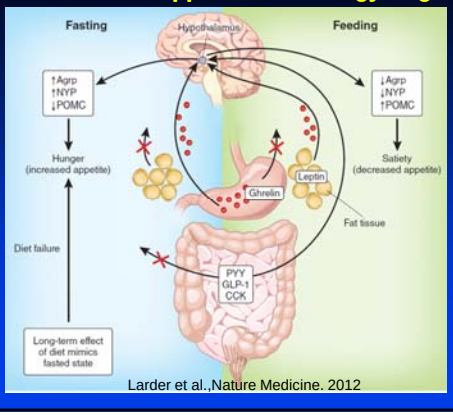
Yanovski S et al, JAMA 2014

## Studies on Orlistat in Children

| Study | Design | Duration | Study Population | Number of Patients (n) | Baseline Therapy | Treatment Groups | Change in BMI (kg/m2) | Change in Weight (kg) |
|---|---|---|---|---|---|---|---|---|
| McDuffie et al, 2002[13] | OL, SC | 3 Months | 12-17 Years old, BMI >95th percentile for age, race, sex plus one obesity-related comorbidity | 20 | Lifestyle modifications | Orlistat 120 mg tid | −1.9[a] | −4.4[a] |
| McDuffie et al, 2004[18] | OL, SC, extension | 6 Months | 12-17 Years old, BMI >95th percentile for age, race, sex, plus 1 obesity-related comorbidity | 20 | Lifestyle modifications | Orlistat 120 mg tid | −2.0[a] | −5.4[a] |
| Ozkan et al, 2004[11] | R, OL, PC | 12 Months | 10-16 Years old, weight-for-height index >140% of healthy individuals | 44 | Lifestyle modifications and multivitamin | Orlistat 120 mg tid<br>PBO | −4.09[a]<br>+0.11 | −6.27[a]<br>+4.16 |
| Chanoine et al, 2005[12] | R, DB, PC | 54 Weeks | 12-16 Years old, BMI ≥2 units above the 95th percentile | 539 | Lifestyle modifications | Orlistat 120 mg tid<br>PBO | −0.55[a]<br>+0.31 | +0.53[a]<br>+3.14 |
| Maahs et al, 2006[13] | R, DB, PC | 6 Months | 14-18 Years old, BMI >85th percentile | 40 | Lifestyle modifications | Orlistat 120 mg tid<br>PBO | −1.3<br>−0.8 | −5.5<br>−1.6 |

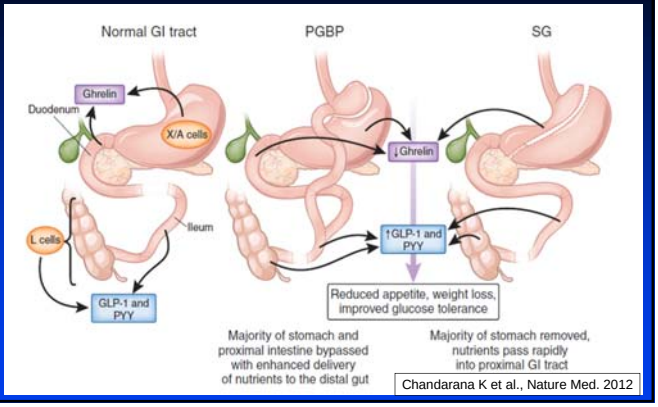
Boland et al, Annals of Pharmacol. 2014

## Hormonal Control of Appetite and Energy Regulation




Larder et al.,Nature Medicine. 2012

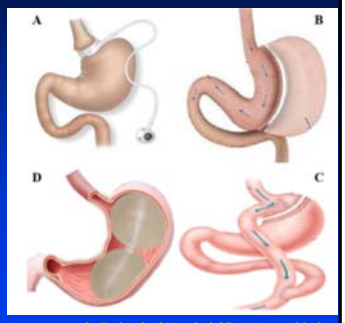
## Hormonal Alterations from Bariatric Interventions




Chandarana K et al., Nature Med. 2012

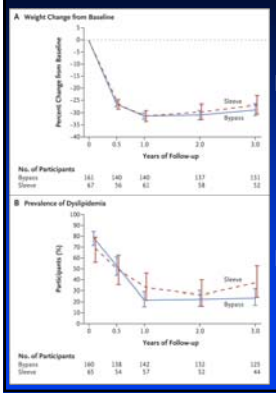
## Adolescent Bariatric Intervention Questions

- Who to operate on?
- Who should pay for it?
- When to do it?
- Who decides?
- How to decide?
- Who operates?
- What operation/procedure?
- How to prepare?
- How to follow-up?




Azagury et al., Endocrinol Metabol Clin N Amer. 2016

## Adolescent Bariatric Surgery Outcomes: TeenLABS




**Most common problems:**

**Nutritional (3 years post surg)**

- Low folate
- Low vitamin D3
- Low vitamin A
- Low vitamin B12
- Low thiamine

**Post-op surgical (RYGB, N=161)**

- Exploratory laparotomy (3)
- Lysis of adhesions (6)
- Gastrostomy (5)

Inge et al., NEJM. 2016

## What Should Be Done (1)?

- Physician identification of modifiable prenatal factors
- Physician promotion of infant breast feeding and appropriate infant feeding practices
- Physician identification of infant and toddlers at risk for overweight and obesity by weight/height trajectory
- Physician discussions around limiting refined sugars and fat added foods, beverages, portion sizes
- Advocacy in public schools for healthy lunches and PE

## What Should Be Done (2)?

- Identification by physicians of children with obesity co-morbidities and appropriate referrals
- Appropriate antibiotic stewardship for frequency, duration, dose and type of antibiotic
- Promote family engagement in weight interventions
- Consider referral for pharmacologic/surgical intervention when appropriate

## Summary: Nutrition in Obese Children

- Obesity and related co-morbidities are the most prevalent worldwide health problems in children
- Environment, genetics, microbiome all important; environment mostly
- Physician opportunity for lifestyle intervention is first line for prevention and treatment
- Orlistat is the only drug FDA approved, many others in trials
- Bariatric surgery for morbid obesity with co-morbidities in adolescents

Ann & Robert H. Lurie Children's Hospital of Chicago

# Intestinal Failure: The Long and Short of the Matter

Valeria Cohran M.D.
Ann & Robert H. Lurie
Children's Hospital of Chicago
Division of Gastroenterology
October 5, 2016

## Objectives

- List the prognostic indicators of achieving enteral autonomy
- Describe the rationale for the use of prebiotics
- Discuss the evidence that supports the use of breast milk in patients with short bowel syndrome
- Define dysbiosis in patients with short bowel syndrome

## Disclosures

- Speaker's bureau
  - Abbott Nutrition
  - Nutricia

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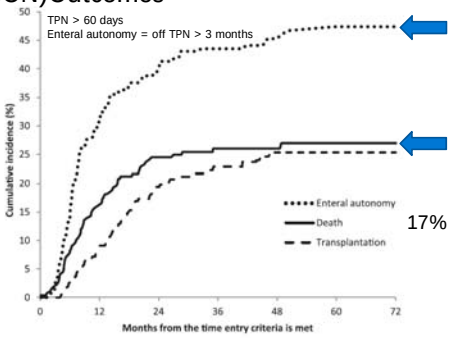
# Prognostic indicators for Enteral Autonomy

## Pediatric Intestinal Failure Consortium (PIFCON)Outcomes

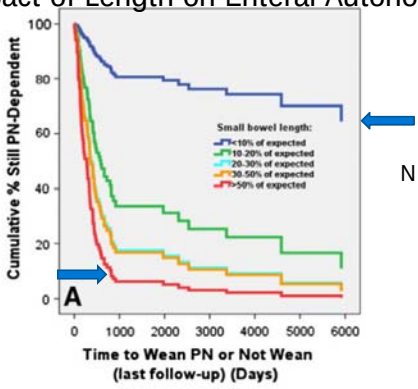



17% died

Squires et al *J Pediatr* 2012;161:723-8

5

## Impact of Length on Enteral Autonomy



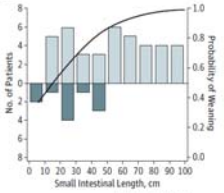

N=171

Demeheri et al *J Peds Surgery* 2015 Jan;50(1):131-5

6

## Predicting outcome based on small intestinal (SI) length

N=63
Maximum of 100 cm of SI
Gestational age: 31 weeks
Median length: 41 cm
8% Died
6% Transplant




| Small Intestinal Length, cm | Predicted Probability of Weaning, Estimate (95% CI) |
|---|---|
| 10 | 0.43 (0.19-0.70) |
| 20 | 0.56 (0.35-0.76) |
| 30 | 0.69 (0.51-0.82) |
| 40 | 0.79 (0.63-0.90) |
| 50 | 0.87 (0.70-0.95) |
| 60 | 0.92 (0.74-0.98) |
| 70 | 0.95 (0.78-0.99) |
| 80 | 0.97 (0.81-1.00) |
| 90 | 0.98 (0.83-1.00) |
| 100 | 0.99 (0.85-1.00) |

Fallon et al *JAMA Surgery* 2014 Jul;149(7):663-70

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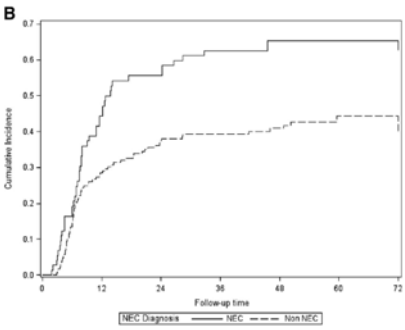
## Impact of NEC on Enteral Autonomy

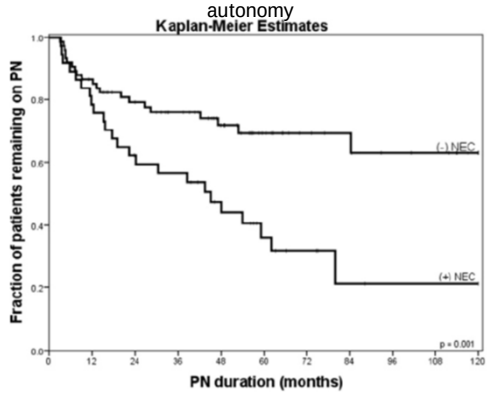



P< 0.001

Khan et al *J Peds* 2015 Jul;167(1):29-34

8

NEC is associated with increased likelihood to attain enteral autonomy




Sparks et al *Journal of Peds Surgery* 2016;51:92-95

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## Breast Milk

- Breast milk always been encouraged
  - 19% of PIFCON cohort
  - Mean duration of TPN 290 vs 720 days in non-breast milk infants
- Growth Factors
  - Glucagon like peptide-2
  - Epidermal growth factor
  - Secretory immunoglobulins
  - Lysozyme
  - Interferon
- Improved outcomes with intestinal autonomy

Squires et al *J Pediatr* 2012;161:723-8
Andorsky et al. *J Pediatr* 2001; 139:27-33

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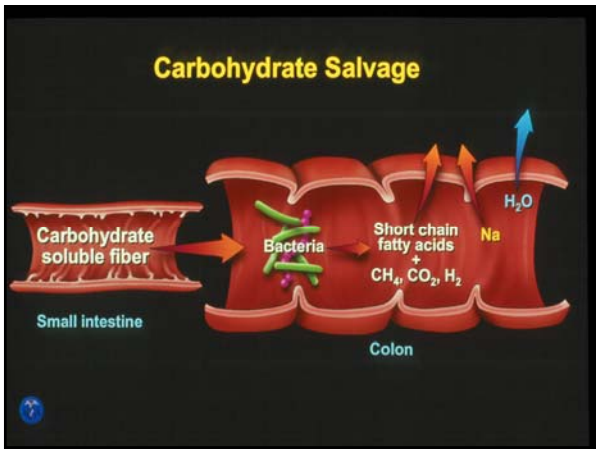
## Prebiotics: The How and Why?

## Prebiotics

- Food product that is not hydrolyzed in the upper GI tract
- Stimulate growth of more beneficial bacteria
- Short chain carbohydrates (oligosaccharides)
  - Inulin
- Serves as an energy source for colonic bacteria
  - Short chain fatty acids: butyrate, propionate and acetate
    - Increase epithelial cell proliferation
    - Decrease epithelial cell apoptosis

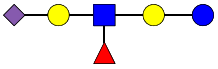
Cow's milk based, extensively hydrolyzed, soy based pediatric and infant formulas containing prebiotics that are commercially available

Stoiodis et al. *Nutrition Research Reviews* 2011;24:2130

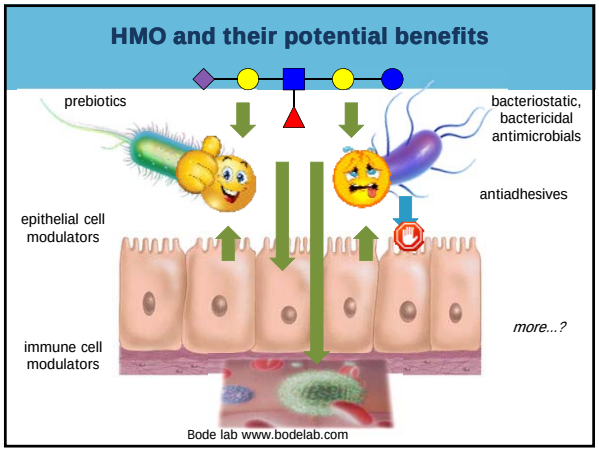



## Human Milk Oligosaccharides (HMO)

- > 200 human milk oligosaccharides
- Carbohydrate polymers
- 3rd most common component after carbohydrates and lipids, > protein
- Minimal present in bovine based formula
- Components
  - Glucose
  - Galactose
  - N-acetylglucasamine
  - Fucose
  - N-acetylneuraminic acid

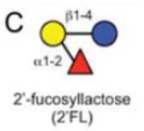


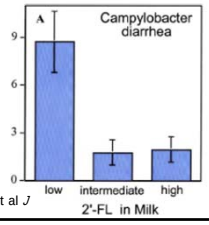
Bode lab www.bodelab.com 14



## 2-Fucosyllactose (2'FL)

- Most abundant HMO in human breast milk
- Prebiotic
- Varying amounts and types depending on genetic predisposition
- Nutrition and environment may also play a role
- Decreasing incidence
  - NEC
  - Norovirus
  - Urinary Tract Infections




Bode et al *Glycobiology* 2012:22:1147-1162 Morrow et al *J Peds* 2004;145:297-303

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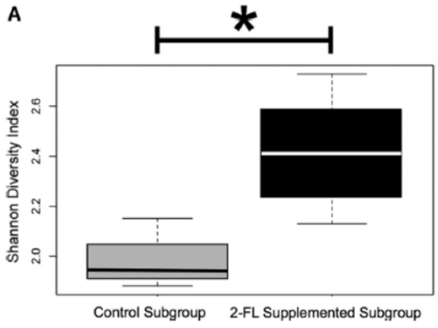
## Increased diversity in 2-FL supplementation after Ileocecal Resection




*Mezoff et al Am J Gastroint Liver Phys* 2015;310:427-38

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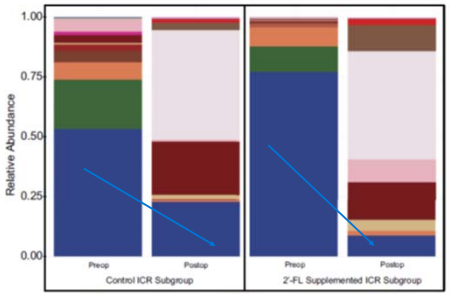
## Effect on abundance of bacteria in 2-FL supplemented animals after ICR




*Mezoff et al Am J Gastroint Liver Phys* 2015;310:427-38

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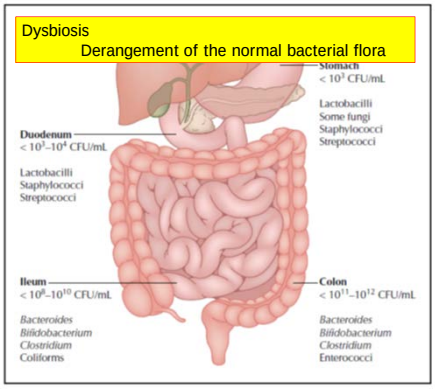
# Dysbiosis and Short Bowel Syndrome

Dysbiosis
Derangement of the normal bacterial flora




Current Gastro Reports 2007;9:456-62

20

## Definitions

- 16S rRNA
  - Allows delineation between different species of bacteria
- Phylum
  - 29 different phyla for bacteria
  - Actinobacteria
    - Bifidobacteria
  - Firmicutes
    - Lactobacillus
  - Proteobacteria
    - the most known phyla, containing species such as Escherichia Coli

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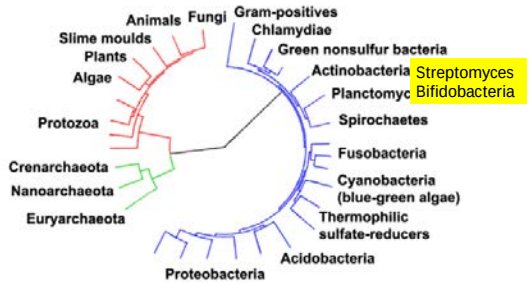
## Bacteria Classification




Streptomyces
Bifidobacteria

Proteus, Klebsiella
Escherichia, Shigella

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## Common organisms in small bowel bacterial overgrowth (SBBO) in Intestinal Failure (IF)

- N=57 IF
- Median age of 5 (2-9.2 years)
- Small bowel bacterial overgrowth defined as $>10^5$ CFU/ml
- Diagnoses
  - 28% Motility Disorders
  - 16% NEC
  - 16% Atresia
  - 14% Gastroschisis
  - 10.5% Hirschsprung's disease

*Gutierrez et al Journal of Pediatric Surgery* 2012;47:1150-1154

23

## Common organisms in small bowel bacterial overgrowth (SBBO) in IF

- 70% (n=40) had SBBO
  - Patients on PN were more likely to have SBBO 70% vs 35%, p=0.02
  - PN administration was associated with adjusted OR 5.1 (95% CI 1.4-18.3;p=0.01)
- 40 patients with SBBO
  - Gram Negative organism
    - N=23 E. Coli
    - N=11 Klebsiella pneumoniae
    - N=4 Klebsiella oxytoca

*Gutierrez et al Journal of Pediatric Surgery* 2012;47:1150-1154

24

## Impact of SBBO

- N=10 NEC
  - 80% had blood stream infection
  - 50% had SBBO
    - Increased the odds for a blood stream infection > 7 times, p=0.009
- N=49
  - SBBO identified prior to tapering of TPN
  - TPN duration
    - N= 12 Diagnosed while on TPN 28 ± 17 months
    - N=11 After tapering from TPN 16 ± 13 months, p<0.05
- N=42 Age of first infection
  - 28±5 Liver failure
  - 48±14 cholestasis
  - 167± 43 days

Suggests that SBBO has a negative impact on enteral adaptation and liver recovery

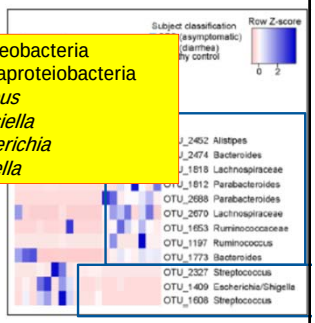
Cole et al *J Peds* 2010;156:941-7
Kaufman et al *J Peds* 1997;131:556-61
Sondheimer et al *JPGN* 1998;27:131-7

25

## Fecal Microbiome in SBS

- N=9 SBS
  - 2.2±0.4 years
  - All had received an
    last 6 months
  - 7/9 metronidazole
  - No motility agents
  - No probiotics
- N= 8 healthy controls
  - 7.6 ± 0.2 years
  - No antibiotics usage within 6 months

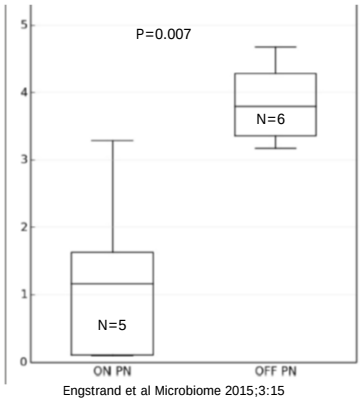
Phylum proteobacteria
class gammaproteiobacteria
*Proteus*
*Klebsiella*
*Escherichia*
*Shigella*




Davidovics et al. *JPEN* 2015

26

## Shannon Diversity Index in SBS patients on and off PN

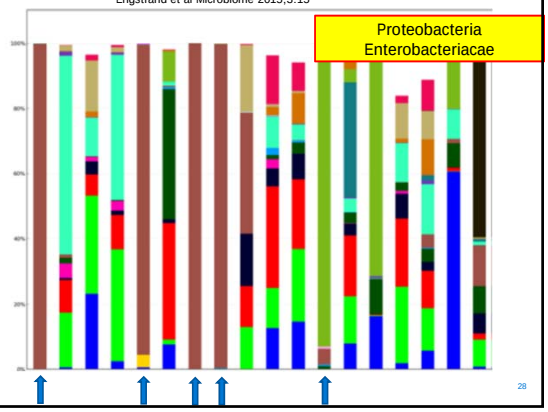



Engstrand et al Microbiome 2015;3:15

27

## Microbial Communities in SBS patients on and off PN

Engstrand et al Microbiome 2015;3:15

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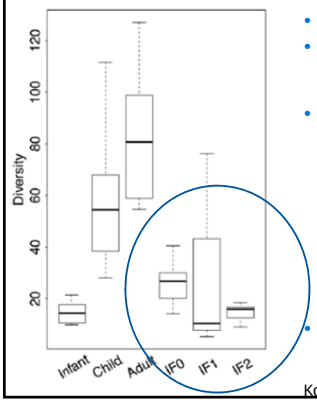
## Intestinal Microbiota Signatures and steatosis in Pediatric IF

- N=23 IF
- N=58 controls
- Overabundance of *Lactobacilli, Proteobacteria, and Actinobacteria*
- Assessed intestinal microbiota based on microarrays
- Proteobacteria ( E. Coli, Klebsiella, Proteus)
  - Liver steatosis and fibrosis
  - Prolonged PN
  - Liver and intestinal inflammation
  - Produces lipopolysaccharides

Korpela et al *JPEN* 2015 in press

29

## Intestinal Microbiota Signatures associated with steatosis with IF

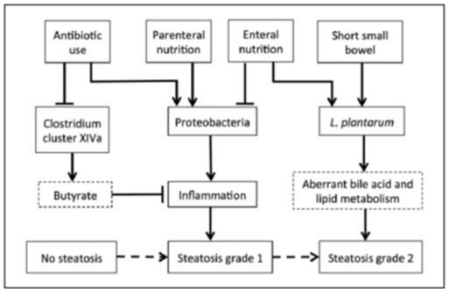



- N=23 IF
- 3 predominant bacteria
  - Clostridium, Proteobacteria, Lactobaccilus planatarum
- Steatosis grades 2-3
  - 2-5 fold increase in Bacilli vs grade 0 or 1
  - Actinobacteria, primarily Bifidobacterium sp, 1.5-6 fold increase
  - Short Bowel syndrome
    - Lactobacillus
  - Prolonged TPN
    - Proteobacteria
- Overall lack of diversity as compared to controls

Korpela et al *JPEN* 2015 in press

30

## Proposed mechanism of steatosis in Intestinal Failure/SBS




Korpela et al *JPEN* 2015 in press

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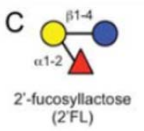
## Conclusion

- Enteral Autonomy
  - Intestinal Length
  - Diagnosis of NEC
  - Use of Breast Milk
- Prebiotics may be beneficial in SBS
  - Improve carbohydrate salvage
  - Water reabsorption




2'-fucosyllactose (2'FL)

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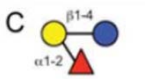
## Conclusion

- Human Milk Oligosaccharides
  - 3rd largest component
  - Protective against viral and bacterial infections
  - Improves diversity after ICR in mice
- Dysbiosis in SBS
  - Proteobacteria
  - Steatosis and hepatitis




2'-fucosyllactose (2'FL)

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# Diet in IBD: Food For Thought

Sandra C. Kim, MD
Associate Professor of Clinical Pediatrics
The Ohio State University College of Medicine
Co - Director
Center for Pediatric and Adolescent IBD
Nationwide Children's Hospital

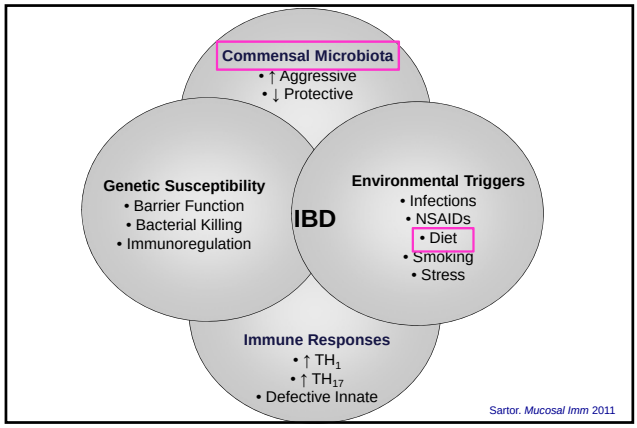
NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.

## Disclosure

The speaker has the following disclosures:
Speakers Bureau (Abbott Laboratories)

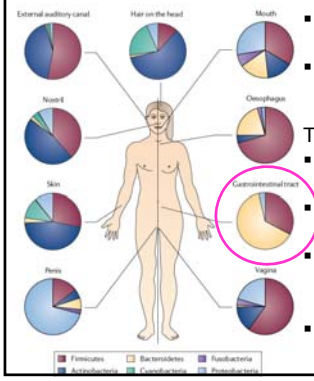
## Objectives

- Address how diet impacts the gastrointestinal tract
- Review the efficacy of enteral therapy in Crohn's disease
- Discuss specific defined diets which have been utilized in IBD




Sartor. *Mucosal Imm* 2011

## The Human Microbiome



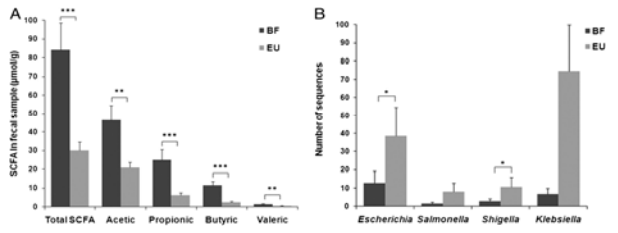
- Comprised of Bacteria, Viruses, others (Archaea, Eukaryotes)
- Distinctive microbiomes at each body site (i.e gut, lung, skin)

The Gut Microbiota

- Human gut is home to ~ 100 trillion bacterial cells
- Density of $10^{11}$ to $10^{12}$ per gram in the colon
- Genome size of microbiota at least 150-fold greater than human
- Large numbers species present, most uncultured

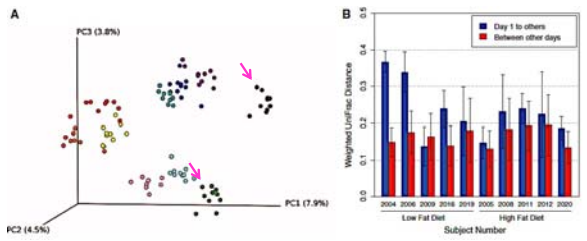
*Nat Rev Micro*. 2011

## SCFA-Producing Bacteria Suppress Potentially Pathogenic Intestinal Bacteria



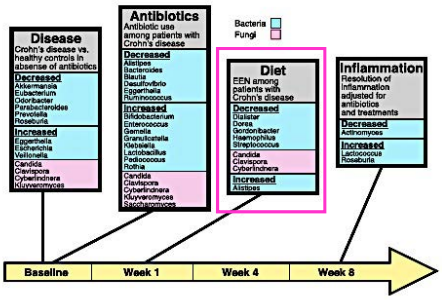

De Filippo, *et al, PNAS*. 2010

## Dietary Impact on Microbiome Composition within 24 Hours




Wu, *et al. Science* 2011

## Diet, Antibiotics, and Inflammation Independently Impact GI Microbiota



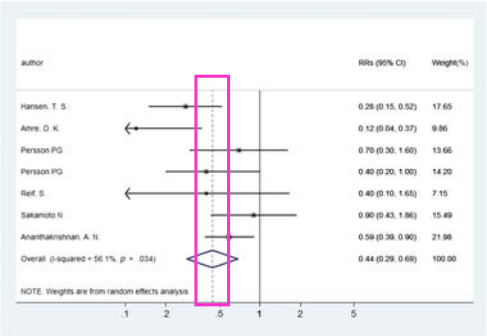

Lewis, et al. *Cell Host Microbe* 2015

## Impact of Diet and IBD Development

- Women in highest quartile of prudent diet score (fish, fruits/vegetables) during high school with 53% lower CD (but not UC) risk
  - Fish ($p = 0.01$) and fiber ( $p = 0.06$)
- Risk of CD decrease by 13% for every 10 gram in fiber intake
- High fat diet could lead to increased intestinal permeability (bile acid exposure; mast cell activation

Ananthakrishnan, *et al. Inflamm Bowel Dis* 2015
Liu, *et al. Nut Res* 2015
Devkota, *et al. Nature* 2012

## Fiber Intake and Crohn's Disease Risk




Liu, *et al. Nut Res* 2015

## ECCO/ESPGHAN Guidelines

- Evidence – based review of existing data
- Individualized treatment algorithms
- Exclusive enteral nutrition (EEN) first choice for induction therapy in children who have not finished growth over corticosteroids
- Predictors for poor outcomes with EEN
  - Severe perianal fistulizing disease
  - Severe stricturing/penetrating disease
  - Severe growth failure
  - Pan-enteric disease

Ruemmele, et al. *J Crohns Colitis* 2014

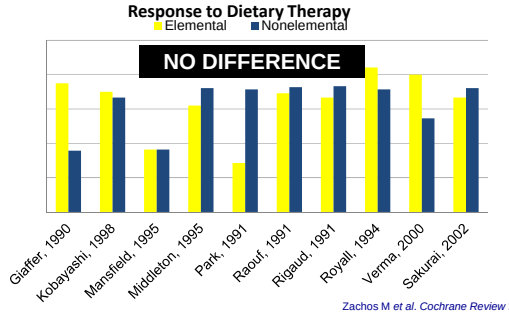
## Enteral Therapy (EN) in Crohn's Disease

- Effective in children and adults with Crohn's disease for induction and maintenance (50-75%)
- EN vs. corticosteroids in pediatric Crohn's
  - 5 prospective randomized clinical trials: EN (4-8 wks) vs. corticosteroids (1-3 wks)
  - Better remission rates
  - *Positive effect on growth
  - *Mucosal healing
- EN may be more effective in children than adults
- Efficacy has not been demonstrated in UC

Lochs, *et al. Gastroenterology* 1991
Seidman, *et al. Gastroenterology* (Abst) 1993
Griffiths, *et al. Gastroenterology* 1995

Day, *et al. Aliment Pharmacol Ther* 2008
Zachos, *et al. Cochrane Database* 2007
Gupta, *et al. Inflamm Bowel Dis* 2013

## Is Elemental Formula Better than Polymeric Formula?




Zachos M *et al. Cochrane Review* 2007

## Induction Therapy: Polymeric Formula vs. Steroids for Pediatric Crohn's

- Prospective 10 week randomized controlled open-label trial
- Newly diagnosed children receive:
  - Polymeric formula (n=18) or steroids (n=19)
- Primary outcomes at 10 weeks
  - Remission (PCDAI≤10): EN (79%); steroids (67%)
  - Mucosal healing: EN (74%); steroids (33%)
    - Decrease in both endoscopic and histologic scores by > 50% when compared to baseline in EN group only

Borrelli, *et al*. *Clin Gastroenterol. Hepatol* 2006

## Exclusive Enteral Therapy Has Improved Clinical Outcomes versus Corticosteroids

- Retrospective chart review with 2 year follow - up
  - N = 89
  - Induction: EEN or corticosteroids
  - Maintenance: Thiopurine
- *Better outcomes in EEN vs. steroid induction
  - Reduced linear growth failure (7% vs. 26%, p = 0.02)
  - Decreased steroid dependence (7% vs. 43 %, p = 0.002)
  - Improved infliximab response (86% vs. 68 %, p = 0.02)

Grover, *et al. Dig Dis Sci* 2015

## Induction Therapy with Partial Enteral Nutrition for Crohn's Disease

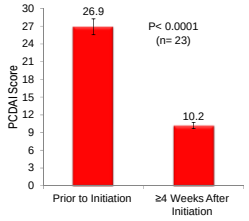
| N = 36 | Week 0 | Week 12 | *P* |
|---|---|---|---|
| HBI, mean | 5.9 ± 2.7 | 0.75 ± 1.75 | 0.000 |
| HBI, median (range) | 6.0 (0–13) | 0.0 (0–6) | 0.000 |
| PCDAI (n = 24) | 25.7 ± 8.9 | 6.44 ± 8.07 | 0.000 |
| CRP | 2.3 ± 2.3 | 0.81 ± 0.64 | 0.002 |
| ESR | 25.7 ± 12.7 | 17 ± 8.2 | 0.001 |
| Hemoglobin | 12.0 ± 1.4 | 12.6 ± 1.3 | 0.1 |
| Albumin | 3.8 ± 0.42 | 4.12 ± 0.39 | 0.000 |

Pairwise comparisons only in subjects with parameters at both time points. Abnormally distributed variables are present as median values. HBI (used in all patients). PCDAI calculated only for children and adolescents through age 18 years.
PCDAI, pediatric Crohn's disease activity index.

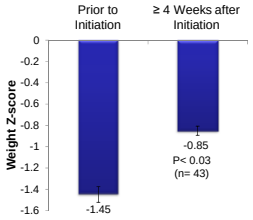
Sigall-Boneh, *et al. Inflamm Bowel Dis* 2014

## CHOP Enteral Nutrition Experience

Mean Change: PCDAI Score




Mean Change: Weight Z-score

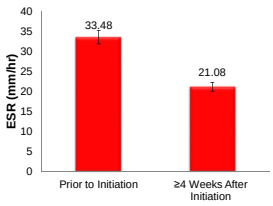



Gupta. *et al. Inflamm Bowel Dis* 2013

## CHOP Enteral Nutrition Experience

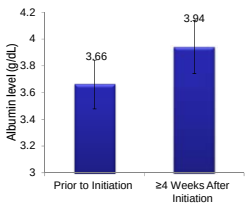
Mean Change: ESR

p=0.0001
n=43




Mean Change: Albumin

p=0.03
n=43




Gupta. *et al. Inflamm Bowel Dis* 2013

## Comparative Effectiveness: Enteral Nutrition (Partial and Exclusive) and anti-TNF

- Prospective study
  - N = 90
  - Anti-TNF (n=52), EEN (n=22), or PEN (formula plus unrestricted diet) (n=16)
- Clinical remission
  - PCDAI: Anti – TNF (84%); EEN (88%); PEN (64%)
  - Calprotectin ≤250 μg/g: Anti – TNF (62%); EEN (45%); PEN (14%)
- QOL improved with EEN in body image (p=0.03) and anti – TNF in emotional domain (p=0.04)

Lee, *et al. Inflamm Bowel Dis* 2015

## Preoperative EEN Reduce Post-Operative Complications in Active Crohn's Disease

- Patients undergoing resection for fibrostenotic ileal +/- colonic Crohn's
  - N = 81 (EN = 42; non – EN = 39)
  - No other treatments for 3 months pre-operatively
- Post – operative complications
  - Significantly less infectious ($p < 0.03$) and non-infectious ($p < 0.02$) in EN vs. non - EN patient groups
- Cumulative recurrence
  - Endoscopic (Rutgeerts): 3 vs 10 (6 months; $p<0.03$); 20 vs 22 (24 months; $p<0.43$); clinical recurrence rates similar at all points

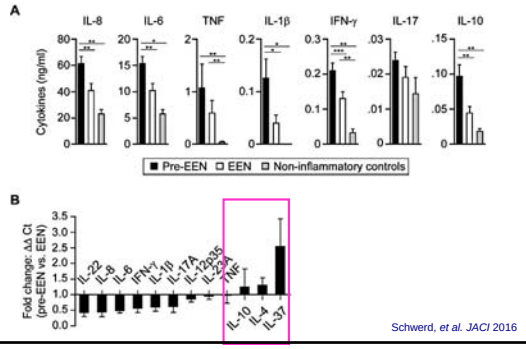
Wang, *et al. World J Gastro* 2016

## Enteral Therapy and the Impact on Microbial Diversity

- Potential efficacy of EEN on fecal microbiota
- Recent studies show decrease/little change in overall microbial diversity in children on EEN
- Changes in specific species associated with disease activity (increases in *Firmicutes, Ruminococcia*e)
  - Includes decrease in presumed protective bacteria *(F. prausnitizii)*
- While EEN does affect composition, need additional studies to look at associative vs. causative role

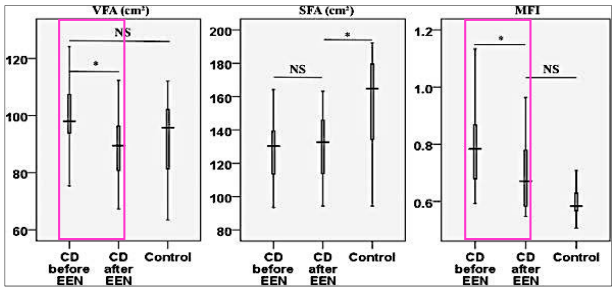
Gerasimidas, *et al. Inflamm Bowel Dis* 2014
Kaakoush, *et al. Clin Transl Gastro* 2015
Schwerd, *et al. JACI 2016*

## Enteral Therapy is Associated With Decreased Pro-inflammatory Cytokines



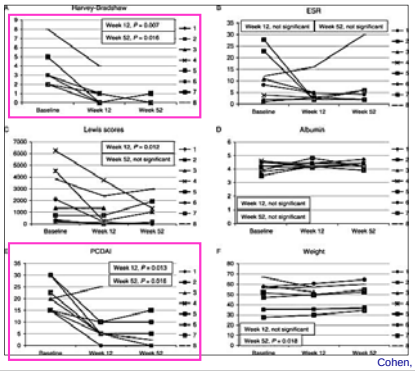

Schwerd, *et al. JACI* 2016

## Enteral Therapy and Impact on Visceral Fat




Li, *et al. Inflamm Bowel Dis* 2014

## Specific Carbohydrate Diet in Crohn's




Cohen, *et al. JPGN* 2014

## Specific Carbohydrate Diet in Crohn's

Albumin levels, g/dL

| Study ID | Before diet intervention | 3 mo after | 6 mo after | 12 mo after | 15 mo after | 18 mo after |
|---|---|---|---|---|---|---|
| 1 | 3.2 | 3.9 | 4.2 | | | |
| 2 | 3.4 | 3.9 | 4.3 | | | |
| 3 | 3.5 | | 4.5 | 4.1 | | 4.1 |
| 4 | 3.8 | 4.5 | 4.3 | 4.5 | 4.3 | 4.3 |
| 5 | 3 | 3.2 | 3.8 | 3.4 | | |
| 9 | 3.6 | | 4.1 | | | |
| 10 | 3.2 | 4.6 | 4.2 | 4.1 | | |

C-reactive protein, mg/dL

| Study ID | Before diet intervention | 3 mo after | 6 mo after | 12 mo after | 15 mo after | 18 mo after |
|---|---|---|---|---|---|---|
| 1 | 4.2 | 0.8 | 1.2 | | | |
| 2 | 2.4 | 0.8 | 0.6 | | | |
| 3 | 5.8 | | 0.8 | 0.8 | | 0.8 |
| 4 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 |
| 5 | 2.8 | 0.9 | 0.8 | 0.8 | | |
| 9 | 2.1 | | 0.8 | | | |
| 10 | 0.4 | 0.8 | 0.8 | 0.8 | | |

Hematocrit (%)

| Study ID | Before diet intervention | 3 mo after | 6 mo after | 12 mo after | 15 mo after | 18 mo after |
|---|---|---|---|---|---|---|
| 1 | 36.3 | 39.9 | 40.1 | | | |
| 2 | 35.5 | 37.7 | 37.7 | | | |
| 3 | 35.3 | | 38.2 | 42.5 | | 42.5 |
| 4 | 41 | 41.7 | 40.6 | 39.7 | 37.7 | 39.6 |
| 5 | 33.9 | 34.9 | 34.6 | 36.7 | | |
| 9 | 36.9 | | 36.2 | | | |
| 10 | 42.3 | 45.8 | 47 | 44.5 | | |

*For Seattle Children's laboratory normal values for albumin is between 3.8 and 5.4 g/dL; normal range for C-reactive protein <0.8; normal range for hematocrit between 34% and 40%.

Suskind, *et al. JPGN* 2014

## Specific Carbohydrate Diet in Crohn's

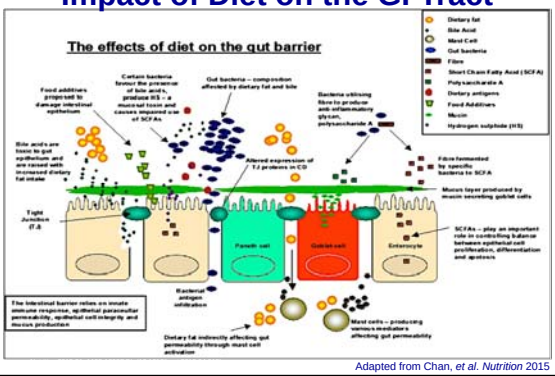
Crohn's disease

| Parameter | Before diet | | 2–6 wk | | 4–6 mo | | 7–11 mo | | 12 mo | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| PCDAI (all) | 14.5 | 16.4 | 8.5 | 13.4 | 3.1 | 5.1 | 7.5 | 6.5 | 0 | |
| PCDAI (diet initiated during active disease) | 32.8 | 13.2 | 20.8 | 16.6 | 8.8 | 8.5 | 10 | 8.7 | 0 | |
| ESR (mm/h) | 19 | 15.9 | 12.2 | 7.6 | 9.5 | 5.2 | 11.8 | 10.1 | 14 | 16.1 |
| CRP (mg/dL) | 1.8 | 1.0 | 1.3 | 1.1 | 0.9 | 0.2 | 1.3 | 1.6 | 0.9 | 0.3 |
| Albumin (mg/dL) | 4.1 | 0.5 | 4.3 | 0.3 | 4.3 | 0.3 | 4.2 | 0.5 | 4.4 | 0.5 |
| Hematocrit (%) | 35.6 | 2.9 | 37.3 | 3.5 | 39.3 | 2.4 | 38.3 | 3.6 | 39.3 | 3.3 |
| Calprotectin (mcg/g) | 685 | 205.5 | 212.6 | 235 | 504 | 540.6 | | | | |
| Vitamin D, 25-hydroxy | 31.1 | 4.7 | 30.7 | 10.6 | 37.5 | 26.2 | 34.1 | 13.6 | 24.5 | 3.5 |
| BMI | 17.3 | 2.3 | 17.9 | 2.3 | 16.7 | 2.9 | 16.9 | 3.12 | 18.3 | 4 |
| Ulcerative colitis | | | | | | | | | | |
| PUCAI (all) | 20 | 11.4 | 12.5 | 13.7 | 12 | 24.1 | 10 | – | 0 | – |
| PUCAI (diet initiated during active disease) | 28.3 | 10.3 | 20 | 17.3 | 18.3 | 31.7 | 10 | – | 0 | – |
| ESR (mm/h) | 15.6 | 7.0 | 11.4 | 6.9 | 8.5 | 3.5 | 7 | – | 7 | – |
| CRP (mg/dL) | 1.0 | 0.5 | 0.7 | 0.3 | 0.9 | 0.3 | 0.8 | – | 0.8 | – |
| Albumin (mg/dL) | 4.2 | 0.4 | 4.5 | 0.2 | 4.4 | 0.3 | | | 4.1 | – |
| Hematocrit (%) | 35.1 | 2.6 | 38.9 | 3.2 | 37.5 | 3.0 | 35.5 | – | 38.5 | – |
| Vitamin D, 25-hydroxy | 25.5 | 3.5 | 28 | 0 | | | | | | |
| BMI | 17.2 | 2.1 | 17.6 | 1.6 | 18.0 | 1.9 | 18.9 | – | 20.1 | – |

- 12/26 patients improved (clinical and inflammatory markers)
- Potential component of therapeutic regimen

Obih, *et al. Nutrition* 2016

## Impact of Diet on the GI Tract




Adapted from Chan, *et al. Nutrition* 2015

## Summary and Take Home Points

- The impact of dietary factors on IBD is multifactorial
  - GI tract permeability
  - Immune cell activation
  - Food antigen recognition
- Enteral therapy is effective as both induction and maintenance regimens in pediatric Crohn's disease
- Defined diets like the specific carbohydrate diet may be effective in IBD but more data needed

## Future Directions

- Clinical research
  - Larger scale studies on elimination diets
- Basic/translational research
  - Delineate the specific protective and inflammatory components of diet (i.e. which food additives)
  - Define how different diets impact the microbiome and metabolome
- Health care delivery
  - Improve accessibility
  - Financial issues

Erasmus MC
University Medical Center Rotterdam

Sophia Children's Hospital

## BIOSIMILARS in IBD

## Lessons from our European Colleagues

Lissy de Ridder, PhD, MD
Associate Professor in Paediatric Gastroenterology

The Paediatric IBD Porto Group
ESPGHAN

## CONFLICT OF INTEREST

Participation in clinical studies sponsored by Abbott, Janssen Biologics, Shire, Hospira and Pfizer as investigator
Consultant of Janssen Biologics, MSD, Abbvie and Shire

Trade names of drugs will be used as little as possible
but cannot be completely avoided due to the topic

## Learning objectives

- Know the differences between generics and biosimilars
- Understand the benefits and limitations of the use of anti-TNF biosimilars in paediatric IBD
- Be aware of ESPGHAN paediatric IBD Porto Group recommendations concerning biosimilars and paediatric IBD

## Content

- Challenge 1
  - Find the differences
- Challenge 2
  - Where are the paediatric data?
- Challenge 3
  - To switch or not to switch?
- Challenge 4
  - Should we fear immunogenicity?
- Challenge 5
  - Is it all about the money?

## Definition of biosimilar

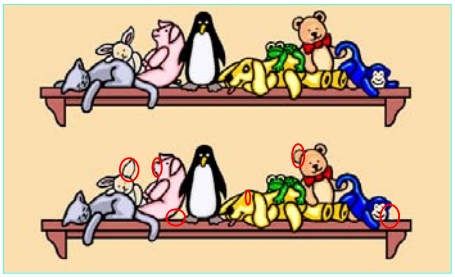
- WHO

  A biologic medicinal product which is similar in terms of quality, safety and efficacy to an already licensed reference biologic medicine

- European Medicines Agency

  A biosimilar is a medicinal product that contains a version of the active substance of an already authorised original biological medicinal product. A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise

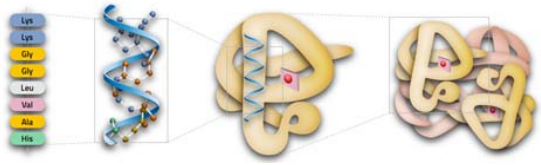
## Challenge 1: **Find the differences!**



Are we, as paediatric gastroenterologists, able to detect the differences?

## Very complex structure

Primary structure | Secondary structure | Tertiary structure | Quaternary structure



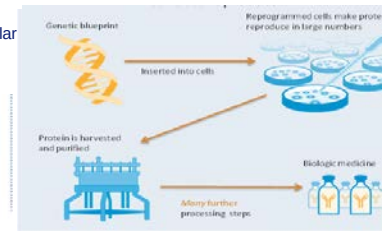

Amino acid residues | α Helix | Polypeptide chain | Assembled subunits

Lehninger Al, Nelson DL and Cox MM. 1993. Chapter 7. The three-dimensional structure of proteins. In Principles of Biochemistry. Second edition. Worth Publishers, New York.1993

## Chemically synthesized medicines are made; biologics are grown

Chemicals; small molecular structures, exactly the same product

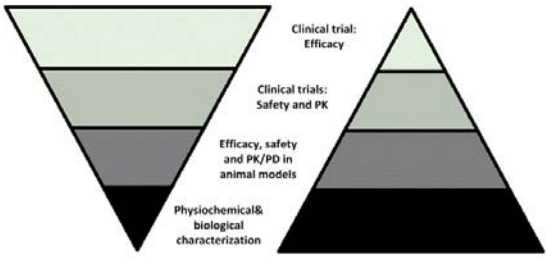
Biologics; grown from living things




## Need to rely on experts EMA (European Medicine Agency) for medicinal products for human use

A very well defined pathway for approval of monoclonal antibody biosimilars:

- Clinical **pharmacokinetic** (PK) and **pharmacodynamic** (PD) studies
- Two or three-arm **clinical efficacy** studies
- Finally, **clinical safety** should be compared in clinical studies assessing the adverse event profile and immunogenicity
- Plans for **post-marketing surveillance** (pharmacovigilance and risk management) – should be provided



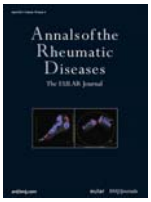

Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

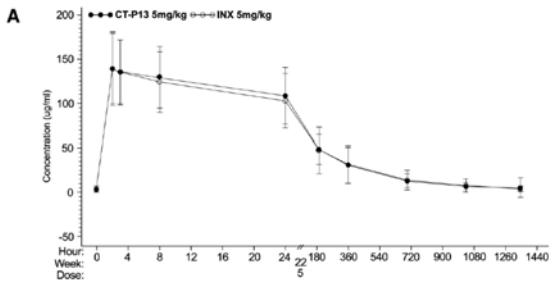
## A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study

Won Park,[1] Pawel Hrycaj,[2] Slawomir Jeka,[3] Volodymyr Kovalenko,[4] Grygorii Lysenko,[5] Pedro Miranda,[6] Helena Mikazane,[7] Sergio Gutierrez-Ureña,[8] Miejin Lim,[1] Yeon-Ah Lee,[9] Sang Joon Lee,[10] HoUng Kim,[11] Dae Hyun Yoo,[12] Jürgen Braun[13]




(Park et al, Ann Rheum Dis 2013)

## Pharmacokinetic Profile; Planetas study



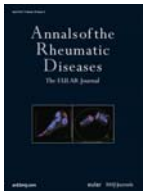

Park et al, Ann Rheum Dis 2012

OPEN ACCESS

EXTENDED REPORT

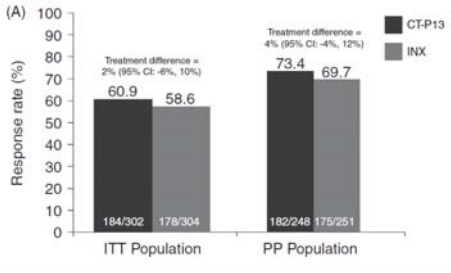
A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

Dae Hyun Yoo,[1] Pawel Hrycaj,[2] Pedro Miranda,[3] Edgar Ramiterre,[4] Mariusz Piotrowski,[5] Sergii Shevchuk,[6] Volodymyr Kovalenko,[7] Nenad Prodanovic,[8] Mauricio Abello-Banfi,[9] Sergio Gutierrez-Ureña,[10] Luis Morales-Olazabal,[11] Michael Tee,[12] Renato Jimenez,[13] Omid Zamani,[14] Sang Joon Lee,[15] HoUng Kim,[16] Won Park,[17] Ulf Müller-Ladner[18]




Yoo et al, Ann Rheum Dis 2013

## ACR20 response rate at week 30 (intention to treat and per protocol)




Yoo et al, Ann Rheum Dis 2012

## Infliximab..s



Remicade® Janssen Biotech (USA)

Remsima® Celltrion (South Korea)

Inflectra® Hospira (USA)

Flixabi® Samsung (South Korea)

## Recommendation for infliximab biosimilars
**EMA**

- Remsima® and Inflectra® are biosimilar to infliximab
  - **Same non-proprietary name**
- Randomized controlled trials have demonstrated **comparable quality, safety, and efficacy** profiles to infliximab in:
  - **AS (Phase I: 250 patients)**
  - **RA (Phase III: 606 patients)**

## Recommendation for infliximab biosimilars
**EMA**

- **Extrapolated data to all approved Remicade® indications:** RA, adult and pediatric Crohn's disease, adult and pediatric ulcerative colitis, AS, psoriatic arthritis, and psoriasis
  - A pharmacovigilance plan for Remsima® is implemented as part of the marketing authorization
- **Same label (Summary of Product Characteristics) as Remsima® and Inflectra®**

## FDA

U.S. Food and Drug Administration
Protecting and Promoting Your Health

- Approval biosimilar across all indications (April 2016)
  - Except for pediatric UC (still under patent)

## Health Canada

Health Canada

- Approval biosimilar for indications CD, fistulizing CD, UC (June 2016)

## Challenge 2: **Where are the paediatric data?**

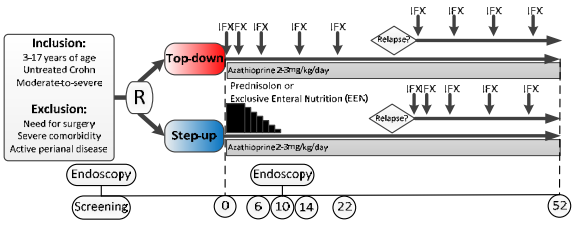
- Poland, 3 academic centers, Dr Kierkus et al (ECCO 2015 abstracts)
  - 12 paediatric CD pts, median age 15.1 yrs
  - 6 paediatric UC pts, median age 12.3 yrs
  - 32 paediatric CD pts switched
- So far, efficacy and safety comparable, but very small numbers and short follow-up
- Crucial to continue close monitoring

## Extrapolation from adult rheumatic disease to paediatric IBD

- Different age group
  - Different lifespan with chronic disorder
- Different disease pathogenesis
- Monotherapy vs combo therapy, different dosing
  - PLANETRA 3mg/kg IFX combined with MTX

## But also study in children!

**Top-down vs Step-up: TISKids study**



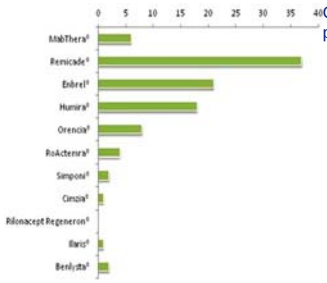
## Challenge 3: **To switch or not to switch?**

- Government funded study
- 18 participating hospitals across the country
- Phase IV study
- Enroll 500 patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis
- Assess the safety and efficacy of switching from infliximab to the biosimilar
- Results expected this autumn

## Challenge 4: **What about immunogenicity?**

- Lifelong disease
- More severe phenotype
- Less alternative drugs available for paediatric IBD patients

## **Manufacturing changes in Biologicals**




Changes in manufacturing process since approval

ICH Harmonised tripartite guideline of biotechnological/biological products subject to changes in their manufacturing process Q5E comparability 2004

A.K. Schneider, Ann Rheum Dis 2013;72:315-318

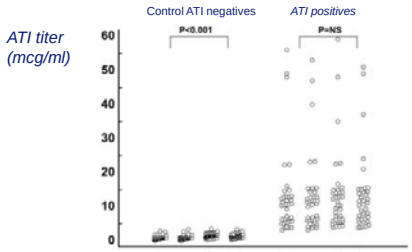
## Cross-immunogenicity

ORIGINAL ARTICLE

Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima

Shomron Ben-Horin,[1] Miri Yavzori,[1] Itai Benhar,[2] Ella Fudim,[1] Orit Picard,[1] Bella Ungar,[1] SooYoung Lee,[3] SungHwan Kim,[3] Rami Eliakim,[1] Yehuda Chowers[4]

## All remicade treated IBD patients with ATI's crossreactivity with Remsima




*2 a-Remicade and 2 a-remsima batches*

## Challenge 5:
## Is it all about the money?

- Availibility of biosimilars is expected to result in a substantial cost expenditure reduction
- Estimated around 30%

## Expiration date for biologics

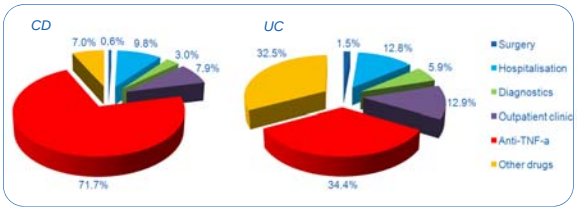
| INN | EU patent exp date | US patent exp date | Biosimilars in development * |
|---|---|---|---|
| **Adalimumab** | **2018** | **2016** | 13 |
| Etanercept | 2015 | 2028 | 21 |
| **Infliximab** | **2014** | **2018** | 9 |
| Insulin Glargine | 2014 | 2014 | 5 |
| Rituximab | 2013 | 2016 | 30 |
| Bevacizumab | 2019 | 2017 | 14 |
| Interferon B-1a | Expired | Expired | N/A |
| Trastuzumab | 2015 | 2015 | N/A |
| Insulin Aspart | 2014 | 2019 | N/A |
| Glatiramer acet | 2017 | 2015 | N/A |
| Pegfilgrastim | 2015 | 2014 | 14 |
| Ranibizumab | 2016 | 2016 | 2 |

Source: IMS MIDAS, 09/2012, IMS Patent focus, Adapted from G. Morelli, IMS Health
*Rader RA, Biosimilars markets. BioProcess International 2013;11(6)suppl:16-23

## Anti tumour necrosis factor-α therapy is a major cost driver in IBD

*M.E. van der Valk[1], M.J. Mangen[2], G. Dijkstra[3] D.J de Jong[4], A.A. van Bodegraven[5], H.H. Fidder[1], M. Pierik[6], C.J. van der Woude[7], C.Y. Ponsioen[8], M.J.L. Romberg-Camps[9], C. Bolwerk[10], J. Jansen[11], N. Mahhmod[12], J.R. Vermeijden[13], C.H.M. Clemens[14], P. van de Meeberg[15], P.D. Siersema[1], M.G.H. van Oijen[1], B. Oldenburg[1] on behalf of the Dutch Initiative on Crohn and Colitis and COIN study*

## Results: healthcare cost (adult IBD)



Erasmus MC
University Medical Center Rotterdam

Sophia Children's Hospital
The Paediatric IBD Porto Group
ESPGHAN

**Societal paper**

**USE OF BIOSIMILARS IN PAEDIATRIC INFLAMMATORY BOWEL DISEASE: A POSITION STATEMENT OF THE (PORTO) ESPGHAN IBD WORKING GROUP**

**Lissy de Ridder, Matti Waterman, Dan Turner, Jiri Bronsky, Almuthe Christina Hauer, Jorge Amil Dias, Caterina Strisciuglio, Frank M Ruemmele, Arie Levine, Paolo Lionetti**

## What about the introduction of biosimilars in paediatric IBD?

- Decrease costs of anti-TNF drugs, enabling to lower the threshold of using these highly effective but expensive drugs in IBD
- But! Absence of published trials on the usage of biosimilars in adult and paediatric IBD

## STATEMENTS

- **The ESPGHAN paediatric IBD Porto group advocates high priority to performing paediatric trials with long term follow-up to support this decision.** 97% *agreement*
- **Treatment of a child with sustained remission on a specific medication: do not switch to a biosimilar until clinical trials in IBD support the safety and efficacy of this.** 94% *agreement*
- **Post-marketing surveillance programs for efficacy, safety and immunogenicity in children with IBD are mandatory.** 100% *agreement*

## Where are we now..

September 2013: Inflectra received EMA marketing authorization

February 2015: Expiration of Remicade


*TISKids*

*PLANETRA*
*606 RA patients*

*PLANETAS*
*250 SA patients*

## To summarise..

- Biosimilars infliximab have comparable efficay and safety data
- Paediatric data are on the way
- So far, switching in paediatric IBD is not recommended
- No reason to fear for increased immunogenicity
- Costs play an important role in the choice of prescription

## Challenge 6: **Predict the future**

Thank you for your attention!

## The role of objective disease monitoring in IBD

**Anne M Griffiths, MD**

**Hospital for Sick Children**

**University of Toronto,**

**Toronto, CANADA**

I have the following financial relationships to disclose:

Janssen: consultant; speaker; research support; IBD program support
Abbvie: speaker; consultant; research support; IBD program support
Merck: consultant
Takeda: consultant

## Specified learning objectives

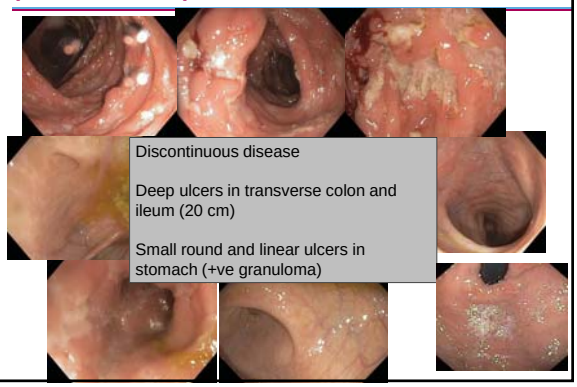
As a result of the talk, the audience will be able to:

1. Establish treatment targets in IBD
2. Understand the utility and limitations of serum and fecal inflammatory biomarkers.
3. Utilize and interpret imaging and/or endoscopic findings appropriately

## Let's initiate discussion with a patient

- 10 year old girl presents with background of vague abdominal discomfort, low grade fevers, lack of weight gain (1 year), poor linear growth (<2 cm in 1 year)
- Rapid deterioration! Within 2-3 weeks: anorexia, weight loss (3 kg), fatigue, fevers, transient E.nodosum

## Ileocolonic Crohn's Disease at first evaluation (Paris: L3 + L4a)



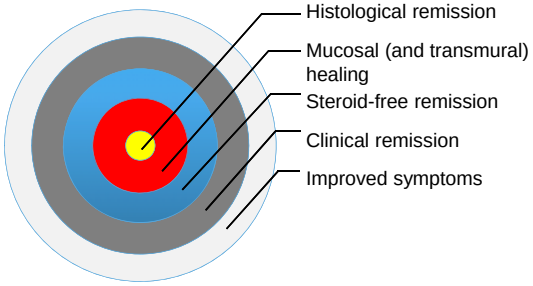

## Outline: In planning management of this (and all) patient(s)....

- What should our treatment targets be and why?
- How can we objectively monitor achievement of targets non-invasively?
- When should we reassess endoscopically and/or with imaging?

## The role of objective disease monitoring

- What should our treatment targets be and why?
- How can we monitor for intestinal healing non-invasively?
- When should we reassess endoscopically and/or with imaging?

## Evolution of IBD treatment goals

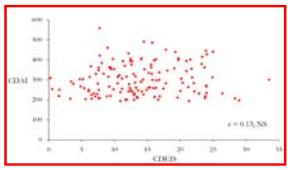



## Why have treatment goals in pediatric IBD have moved "beyond symptoms"?

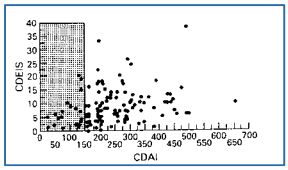
- Recognition of the discrepancy between symptoms and status of intestine particularly in Crohn's disease
- Aiming to heal the intestine and thereby alter natural history, and improve outcomes
- Possible because of emergence of therapies with greater potential to achieve healing

STRIDE "Selecting therapeutic targets in Inflammatory Bowel Disease"
Peyrin-Biroulet et al, Am J Gastro 2015; 110: 1324-1338

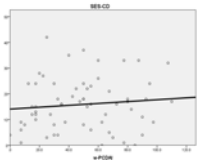
## Discrepancy between symptoms and endoscopic appearance in Crohn's disease!



Modigliani R et al. Gastroenterology 1990;98:811

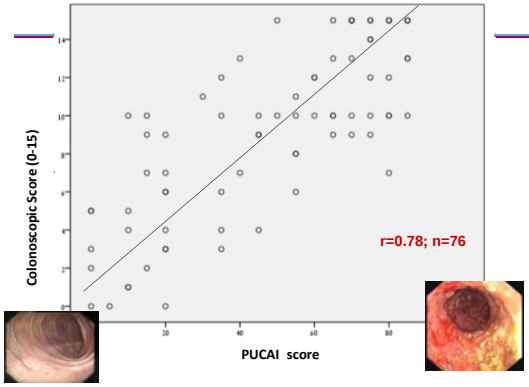



Cellier C. et al. Gut 1994;35:231-235



Carman N et al
Canadian Children IBD Network
CDDW 2015

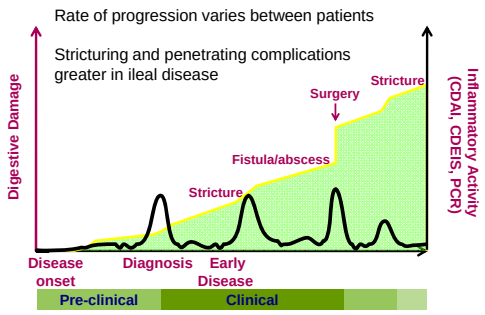
## What about ulcerative colitis?




Turner D et al, Gastroenterology 2007;133:423–432

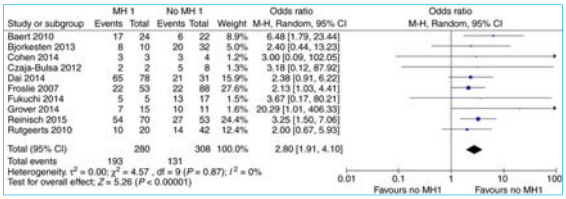
## Crohn's disease: A progressive disease

### Progression of digestive damage and inflammatory activity



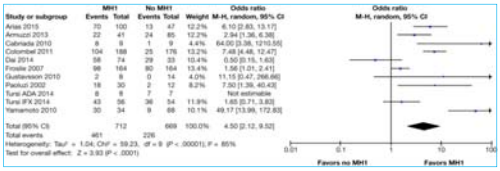

Pariente et al. Inflamm Bowel Dis 2011;17:1415-1422

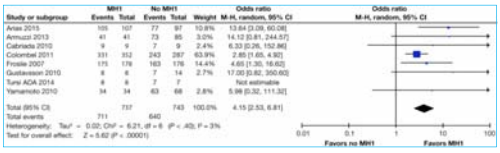
## Association of mucosal healing with long-term clinical remission and avoidance of surgery: CD




Shah SC et al, APT 2015; 43: 317-333

## Association of mucosal healing with long-term clinical remission and avoidance of colectomy: UC




Shah SC et al, Clin Gastro Hepatol 2016

## Practically defining mucosal/intestinal healing as the target: what is adequate to improve outcomes?

| Crohn's disease | Ulcerative colitis |
|---|---|
| • Absence of ulcers?<br>• Absence of deep ulcers?<br>• SES-CD/ CDEIS definition of endoscopic remission?<br>• Deeper than mucosal…also MRE normalization? | • Mayo subscore 0?<br>• Mayo subscore 0 or 1?<br>• Also absence of inflammation histologically? |

## The role of objective disease monitoring

What should our treatment targets be and why?

- How can we monitor for achievement of intestinal healing..... non-invasively?

When should we reassess endoscopically and/or with imaging?

## Beyond symptoms: Objective monitoring during regular follow-up

- Linear growth: adequacy for pubertal stage
- Serologic inflammatory markers (C-reactive protein)
  - Sensitivity and specificity for significant persistent endoscopic or (MR enterographic) inflammation?
- Fecal inflammatory markers
  - *Fecal calprotectin (FCP), lactoferrin, S100A12
  - Sensitivity and specificity for significant persistent endoscopic (or MR enterographic) inflammation?

## Diagnostic accuracy for endoscopically active IBD

Meta-analysis of 19 studies (2499 patients) total)

| Marker | Sensitivity | Specificity | Positive LR | Negative LR | AUC |
|---|---|---|---|---|---|
| **CRP** | | | | | |
| IBD | 0.49 (0.34,0.64) | 0.92 (0.72, 0.98) | 6.3 (1.9, 21.3) | 0.56 (0.44, 0.71) | 0.72 (0.68, 0.76) |
| **FCP** | | | | | |
| IBD | 0.88 (0.84,0.90) | 0.73 (0.66, 0.79) | 3.2 (2.6, 4.1) | 0.17 (0.14, 0.20) | 0.89 (0.86, 0.91) |
| CD | 0.87 (0.82, 0.91) | 0.67 (0.58, 0.75) | 2.7 (2.1, 3.4) | 0.19 (0.14, 0.27) | 0.85 (0.82, 0.88) |
| UC | 0.88 (0.84, 0.92) | 0.79 (0.68, 0.87) | 4.2 (2.8, 6.4) | 0.15 (0.11, 0.20) | 0.91 (0.89, 0.94) |

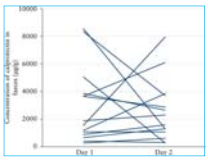
Mosli MH et al, Am J Gastro 2015; 110: 802-819

## Fecal inflammatory markers in monitoring IBD

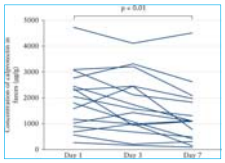
- Beware generic issues around stool collection and assays
- Distinguish from use as a screening test for IBD versus IBS in patients presenting with GI symptoms
  - Relatively clear cut-offs giving reassurance of no IBD
- More controversy around use in the monitoring of known IBD
  - Cut-offs reliably indicating significantly active disease less clear
  - Utility may vary according to type and location of IBD

## Generic issues in interpretation of values

Variability of FCP day to day (UC patients)



Stability at room temperature



- First morning stool recommended

Lasson A et al. J Crohns Colitis 2015;9:26-32
Moum B et al, Inflamm Bowel Dis 2010; 16: 1090-1091

## Interpretation of FCP Results in Monitoring IBD

- A meta-analysis of 13 studies (n=1471) compared cut-off FC levels of 50 µg/g, 100 µg/g and 250 µg/g, and found that with higher levels, the sensitivity decreased, while the specificity increased.

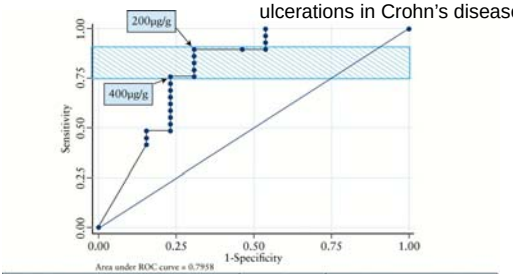
| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| IBD remission vs. active at FC 50 µg/g | 55.2 | 98.9 | 97.0 | 77.4 |
| IBD remission vs. active at FC 100 µg/g | 72.4 | 95.6 | 91.3 | 84.3 |
| IBD remission vs. active at 250 µg/g | 89.7 | 75.6 | 70.3 | 91.9 |

FC: faecal calprotectin; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; NPV: negative predictive value; PPV: positive predictive value.

Lin JF et al, Inflamm Bowel Dis 2014;20:1407-15.

## Monitoring of known IBD

Detection of superficial or deep ulcerations in Crohn's disease.

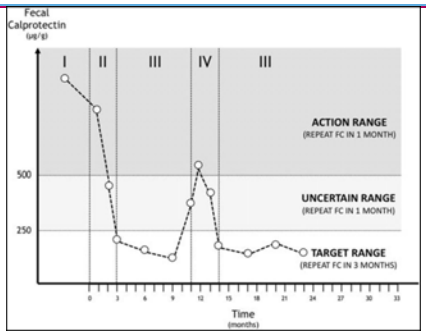



| Fecal calprotectin thresholds | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| ≥200μg/g | 0.86 [0.68-0.96] | 0.69 [0.39-0.91] | 0.86 [0.68-0.96] | 0.69 [0.39-0.91] |
| ≥400μg/g | 0.76 [0.53-0.87] | 0.77 [0.46-0.95] | 0.88 [0.67-0.97] | 0.56 [0.31-0.79] |

[95% confidence interval]; PPV: positive predictive value; NPV: negative predictive value

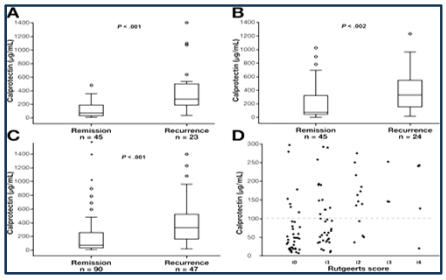
Goutorbe F et al. J Crohns Colitis 2015;9:1113-1119

## Monitoring for intestinal healing




Van Rheenen P. Inflamm Bowel Dis 2014; 20:1416-1417.

## Fecal calprotectin in monitoring for endoscopic recurrence following intestinal resection




Data from the POCER study

Wright EL et al Gastroenterology 2015; 148: 938-947

## The role of objective disease monitoring

- When should we reassess endoscopically and/or with imaging?

## Personal approach to new onset (or established) IBD

- Careful phenotypic characterization (Risk assessment)
- Selection of initial and maintenance treatment plan that is endorsed by family and patient
  - Discuss targets
- Implementation of chosen therapies optimally
- Monitoring of outcomes including re-assessment of intestinal healing….but at variable times

## When to reassess endoscopically or with cross-sectional imaging? Principles in planning

- Symptoms, growth, serologic and fecal markers of inflammation are our guide as to whether we think the intestine has healed
- Consider baseline localization of IBD
- Consider implications of disease progression (based on known extent and localization): “disease burden”
- Consider known effectiveness of ongoing therapy
- Consider actions that would be taken based on findings at reassessment

## Endoscopy in Paediatric IBD: from PORTO/ESPGHAN Guidelines in progress

- Endoscopic reassessment on a case by case basis in patients not responding to therapy, with frequent relapses, or steroid dependency
- Endoscopy indicated before major treatment changes are considered to assess severity-extent of disease and to explore for complications (EL3; RGC)
- Routine endoscopy for children in complete sustained clinical remission (PUCAI <10) is generally unnecessary in UC, especially when MH has been confirmed by fecal inflammatory markers
- Endoscopy may be considered 6-9 months following bowel resection to identify post-operative recurrence (Adult data, EL3; RGC)

S Cucchiara ESPGHAN meeting 2016

## Simple endoscopic score (SES-CD) grading vs CDEIS grading

SES-CD overestimates severity vs CDEIS in inactive / mild CD

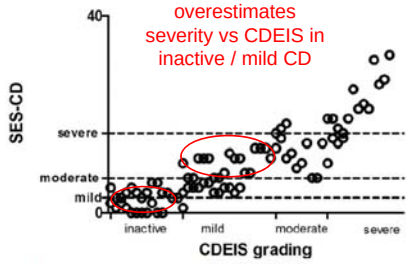
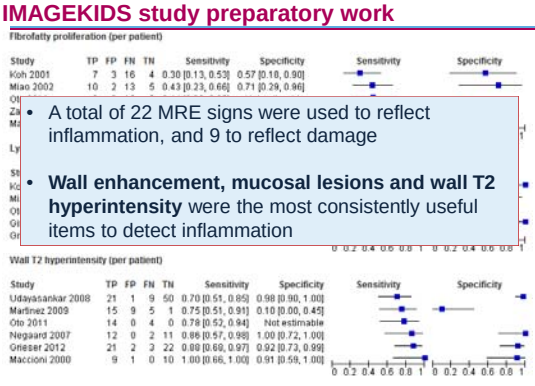



FIGURE 2. The SES-CD results according to the CDEIS grading.

Sipponen T et al. Inflam Bowel Dis 2010

## Meta-analysis of individual MRE items: IMAGEKIDS study preparatory work




- A total of 22 MRE signs were used to reflect inflammation, and 9 to reflect damage
- **Wall enhancement, mucosal lesions and wall T2 hyperintensity** were the most consistently useful items to detect inflammation

Church P et al. Aliment Pharm Therapeutics 2015; 41: 153-166

## Summary: take-home messages

- What should our treatment targets be and why?
  - alleviation of symptoms, facilitation of growth and well-being

    AND
  - control/healing of intestinal inflammation to prevent future complications

## Summary: take-home messages

- How can we monitor for intestinal healing non-invasively?
  - Attention to linear growth and serologic markers of inflammation
  - Fecal inflammatory markers are an adjunctive means of non-invasive monitoring
  - Their role in routine monitoring in improving long-term outcomes has not yet been fully assessed

## Summary: take-home messages

- When should we reassess endoscopically and/or with imaging?
  - Maintaining goal of healing/prevention of progression is important
  - Interpretation of endoscopic/imaging findings essential
  - Timing of reassessment based on principles outlined
- Ongoing cohort studies within phenotypic subgroups of IBD under specific treatment algorithms needed

# Autoimmune Liver Diseases

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## Autoimmune Liver Diseases

No conflict of interest to declare.

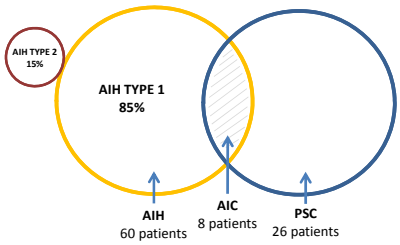
## Autoimmune Liver Diseases

*Objectives*

- Differential diagnosis of liver autoimmune disorders.
- Characterization of clinical and biochemical phenotypes.
- Histologic features of liver autoimmune diseases.
- Prognosis according to particular diagnosis.

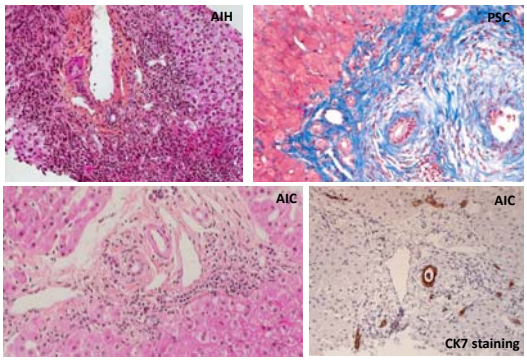
## Autoimmune Liver Diseases

*Review of a cohort from CHU Sainte-Justine*




**AIH :** Autoimmune hepatitis
**AIC :** Autoimmune cholangitis
**PSC :** Primary sclerosing cholangitis

## Histology of AIH, PSC and AIC




## Autoimmune Hepatitis in Children

*Clinical features*

| Clinical features | Type 1 AIH | Type 2 AIH |
|---|---|---|
| Mean age at onset | 10 years | 6,5 years |
| Females (%) | ~75% | 90% |
| Duration of illness | 4m (2w-24m) | 2m (1w-16m) |
| Form of presentation [a] : | | |
| Acute hepatitis [b] | ~45% | ~50% |
| Chronic hepatitis | 35% | 30% |
| Others | 20% | 20% |

(a) These percentages are obtained from previously published series.
(b) Including fulminant and subfulminant liver failure.

*Alvarez F. Clinics in Liver Disease, 2006;10:89-107*

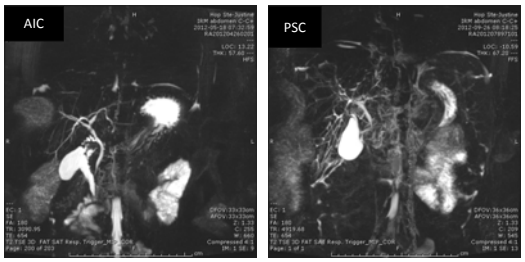
## Autoimmune Hepatitis in Children

*Types of AIH*

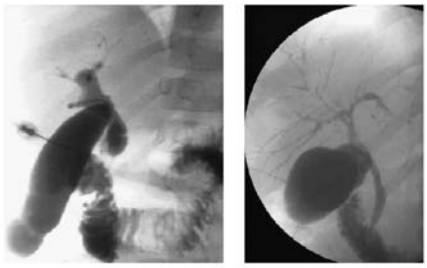
| Autoantibody | Antigen | Type 1 AIH | Type 2 AIH |
|---|---|---|---|
| SMA | Actin filaments | + (90-100%) | – |
| ANA | Various | + (0-10%) | ± |
| SMA/ANA | — | (40-60%) | – |
| LKM1 | Cytochrome P450 2D6 | | + (40-50%) |
| LC1 | Formiminotransferase cyclodeaminase | | + (10-15%) |
| LKM1/LC1 | | | (35-45%) |

*Alvarez F. Clinics in Liver Disease, 2006;10:89-107*

## AIC and PSC images




## PSC images



## Autoimmune Liver Diseases

*Association with IBD*

| AIH | AIC | PSC |
|---|---|---|
| 4/60 pts | 3/8 pts | 19/26pts |
| 6.6% | 37.5% | 73% |
| UC: 1<br>Crohn: 3 | UC: 3 | UC or IC: 10<br>Crohn: 9 |

## Autoimmune Liver Diseases

*Question*

When is a cholangiogram and/or a colonoscopy indicated in patients with AIH type 1?

*Answer*

a) When symptoms of IBD are present;
b) When serum GGT levels are elevated at onset or remain even slightly elevated during treatment;
c) When ANCA antibodies are positive (?!)

## Autoimmune Liver Diseases

*Clinical features*

| | AIH | AIC | PSC |
|---|---|---|---|
| **Mean age (years)** | 10.3 | 13.3 | 1.4 |
| **Females** | 70% | 50% | 42% |
| **Jaundice** | 50% | 37.5% | 7.6% |
| **Cirrhosis** | 49% | 43% | 38.5% |
| **Hepatitic failure** | 42% | 37.5% | 0% |

## Autoimmune Liver Diseases

*Clinical features*

| Biochemical features [mean (range)] | AIH | AIC | PSC |
|---|---|---|---|
| Total Bi (µmol/l) | 69.2 (2-515) | 33 (6-78) | 16 (4-200) |
| ALT (IU/l) | 730 (87-4800) | 261 (26-520) | 130 (14-413) |
| GGT (IU/l) | 79 (10-190) | 177 (63-431) | 244 (37-834) |
| Auto Abs (%) | 90% | 85% | 65% |
| IgG (g/l) | 30 (6.5-63) | 24 (15.3-31) | 17 (8.7-37) |
| Albumin (g/l) | 32 (15-48) | 38 (20-45) | 37 (23-44) |
| INR | 1.7 (1-5.6) | 1.25 (0.9-1.8) | 1.05 (0.9-1.2) |

AIH – 25 out of 60 showed signs of hepatic failure
AIC – 3 out of 8 showed signs of hepatic failure
PSC – No patient present with hepatic failure at onset

## Autoimmune Liver Diseases

*Summary of differential diagnosis*

- When AIH biochemistry is compared to AIC and PSC, these patients show:
  - Higher serum Bi, ALT and IgG levels.
  - Lower serum GGT levels (this is a good marker of bile duct injury).

## Autoimmune Liver Diseases

*Summary of differential diagnosis*

- Females are predominant only in the AIH group
- An « acute hepatitis » syndrome is more common in AIH patients.
- Cirrhosis at presentation is more frequent in patients with AIH/AIC than in those with PSC.
- At onset, AIH and AIC are more severe diseases; around 40% of AIH patients show signs of liver failure.

## Autoimmune Liver Diseases

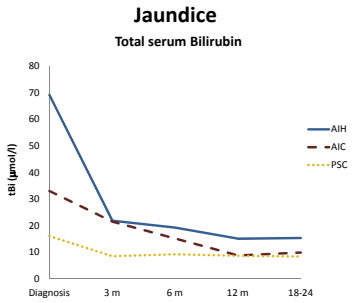
*Follow-up under treatment*

***Treatments:***

- AIH: immunosuppressors
- AIC: immunosuppressors + UDCA
- PSC: UDCA

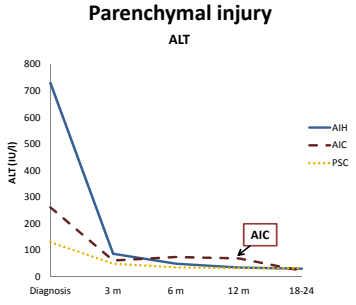
## Autoimmune Liver Diseases

*Prognosis*




## Autoimmune Liver Diseases

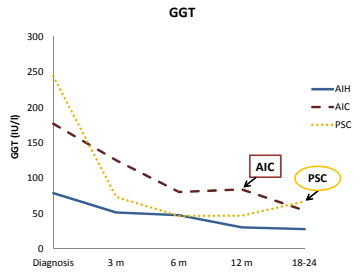
*Prognosis*



# Autoimmune Liver Diseases

*Prognosis*

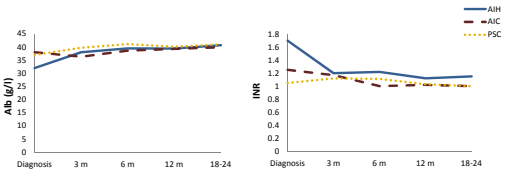
**Bile ducts injury**




# Autoimmune Liver Diseases

*Prognosis*

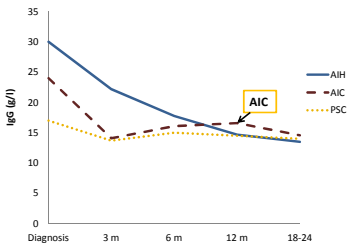
**Liver failure**




# Autoimmune Liver Diseases

*Prognosis*

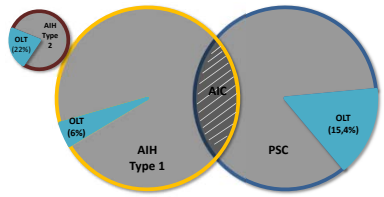
**Liver-Immune-Inflammation**



## Autoimmune Liver Diseases

*Prognosis*

**Liver transplantation**




## Autoimmune Liver Diseases

*Conclusions (Treatment)*

- Patients with AIC do not completely respond to immunosuppressors + URSO association.
- AIC patients show frequent relapses when corticosteroids are tapering.
- Liver transplantation is more frequently indicated for patients with type 2 AIH.

## Autoimmune Liver Diseases

*Future direction*

- When to indicate a colonoscopy.
- How frequently should it be made in patients with colitis.
- Establish the long-term outcome of autoimmune cholangitis.
- Individualize the immunosuppressive treatment according to specific markers.

SickKids
THE HOSPITAL FOR SICK CHILDREN

UNIVERSITY of TORONTO

Binita M. Kamath, MBBChir
Associate Professor
The Hospital for Sick Children, Toronto

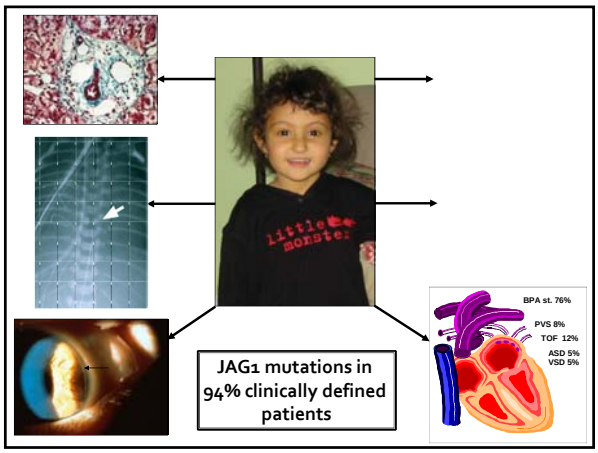
# Alagille Syndrome: What's New?

## Disclosures

- Financial disclosures:
  - Retrophin – Consultant
  - Shire – Travel expenses
- I will be discussing the following investigational drugs:
  - LUM001 (Shire)

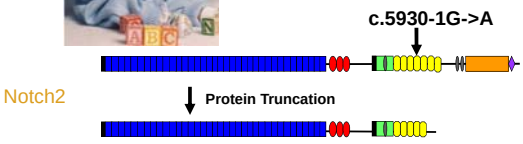
## Objectives

1. To recognize the broader genotype and phenotype associated with Alagille syndrome (ALGS).
2. To identify a novel method to predict liver disease outcomes in Alagille syndrome.
3. To discover a potential novel therapy for pruritus in Alagille syndrome.
4. To explore advances in stem-cell based technologies that may shed light on disease mechanisms in Alagille syndrome and other biliary disorders.




## *NOTCH2* Mutation in Alagille Proband

- Facies
- Cholestasis
- Pulmonic stenosis
- Neonatal renal failure
- No *JAG1* mutation




*McDaniell et al, AJHG 2006*

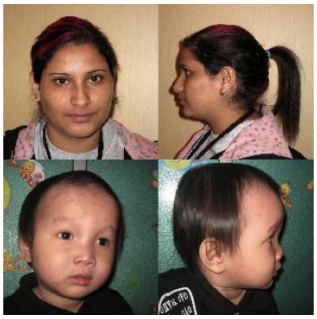
## *JAG1* vs. *NOTCH2* ALGS

**Table 2: Phenotypic comparison between *JAG1*(+) and *NOTCH2*(+) individuals**

| Frequency of clinical findings (%) | Liver | Cardiac | Renal | Eye | Skeletal | Facies |
|---|---|---|---|---|---|---|
| *NOTCH2* probands N=10 | 100 | 60 | 44 | 63 | **10** | **20** |
| *JAG1* probands* N=34 | 100 | 100 | 40** | 75 | 64 | 97 |

*Kamath et al, Hum Mut 2012*

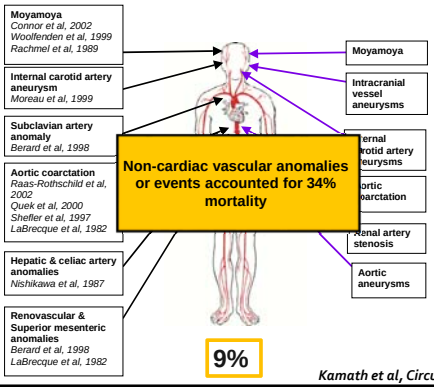
## Facial Features in ALGS



*NOTCH2*-related

*JAG1*-related

## Spectrum of Vascular Anomalies in CHOP ALGS Cohort and in Previous Reports




*Kamath et al, Circulation 2004*

## Vasculopathy is Treatable in ALGS: Need to Look!

CLINICAL AND LABORATORY OBSERVATIONS www.jpeds.com • THE JOURNAL OF PEDIATRICS

Moyamoya Syndrome Associated with Alagille Syndrome: Outcome after Surgical Revascularization

Lissa C. Baird, MD[1,2], Edward R. Smith, MD[3,4], Rebecca Ichord, MD[5,8], David A. Piccoli, MD[6,7], Timothy J. Bernard, MD[8,9], Nancy B. Spinner, PhD[6,10], R. Michael Scott, MD[3,4], and Binita M. Kamath, MBBChir[11,12]

- MRI/MRA head prior to liver transplant or any major surgery
- Personal recommendation is for a baseline MRA in children who do not require sedation

*Baird et al, J Peds 2015*

# Renal Anomalies in ALGS

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics

## Renal Anomalies in Alagille Syndrome: A Disease-Defining Feature

Binita M. Kamath,[1,2]* Gisele Podkameni,[3,4] Anne L. Hutchinson,[5] Laura D. Leonard,[5] Jennifer Gerfen,[5] Ian D. Krantz,[4,6,7] David A. Piccoli,[3,4] Nancy B. Spinner,[5,7] Kathleen M. Loomes,[3,4] and Kevin Meyers[4,8]

- 466 *JAG1* mutation positive individuals
- **39%** with renal anomaly
- Renal dysplasia most common finding

*Kamath et al, AJMG 2012*

# Renal Insufficiency in ALGS Following Liver Transplantation

| | 30 days | | | 1 year | | | 2 years | | |
|---|---|---|---|---|---|---|---|---|---|
| | ALGS (n=91) | BA (n=236) | P value | ALGS (n=69) | BA (n=195) | P value | ALGS (n=59) | BA (n=159) | P value |
| Biliary tract complications | 15.4% | 9.7% | 0.1868 | 4.3% | 5.1% | 0.7781 | 0.0% | 1.3% | 0.3904 |
| Vascular complications | 20.9% | 15.7% | 0.3325 | 2.9% | 2.1% | 0.6984 | 3.4% | 1.3% | 0.2909 |
| CNS complications | 7.7% | 4.2% | 0.2352 | 1.4% | 0.0% | 0.0947 | 0.0% | 0.0% | NA |
| Renal complications | 9.9% | 3.4% | **0.0220** | 4.3% | 0.5% | **0.0265** | 1.7% | 0.0% | 0.0973 |
| Calculated GFR <=90 mL/min/1.73m2 | No data collected | | | 21.7% | 8.2% | **0.0014** | 16.9% | 6.9% | **0.0252** |
| Serum creatinine (mg/dL) mean±SD | 0.49±0.31 | 0.36±0.24 | **0.0012** | 0.54±0.31 | 0.47±0.27 | 0.0565 | 0.57±0.28 | 0.48±0.17 | **0.0117** |

**NEED FOR RENAL-SPARING PROTOCOL**

*Kamath et al, Liver Transpl 2012*

# Immune Dysregulation in ALGS

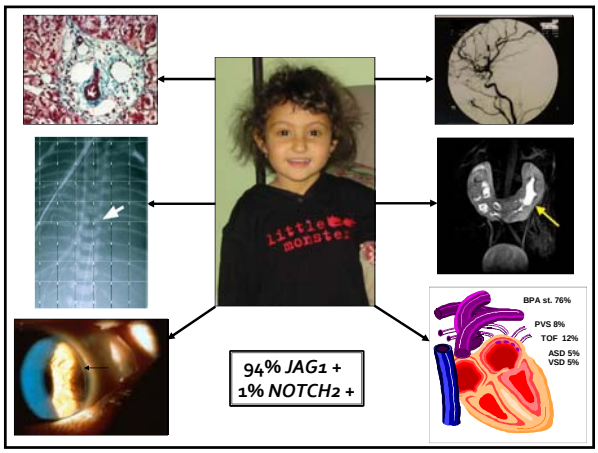
**The CD46 and Jagged1 interaction is critical for human T helper 1 immunity**

Gaëlle Le Friec[1], Devon Sheppard[2], Pat Whiteman[3,14], Christian M. Karsten[4,14], Salley Al-Tilib Shamoun[5,14], Adam Laing[1], Laurence Bugeon[6], Margaret J. Dallman[6], Teresa Melchionna[1], Chandramouli Chillakuri[3], Richard A. Smith[1], Christian Drouet[7], Lionel Couzi[8], Veronique Fremeaux-Bacchi[9,10], Jörg Köhl[4,11], Simon N. Waddington[12], James M. McDonnell[13], Alastair Baker[5,15], Penny A. Handford[3,15], Susan M. Lea[2], and Claudia Kemper[1]

Immune dysregulation in Alagille syndrome: A new featu… 25% ALGS cohort with …enotype frequent infections

S. Tilib Shamoun … Kemper[b], A.J. Baker[a,*]

*Le Friec et al, Nat Imm 2013*
*Shamoun et al, Clin Res in Hep and Gastro 2015*

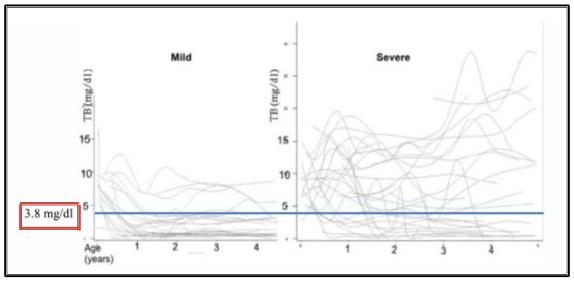



## Liver Disease in ALGS

- Unique natural history
- Children with mild liver disease do not show disease progression
- Cholestasis in infancy may
  a) Persist unchanged
  b) Progress to unremitting cholestasis/ESLD
  c) Resolve or significantly improve, usually around the age of 4-5 years
- Inability to predict outcome poses management challenge - ?unnecessary liver transplantation

**Early life predictive markers of liver disease outcome in an International, Multicentre Cohort of children with Alagille syndrome**

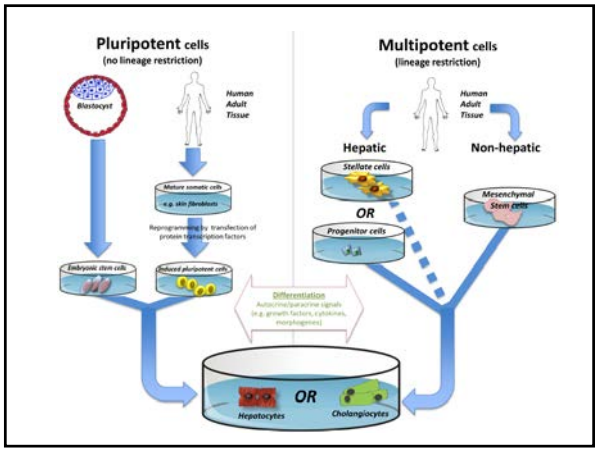
Marialena Mouzaki[1], Lee M. Bass[2], Ronald J. Sokol[3], David A. Piccoli[4], Claudia Quammie[1], Kathleen M. Loomes[4], James E. Heubi[5], Paula M. Hertel[6], Rene Scheenstra[7], Katryn Furuya[8], Erika Kutsch[8], Nancy B. Spinner[9], Kristen N. Robbins[3], Veena Venkat[10], Philip Rosenthal[11], Joseph Beyene[12], Alastair Baker[13] and Binita M. Kamath[1]



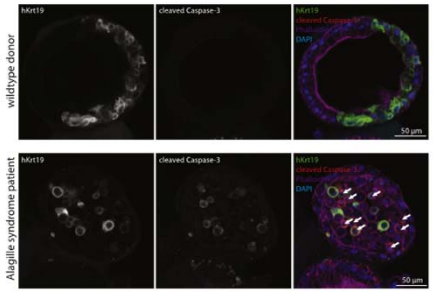

*Mouzaki et al, Liver Int 2016*

## Novel Therapy for ALGS: Chemical Diversion


## ALGS: The Promise of Stem Cells

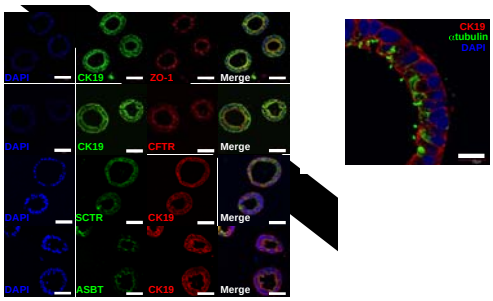


## Biliary Organoids from Adult Liver




*Huch et al, Cell 2015*

## Cholangioids from iPSCs

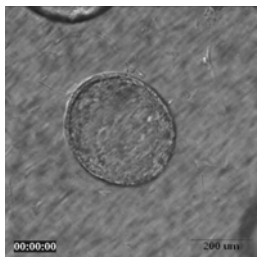






*Ogawa et al, Nature Biotech 2015*

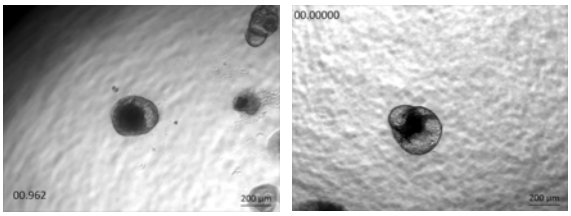
## Cholangioids from iPSCs




*Ogawa et al, Nature Biotech 2015*

## CF cholangioids: Impaired Function can be rescued with CFTR correctors

**Without correction** | **WITH correction**




*Ogawa et al, Nature Biotech 2015*

## Take Home Messages

1. Clinical manifestations of ALGS are highly variable
   1. Managed by Gastroenterologists but requires multisystem knowledge!
   2. 7 potential organ systems involved – look for renal & vascular
2. Cholestasis stabilizes or improves in the majority – use predictive tools
3. Liver Transplantation is only required for 15-20% and renal sparing protocol necessary
4. New therapies are coming

# Steatorrhea: What if it's not Cystic Fibrosis?

Mark Lowe MD, PhD

Children's Hospital of Pittsburgh of UPMC



## Conflict of interest

- Consultant
  - AbbVie Inc
  - Up-to-Date
  - Nordmark Arzneimittel GmbH & Co KG
- Royalties
  - EMD Millipore Corp



## Learning objectives

1. Explain the physiology of dietary fat digestion and absorption
2. Discuss the pros and cons of tests for exocrine pancreatic insufficiency (EPI)
3. Recall the differential diagnosis of fat malabsorption

## Dietary fat digestion

*Sources of Intestinal Lipids*

**Input**

- Dietary fats
  - 92-96 g of triglyceride (TG)
  - 4-6 g of phospholipid (PL)
  - 0.5 g of cholesterol (Ch)
- Biliary lipids
  - 10-15 g phospholipid
  - 1-2 g cholesterol
- Desquamated intestinal cells
  - 2-6 g of mixed membrane lipids
- Dead Bacteria
  - 10 g of mixed membrane lipids

**Output**

- 4 g of fatty acids
- Rare to detect glycerides in stool

Carey MC, Hernell O, *Gastrointest Dis*. 1992;3:189-208.



## Assimilation of dietary fats in the gut

- Intraluminal Digestion
  - Action of lipases to break down dietary fats into their component parts
  - Bile acids to facilitate digestion
- Mucosal Absorption
  - Bile acids to facilitate micelle formation and absorption
  - Uptake of digestion products into intestinal enterocytes
- Secretion of fats from enterocytes into bloodstream

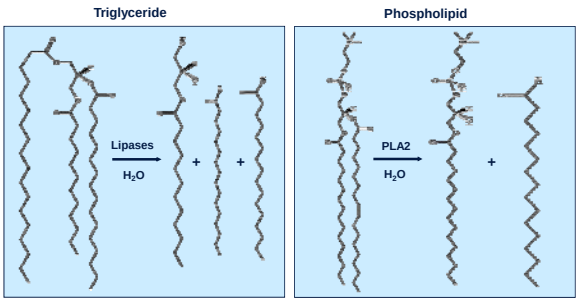


## Digestive Lipases

- Stomach
  - Gastric lipase
- Pancreas
  - Pancreatic Triglyceride Lipase-Colipase Complex
  - Carboxyl Ester Lipase
  - Pancreatic Lipase Related Protein 2
  - Phospholipase A2 (PLA2)

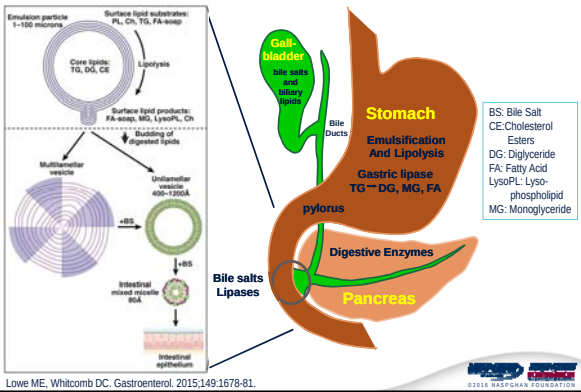
Whitcomb DC, Lowe ME. Dig Dis Sci. 2007;52:1-17.

## Digestion of Dietary Lipids






## Dietary Fat Digestion




Lowe ME, Whitcomb DC. Gastroenterol. 2015;149:1678-81.



## Fat maldigestion

- Changes in stools
- Weight loss or poor growth
- Flatulence
- Bloating
- Abdominal pain
- Fat soluble vitamin deficiency

## Tests for exocrine pancreatic insufficiency

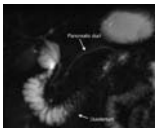
- Direct tests
  - Measure exocrine secretory function
    - Hormonal stimulation and collection of pancreatic juice
- Indirect tests
  - Generally measure digestive function
    - Fat digestion is most common target
    - Estimates of pancreatic enzyme levels

No test measures both secretory and digestive function

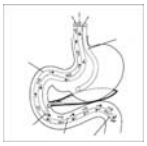


## Direct tests

- Secretin stimulated MRI
  - Highly subjective
  - Not suitable for grading degree of EPI



- Dreiling tube
  - Perhaps most sensitive and specific test
  - Time-consuming
  - Tube placement can be difficult
  - Uncomfortable for patient
  - Very few centers to the test





## Direct tests

- Endoscopic pancreatic function test
  - Rapidly gaining favor
  - Equipment readily available
  - Prolonged sedation or, in children, prolonged anesthesia
  - Variability
  - Gastric fluid contamination
  - Lack of standard protocol
    - What to measure: bicarbonate versus pancreatic enzymes

## Indirect tests

- 72 hour fecal fat test
  - Still considered the gold standard
  - Unpleasant to perform
  - Improper storage of stool
  - Missed stool samples
  - Incomplete documentation of the diet
  - Not suited for repeated measures



## Indirect Tests

- Fecal elastase
  - Not validated in all patient groups
  - Only useful for detecting severe EPI
  - Affected by stool consistency
  - Test-to-test variability
  - Primarily a screening test

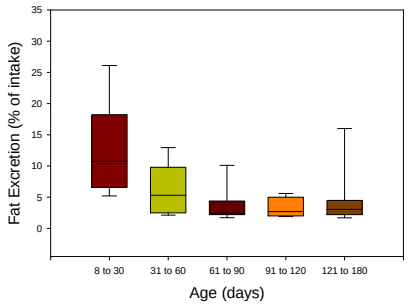


## Indirect tests

- $^{13}C$-mixed triglyceride breath test
  - Wide variability
  - Amount of expired $^{13}C$-labelled $CO_2$ varies with activity
  - Influenced by other factors
  - Difficult to perform in infants and toddlers
  - Lack of availability

## Fat malabsorption in human newborns

Can be physiological




Fomon SJ, Ziegler EE, Thomas LN, et al. Am J Clin Nutr. 1970;23:1299.



## Shwachman-Diamond syndrome (SDS)

- If you think an infant has CF and they don't, think of SDS
- Clinical findings
  - Exocrine pancreatic insufficiency
    - Duct function is normal
  - Short stature
  - Hematological abnormalities
    - Mostly neutropenia
  - Skeletal changes
- Diagnosis is made by demonstration of genetic mutation in *SBDS*
  - Present in about 90%



## Developmental disorders

- Johanson-Blizzard syndrome
  - Mutations in *UBR1* which encodes an E3 ubiquitin ligase
  - Pancreatic acini replaced by fibrous tissue
  - Islet and duct function are normal
- Jeune syndrome
  - Pancreatic fibrosis and cyst formation
  - Skeletal, renal and liver abnormalities
- Pearson's syndrome
  - Bone marrow failure and pancreatic insufficiency
  - Deletions in mitochondrial DNA

## Anatomical anomalies

- Pancreatic aplasia
  - Inactivation of *PDX1 or* PTF1A
  - *GATA6* mutations may be most common cause
  - Neonatal diabetes predominates
- Pancreatic hypoplasia
  - Inactivation of Notch signaling pathway
  - May also present with diabetes
  - May be incidental finding



## Isolated enzyme deficiencies

- Pancreatic lipase deficiency
  - Multiple reports in the literature
    - Only one has genetic explanation
      - Missense mutation in *PNLIP*
- Colipase deficiency
  - No convincing reports in humans
  - In utero loss and increased newborn death in mice



## Inflammatory disorders of the pancreas

- Acute pancreatitis
  - Exocrine pancreatic insufficiency in up to 20% of adults
  - Did not depend on severity of acute pancreatitis
- Chronic pancreatitis
  - About 10% of children present with steatorrhea
    - May be as common as SDS
  - About 35% develop steatorrhea in childhood

Vujasinovic M, Tepes B, Makuc J et al. World J Gastroenterol. 2014;20:18432-8.
Schwarzenberg SJ, Bellin M, Husain SZ et al. J Pediatr. 2015;166:890-6.

## Liver disease and steatorrhea

- Lysosomal acid lipase deficiency
  - Infants
- Cholestatic liver disease
  - Bile acid deficiency or exocrine pancreatic insufficiency



## Intestinal causes of steatorrhea

- Celiac disease
  - Reported frequency of exocrine pancreatic insufficiency ranges from 11 to 55%
    - Various methods to determine insufficiency
      - Fecal elastase most common
  - Pathophysiology is uncertain
  - Improves with gluten-free diet
- Crohn disease
  - Evidence is not strong
  - Extensive small bowel disease or terminal ileal resection



## Intestinal causes of steatorrhea

- Small bowel bacterial overgrowth
- Short-gut
- Giardiasis
- Gastric bypass surgery
- Glucogonoma or somatostatinoma
- Abetalipoproteinemia
- Hypobetalipoproteinemia
- Chylomicron retention disease
- Neurogenin 3 mutations
- Intestinal lymphangiectasia

## Summary

Physiology of dietary fat digestion and absorption

- Triglycerides are predominant dietary fat
- Lipid absorption depends on luminal digestion and on uptake and secretion by enterocytes
- Lipases and bile salts are essential for dietary fat digestion



## Summary

The pros and cons of tests for exocrine pancreatic insufficiency

- No test measures both secretory and digestive function
- All tests have drawbacks
- Fecal elastase is a screening test
- Endoscopic pancreatic function testing has gained favor but there remain many questions about the protocol



## Summary

The differential diagnosis of fat malabsorption

- Fat malabsorption is physiological in human newborns
- Cystic fibrosis remains the most common cause of pathological steatorrhea in children
- Shwachman-Diamond Syndrome is probably the second most common cause
- Chronic pancreatitis can present with steatorrhea and may be as common as SDS
- Other causes are rare and often associated with dysfunction of multiple organ systems

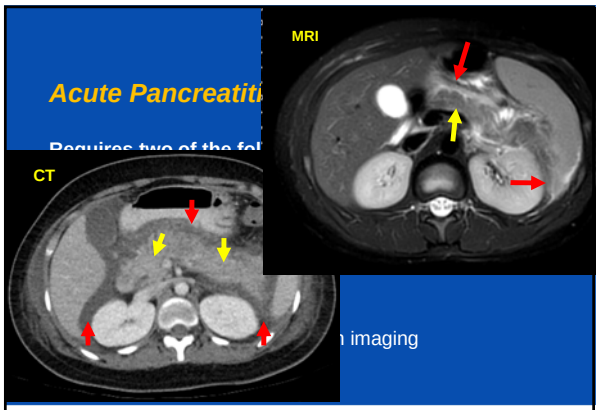
## *"Bienvenue"*
## *2016 Updates in Pediatric Acute Pancreatitis*

***Maisam Abu-El-Haija, MD***
*Assistant Professor of Pediatrics*
*Pancreas Care Center, Medical Director*
*Cincinnati Children's Hospital Medical Center*

I have no financial relationships to disclose.

Objectives

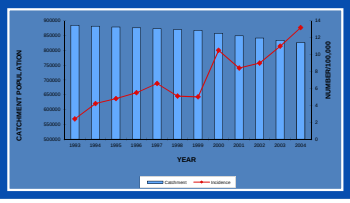
- Recognize the Impact of acute pancreatitis in pediatrics.
- Identify background, prevalence & etiologies of pediatric pancreatitis.
- Recognize the advances in Management of acute pancreatitis up to the year 2016.
- Recognize and manage severe acute pancreatitis




*Banks. Gut. 2013;62:102-11.*
*Morinville. JPGN. 2012.*

## Background

- Historically: acute pancreatitis (AP) believed to be an uncommon problem in pediatrics
- Recently: an increased incidence of AP has been observed in the pediatric population




*Morinville VD et al Pancreas. 2010.*

## Acute Pancreatitis in Pediatric Patients: 2006, 2009, 2012

KID The Kids' Inpatient Database (KID) is part of a family of databases and software tools developed for the Healthcare Cost and Utilization project (HCUP)

- A total of 27,983 discharges with principal diagnosis of AP
- Incidence increases with age in the pediatric population

| | Age<5 | Age 5-14 | Age >14 | p-value |
|---|---|---|---|---|
| Age | 2.66 (2.57,2.75) | 10.53 (10.43,10.62) | 17.99 (17.95, 18.03) | **<0.001** |
| Number of cases in 3 years | **1,279** | **8,012** | **18,692** | |

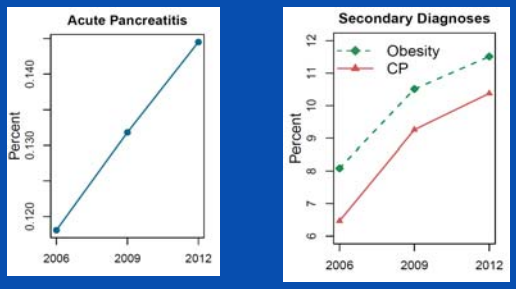
***Unpublished Data.***

## *Patient outcomes for pediatric patients with a principal diagnosis of AP*

| | Age <5 (n = 1,279) | Age 5-14 (n = 8,012) | Age >14 (n = 18,692) | p-value |
|---|---|---|---|---|
| Mortality | ≤10 0.24% | 17 0.22% | 23 0.12% | 0.3024 |
| Length of Stay (days) | 7.18 (6.34, 8.02) | 5.79 (5.51, 6.07) | 4.77 (4.65, 4.89) | **<0.0001** |
| Costs (US$) | $15,387 (12,672, 18,102) | $11,404 (10,575, 12,233) | $9,306 (8,955, 9,656) | **<0.0001** |

*Unpublished Data*

## *AP Admissions Trend: Obesity and Chronic Pancreatitis*

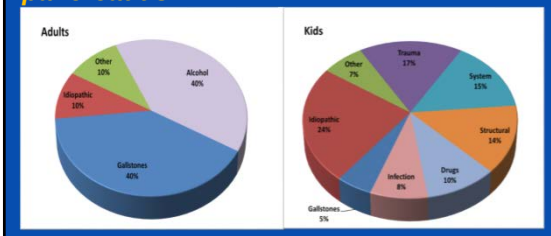






*Unpublished Data.*

## *Etiologies are distinct from adult pancreatitis*




*Pie chart prepared by Lindsey Hornung*

*Park AJ, et al JPGN 2010.*
*Yadav D et al, Nat Rev Gastroenterol Hepatol 2010.*
*Wang GJ et al, WJG 2009.*
*Bai HX et al, JPGN 2001.*

## Enteral nutrition (EN)

INTERNAL MEDICINE

ORIGINAL ARTICLE

**Meta-analysis: Total Parenteral Nutrition Versus Total Enteral Nutrition in Predicted Severe Acute Pancreatitis**

Fengming Yi, Linqing Ge, Jie Zhao, Yuan Lei, Feng Zhou, Zhifen Chen, Youqing Zhu and Bing Xia

Total enteral nutritional support is associated with:

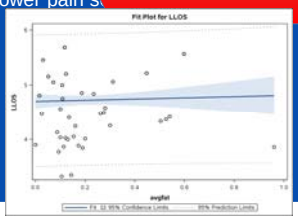
- Decreased organ failure
- Decreased surgical intervention rate
- Mortality and Infections

Yi F. Intern Med. 2012

## Are Feeds f… …P?

- Early nutri… …associated with adv…
- Patients … …ilar pain scores co…
- Figure sho… …ociated with lower pain s…

**Is a low fat diet needed in AP???**



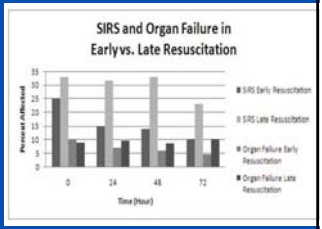

**38 total admissions of mild AP (p<0.001)**

*Abu-El-Haija. et al JPGN. 2015.*

## Adult studies support early aggressive fluid resuscitation

Early resuscitated group: received >⅓ of administered 72 hr IVF volume within 24 hr [1,2]

Outcomes: SIRS, organ failure, ICU, LOS, death




Early fluid resuscitation was associated with reduced SIRS and organ failure at 72 hr.[2]

[1]*Garnder TB. Pancreatology. 2009.*
[2]*Warndorf MG. Clinical gastroenterology and hepatology. 2011.*

## *Lactated Ringer vs Normal Saline in AP*

- 40 adult patients
- randomized to:
  - Goal-directed fluid resuscitation LR vs normal saline (goal-directed = 20 mL/kg, 3.0 mL/kg/h)

Results:

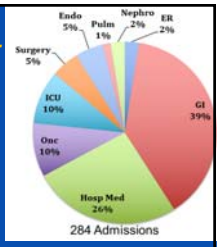
- Early resuscitation with LR lead to reduced systemic inflammation (SIRS and CRP at 24 hrs)

Lactated Ringer's Solution Reduces Systemic Inflammation Compared With Saline in Patients With Acute Pancreatitis

*Wu. Clin Gastro and Hep 2011.*

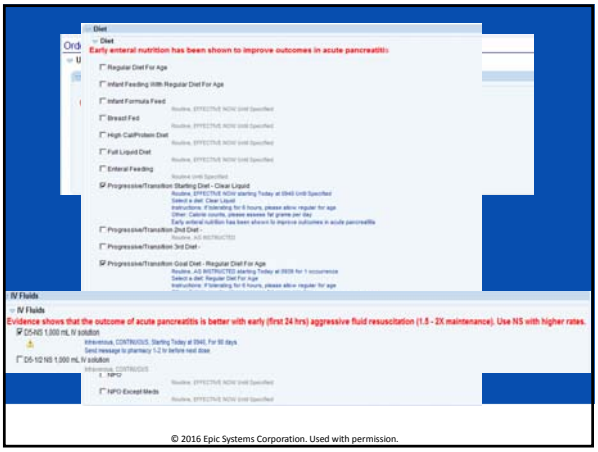
## *Survey on AP management*

- Surveyed 84 providers at CCHMC that mostly manage AP (Emergency, Hospitalists and gastroenterologists), response 80%
- Discrepancy in management between physicians from GI and non-GI, as well as within providers from the same specialty.



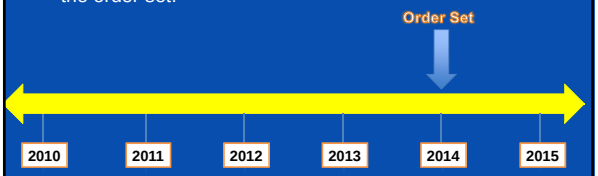

**Standardizing care** is needed in AP to eliminate practice variability → facilitate comparative effectiveness studies → Improve Patient Outcomes

*Abu-El-Haija. et al Pancreas 2016.*



## AP standard management & outcomes

- Order set was used on acute pancreatitis admissions from January 2014 until now -65% of cases use rate
- Analyzed outcomes from AP admissions before and after the order set:




## 201 cases with mild AP on admission

Managed according to 4 different pathways

| Response Variable (SE) | NPO + IVF lo (a) | NPO + IVF hi (b) | PO + IVF lo (c) | PO + IVF hi (d) | Overall F-test | Significantly different pairs |
|---|---|---|---|---|---|---|
| Patients (n) | 20 | 30 | 55 | 96 | | |
| LOS mean days | 7.1 (1.01) | 5.0 (0.58) | 2.8 (0.24) | 3.2 (0.22) | <0.001 | ad, bd, bc, ab |
| SAP Rate | 35% | 17% | 9.1% | 4.2% | 0.0026 | ad, bd, ac |
| ICU Transfers | 20% | 13% | 1.8% | 1.0% | 0.0043 | ad, bd, ac |

Severe AP (SAP):

Resp complications, Local complications , Need for surgery ICU admission with (SIRS, Multi Organ Failure) or Death

F-test is either from ANOVA for LOS, or mixed effect logit model rates. LOS and rates analyzed via a mixed effect linear model, p values adjusted.

*F. Szabo. et al J Pediatr. 2015.*

## Could we have predicted SAP?

| Variables | | NPO + IVF lo (a) | NPO + IVF hi (b) | PO + IVF lo (C) | PO + IVF hi (d) | p-value |
|---|---|---|---|---|---|---|
| Patients | N | 20 | 30 | 55 | 96 | |
| Sex† | Male | 9 (45%) | 17 (56.7%) | 31 (56.4%) | 37 (38.5%) | 0.11 |
| Age* | Mean (SD) | 13.5 (4.92) | 13.3 (4.3) | 12.8 (4.73) | 13 (4.28) | 0.92 |
| BMI pct* | Mean (SD) | 67.7 (28) | 60.9 (37.8) | 65 (34.3) | 60.8 (34.4) | 0.63 |
| Lipase* | Mean (SD) | 3139 (2982) | 5634 (6045) | 3926 (4963) | 5670 (7803) | 0.09 |
| WBC* | Mean (SD) | 13.6 (6.44) | 13.3 (4.76) | 9.89 (3.89) | 11.3 (5.25) | 0.01 |

Clinical Variables and Patient Demographics on Admission.
† Fisher's exact test, * Kruskal-Wallis test

## First initiative to predict SAP in pediatrics

Acute Pancreatitis in Children

John R. DeBanto, M.D., Praveen S. Goday, M.D., Martha R. A. Pedroso, M.D., Rehan Iftikhar, M.D., Ali Fazel, M.D., Sanjay Nayyar, M.D., Darwin L. Conwell, M.D., Mark T. DeMeo, M.D., Frank R. Burton, M.D., David C. Whitcomb, M.D., Ph.D., Charles D. Ulrich II, M.D., and Lawrence K. Gates, Jr., M.D., for the Midwest Multicenter Pancreatic Study Group

Admission: age <7 yrs, weight <23 kg, WBC >18.5

48 hrs: LDH >2000, 48 hr fluid seq, BUN rise >5 mg/dL, alb <2.6 g/dL

*DeBanto. Am J Gastroenterol 2002.*

## Lipase as a single marker of severity in 24 hours

Serum Lipase as an Early Predictor of Severity in Pediatric Acute Pancreatitis

*[*]Michael J. Coffey, [†]Scott Nightingale, and [†]Chee Y. Ooi*

73 cases of AP and 34% were classified as SAP

Lipase >7 ULN predicted SAP with a 85% sensitivity and 63% specificity

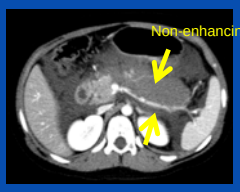
*Coffey. et al JPGN 2013.*

## SAP in pediatrics

- Occurs in 15-30% depending on the definitions used
- Studies that looked at prediction of SAP, used variable definitions

*DeBanto. et al Am J Gastroenterol 2002.*
*Coffey et al, JPGN 2013*
*Szabo. et al. Pancreatology 2016.*

## SAP cases in pediatrics




Necrotizing Pancreatitis CT

## Knowledge gap

- No agreed upon definition for SAP
- New definition on the way
- NASPGHAN Pancreas Committee has undertaken this effort to define SAP in pediatrics
  - We also need to be able to predict severity in pediatric AP … designed a study that looks at early markers of SAP

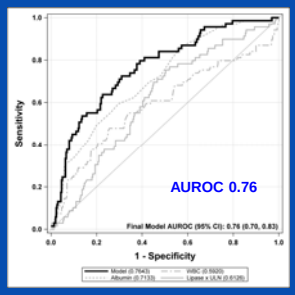
## Derivation and Validation Cohorts

- Derivation: Review of admission encounters of patients ≤21 years, who presented with AP to Cincinnati Children's November 2009 – August 2013 (n=284)
- Validation: The validation cohort included admission encounters Sept 2013 – June 2014 (n = 146)
  - **Cincinnati Children's**
  - **Children's Hospital of Los Angeles**
  - **Children Hospital of Pittsburgh**

*F. Szabo. L. Hornung et al. Pancreatology 2016.*

AUROC of the multivariable model based on combined data of the derivation and validation cohorts (n=369)

| Predicted score | Sensitivity | Specificity |
|---|---|---|
| ≥ 20 | 73% | 66% |




*F. Szabo. L. Hornung et al. Pancreatology 2016.*

## *Acute Recurrent (ARP) and Chronic Pancreatitis (CP)*

- The natural history of progression of acute pancreatitis to acute recurrent pancreatitis and chronic pancreatitis remains unknown
- INSPPIRE (**In**ternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n search for a cu**re**)
  - Developed criteria for pediatric AP, ARP and CP

*Morinville. et al JPGN. 2012.*

## *Prospective studies in pediatric AP*

- The Cincinnati Children's AP Registry
- Designed to follow pediatric patients from first attack of AP
- Data collected includes clinical, predictive, management, and outcomes data, as well as natural history longitudinally

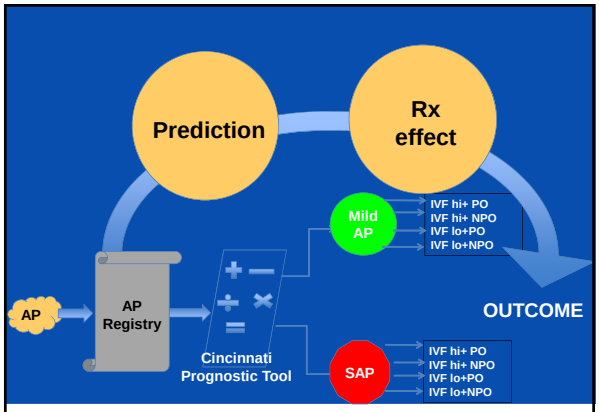
## *Longitudinal Studies from the AP registry*

**ARP within 3 months vs not: First AP Attack Characteristics**

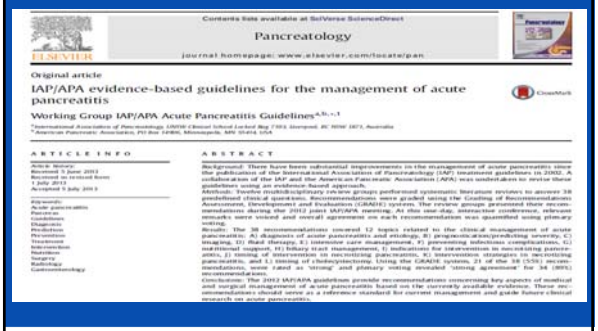
| | ARP within 3 months (n=11) | No ARP within 3 months* (n=72) | P-value |
|---|---|---|---|
| Duration follow-up (years) | 2.0 (1.3, 2.6) n=11 | 1.8 (0.9, 2.5) n=72 | 0.53 |
| Age (years) | 15.3 (12.7, 16.5) n=11 | 13.6 (9.6, 15.7) n=72 | 0.25 |
| Sex (male) | 9 (82%) | 41 (57%) | 0.19 |
| Weight percentile | 89.4 (78.6, 92.9) n=9 | 47.3 (22.0, 78.8) n=70 | 0.03 |
| BMI percentile | 84.6 (69.0, 92.1) n=9 | 52.8 (23.6, 81.4) n=67 | 0.18 |
| Lipase x ULN | 4.2 (3.3, 10.7) n=10 | 8.2 (4.0, 22.3) n=66 | 0.30 |
| Amylase | 221.0 (101.0, 774.0) n=9 | 197.0 (108.0, 416.0) n=52 | 0.69 |
| Albumin | 3.7 (2.3, 3.8) n=10 | 3.6 (3.1, 4.0) n=58 | 0.41 |
| WBC | 8.0 (7.3, 12.2) n=9 | 11.6 (8.4, 17.3) n=54 | 0.18 |
| ICU part of admission (yes) | 1/11 (9%) | 12/71 (17%) | 1.00 |
| Pancreatic necrosis | 2 (18%) | 0 | 0.02 |
| Pancreatic pseudocyst | 1 (9%) | 4 (6%) | 0.52 |
| Family history of pancreatitis | 2/10 (20%) | 8/67 (13%) | 0.62 |
| Severe AP | 3 (27%) | 13 (18%) | 0.44 |

N=83 patients
Data presented as median (25th, 75th percentile) or frequency (%).
*AP patients had at least 3 months of follow-up without developing ARP.

***Unpublished data***




## *Management Guidelines are Available for Adults*


Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

IAP/APA evidence-based guidelines for the management of acute pancreatitis

Working Group IAP/APA Acute Pancreatitis Guidelines

## Management of SAP

- Systemic inflammatory response syndrome (SIRS) predicts SAP
- Intravenous antibiotic prophylaxis is not recommended as a prophylaxis
- The use of antibiotics is restricted to cases of infected necrosis.
- Parenteral nutrition can be administered as second-line therapy if nasojejunal or nasogastric tube feeding is not tolerated and nutritional support is required.

*Working Group IAP/APA Acute Pancreatitis Guidelines / Pancreatology 13 (2013)*

## Procedural Management of SAP

- ERCP is indicated in biliary pancreatitis with common bile duct obstruction, and in biliary pancreatitis and cholangitis
- Infected necrotizing pancreatitis, invasive interventions (percutaneous, endoscopic, or open necrosectomy) should be delayed where possible until at least 4 weeks to allow the collection to become 'walled-off

*Working Group IAP/APA Acute Pancreatitis Guidelines / Pancreatology 13 (2013)*

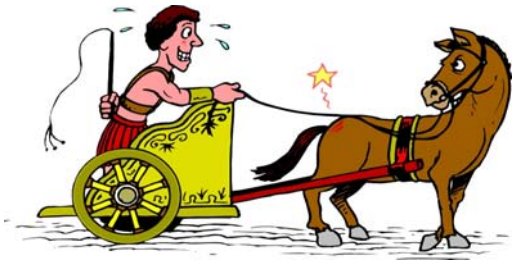
## Conclusions and Future Directions

- AP is an emerging problem in pediatrics
- A subset of children progress to SAP
- A subset progresses to ARP/CP
- More studies are needed to predict AP, SAP, ARP/CP
- Early nutrition/aggressive fluid resuscitation is associated with improved outcomes of pancreatitis
- Future studies are needed to study markers of SAP and outcomes from fluid and nutrition management

## Thank You!

maisam.haija@cchmc.org

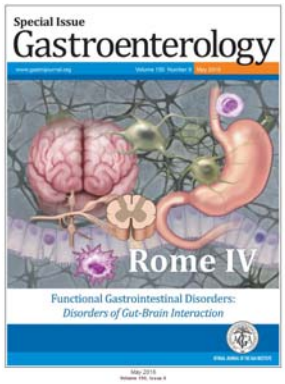
## Functional gastrointestinal disorders in the first 4 years of life; The new Rome IV criteria

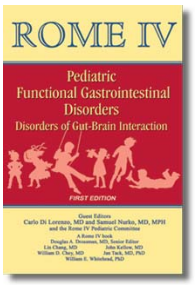


Marc Benninga, Pediatric Gastroenterologist
Emma Children's Hospital / AMC

## Outline of the presentation

- Rome IV
- Regurgitation
- Infant Colic
- Constipation


## Changes in Rome criteria
## Major Points:

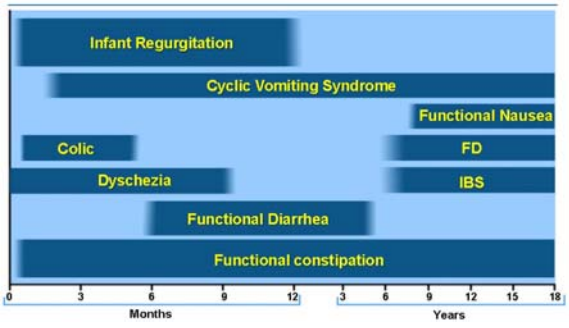

- Criteria have been refined
- Added section on neurobiology, development and assessment of pain
- Issues related to the possibility of adding new feeding disorders criteria

## Functional Disorders: infants and toddlers

G1. Infant Regurgitation
G2. Infant rumination syndrome
G3. Cyclic vomiting syndrome
G4. Infant colic
G5. Functional diarrhea
G6. Infant dyschezia
G7. Functional constipation

Benninga MA, et al. Gastroenterology 2016

## Role of Development of Pediatric FGIDs



## Pediatric FGID Are Common

| | Age | % |
|---|---|---|
| Regurgitate at least 4 times/day | 4 month old infants | 26 |
| Rumination syndrome | infants | 2 |
| Cyclic vomiting syndrome | infants<br>toddlers | 0.2-1<br>3.4 |
| Colic | infants | 20 |
| Functional diarrhea | toddlers | 8 |
| Infant dyschezia | 1 month old | 4 |
| | 3 month old | 1 |
| Functional constipation | 1st year | 3 |
| | 2nd year | 10 |

Benninga MA, et al. Gastroenterology 2016

## Infant regurgitation

**Must include <u>all</u> of the following in otherwise healthy infants 3 weeks to 12 months of age:**

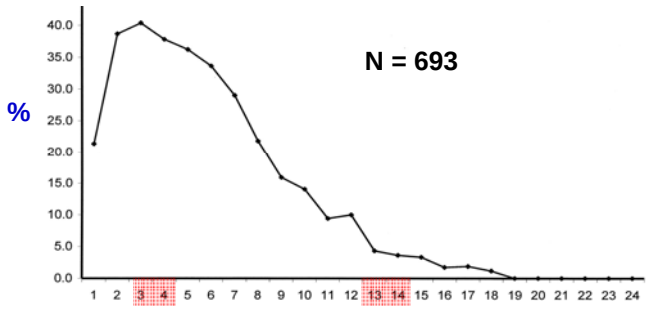
- Regurgitation two or more times per day for three or more weeks
- No retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties or abnormal posturing

## Infant regurgitation

- Global consensus and NASPGHAN/ESPGHAN guidelines
  - "Bothersome symptoms". Criterion to differentiate infant regurgitation from GERD
  - Quantitative methods to define "bothersome" are missing
  - Infants cannot communicate if they are bothered
  - Variation in clinician's interpretation of "bothersome" resulted in unnecessary evaluation and treatment of many infants with regurgitation, not GERD

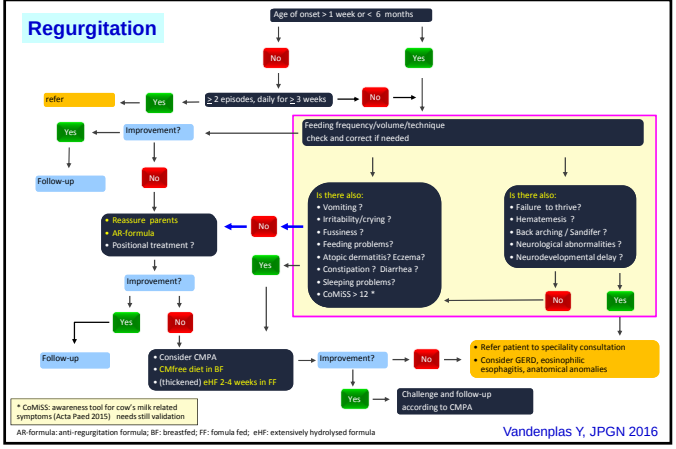
***Did not use bothersome***

## Natural history of regurgitation




Martin AJ, et al. Pediatrics 2002

## Regurgitation




Vandenplas Y, JPGN 2016

## Infant rumination syndrome

- **Old literature (1970-1980)**
- **New population based study using Rome III showed prevalence of 1.9%**
- **Old conceptualization of infants relationships and development**

Tilburg MA, et al. J Pediatr 2015

## Infant rumination syndrome

**Must include <u>all</u> of the following for at least 2 months:**

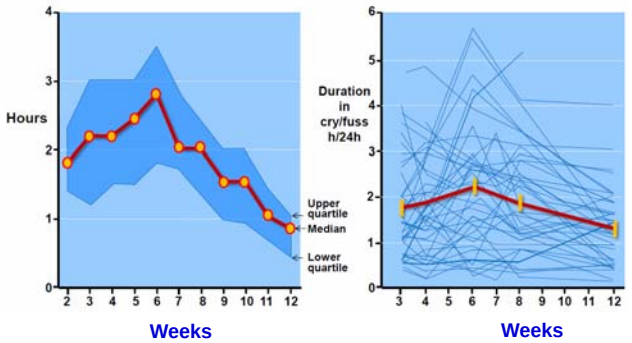
1. **Repetitive contractions of the abdominal muscles, diaphragm, and tongue**
2. **Effortless regurgitation of gastric contents which is either expelled from the mouth or rechewed and reswallowed**
3. **Three or more of the following:**
   a) **Onset between 3 and 8 months**
   b) **Does not respond to management for GERD**
   c) **Unaccompanied by signs of distress**
   d) **Does not occur during sleep and when the infant is interacting with individuals in the environment**

## Cyclic vomiting syndrome

**Must include <u>all</u> of the following:**

1. ***Two or more*** **periods of intense ~~nausea and~~ unremitting *paroxysmal* vomiting with or without retching, lasting hours to days *within a 6 month period***
2. **Episodes are stereotypical in each patient**
3. **Episodes are separated by weeks to months**

## Duration of crying




Brazelton TB, Pediatrics, 1962

Barr RG. Dev Med Child Neurol 1990

## Non gastrointestinal tract origin

- **Unexplained excessive infant crying is a developmental phenomenon**

St James-Roberts I. JPGN 2013

Barr RG. New evidence on unexplained infant crying: Its origins, Nature and management. Ed. Barr, St James-Roberts, Keefe. 2001 Johnson & Johnson Pediatric Institute

## GIT origin* ("Colic")

- **Maturing gut sensitive to substances such as lactose, etc**
- **Gastro-esophageal reflux disease**
- **Motility disorder of esophagus and GIT**
- **Interaction between probiotics and upper GI motility**

Indrio F, et al. JPGN 2013

## Definition

- **Rule of threes:**
  - **Three hours**
  - **Three times a week**
  - **Three weeks**
- **Difficult to validate**
- **Questionnaires**

Wessel MA, et al. Pediatrics 1954

## Wessel criteria

- They are arbitrary
  - no evidence that infants who cry >3hrs/day are in any important respect different from infants who cry 2hrs 50mins/day
- They are culturally dependent
- They are impractical to use
  - The most accepted measurement method is caregiver-kept behavior diaries, but some caregivers are reluctant to keep those for 7 days to decide whether their infant meets diagnostic criteria

## Infant colic

For Clinical purposes must include all of the following:

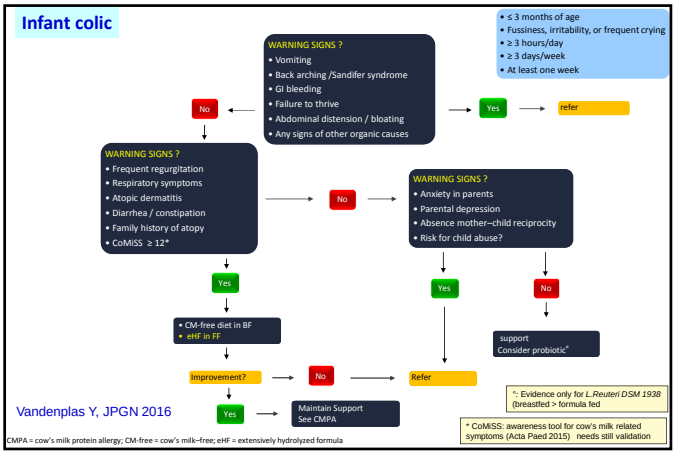
1. An infant who is less than 5 months of age:
2. *Recurrent* prolonged periods of infant irritability, fussing, or crying *reported by parents* that occur without obvious cause and cannot be prevented or resolved by *caregivers*
3. No evidence of infant failure to thrive, fever or ill health

## Infant colic

The Committee also decided that for Clinical Research purposes, to diagnose infant colic the child must meet the clinical criteria PLUS both of the following:

1. Caregiver reports infant has cried or fussed for three or more hours/day during three or more days in seven days in a telephone or face-to-face screening interview with a researcher or clinician
2. Total 24-hour crying plus fussing in the selected group of infants is confirmed to be 3 hours or more when measured by a single, prospectively-kept, 24-hour behavior diary

## Infant colic




Vandenplas Y, JPGN 2016

CMPA = cow's milk protein allergy; CM-free = cow's milk–free; eHF = extensively hydrolyzed formula

## Colicky infants compared with control infants

**Slower colonization**
**Lower diversity and stability**

**↑ Proteobacteria including species producing gas and inflammation**

**↓ Butyrate- producing species**

**↓ Lactobacilli & Bifidobacteria including species with anti-inflammatory effects)**

De Weerdt C, et al. Gut Microbes 2013

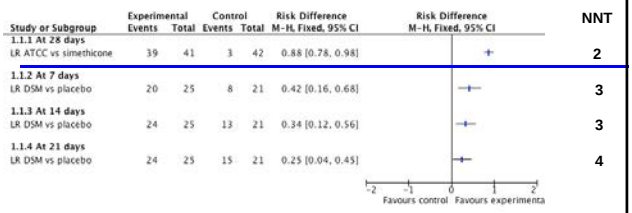
## Altered Fecal Microflora and Increased Fecal Calprotectin in Infants with Colic

- **Fecal calprotectin levels were 2-fold higher in infants with colic than in control infants**
- **Klebsiella species were detected in more colic patients than in control patients**
- **Enterobacter/Pantoea species were detected only in the control patients**
- **Differences could not be attributed to differences in formula versus breast milk feeding, consumption of elemental formula, or exposure to antibiotics**

Rhoads JM, et al. J Pediatr 2009

# Responders

## (50% reduction in crying time from baseline)




**These studies suggest the benefit of supplementation with L reuteri in infantile colic**

Savino F, et al. Pediatrics 2007; Savino F, et al. Pediatrics 2010

## Lactobacillus reuteri DSM 17938 for the Management of Infantile Colic in Breastfed Infants: A RDBPCT

| Outcome | Probiotic group (n = 40) | Placebo group (n = 40) | RR (95% CI) | NNT (95% CI) | *P* value* |
|---|---|---|---|---|---|
| Treatment success (reduction in the daily average crying time ≥50%) | | | | | |
| Day 7 | 6 | 0 | - | 7 (4-19) | .026 |
| Day 14 | 30 | 7 | 4.3 (2.3-8.7) | 2 (2-3) | <.001 |
| Day 21 | 29 | 15 | 2.6 (1.8-4.0) | 2 (2-3) | <.001 |
| Day 28† | 30 | 19 | 1.6 (1.3-2.1) | 3 (2-5) | <.001 |
| | | | Median difference (95% CI) | | |
| Duration of crying (min/d) (median, IQR) | | | | | |
| Baseline | 240 (210-270) | 240 (203-278) | 0.0 (−30 to 30) | N/A | .8 |
| Day 7 | 180 (149-180) | 180 (150-210) | 0.0 (−60 to 0) | N/A | .002 |
| Day 14 | 105 (101-120) | 150 (120-180) | −45 (−75 to −30) | N/A | <.0001 |
| Day 21 | 75 (60-90) | 128 (116-150) | −53 (−83 to −45) | N/A | <.0001 |
| Day 28† | 52 (45-75) | 120 (90-128) | −68 (−75 to −60) | N/A | <.0001 |

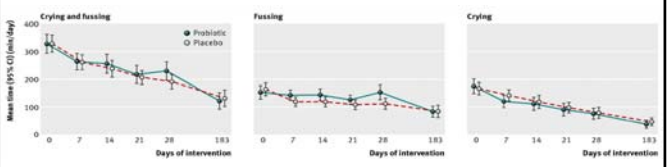
Szajewska H, et al J Pediatr 2013

## Treating infant colic with the probiotic Lactobacillus reuteri: DBPCRT

- **Design: Double blind, placebo controlled randomised trial.**
- **Setting: Community based sample (primary and secondary level care centres) in Melbourne, Australia.**
- **Participants: 167 breastfed infants or formula fed infants aged < 3 months meeting Wessel's criteria for crying or fussing.**
  - **85 were randomised to receive probiotic and 82 to receive placebo.**
- **Interventions Oral daily *L reuteri* (1×108 colony forming units) versus placebo for one month.**

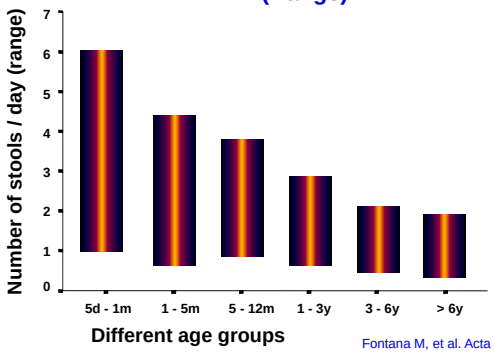
Sung V, et al. BMJ 2014

## Daily duration of cry or fuss over study period and at 6 month follow-up




Sung V, et al. BMJ 2014

## Bowel frequency in different age groups (Range)




Fontana M, et al. Acta Pediatr Scand 1989

## Functional diarrhea

**Must include <u>all</u> of the following:**

1. **Daily painless, recurrent passage *of 4 or more* large, unformed stools**
   ~~***Eliminated during sleep***~~ **(25% have a bowel movement when sleeping)**
1. **Symptoms that last more than 4 weeks**
2. **Onset of symptoms that begins between 6 and 60 months of age**
3. **No failure-to-thrive if caloric intake is adequate**

## Infant dyschezia

**Diagnostic Criteria for Infant Dyschezia**

- Must include *both* of the following in an infant younger than 6 (9) months of age:

1. At least 10 minutes of straining and crying before (un)successful passage of soft stools
2. No other health problems

**Physiological factors:**
Failure to coordinate increased intra-abdominal pressure with relaxation of the pelvic floor

## Treatment of infant dyschezia

- **For the parents**
  - Reassurance
  - Education
  - Patience
- **For the baby**
  - Nothing

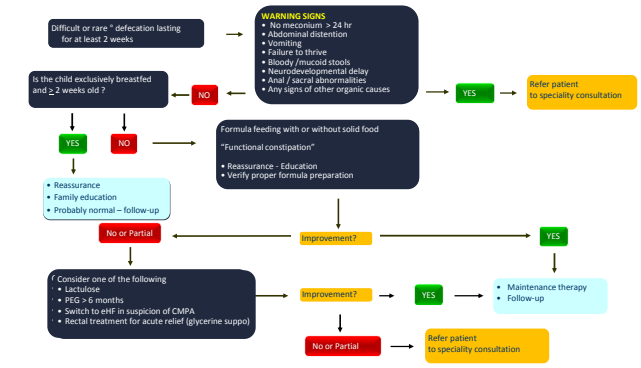

## Functional constipation

- Must include <u>one month of at least two</u> of the following in infants up to 4 years of age:
  - 1. Two or fewer defecations per week
  - 2. History of excessive stool retention
  - 3. History of painful or hard bowel movements
  - 4. History of large diameter stools ~~*which may obstruct the toilet*~~
  - 5. Presence of a large fecal mass in the rectum

*In toilet trained children the following additional criteria may be used*

  - *6. At least 1 episode/week of incontinence after the acquisition of toileting skills*
  - *7. History of large diameter stools which may obstruct the toilet*

## Constipation (<1 year)




Artificial feeding = formula feeding; FC = functional constipation PEG = polyethylene glycol pHF: partially hydrolyzed formula Vandenplas Y, JPGN 2016

## Rome V…..

**New disorders:**

- **Feeding disorders**
  - **FTT vs no FTT**
  - **Disorders related to parent/infant interaction**
  - **Lack of validation**
- **Outcome studies**
- **More epidemiologic, cross cultural, quality of life and health care utilization studies are needed**

# "Not everything that comes up IS reflux: vomiting in the older child"

Samuel Nurko MD MPH
Center for Motility and Functional Gastrointestinal Disorders
Boston Children's Hospital

## DISCLOSURE

- Nothing to disclose

## OBJECTIVES

a) Recognize the differential diagnosis of vomiting in the older child

b) Describe the evaluation of the child with vomiting

c) Understand the treatment of the older child with vomiting

## VOMITING

- Forcible ejection of contents of stomach through the mouth

## SYMPTOMS

- Esophagus
  - Dysphagia, odynophagia, regurgitation/*vomiting*, chest pain, respiratory problems, GERD
- Stomach
  - Early satiety, abdominal distention, *vomiting*, pain, dyspepsia
- Small bowel
  - Abdominal distention, pain, *vomiting*, inability to tolerate feedings, diarrhea

## VOMITING

- Forcible ejection of contents of stomach through the mouth
  - Stomach contents?
  - Forceful?
  - Periodicity
  - Other factors

## VOMITING

Stomach contents?
Characteristics
- Relation with meals
  - During
  - After (timing)
- Digested vs undigested
  - Gastric vs esophageal
- Other content
  - Dry
  - Bile, fecal

Forceful?
- Retching, gagging
- Effortless
- Projectile

Periodicity ?
- Episodic
- Constant
- Cyclic

## TYPE OF VOMITING

| | Contents | Forceful | Periodicity | Other symptoms |
|---|---|---|---|---|
| Esophagus | Undigested food | none to + | Episodic Constant | Heartburn, Dysphagia Respiratory Swallowing difficulties |
| Gastric | Partially digested food, liquid | + to +++ Effortless volitional | Episodic cyclic | Pain, retching, nausea |
| Small bowel | Liquid, bilious | + to +++ | Episodic cyclic | Pain , retching nausea, distention |
| | | | | |
| | | | | |

## VOMITING

- Other factors present
  - Congenital malformations
    - Esophagus
    - Upper GI tract
  - Fundoplication
  - Inflammation
    - EoE, infections, ulcers
  - Extra-intestinal
    - Metabolic, RTA

ESOPHAGUS
Anatomic problems

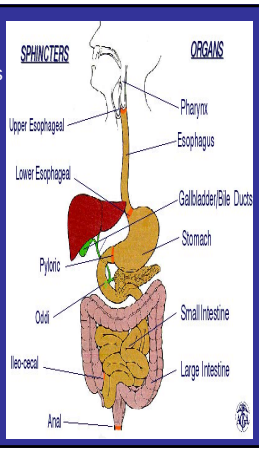
GERD

Swallowing problems
Feeding disorders
Aspiration

Achalasia

EoE
Fundoplication

Metabolic, extraintestinal




GASTRO/ INTESTINAL
Anatomic problems

Gastroparesis
Pseudobstruction

Accommodation

Cyclic vomiting

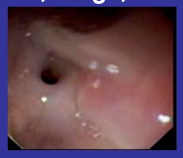
Rumination

Mucosal disease

## IS THERE A MOTILITY DISORDER?

- Exclude anatomic obstruction
  - PE, x-ray, endoscopy
- Look for an etiology
  - Mucosal, r… …stemic, drugs, …ogi…
- … tra…

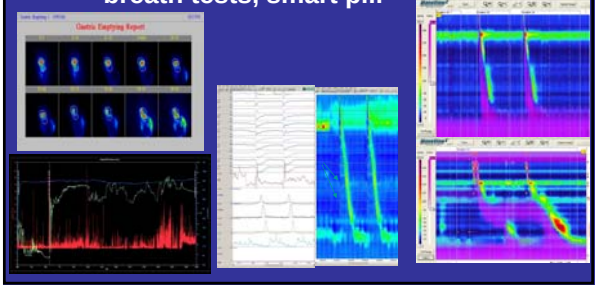




## IS THERE A MOTILITY DISORDER?

**Evaluate transit**

**Impedance, scintigraphy, markers, breath tests, smart pill**



# 4 HOUR GASTRIC EMPTYING

TABLE 1. Comparison of GES results at 2 and 4 hours

| | Abnormal GES at 2 h | Normal GES at 2 h |
|---|---|---|
| Abnormal GES at 4 h | 32 | 8 (23%) |
| Normal GES at 4 h | 4 (11%) | 27 |

Individual data for GES comparison

| 2 h | 2 h | 4 h | 4 h |
|---|---|---|---|
| Normal | Delayed | Normal | Delayed |
| 35 (49%) | 36 (51%) | 31 (44%) | 40 (56%) |

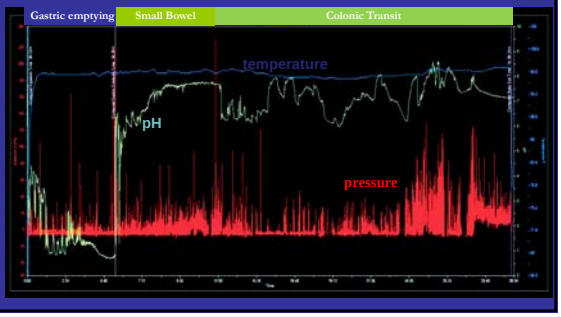
Cumulative data for GES comparison

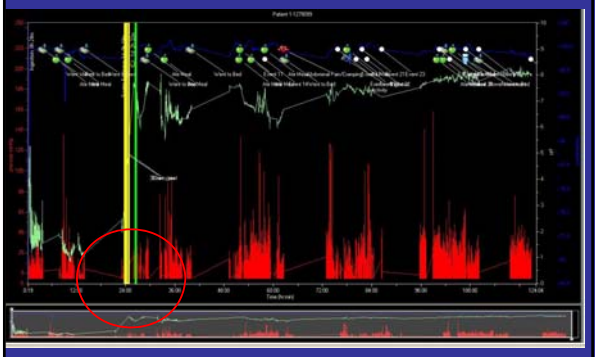
| 2 h | 2 h | 4 h | 4 h |
|---|---|---|---|
| Normal | Delayed | Normal | Delayed |
| 35 (49%) | 36 (51%) | 27 (38%) | 44 (62%) |

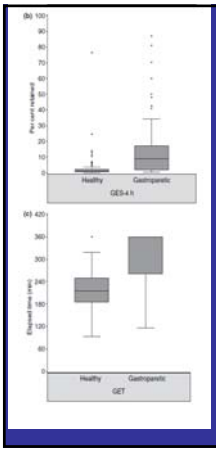
**23 % with normal 2 hr emptying were abnormal at 4 hrs**
**11% with abnormal at 2 hrs , were normal at 4 hrs**
**28% abnormal at the first hour were abnormal at 2 and 4 hrs**

**JPGN 2013**

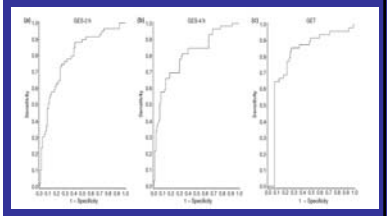
# SMART PILL





## SCINTIGRAPHY VS SMART PILL



APT 2008

Table II. Contractility parameters by the wireless motility capsule test for normal, mild gastroparetic, and severe gastroparetic patients and their ADM final diagnoses, scintigraphic gastric emptying percentages at 2 hours, and SBTT

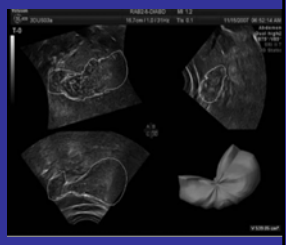
| Patient | Gastric contractility | SB contractility | ADM | Scintigraphic gastric emptying at 2 hours, % | SBTT (hours: minutes) |
|---|---|---|---|---|---|
| 21 | Missing data | Missing data | Rumination | 67 | 1:03 |
| Normal GET | | | | | |
| 1 | No abnormalities | No abnormalities | Normal ADM | 79 | 5:45 |
| 2 | Abnormalities | Abnormalities | Normal ADM | 97 | 3:41 |
| 3 | No abnormalities | Abnormalities | Normal ADM | 68 | 5:22 |
| 4 | Abnormalities | Abnormalities | Normal ADM | 57 | 5:01 |
| 5 | No abnormalities | No abnormalities | Normal ADM | 97 | 3:24 |
| 6 | No abnormalities | No abnormalities | Rumination | 84 | 2:37 |
| Mild prolonged GET | | | | | |
| 7 | No abnormalities | No abnormalities | Hyperactivity/rumination | 89 | 3:54 |
| 8 | No abnormal | | | | 15:45 |
| 9 | No abnormal | | | | 5:20 |
| 10 | No abnormal | | | | 6:15 |
| Severely prolonged GET | | | | | |
| 11 | Abnormalities | Abnormalities | Rumination | 34 | 5:31 |
| 12 | Abnormalities | No abnormalities | Rumination | 62 | 5:44 |
| 13 | No abnormalities | No abnormalities | Rumination | 22 | 0:47 |
| 14 | Abnormalities | No abnormalities | Rumination | 74 | 8:40 |
| 15 | Missing data | Missing data | Normal ADM | 72 | 5:32 |
| 16 | Abnormalities | No abnormalities | Antral hypermotility disorder | 42 | 7:00 |
| 17 | Abnormalities | Missing data | Normal motility | 30 | 8:04 |
| 18 | No abnormalities | No abnormalities | Normal motility | 77 | 5:52 |
| 19 | Missing data | No abnormalities | Rumination | 47 | 7:21 |
| 20 | Missing data | Missing data | Normal motility | 43 | 3:48 |

When compared with scintigraphy smart pill has a high sensitivity to detect gastroparesis

J Peds 2013

## OTHER

- Ultrasound
- Breath tests
  - Octanoic
  - Spirulina



## IS THERE A MOTILITY DISORDER?

- Exclude anatomic obstruction
  - PE, x-ray, endoscopy
- Look for an etiology
  - Mucosal, metabolic, systemic, drugs, psychological
- Evaluate transit
- Motility testing

## IS THERE A MOTILITY DISORDER?

- Are there any contractions?
- Are they strong enough?
- Are they coordinated?
- Can we correlate with transit?

**MOTILITY TESTING**

## IS THERE A MOTILITY DISORDER?

Is the problem secondary to muscle, ENS, autonomic or central nerve dysfunction?

***The phenotypic presentation of the different alterations may be similar***

Motility testing is necessary

## IS THERE A MOTILITY DISORDER?

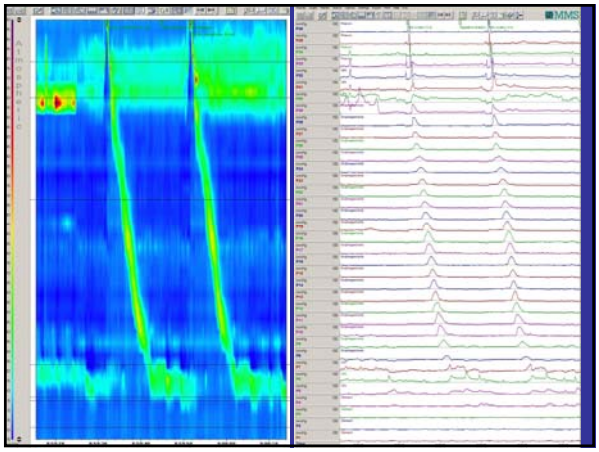
**Evaluate Motility**

**Manometry**

***High resolution manometry***

***Smart pill?***

***Flip?***



ESOPHAGUS
Anatomic problems

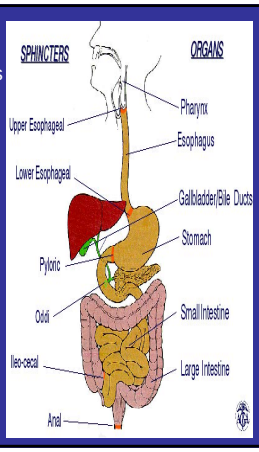
GERD

Swallowing problems
Feeding disorders
Aspiration

Achalasia

EoE
Fundoplication

Metabolic, extraintestinal




GASTRO/
INTESTINAL
Anatomic problems

Gastroparesis
Pseudobstruction

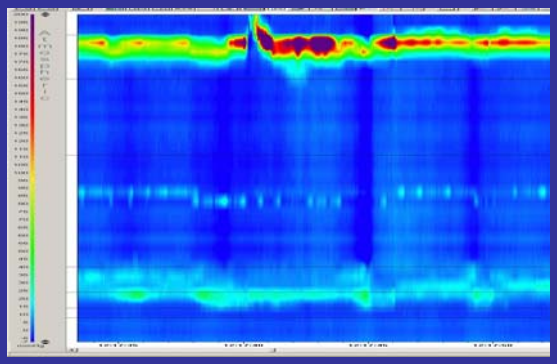
Accommodation

Cyclic vomiting

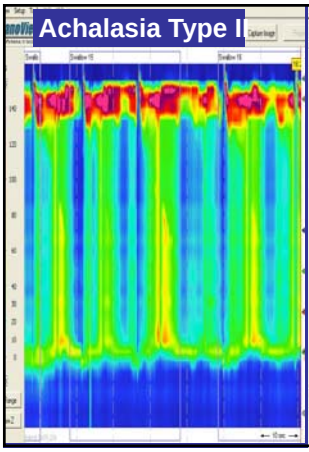
Rumination

Mucosal disease

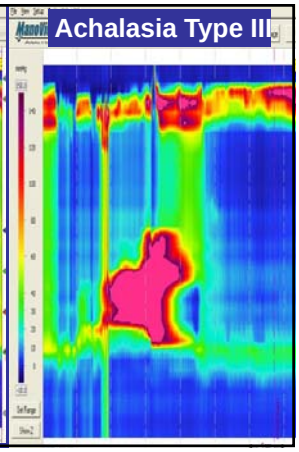
## Achalasia Type I

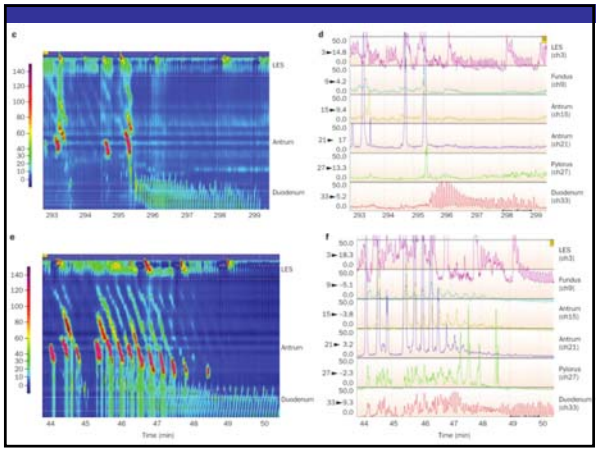


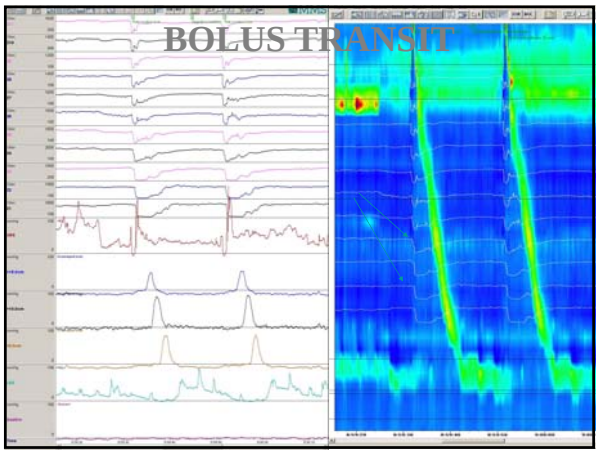
## Achalasia Type II



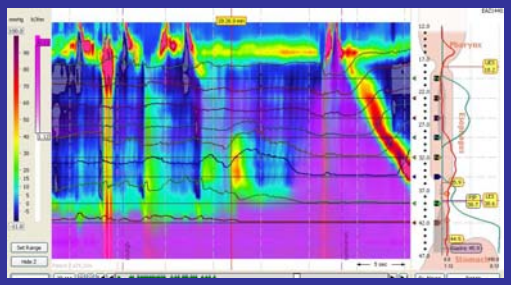
## Achalasia Type III

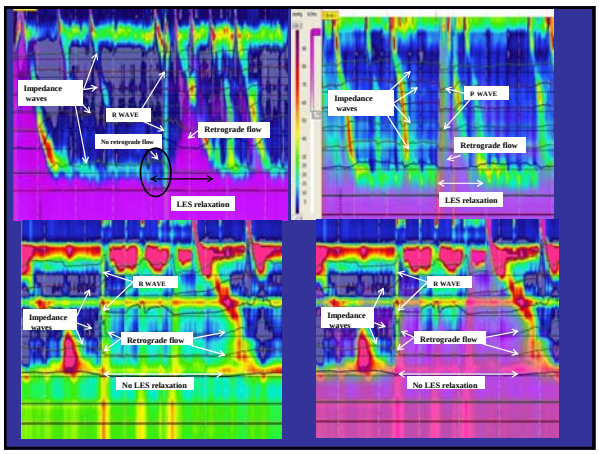




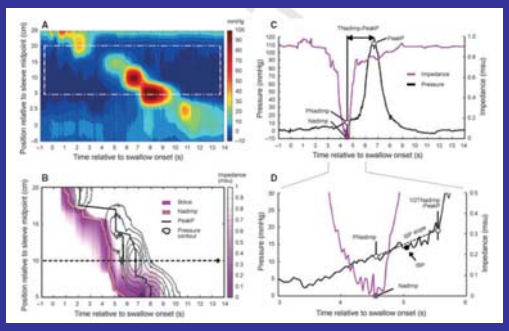



## Cough versus Rumination: You need impedance or you need to be there





## Automated Impedance Manometry analysis (AIM)

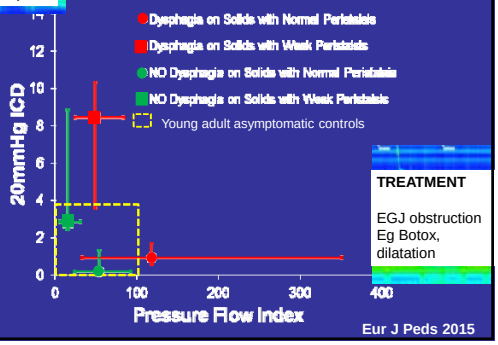


NGM 2012

## Results

**TREATMENT**

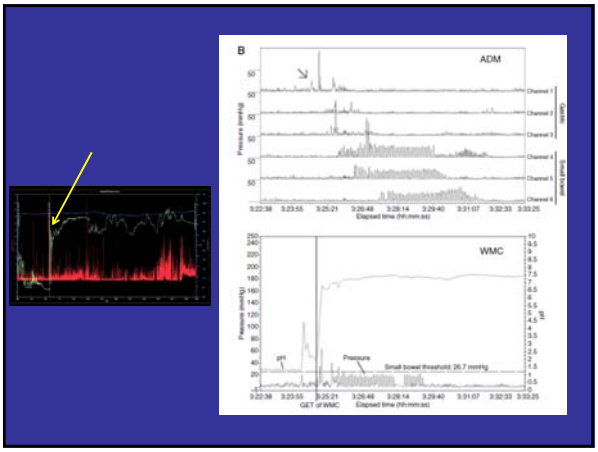
Weak peristalsis
Cholinergic agent
(eg Bethanecol )




**TREATMENT**

EGJ obstruction
Eg Botox, dilatation

Eur J Peds 2015



# SMART PILL

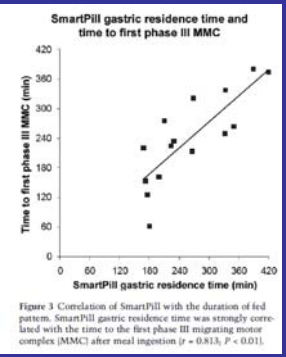



Figure 3 Correlation of SmartPill with the duration of fed pattern. SmartPill gastric residence time was strongly correlated with the time to the first phase III migrating motor complex (MMC) after meal ingestion ($r = 0.813$; $P < 0.01$).

NGM 2008

# SMART PILL

Table II. Contractility parameters by the wireless motility capsule test for normal, mild gastroparetic, and severe gastroparetic patients and their ADM final diagnoses, scintigraphic gastric emptying percentages at 2 hours, and SBTT

| Patient | Gastric contractility | SB contractility | ADM | Scintigraphic gastric emptying at 2 hours, % | SBTT (hours: minutes) |
|---|---|---|---|---|---|
| 21 | Missing data | Missing data | Rumination | 67 | 1:03 |
| Normal GET | | | | | |
| 1 | No abnormalities | No abnormalities | Normal ADM | 79 | 5:45 |
| 2 | Abnormalities | Abnormalities | Normal ADM | 97 | 3:41 |
| 3 | No abnormalities | Abnormalities | Normal ADM | 68 | 5:22 |
| 4 | Abnormalities | Abnormalities | Normal ADM | 57 | 5:01 |
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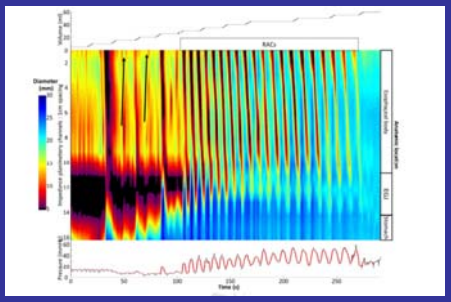
| 6 | No abnormalities | | | | 2:37 |
| Mild prolonged GET | | | | | |
| 7 | No abnormalities | | | | 3:54 |
| 8 | No abnormalities | | | | 15:45 |
| 9 | No abnormalities | | | | 5:20 |
| 10 | No abnormalities | | | | 6:15 |
| Severely prolonged GET | | | | | |
| 11 | Abnormalities | | | | 5:31 |
| 12 | Abnormalities | No abnormalities | Rumination | 62 | 5:44 |
| 13 | No abnormalities | No abnormalities | Rumination | 22 | 0:47 |
| 14 | Abnormalities | No abnormalities | Rumination | 74 | 8:40 |
| 15 | Missing data | Missing data | Normal ADM | 72 | 5:32 |
| 16 | Abnormalities | No abnormalities | Antral hypomotility disorder | 42 | 7:00 |
| 17 | Abnormalities | Missing data | Normal motility | 30 | 8:04 |
| 18 | No abnormalities | No abnormalities | Normal motility | 77 | 5:52 |
| 19 | Missing data | No abnormalities | Rumination | 47 | 7:21 |
| 20 | Missing data | Missing data | Normal motility | 43 | 3:48 |

SB, small bowel.

When compared with scintigraphy smart pill has a high sensitivity to detect gastroparesis and may be more sensitive than ADM to detect motor abnormalities

J Peds 2013

# FLIP



Gastroenterology 2015

## TREATMENT

**Supportive care**

**Specific**

## SUPPORTIVE THERAPY

- Supportive
  - Fluids
  - Metabolic imbalance
  - Nutrition
    - *enteral* vs TPN
  - Complications
- Medications
- Pain management
- Surgery
  - G-tube
  - J-tube

## SUPPORTIVE THERAPY

- Supportive
  - Fluids
  - Metabolic imbalance
  - Nutrition
    - *enteral* vs TPN
  - Complications
    - Bacterial overgrowth
- Medications
  - Modify Transit
  - Pain
  - Cyclic vomiting

## SUPPORTIVE THERAPY

- Supportive
  - Fluids
  - Metabolic imbalance
  - Nutrition
    - *enteral* vs TPN
  - Complications
    - Bacterial overgrowth
- Medications. Modify Transit
  - Augment transit: Cholinergics, EES, Cisapride, reglan, domperidone, zelnorm, octreotide, augmentin
- Botox

## SUPPORTIVE THERAPY

- Supportive
  - Fluids
  - Metabolic imbalance
  - Nutrition
    - *enteral* vs TPN
  - Complications
    - Bacterial overgrowth
- Medications
  - Pain
    - Cyproheptidine
    - Nerve modulators

## THERAPY

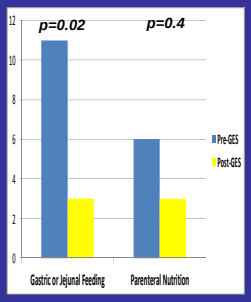
- Supportive
  - Fluids
  - Metabolic imbalance
  - Nutrition
    - *enteral* vs TPN
  - Complications
    - Bacterial overgrowth
- Medications
- Pain management
- Relieve the obstruction
  - Surgery

## Therapies

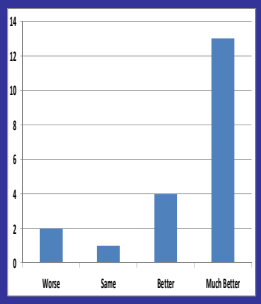
- Surgery
  - Goal: Cure, keep alive, improve quality of life
  - Provide access for enteral nutrition, IV support/ PN, reduce vomiting, shorten gut, facilitate transit, decompress, decrease hospitalizations
    - Gastrostomy, jejunostomy
    - Ileostomy
    - Resections: focal/ total
    - Treat complications
    - Pacing
    - Transplant
  - Remember: Adhesions

## Gastric pacing

**26 children, age 4-21 years**




Route of nutrition




Global health

NGM 2013

## SUMMARY

- Vomiting is a symptom that requires careful evaluation
- May be associated with anatomic, motility or extra-intetsinal disorders
- There are new evaluation techniques
- Therapy is multidisciplinary
  - Supportive
  - Specific

# How to make the bowel less irritable: Update on treatment of IBS

Carlo Di Lorenzo, M.D.
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NATIONWIDE CHILDREN'S
*When your child needs a hospital, everything matters.*

THE OHIO STATE UNIVERSITY

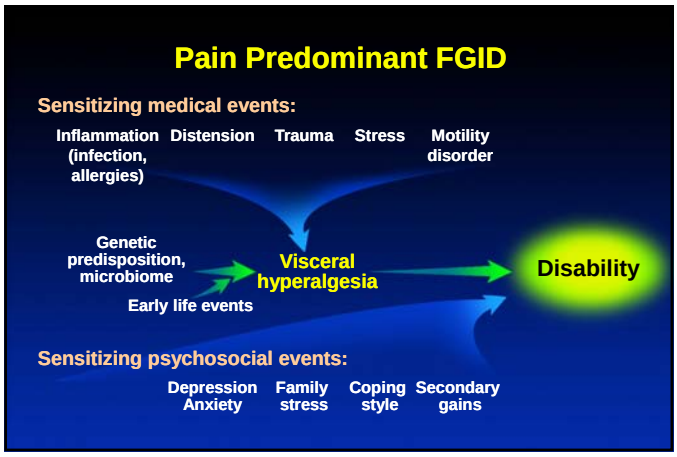
## Conflicts of interest regarding this presentation

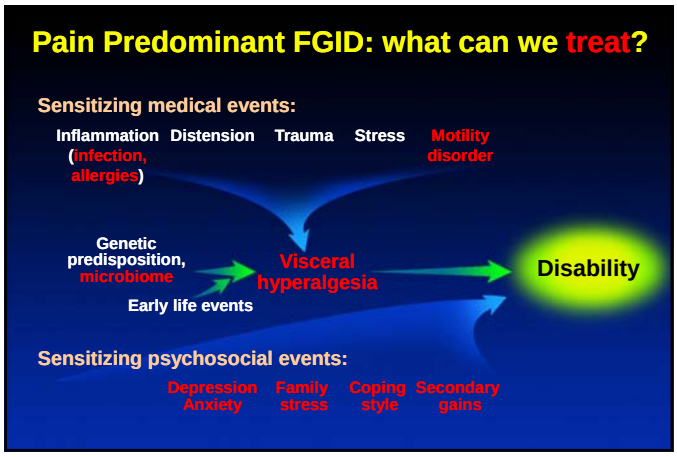
QOL Medical (consultant)

IM HealthScience™ (consultant)

## Outline

- Become familiar with the central and peripheral pathogenetic mechanisms of IBS
- Recognize the role of dietary treatment of childhood IBS
- Understand the value of pharmacological and non-medical treatment of childhood IBS


Pain Predominant FGID
Sensitizing medical events:
Inflammation (infection, allergies)
Distension
Trauma
Stress
Motility disorder
Genetic predisposition, microbiome
Early life events
Visceral hyperalgesia
Disability
Sensitizing psychosocial events:
Depression Anxiety
Family stress
Coping style
Secondary gains


Pain Predominant FGID: what can we treat?
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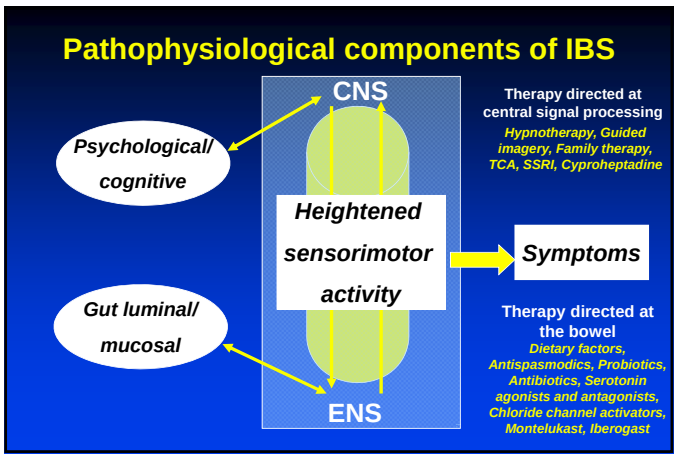
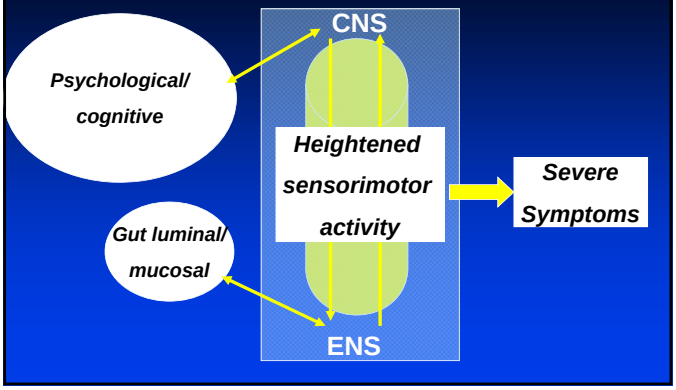
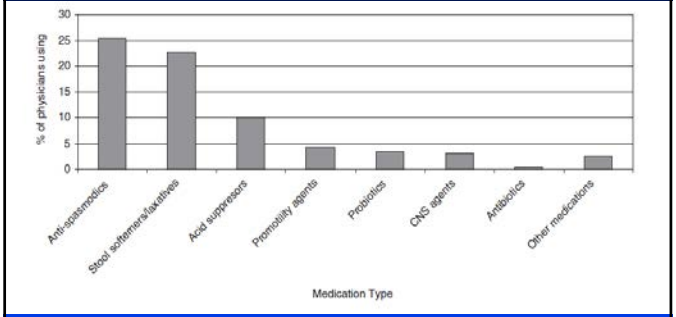

Pathophysiological components of IBS
CNS
Psychological/ cognitive
Heightened sensorimotor activity
Symptoms
Gut luminal/ mucosal
ENS
Therapy directed at central signal processing
Hypnotherapy, Guided imagery, Family therapy, TCA, SSRI, Cyproheptadine
Therapy directed at the bowel
Dietary factors, Antispasmodics, Probiotics, Antibiotics, Serotonin agonists and antagonists, Chloride channel activators, Montelukast, Iberogast

## Pathophysiological components of IBS



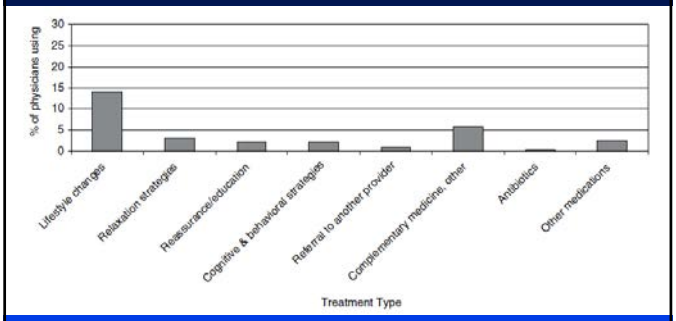

## Treatment:
## What do pediatric gastroenterologists do?

## Medical treatment - 2009




Schurman et al, JPGN 2010;50: 32–37

## Non-medical treatment - 2009




Schurman et al, JPGN 2010;50: 32–37

## The evidence: what are the DBPC studies in pediatric FGIDs?

## Medications: DBPC studies

| Ref. | Treatment | Diagnosis | Sample size (enrolled/completed) | Superior to placebo for pain relief |
|---|---|---|---|---|
| Symon and Russell[56] (1995) | Pitofiten | Abdominal migraine | 16/14 | Yes |
| Kline *et al*[65] (2001) | Enteric coated peppermint oil capsules | Irritable bowel syndrome | 50/42 | Yes |
| See *et al*[66] (2001) | Famotidine | Abdominal pain and dyspepsia | 25/25 | Yes |
| Friesen *et al*[67] (2004) | Montelukast | FD with duodenal eosinophilia | 40/37 | Yes |
| Bahar *et al*[68] (2008) | Amitriptyline | Irritable bowel syndrome | 35/33 | Yes |
| Sadeghian *et al*[69] (2008) | Cyproheptadine | Functional abdominal pain | 36/28 | Yes |
| Saps *et al*[58] (2009) | Amitriptyline | FD, irritable bowel syndrome, and functional abdominal pain | 90/83 | No |
| Pourmoghaddas *et al*[70] (2014) | Mebeverine | Functional abdominal pain | 115/87 | No |

## Evaluation of the Efficacy of Amitriptyline in Children with Abdominal Pain of Non-Organic Origin: A DBPC trial

Miguel Saps, Nader Youssef, Samuel Nurko, Paul Hyman, Jose Cocjin, Adrian Miranda, Carlo Di Lorenzo

Gastroenterology 2009;137:1261-9

## Overall Assessment Intention To Treat

| | Total | Placebo | | Amitriptyline | |
|---|---|---|---|---|---|
| Failed | 16% | 16 % | | 15 % | |
| Poor | 11% | 7 % | | 15 % | |
| Fair | 18 % | 23 % | | 13 % | |
| Good | 37 % | 39 % | 46 % | 35 % | 50 % |
| Excellent | 11 % | 7 % | | 15 % | |

- No significance difference between arms , (p=0.76).
- Excellent or Good vs. Fair, Poor or Failed, (p=0.68).

## Rifaximin

**Pediatric RCT**

- IBS/FAP/FD (n=75) treated with 550 mg rifaximin or placebo TID for 10 d
- No significant difference in symptom improvement between groups, regardless of initial phenotype
- Only 20% of children treated with rifaximin achieved a normalized repeat LBT

Collins BS. JPGN 2011;52:382-6

# What are the treatments that have been demonstrated to "work"?

## Placebo

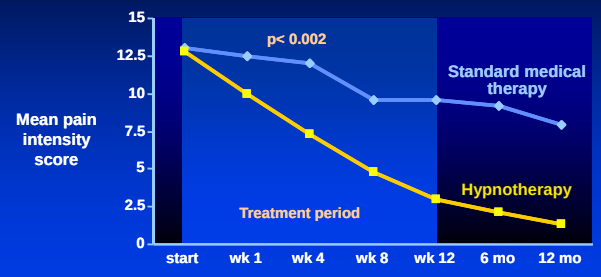

- Peppermint oil (n=50): Improvement in symptoms 43%
- Amitriptyline (n=90): Feeling better 53%
- Famotidine (n=25): Improvement 15.4%
- Cyproheptadine (n=29): Global improvement 35.7%
- Mebeverine (n=115): Treatment response 53.4%

Korterink et al. Pediatrics. 2015;135:522-35

## Probiotics in children with FGID: Summary

| | Agent | Design | Sample size | Age | Effect |
|---|---|---|---|---|---|
| Bausserman | Lactobacillus GG | DBPC | 50 | 6-20 yr | ↓ bloating |
| Gawrońska | Lactobacillus GG | DBPC | 104 | 6-16 yr | ↓ frequency pain |
| Romano | Lactobacillus reuteri | DBPC | 60 | 6-16 yr | ↓ intensity pain |
| Guandalini | VSL # 3 | DBPC-CO | 64 | 4-18 yr | ↓ global assessment of sx |
| Francavilla | Lactobacillus GG | DBPC | 141 | 5-14 yr | ↓ Frequency and severity pain |

## Hypnotherapy in Children with FAP

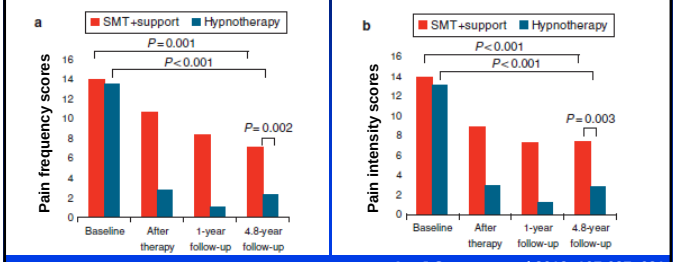



Vlieger et al. Gastroenterology 2007;133:1430-6

## 5 years later…

## Long-Term Follow-Up of Gut-Directed Hypnotherapy vs. Standard Care in Children With Functional Abdominal Pain or Irritable Bowel Syndrome

Anne M. Vlieger, MD, PhD[1], Juliette M.T.M. Rutten, MD[2], Anita M.A.P. Govers, MD[2], Carla Frankenhuis[2] and Marc A. Benninga, MD, PhD[2]



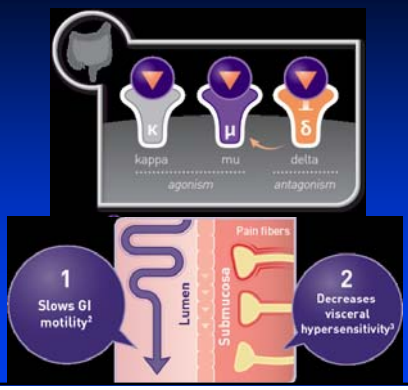

Am J Gastroenterol 2012; 107:627–631

# New kids on the block

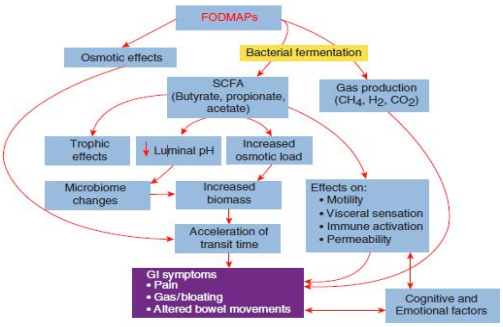
## Linaclotide (Linzess): Mechanism of Action


**Peptide agonist of guanylate cyclase 2C**

## Viberzi (eluxadoline)




## How does food cause GI symptoms?




Adapted from Spencer M, et al. Cur Tx Opt GI. 2014;12:424-440

AP&T Alimentary Pharmacology and Therapeutics

**Randomised clinical trial: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome**

B. P. Chumpitazi*, J. L. Cope†,§, E. B. Hollister†,§, C. M. Tsai*, A. R. McMeans*, R. A. Luna†,§, J. Versalovic†,§ & R. J. Shulman*,†

*Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA
†Children's Nutrition Research Center,

**Aliment Pharmacol Ther. 2015;42:418-27**

SUMMARY

Background

33 children completed the study. Less abdominal pain occurred during the low FODMAP diet vs. TACD. Compared to baseline (1.4  0.2), children had fewer daily abdominal pain episodes during the low FODMAP diet but more episodes during the TACD.

Responders were enriched at baseline in taxa with known greater saccharolytic metabolic capacity (Bacteroides, Ruminococcaceae, Faecalibacterium prausnitzii) and three Kyoto Encyclopedia of Genes and Genomes orthologues, of which two relate to carbohydrate metabolism.

## What about fiber?

ARTICLE IN PRESS

Clinical Gastroenterology and Hepatology 2016;■:■–■

### Psyllium Fiber Reduces Abdominal Pain in Children With Irritable Bowel Syndrome in a Randomized, Double-Blind Trial

Robert J. Shulman,[*,‡,§,a] Emily B. Hollister,[§,‖,¶,#,a] Kevin Cain,[**] Danita I. Czyzewski,[§,‡‡] Mariella M. Self,[§,‡‡] Erica M. Weidler,[*,‡,§] Sridevi Devaraj,[§,‖,¶,#] Ruth Ann Luna,[§,‖,¶,#] James Versalovic,[§,‖,¶,#] and Margaret Heitkemper[§§]

[*]Department of Pediatrics, [‡‡]Menninger Department of Psychiatry and Behavioral Sciences, [¶]Department of Pathology and Immunology, Baylor College of Medicine; [‡]Children's Nutrition Research Center; [#]Department of Pathology, [§]Texas Children's Hospital; [‖]Texas Children's Microbiome Center; [**]Department of Biostatistics and Office of Nursing Research, [§§]Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle, Washington

## Fiber

- RDBC trial of 103 children (13±3 y) with IBS.
- 8 day diet excluding carbohydrates thought to cause symptoms of IBS

**Conclusions: "Psyllium fiber reduced the number of abdominal pain episodes in children with IBS, independent of psychological factors. Psyllium did not alter breath hydrogen or methane production, gut permeability, or microbiome composition."**

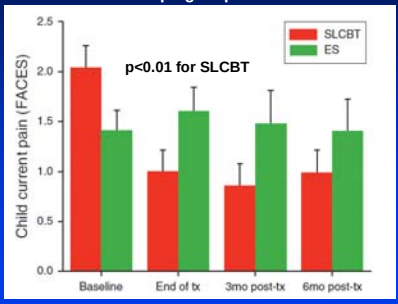
(n=37) or placebo (maltodextrin, n=47) for 6 weeks. Breath hydrogen and methane production, intestinal permeability, and the composition of the microbiome before and after treatment.

*Shulman R, et al. Clinical Gastroenterology and Hepatology (in press)*

## Treating the parents?

## Social learning: parents-children

200 children, 7-17 yr, 3-session intervention of social learning-cognitive-behavioral treatment (SLCBT) targeting parents' responses to their children's pain complaints and children's coping responses vs education support (ES)



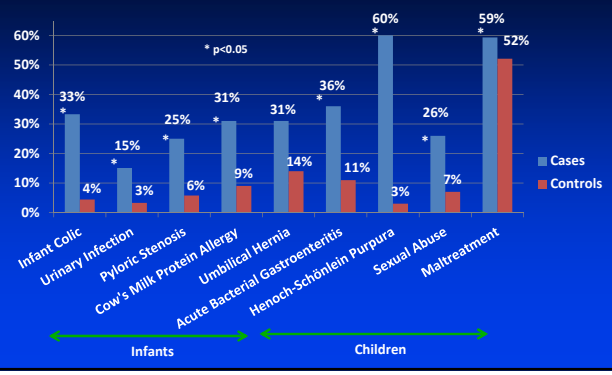

Levy RL et al. Am J Gastroenterol 2010;105:946-56

## But we do not treat every IBD in the same way!

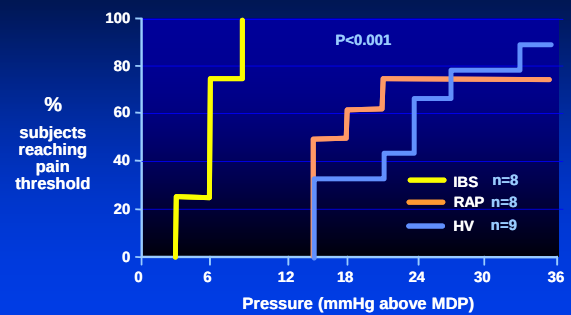
## Are we looking at the forest and missing the trees?

## Different pathophysiology

## Early Life Events as Predictors of Pediatric FAP/IBS




## Rectal Barostat Demonstrates Visceral Hyperalgesia




Van Ginkel R et al. Gastroenterology 2001; 120:31

## Inflammation and Permeability in Functional Abdominal Pain Syndrome and IBS vs Controls

- Increased gastrointestinal permeability
- GI inflammation- greater fecal calprotectin concentration in FAP/IBS = 65.5 ± 75.4
- Fecal calprotectin concentration correlated with pain interference with activities

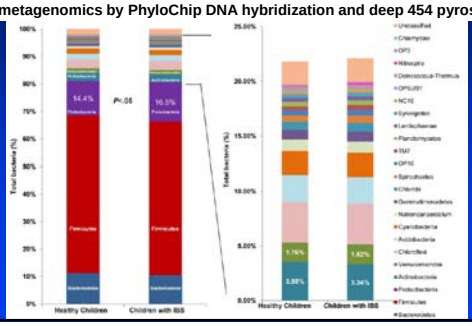
Shulman RJ, et al. J Pediatr. 2008;153:646-650

## Gastrointestinal Microbiome Signatures of Pediatric Patients With Irritable Bowel Syndrome

GASTROENTEROLOGY 2011;141:1782–1791

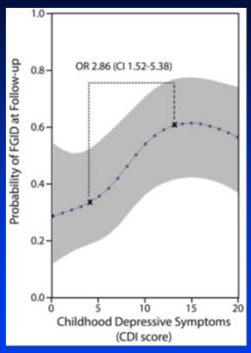
DELPHINE M. SAULNIER,*,‡,§ KEVIN RIEHLE,‖,¶ TONI-ANN MISTRETTA,*,‡ MARIA-ALEJANDRA DIAZ,*,‡ DEBASMITA MANDAL,# SABEEN RAZA,*,‡ ERICA M. WEIDLER,**,‡‡ XIANG QIN,§§ CRISTIAN COARFA,‖,¶ ALEKSANDAR MILOSAVLJEVIC,‖,¶ JOSEPH F. PETROSINO,§§,‖‖,¶¶ SARAH HIGHLANDER,§§,‖‖ RICHARD GIBBS,§§ SUSAN V. LYNCH,# ROBERT J. SHULMAN,**,‡‡ and JAMES VERSALOVIC*,‡,§,**,‡‡

Using16S metagenomics by PhyloChip DNA hybridization and deep 454 pyrosequencing




## Does it make sense to treat them all in the same way?

## Can we predict who will do well?




Horst S, et al Clin Gastroenterol Hepatol. 2014;12:2026-32

## Take home messages

- Become comfortable in dealing with both peripheral AND central components of IBS
- Many treatments that target either the bowel or the brain are available
- Use the treatment most likely to benefit your patient (no cookie cutter approach)
- Most effective (and safest!) treatment is placebo

## Some of the gaps and how to close them

- How do we prevent a young child with IBS from becoming an adult with IBS?
- Development of consortia
- Validation of pediatric PROs
- Define the physiology (point of care testing with non invasive physiological studies and screening for internalizing disorders?)
- Augmentation/layering treatments?