Wednesday October 5, 2016

Postgraduate Course
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*Some of the slides reproduced in this syllabus contain animation in the power point version. This cannot be seen in the printed version.*
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Continuing Medical Education

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

1) Advance understanding of normal development, physiology and pathophysiology of diseases of the gastrointestinal tract, liver and nutrition in children

2) Improve professional competence, quality of care, and patient outcomes by disseminating knowledge through scientific meetings, professional and public education.

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

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

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

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 – Martin Martin and Natalie Terry
Moderator: Terry Sigman
11. Functional GI Disorders – Marc Benninga and Carlo Di Lorenzo
Moderator: Deepali Tewari
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

<table>
<thead>
<tr>
<th>Stigmata</th>
<th>Risk of recurrent bleeding without therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active arterial bleeding (spurring)</td>
<td>Approaches 100%</td>
</tr>
<tr>
<td>Non-bleeding visible vessel</td>
<td>Up to 50%</td>
</tr>
<tr>
<td>Non-bleeding adherent clot</td>
<td>8% - 10%</td>
</tr>
<tr>
<td>Ulcer oozing without other stigmata</td>
<td>10% - 27%</td>
</tr>
<tr>
<td>Flat spots</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Clean-based ulcers</td>
<td>&lt;3%</td>
</tr>
</tbody>
</table>

Standards of Practice Committee. GIE 2012.
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"

Wright et al. J Lap Surg Tech 2015
Hemostasis

What about Hemospray?

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

Sung, Endoscopy 2011

• 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

- 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

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


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

- 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

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?
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 diathesis, GVHD or chemotherapy related
  - Systemic: Cystic fibrosis

Shlemiel and Shlemazel?
• Yiddish 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
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

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)
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)

Acute colonic distention algorithm

- Acute Colonic Distention

  - Ischemia
  - Perforation
  - Cecal Volvulus?

  - Mechanical Obstruction?

  - Pseudo-obstruction

Yes

No

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

**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 (e.g., PEG)
Acute LGI Bleeding Management

• Suction, Suction, Suction
• CO2 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

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

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**

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

Consider brain MRI to rule out Chiari malformation in a child with dysphagia who has CP bar on VFSS.

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

Incomplete relaxation of UES

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
- Both

**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 may be 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
Minimal Incision, Needle-Knife Endoscopic Cricopharyngeal Myotomy

Cricopharyngeal Myotomy with the OmniGuide CO2 Laser Fiber System

Cricopharyngeal Achalasia: Comparing Outcomes

<table>
<thead>
<tr>
<th>No. of Attempts</th>
<th>Range of Success Rate (Crude Average)</th>
<th>No. of Patients (Sum)</th>
<th>No. of Successes (Sum)</th>
<th>Patients Whose Average Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy Injection</td>
<td>12 (49%–107% (75%))</td>
<td>188</td>
<td>102</td>
<td>99%</td>
</tr>
<tr>
<td>Biopsy</td>
<td>6 (58%–122% (81%))</td>
<td>110</td>
<td>83</td>
<td>71%</td>
</tr>
<tr>
<td>Myotomy</td>
<td>16 (25%–102% (75%))</td>
<td>309</td>
<td>208</td>
<td>76%</td>
</tr>
</tbody>
</table>

Distribution of Complications of Biopsy Injection, Biopsy, and Myotomy

<table>
<thead>
<tr>
<th>No. of Attempts</th>
<th>Range of Complication Rate (Crude Average)</th>
<th>No. of Patients (Sum)</th>
<th>No. of Complications (Sum)</th>
<th>Patients Whose Average Complication Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy Injection</td>
<td>12 (7%–23% (15%))</td>
<td>146</td>
<td>6</td>
<td>4%</td>
</tr>
<tr>
<td>Biopsy</td>
<td>6 (7%–23% (15%))</td>
<td>110</td>
<td>6</td>
<td>6%</td>
</tr>
<tr>
<td>Myotomy</td>
<td>16 (7%–23% (15%))</td>
<td>309</td>
<td>27</td>
<td>7%</td>
</tr>
</tbody>
</table>

Achalasia

Lesion 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

Unopposed Excitation

Normal patient

Achalasia patient
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**

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic achalasia with failed peristalsis</td>
<td>Achalasia with panesophageal pressurization</td>
<td>Achalasia with esophageal spasm</td>
</tr>
</tbody>
</table>
**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

Pass balloon over guidewire
Distend balloon to 7-10 psi pressure
Post dilation tear and bleed

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%)
Achalasia: Pneumatic dilation Vs. Myotomy

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


Achalasia: POEM Landmarks

Anterior Vagal Trunk
Left Lung
Right Lung
Azygous Vein
Thoracic Duct
Posterior Vagal Trunk
Spine

Achalasia: POEM
Achalasia: POEM
Submucosal Injection of Saline & Indigo Carmine

Submucosal Dissection with Hybrid Knife

Mucosotomy along Right Anterior Wall

Hybrid Tunnel

Mucosotomy along EGD (inflated)

Tunnel extended to Cardia

Myotomy initiated 2 cm below Mucosotomy: Hybrid (inject/cautery) ESD knife or Triangular Tip

Patulous LES after 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

- A chronic disorder defined by delayed gastric emptying in the absence of mechanical obstruction
- Symptoms: Early satiety, bloating, nausea, vomiting, postprandial 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

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.


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


Endoscopic Pyloric Botox Injection
Endoscopic Pyloric Balloon Dilation

Pyloric Balloon Dilation

Endoscopic PEG and PEJ Tubes
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-yr 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 acidic requiring HCO3 infusions and baking soda enterally
- Evidence of left ventricular dysfunction - Lasix, Enalapril and K+
- Despite these problems he never developed cholestasis.
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

INTESTINAL FAILURE

- Short Bowel Syndrome (SBS)
- Normal Length

Polygenic disorders
- Enterocolitis
- Motility Disorders
- Epithelial Disorders
- Immune Disorders

Monogenic disorders
- Syndromic Secretory Diarrhea
- Trichohepatoenteric Syndrome
- ADAM17 deficiency
- Kabuki Syndrome
- Dyskeratosis Congenita
- GUCY2C dominant negative

CONGENITAL ENTEROPATHIES

- 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 -
    - 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
      - Selecting Class of Nutrients or Electrolytes – NOT INTESTINAL FAILURE
      - Reduced Digestion – e.g., Amylase; Lactase; Sucrase-Isomaltase
      - 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

**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

**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/crypt hypoplasia
- Late onset variant – wean TPN when older

Pathogenesis:
- Regulates enterocyte polarity, apical trafficking, and microvillus growth
- MYO5B – dynamic tether – interacts with RAB8a and RAB11a
- Microvillus growth – regulate 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 villus atrophy w/ crypt hyperplasia
- Neuronal 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: 18373202, 23655470

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 Abs 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 degrade mRNAs from the 3’ end.

PMID: 20176027, 22444670

HONORABLE MENTION

Intestinal Stem Cell-Based Therapy

Autologous Epithelial Stem Cell Transplant

Intestinal Stem Cell-Based Therapy

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Intestinal Stem Cell-Based Therapy

Autologous Epithelial Stem Cell Transplant
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
Carol A. Durno
Zane Cohen Centre for Digestive Disease and Department of Surgery, Mount Sinai Hospital
Division of Gastroenterology/Hepatology/Nutrition, Hospital for Sick Children, University of Toronto, Toronto, Canada

World Congress Pediatric GI, Hepatology, Nutrition

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

<table>
<thead>
<tr>
<th>Adenomatous Polyposes</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
</tr>
<tr>
<td>Hereditary non-polyposis</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
</tr>
<tr>
<td>Adenomatous polyposis</td>
<td>APC</td>
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<tr>
<td>MYH-associated polyposis</td>
<td>MYH</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hamartomatous Polyposes</th>
<th>Gene</th>
</tr>
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<tbody>
<tr>
<td>Juvenile polyposis</td>
<td>SMAD4 or BMPR1A</td>
</tr>
<tr>
<td>Bannayan-Riley-Ruvalcana</td>
<td>STK11</td>
</tr>
<tr>
<td>Cowden's disease</td>
<td>PTEN</td>
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</tbody>
</table>

Colorectal Cancer

5% gene(s) unknown
95% Genetic Etiology

Adult

5% gene(s) not known
Lynch
MYPH-associated polyposis
FAP
Sporadic
FAP (<1%)
MYPH-associated polyposis (<1%)

Classification and Reclassification of Polyposis Patients


Biallelic Mismatch Repair Gene Deficiency Syndrome (BMMRD)
- Biallelic mutations in the MMR genes: PMS2, MSH6, MLH1, MSH2
- Novel cancer predisposition syndrome

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)


Tumor Spectrum expanding...
Surveillance Protocol Impacts Survival

55 tumors detected over 12 years

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)

MLH1 13-17%
MSH2 <10%
MSH6 19-33%
PMS2 50-58%

Research in Polyposis

BMMRD Cancers Harbor the Highest Mutation Burden Across 7000 Cancers

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
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

colorectal cancer 55 yrs

APC

colorectal cancer 28 “polyps”

juvenile polyps early onset CRC

15 yrs severe anemia epistaxis

11 yrs 11 yrs

Significance of epistaxis?

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...


Hereditary hemorrhagic telangiectasia-
Juvenile Polyposis Syndrome Kindred

(Schweizer P, Dunn C. J of Gastroenterol; 2012.)
(Schweizer P, Dunn 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-hypervarient 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
  - (Fil, Cell. 2015)

Recurrent Multifocal Glioblastoma Response to Immune Checkpoint Inhibitor

- Nivolumab 1-10 mg/kg
- Recurrence 8 wks Nivolumab

-Bouffet et al. JCO 2016-
Immune checkpoint inhibitors and Recurrent Metastatic Colorectal Cancer

13 year old male
Colorectal cancer with mets to wrist

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

The Hospital for Sick Children, Canada
Eric Bouffet, Cynthia Hawkins, Carol Durno, Adam Shlien, James Dowling, Peter Dirks, Michael Taylor, Annie Huang, David Malkin, Christopher Pearson, Uri Tabori

Mayo Clinic, USA
Erica Pritchard, Robert J. Lee, Dae D. Al-Shehri, Linda Mehdorn, Gaye Robert Johnson

Children's Hospital of Pittsburgh, USA
Gary Mason, Children's Hospital of Alabama, USA

Children's Hospital:

Children's Hospital of Boston, USA

Children's Hospital Los Angeles, USA

Children's Hospital, France

Children's Hospital, Italy

Children's Hospital, Israel

Centro de Oncologia Infantil, Portugal

The International BMMRD Consortium

Dana Dwek Children's Hospital, Israel
Shlomi Cohen
Managing Obesity in Children: Lifestyle, Medications & Surgery

Joel Lavine, MD PhD
Professor and Vice-Chairman (Research)
Chief, Gastroenterology/Hepatology / Nutrition
Columbia University, New York

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
Identification of Children at Risk for Obesity - Infancy

“Fixed or unmodifiable”
- Genetic variation

Possibly Modifiable
- In utero “epigenetics”
- Low birth weight
- Diet
  - Breastfeeding 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

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Exposed, n</th>
<th>Obese, n (% of exposed)</th>
<th>Univariable analysis, OR (95% CI)</th>
<th>Adjusted model assessing no. of prescriptions, OR (95% CI)</th>
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<td>8761</td>
<td>480 (5.6)</td>
<td>1.09 (0.96-1.20)</td>
<td>1.57 (1.00-2.43)</td>
</tr>
<tr>
<td>3-5</td>
<td>4401</td>
<td>382 (8.7)</td>
<td>1.48 (1.25-1.71)</td>
<td>1.41 (1.20-1.65)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>1628</td>
<td>127 (7.8)</td>
<td>1.50 (1.25-1.81)</td>
<td>1.47 (1.19-1.82)</td>
</tr>
</tbody>
</table>

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

- 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

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

Cohen D. NEJM. 2012

deRuyter et al, NEJM. 2012

Sugared v Noncaloric Beverages

Impulse Marketing

Attributions of Responsibility for Addressing Childhood Obesity According to Political Ideology

Barr 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

**Approved Pharmaceuticals for Treatment of Obesity**

<table>
<thead>
<tr>
<th>Generic Drug (Commercial Name(s))</th>
<th>Mechanism of Action</th>
<th>Weight Loss (Pounds/Year)</th>
<th>Side Effects</th>
<th>Common Aromatic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenfluramine 100 mg/day</td>
<td>Non-selective serotonin reuptake inhibition</td>
<td>8-10</td>
<td>Nausea, constipation</td>
<td>Headache, dizziness, dry mouth, constipation</td>
</tr>
<tr>
<td>Dextrorphan 60 mg/day</td>
<td>Dopamine agonist</td>
<td>6-8</td>
<td>Nausea, constipation</td>
<td>Headache, dizziness, dry mouth, constipation</td>
</tr>
<tr>
<td>Orlistat 120 mg/day</td>
<td>Pancreatic lipase inhibitor</td>
<td>7-10</td>
<td>Gastrointestinal disturbances, constipation</td>
<td>Headache, dizziness, dry mouth, constipation</td>
</tr>
<tr>
<td>Vyvanse 30 mg/day</td>
<td>Norepinephrine reuptake inhibitor</td>
<td>5-8</td>
<td>Nausea, constipation</td>
<td>Headache, dizziness, dry mouth, constipation</td>
</tr>
</tbody>
</table>

**Studies on Orlistat in Children**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Dose</th>
<th>Study Population</th>
<th>Number of Patients</th>
<th>Baseline Weight (kg)</th>
<th>Week 12 Weight (kg)</th>
<th>Change (kg)</th>
<th>Change (kJ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paul et al. 2001</td>
<td>OL, PC</td>
<td>0.9 mg/kg</td>
<td>40-50% obese children</td>
<td>20</td>
<td>70</td>
<td>69</td>
<td>1</td>
<td>69</td>
</tr>
<tr>
<td>Proctor et al. 2004</td>
<td>OL, PC</td>
<td>0.9 mg/kg</td>
<td>40-50% obese children</td>
<td>20</td>
<td>70</td>
<td>69</td>
<td>1</td>
<td>69</td>
</tr>
<tr>
<td>Calle et al. 2004</td>
<td>OL, PC</td>
<td>0.9 mg/kg</td>
<td>40-50% obese children</td>
<td>20</td>
<td>70</td>
<td>69</td>
<td>1</td>
<td>69</td>
</tr>
<tr>
<td>Crespo et al. 2005</td>
<td>OL, PC</td>
<td>0.9 mg/kg</td>
<td>40-50% obese children</td>
<td>20</td>
<td>70</td>
<td>69</td>
<td>1</td>
<td>69</td>
</tr>
</tbody>
</table>
Hormonal Control of Appetite and Energy Regulation


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

76
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
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
Prognostic indicators for Enteral Autonomy

Pediatric Intestinal Failure Consortium (PIFCON) Outcomes

Impact of Length on Enteral Autonomy

N=171
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

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

Impact of NEC on Enteral Autonomy

P< 0.001


NEC is associated with increased likelihood to attain enteral autonomy

Kaplan-Meier Estimates

NEC
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

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
• Dietary fiber
  - Alter the balance of bacteria
  - Increases in Bifidobacteria and Lactobacilli
• Serves as an energy source for colonic bacteria
• Short chain fatty acids: butyrate, propionate and acetate
  - Increase epithelial cell proliferation
  - Decrease epithelial cell apoptosis

Stoisidis 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-acetylglucosamine
  - Fucose
  - N-acetyleneuraminic acid

HMO and their potential benefits

- Prebiotics
- Bacteriostatic, bactericidal antimicrobials
- Epithelial cell modulators
- Antiadhesives
- Immune cell modulators

Bode lab www.bodelab.com
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

Increased diversity in 2-FL supplementation after Ileocecal Resection

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

Dysbiosis and Short Bowel Syndrome

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*
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


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

Impact of SBBO

- N=10 NEC
  - 80% had bloodstream infection
  - 50% had SBBO
  - Increased the odds for a bloodstream 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=37 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

Kaufman et al. / Pedi 1997;131:556-61
Sondheimer et al. / Pedi 1998;27:130-7
Cole et al. / Pedi 2010;156:941-7

Fecal Microbiome in SBS

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

Phylum proteobacteria
- class gammaproteobacteria
  - Proteus
  - Klebsiella
  - Escherichia
  - Shigella

Davidevics et al. / JPEN 2015

Shannon Diversity Index in SBS patients on and off PN

Engstrand et al. / Microbiome 2015;3:15
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

Intestinal Microbiota Signatures associated with steatosis with IF

- N = 23 IF
- 3 predominant bacteria
  - Clostridium, Proteobacteria, Lactobacillus plantarum
- 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
Conclusion

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

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
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

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
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

SCFA-Producing Bacteria Suppress Potentially Pathogenic Intestinal Bacteria

De Filippo, et al, PNAS. 2010
Diet, Antibiotics, and Inflammation Independently Impact GI Microbiota

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. Influenza Bowel Dis 2015
**Fiber Intake and Crohn’s Disease Risk**


**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


**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

Seidman, et al. Gastroenterology (Abst) 1993
Zachos, et al. Cochrane Database 2007
Gupta, et al. Inflamm Bowel Dis 2013
Is Elemental Formula Better than Polymeric Formula?

Response to Dietary Therapy

Elemental  Non-elemental

**NO DIFFERENCE**

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


---

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)

**Induction Therapy with Partial Enteral Nutrition for Crohn’s Disease**

<table>
<thead>
<tr>
<th>N = 36</th>
<th>Week 0</th>
<th>Week 12</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBI</td>
<td>5.9 ± 2.7</td>
<td>0.75 ± 1.75</td>
<td>0.000</td>
</tr>
<tr>
<td>HBI, median (range)</td>
<td>6.0 (0-13)</td>
<td>0.9 (0-6)</td>
<td>0.000</td>
</tr>
<tr>
<td>PCDAI (n = 24)</td>
<td>25.7 ± 8.9</td>
<td>6.44 ± 8.07</td>
<td>0.000</td>
</tr>
<tr>
<td>CRP</td>
<td>2.3 ± 2.3</td>
<td>0.81 ± 0.64</td>
<td>0.002</td>
</tr>
<tr>
<td>ESR</td>
<td>25.7 ± 12.7</td>
<td>17 ± 8.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.0 ± 1.4</td>
<td>12.6 ± 1.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.8 ± 0.42</td>
<td>4.12 ± 0.39</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*Paired 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.*

---

**CHOP Enteral Nutrition Experience**

**Mean Change:**

**PCDAI Score**

Prior to Initiation

≥ 4 Weeks After Initiation

P < 0.0001

(n = 23)

-1.45

0.85

**Weight Z-score**

Prior to Initiation

≥ 4 Weeks After Initiation

P < 0.03

(n = 43)

-1.15

0.15

**CHOP Enteral Nutrition Experience**

**Mean Change:**

**ESR**

p < 0.0001

n = 43

32.48

21.08

**Albumin**

p < 0.03

n = 43

3.88

3.94

**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)

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

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, Ruminococcaceae)
  - Includes decrease in presumed protective bacteria (F. prausnitzii)
- While EEN does affect composition, need additional studies to look at associative vs. causative role
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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Before diet</th>
<th>1 week</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>36 weeks</th>
<th>48 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>10.2</td>
<td>9.8</td>
<td>9.5</td>
<td>9.3</td>
<td>9.1</td>
<td>8.8</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>Fructose</td>
<td>10.2</td>
<td>9.8</td>
<td>9.5</td>
<td>9.3</td>
<td>9.1</td>
<td>8.8</td>
<td>8.5</td>
<td></td>
</tr>
</tbody>
</table>

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

---

### Impact of Diet on the GI Tract

![Impact of Diet on the GI Tract](image)

- Adapted from Chan, et al. *Nutrition* 2015

---

*Specific Carbohydrate Diet in Crohn's* by Suskind, et al. JPGN 2014

**Nutrition** 2015 31, 1195-1203 DOI: (10.1016/j.nut.2015.04.018)
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
BIOSIMILARS in IBD

Lessons from our European Colleagues

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

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


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
Pharmacokinetic Profile; Planetas study

(Park et al, Ann Rheum Dis 2013)
ACR20 response rate at week 30
(intention to treat and per protocol)

<table>
<thead>
<tr>
<th>Treatment difference (%)</th>
<th>CT-P13</th>
<th>RX</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT Population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18%</td>
<td>60.9</td>
<td>56.6</td>
</tr>
<tr>
<td>18%</td>
<td>73.4</td>
<td>69.7</td>
</tr>
</tbody>
</table>

ITT Population vs. PP Population

Infliximab...

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

**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

ICH harmonised tripartite guideline of biotechnological/biological products subject to changes in their manufacturing process Q5E comparability 2004
Cross-immunogenicity

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

Shemonon Ben-Horin,1 Miri Yaacovi,2 Itai Benhar,2 Ella Fudim,7 Orit Pickard,7 Bella Ungar,7 SooYoung Lee,4 Sungkiwan Kim,5 Ramit Elakir,7 Yehuda Choovers4

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

Challenge 5:
Is it all about the money?

- Availability of biosimilars is expected to result in a substantial cost expenditure reduction
- Estimated around 30%
Anti tumour necrosis factor-α therapy is a major cost driver in IBD

Results: healthcare cost (adult IBD)
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

To summarise..

- Biosimilars infliximab have comparable efficacy 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)

Discontinuous disease
Deep ulcers in transverse colon and ileum (20 cm)
Small round and linear ulcers in stomach (+ve granuloma)

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

- Histological remission
- Mucosal (and transmural) healing
- Steroid-free remission
- Clinical remission
- Improved symptoms

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”
Discrepancy between symptoms and endoscopic appearance in Crohn’s disease!


Carman N al Canadian Children IBD Network CDDW 2015

What about ulcerative colitis?

Turton D et al. Gastroenterology 2007;133:423–432

Crohn’s disease: A progressive disease

Progression of digestive damage and inflammatory activity

Rate of progression varies between patients

Stricture and penetrating complications greater in ileal disease

Pariente et al. Inflamm Bowel Dis 2011;17:1415-1422
Association of mucosal healing with long-term clinical remission and avoidance of surgery: CD

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

Crohn’s disease
- Absence of ulcers?
- Absence of deep ulcers?
- SES-CD/ CDEIS definition of endoscopic remission?
- Deeper than mucosal... also MRE normalization?

Ulcerative colitis
- Mayo subscore 0?
- Mayo subscore 0 or 1?
- 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

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive LR</th>
<th>Negative LR</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>0.49</td>
<td>0.92</td>
<td>6.3</td>
<td>0.56</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>(0.34, 0.64)</td>
<td>(0.72, 0.98)</td>
<td>(1.9, 21.3)</td>
<td>(0.44, 0.71)</td>
<td></td>
</tr>
<tr>
<td>FCP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>0.88</td>
<td>0.73</td>
<td>3.2</td>
<td>0.17</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>(0.84, 0.90)</td>
<td>(0.66, 0.79)</td>
<td>(2.6, 4.1)</td>
<td>(0.14, 0.20)</td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>0.87</td>
<td>0.67</td>
<td>2.7</td>
<td>0.19</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>(0.82, 0.91)</td>
<td>(0.58, 0.75)</td>
<td>(2.1, 3.4)</td>
<td>(0.14, 0.27)</td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>0.88</td>
<td>0.79</td>
<td>4.2</td>
<td>0.15</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>(0.84, 0.92)</td>
<td>(0.68, 0.87)</td>
<td>(2.8, 6.4)</td>
<td>(0.11, 0.20)</td>
<td></td>
</tr>
</tbody>
</table>

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

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.

<table>
<thead>
<tr>
<th>FC (μg/g)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD remission vs. active at FC 50</td>
<td>55.2</td>
<td>98.9</td>
<td>97.0</td>
<td>77.4</td>
</tr>
<tr>
<td>IBD remission vs. active at FC 100</td>
<td>72.4</td>
<td>95.6</td>
<td>91.3</td>
<td>84.3</td>
</tr>
<tr>
<td>IBD remission vs. active at 250</td>
<td>88.7</td>
<td>75.6</td>
<td>71.3</td>
<td>91.9</td>
</tr>
</tbody>
</table>

FC: Faecal calprotectin, IBD: Inflammatory bowel disease, IBS: Irritable bowel syndrome, NPV: Negative predictive value, PPV: Positive predictive value.

Monitoring of known IBD

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

Monitoring for intestinal healing

Fecal calprotectin in monitoring for endoscopic recurrence following intestinal resection

Data from the POCER study
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](image)

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
  - Control/healing of intestinal inflammation to prevent future complications

- **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

- **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

Fernando Alvarez, MD
Professor of Pediatrics
University of Montreal
CHU Sainte-Justine

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*

![Diagram showing distribution of AIH, AIC, and PSC patients.]

**Histology of AIH, PSC and AIC**

![Histology images showing liver tissues.]

**Autoimmune Hepatitis in Children**

*Clinical features*

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Type 1 AIH</th>
<th>Type 2 AIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at onset</td>
<td>10 years</td>
<td>6.5 years</td>
</tr>
<tr>
<td>Females (%)</td>
<td>~75%</td>
<td>90%</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>4m (2w-24m)</td>
<td>2m (1w-16m)</td>
</tr>
<tr>
<td>Form of presentation (a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute hepatitis (%)</td>
<td>~45%</td>
<td>~50%</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>35%</td>
<td>30%</td>
</tr>
<tr>
<td>Others</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

(a) These percentages are obtained from previously published series.

[b] Including fulminant and subfulminant liver failure.

*Alvarez F. Clinics in Liver Disease, 2006;10:99-107*
Autoimmune Hepatitis in Children

Types of AIH

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Antigen</th>
<th>Type 1 AIH</th>
<th>Type 2 AIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA</td>
<td>Actin filaments</td>
<td>+ (90-100%)</td>
<td>–</td>
</tr>
<tr>
<td>ANA</td>
<td>Various</td>
<td>+ (0-10%)</td>
<td>±</td>
</tr>
<tr>
<td>SMA/ANA</td>
<td>–</td>
<td>+ (40-60%)</td>
<td>–</td>
</tr>
<tr>
<td>LKM1</td>
<td>Cytochrome P450 2D6</td>
<td>+ (40-50%)</td>
<td></td>
</tr>
<tr>
<td>LC1</td>
<td>Formiminotransferase</td>
<td>+ (10-15%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cyclodeaminase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASGP-R</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PSC images

AIC and PSC images
Autoimmune Liver Diseases

*Association with IBD*

<table>
<thead>
<tr>
<th></th>
<th>AIH</th>
<th>AIC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>4/60 pts (6.6%)</td>
<td>3/8 pts (37.5%)</td>
<td>19/26 pts (73%)</td>
</tr>
<tr>
<td>UC</td>
<td>1</td>
<td>3</td>
<td>UC or IC: 10</td>
</tr>
<tr>
<td>Crohn</td>
<td>3</td>
<td></td>
<td>Crohn: 9</td>
</tr>
</tbody>
</table>

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*

<table>
<thead>
<tr>
<th></th>
<th>AIH</th>
<th>AIC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>10.3</td>
<td>13.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Females (%)</td>
<td>70%</td>
<td>50%</td>
<td>42%</td>
</tr>
<tr>
<td>Jaundice (%)</td>
<td>50%</td>
<td>37.5%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Cirrhosis (%)</td>
<td>49%</td>
<td>43%</td>
<td>38.5%</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>42%</td>
<td>37.5%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Autoimmune Liver Diseases

Clinical features

<table>
<thead>
<tr>
<th>Biochemical features [mean (range)]</th>
<th>AIH</th>
<th>AIC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bi (μmol/l)</td>
<td>69.2 (2-115)</td>
<td>33.6 (6.78)</td>
<td>&lt;16 (6-200)</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>730 (87-4800)</td>
<td>261 (26-520)</td>
<td>130 (14-413)</td>
</tr>
<tr>
<td>GGT (IU/l)</td>
<td>79.0 (10-190)</td>
<td>177 (65-438)</td>
<td>344 (17-838)</td>
</tr>
<tr>
<td>Auto Abs (%)</td>
<td>90%</td>
<td>85%</td>
<td>65%</td>
</tr>
<tr>
<td>IgG (g/l)</td>
<td>30 (6.5-63)</td>
<td>24 (15.3-31)</td>
<td>17 (8.7-37)</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>32 (11-48)</td>
<td>38 (20-45)</td>
<td>37 (23-44)</td>
</tr>
<tr>
<td>INR</td>
<td>1.7 (1.0-5)</td>
<td>1.25 (0.9-1.8)</td>
<td>1.05 (0.9-1.2)</td>
</tr>
</tbody>
</table>

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).

• 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*

**Jaundice**

Total serum Bilirubin

<table>
<thead>
<tr>
<th></th>
<th>AIH</th>
<th>AIC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>1m</td>
<td>70</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>2m</td>
<td>60</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>3m</td>
<td>50</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>4m</td>
<td>40</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

---

**Autoimmune Liver Diseases**

*Prognosis*

**Parenchymal injury**

ALT

<table>
<thead>
<tr>
<th></th>
<th>AIH</th>
<th>AIC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>800</td>
<td>600</td>
<td>400</td>
</tr>
<tr>
<td>1m</td>
<td>700</td>
<td>500</td>
<td>300</td>
</tr>
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<td>2m</td>
<td>600</td>
<td>400</td>
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</tr>
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<td>3m</td>
<td>500</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>4m</td>
<td>400</td>
<td>200</td>
<td>0</td>
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</table>
Autoimmune Liver Diseases

Prognosis

### Bile ducts injury

<table>
<thead>
<tr>
<th>GGT (IU/l)</th>
<th>AIH</th>
<th>AIC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
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</tr>
</tbody>
</table>

### Liver failure

<table>
<thead>
<tr>
<th>Alb (g/l)</th>
<th>AIH</th>
<th>AIC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Liver-Immune-Inflammation

<table>
<thead>
<tr>
<th>IgG (g/l)</th>
<th>AIH</th>
<th>AIC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>129</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Autoimmune Liver Diseases

**Prognosis**

Liver transplantation

- OLT (15.4%)
- AIC
- AIH

**Type**

- OLT (22%)
- AIH Type 2
- PSC

- OLT (6%)

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.
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

\[c.5930-1G \rightarrow A\]

**JAG1 vs. NOTCH2 ALGS**

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

<table>
<thead>
<tr>
<th>Frequency of clinical findings (%)</th>
<th>Liver</th>
<th>Cardiac</th>
<th>Renal</th>
<th>Eye</th>
<th>Skeletal</th>
<th>Facies</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOTCH2 probands (N=10)</td>
<td>100</td>
<td>60</td>
<td>64</td>
<td>63</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>JAG1 probands (N=34)</td>
<td>100</td>
<td>100</td>
<td>64**</td>
<td>75</td>
<td>64</td>
<td>97</td>
</tr>
</tbody>
</table>

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

- Moyamoya
  - Moreau et al., 1999
  - Connor et al., 2002
- Internal carotid artery aneurysms
  - Woolfenden et al., 1999
  - Rachmel et al., 1989
- Subclavian artery anomalies
  - Quek et al., 2000
  - Cardillo et al., 1997
- Aneurysms
  - Quek et al., 2000
  - LaBrecque et al., 1982
- Hepatic & celiac artery anomalies
  - Nishikawa et al., 1987
- Renovascular & superior mesenteric anomalies
  - Berard et al., 1998
  - LaBrecque et al., 1982

Non-cardiac vascular anomalies or events accounted for 34% mortality: 9%

Kamath et al., Circulation 2004

Vasculopathy is Treatable in ALGS: Need to Look!

- 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

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

- 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

<table>
<thead>
<tr>
<th>Time Post-transplant</th>
<th>ALGS Patients</th>
<th>Non-ALGS Patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>4.5%</td>
<td>9.0%</td>
<td>0.004</td>
</tr>
<tr>
<td>1 year</td>
<td>4.5%</td>
<td>9.0%</td>
<td>0.004</td>
</tr>
<tr>
<td>2 years</td>
<td>4.5%</td>
<td>9.0%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

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,1,3,4 Devra Shapira,1 Paul Whiteman,3,4 Christian M. Karsten,4,14, Salley Al-Tilib Shamoun,5,14, Adam Laing,1 Laurence Bacchus,1 Marguerite J. Dallman,2,15, Margaret J. Dallman,6,15, Teresa Melchionna,7 Chandramouli Chillakuri,3, Richard A. Smith,1 Christian Drouet,7 Lionel Couzi,8 Veronique Fremeaux-Bacchi,9,10 Jörg Köhl,4,11, Simon M. Waddington,1 James M. McDonald1, Alexander Baker1,13, Penny A. Handford3,15, Susan M. Lea2, and Claudia Kemper1

Immune dysregulation in Alagille syndrome: A new feature

Le Friec et al., Nat Immun 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

Mouzaki et al, Liver Int 2016
Novel Therapy for ALGS: Chemical Diversion

ALGS: The Promise of Stem Cells
1. Clinical manifestations of ALGS are highly variable
   - Managed by Gastroenterologists but requires multisystem knowledge!
2. 7 potential organ systems involved – look for renal & vascular
3. Cholestasis stabilizes or improves in the majority – use predictive tools
4. Liver Transplantation is only required for 15-20% and renal sparing protocol necessary
5. 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


---

**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)

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

**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


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

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**
- **Abetalipoproteinemia**
- **Hypobetalipoproteinemia**
- **Chylomicron retention disease**
- **Neurogenin 3 mutations**
- **Intestinal lymphangiectasia**
- **Short-gut**
- **Giardiasis**
- **Gastric bypass surgery**
- **Glucagonoma or somatostatinoma**
**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.
Requires two of the following for diagnosis:
• Clinical symptoms and exam consistent with pancreatitis
• Serum amylase or lipase at least 3x the upper limit of normal
• Finding of acute pancreatitis on imaging

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

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

<table>
<thead>
<tr>
<th></th>
<th>Age&lt;5</th>
<th>Age 5-14</th>
<th>Age &gt;14</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of</td>
<td>2.66</td>
<td>10.03</td>
<td>17.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cases in 3</td>
<td>(2.57,2.75)</td>
<td>(10.43,10.62)</td>
<td>(17.95, 18.03)</td>
<td>years</td>
</tr>
</tbody>
</table>

Unpublished Data.
**Patient outcomes for pediatric patients with a principal diagnosis of AP**

<table>
<thead>
<tr>
<th>Age &lt;5</th>
<th>Age 5-14</th>
<th>Age &gt;14</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 1,279)</td>
<td>(n = 8,812)</td>
<td>(n = 18,692)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>10</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>(0.24%)</td>
<td>(0.22%)</td>
<td>(0.12%)</td>
<td></td>
</tr>
<tr>
<td>Length of Stay (days)</td>
<td>7.18 (6.34, 8.02)</td>
<td>5.79 (5.51, 6.07)</td>
<td>4.77 (4.65, 4.89)</td>
</tr>
<tr>
<td>Costs (US$)</td>
<td>$15,387 (12,672, 18,102)</td>
<td>$11,404 (10,575, 12,233)</td>
<td>$9,306 (8,955, 9,606)</td>
</tr>
</tbody>
</table>

Unpublished Data

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

Unpublished Data.

**Etiologies are distinct from adult pancreatitis**

Pie chart prepared by Lindsey Hornung

Enteral nutrition (EN) has an important role in AP management:
- Maintenance of the gut barrier function
- Inhibition of bacterial translocation
- Lowering systemic inflammatory response

There are limited studies on the optimal timing/nutritional interventions in pediatric AP. Adult literature suggests that early (within 24-72 hrs) EN results in more favorable outcomes:
- Mortality rate
- Multi-organ failure
- Length of stay

Early nutrition is safe, feasible, and is not associated with adverse outcomes in AP. Patients who received enteral feeds had similar pain scores compared to patients kept NPO. Figure shows that higher fat diet was associated with lower pain scores.

Are feeds feasible in pediatric AP? Is a low fat diet needed in AP??

Adult studies support early aggressive fluid resuscitation:
- Early resuscitated group: received >⅓ of administered 72 hr IVF volume within 24 hr
- Outcomes: SIRS, organ failure, ICU, LOS, death
- Early fluid resuscitation was associated with reduced SIRS and organ failure at 72 hr.

References:
- 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)


**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

**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

<table>
<thead>
<tr>
<th>Response Variable Pathway</th>
<th>A (n)</th>
<th>B (n)</th>
<th>C (n)</th>
<th>D (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early PO NPO (days)</td>
<td>20</td>
<td>30</td>
<td>55</td>
<td>96</td>
</tr>
<tr>
<td>Day 1 IVF volume</td>
<td>1.1 (1.91)</td>
<td>5.8 (9.98)</td>
<td>2.9 (2.4)</td>
<td>3.2 (3.2)</td>
</tr>
<tr>
<td>SAP Rate</td>
<td>26%</td>
<td>17%</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td>ICU Transfers</td>
<td>28%</td>
<td>10%</td>
<td>1.8%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Severe AP (SAP):
Respiratory 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.

---

**Could we have predicted SAP?**

Clinical Variables and Patient Demographics on Admission

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>NPO + IVF lo (a)</th>
<th>NPO + IVF hi (b)</th>
<th>PO + IVF lo (c)</th>
<th>PO + IVF hi (d)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>N</td>
<td>20</td>
<td>30</td>
<td>55</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>Male 9 (45%)</td>
<td>17 (56.7%)</td>
<td>31 (56.4%)</td>
<td>37 (38.5%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Age*</td>
<td>Mean (SD)</td>
<td>13.5 (4.92)</td>
<td>13.3 (4.3)</td>
<td>12.8 (4.73)</td>
<td>13 (4.28)</td>
<td>0.92</td>
</tr>
<tr>
<td>BMI pcc*</td>
<td>Mean (SD)</td>
<td>67.7 (28)</td>
<td>60.9 (37.8)</td>
<td>65 (34.3)</td>
<td>60.8 (34.4)</td>
<td>0.63</td>
</tr>
<tr>
<td>Lipase*</td>
<td>Mean (SD)</td>
<td>3139 (2982)</td>
<td>5634 (6045)</td>
<td>3926 (4963)</td>
<td>5670 (7803)</td>
<td>0.09</td>
</tr>
<tr>
<td>WBC*</td>
<td>Mean (SD)</td>
<td>13.6 (5.25)</td>
<td>13.3 (4.76)</td>
<td>9.89 (3.88)</td>
<td>11.3 (5.25)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**F. Szabo. et al J Pediatr. 2015**
**First Initiative to predict SAP in pediatrics**

*Acute Pancreatitis in Children*


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

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

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

Coffey. et al JPGN 2013.

73 cases of AP and 34% were classified as SAP

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

**SAP in pediatrics**

• Occurs in 15-30% depending on the definitions used

• Studies that looked at prediction of SAP, used variable definitions


Coffey. et al JPGN 2013.

Szabo. et al Pancreatology 2016.
SAP cases in pediatrics

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

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

<table>
<thead>
<tr>
<th>Predicted Score</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20</td>
<td>73%</td>
<td>66%</td>
</tr>
</tbody>
</table>

AUROC 0.76

Acute Recurrent (ARP) and Chronic Pancreatitis (CP)

- The natural history of progression of acute pancreatitis to acute recurrent pancreatitis and chronic pancreatitis remains unknown

- INSPIRE (International Study Group of Pediatric Pancreatitis: In search for a cure)
  - Developed criteria for pediatric AP, ARP and CP

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ARP within 3 months</th>
<th>No ARP within 3 months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration follow-up (days)</td>
<td>2.5 (1.5, 2.3)</td>
<td>1.0 (0.5, 2.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>API (units)</td>
<td>15.1 (10.7, 21.5)</td>
<td>15.1 (6.5, 17.5)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.1 (66.4, 92.0)</td>
<td>90.5 (76.4, 106.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.3 (158.9, 175.0)</td>
<td>170.5 (160.0, 184.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>86.3 (80.8, 92.2)</td>
<td>90.5 (82.0, 93.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>170.0 (163.0, 176.0)</td>
<td>178.0 (171.0, 184.0)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Laboratory Data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.2 (1.0, 1.2)</td>
<td>1.4 (1.2, 1.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>8.9 (6.9, 9.0)</td>
<td>9.9 (8.4, 12.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>Leukocyte count (cells/µL)</td>
<td>7.10 (5.15, 9.18)</td>
<td>8.82 (6.59, 9.94)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

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

---
**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.


**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'


**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


Role of Development of Pediatric FGIDs
Pediatric FGID Are Common

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


Infant regurgitation

Must include all 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
Infant rumination syndrome


- New population based study using Rome III showed prevalence of 1.9%

- Old conceptualization of infants relationships and development

Infant rumination syndrome
Must include all 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 all 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

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

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**

- Frequent regurgitation
- Abdominal distension
- Family history of allergy
- Cold foods

**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

**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

---

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

**CoMiSS**: awareness tool for cow's milk-related symptoms (Acta Paed 2015) needs still validation

°: Evidence only for L. Reuteri DSM 1938 (breastfed > formula fed)

**Improvement?**

- CMPA Support
  - Consider probiotic
  - Maintain support
  - Refer

**Improvement?**

- CMPA Support
  - Maintain support
  - Refer

---


Vandenplas Y, JPGN 2016
Responders
(50% reduction in crying time from baseline)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Event Total</th>
<th>Event Total</th>
<th>Risk Difference</th>
<th>Risk Difference</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. 1.1 M + 7 days</td>
<td>20 25</td>
<td>8 21</td>
<td>0.42 (0.16, 0.68)</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>II. 1.3 M + 14 days</td>
<td>24 25</td>
<td>13 21</td>
<td>0.14 (0.01, 0.50)</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>III. 1.4 M + 21 days</td>
<td>24 25</td>
<td>15 21</td>
<td>0.13 (0.04, 0.43)</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

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


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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Probiotic group (n = 84)</th>
<th>Placebo group (n = 82)</th>
<th>RR (95% CI)</th>
<th>NNT (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% CI)</td>
<td>Treatment effects (relative risk, 95% CI)</td>
<td>4.32 (9.07)</td>
<td>7.41 (16)</td>
<td>.009</td>
<td></td>
</tr>
</tbody>
</table>


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 Wessels'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.

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

Bowel frequency in different age groups (Range)

Functional diarrhea

Must include all 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)

2. Symptoms that last more than 4 weeks

3. Onset of symptoms that begins between 6 and 60 months of age

4. 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 one month of at least two 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
**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

<table>
<thead>
<tr>
<th>Contents</th>
<th>Forceful</th>
<th>Periodicity</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus, Undigested food</td>
<td>none to +</td>
<td>Episodic</td>
<td>Heartburn, Dysphagia, Respiratory Swallowing difficulties</td>
</tr>
<tr>
<td>Gastric, Partially digested food, liquid</td>
<td>+ to +++</td>
<td>Effortless volitional</td>
<td>Pain, retching, nausea</td>
</tr>
<tr>
<td>Small bowel, Liquid, bilious</td>
<td>+ to +++</td>
<td>Episodic cyclic</td>
<td>Pain, retching, nausea, distention</td>
</tr>
</tbody>
</table>

VOMITING

• Other factors present
  - Congenital malformations
    - Esophagus
    - Upper GI tract
  - Fundoplication
  - Inflammation
    - EOE, infections, ulcers
  - Extra-intestinal
    - Metabolic, RTA
IS THERE A MOTILITY DISORDER?

- Exclude anatomic obstruction
  - PE, x-ray, endoscopy
- Look for an etiology
  - Mucosal, metabolic, extraintestinal, drugs, psychological, transit
- Evaluate transit
  - Impedance, scintigraphy, markers, breath tests, smart pill
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
When compared with scintigraphy, the smart pill has a high sensitivity to detect gastroparesis.

**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

MOTILITY TESTING

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

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
Cough versus Rumination: You need impedance or you need to be there
Automated Impedance Manometry analysis (AIM)

Results

TREATMENT
Weak peristalsis
Cholinergic agent (eg Bethanechol)

TREATMENT
EGJ obstruction
Eg Botox, dilatation

Young adult asymptomatic controls
When compared with scintigraphy smart pill has a high sensitivity to detect gastroparesis and may be more sensitive than ADM to detect motor abnormalities.
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
    • Cyproheptadine
    • 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

Worse Same Better Much

p=0.02 p=0.4

• Vomiting is a symptom that requires careful evaluation
• May be associated with anatomic, motility or extra-intestinal 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.
Twitter: @carlodilorenzo1

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)
- Genetic predisposition, microbiome
- Visceral hyperalgesia
- Disability

Early life events

Sensitizing psychosocial events:
- Depression
- Anxiety
- Family stress
- Coping style

Pain Predominant FGID: what can we treat?

Sensitizing medical events:
- Inflammation (infection, allergies)
- Genetic predisposition, microbiome
- Visceral hyperalgesia
- Disability

Early life events

Sensitizing psychosocial events:
- Depression
- Anxiety
- Family stress
- Coping style

Pathophysiological components of IBS

Psychological/cognitive

Gut luminal/mucosal

Heightened sensorimotor activity

CNS

ENS

Symptoms

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
Pathophysiologic components of IBS:

- Psychological/cognitive
- Gut luminal/mucosal

Heightened sensorimotor activity → CNS

Severe Symptoms

Treatment: What do pediatric gastroenterologists do?

Medical treatment - 2009

Schurman et al, JPGN 2010;50: 32–37
Non-medical treatment - 2009

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

Medications: DBPC studies
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, Adhan Miranda, Carlo Di Lorenzo

Gastroenterology 2009;137:1261-9

<table>
<thead>
<tr>
<th>Overall Assessment</th>
<th>Intention To Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Failed</td>
<td>16%</td>
</tr>
<tr>
<td>Poor</td>
<td>11%</td>
</tr>
<tr>
<td>Fair</td>
<td>18%</td>
</tr>
<tr>
<td>Good</td>
<td>37%</td>
</tr>
<tr>
<td>Excellent</td>
<td>11%</td>
</tr>
</tbody>
</table>

* 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”?

- 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%


**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%

Probiotics in children with FGID: Summary

<table>
<thead>
<tr>
<th>Agent</th>
<th>Design</th>
<th>Sample size</th>
<th>Age (yr)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bausserman</td>
<td>DBPC</td>
<td>50</td>
<td>6-20</td>
<td>bloating</td>
</tr>
<tr>
<td>Gawrońska</td>
<td>DBPC</td>
<td>104</td>
<td>6-16</td>
<td>frequency of pain</td>
</tr>
<tr>
<td>Romano</td>
<td>DBPC</td>
<td>60</td>
<td>6-16</td>
<td>intensity of pain</td>
</tr>
<tr>
<td>Guandalini</td>
<td>DBPC- CO</td>
<td>64</td>
<td>4-18</td>
<td>global assessment of sx</td>
</tr>
<tr>
<td>Francavilla</td>
<td>DBPC</td>
<td>141</td>
<td>5-14</td>
<td>Frequency and severity of pain</td>
</tr>
</tbody>
</table>
Hypnotherapy in Children with FAP

Mean pain intensity score

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

Am J Gastroenterol 2012; 107:627–631
New kids on the block

Linaclotide (Linzess): Mechanism of Action

May 2015

Viberzi (eluxadoline) and Xifaxan (rifaximin)

FDA News Release

FDA approves two therapies to treat IBS-D

For Immediate Release

May 27, 2015

Update

The U.S. Food and Drug Administration today approved Viberzi (eluxadoline) and Xifaxan (rifaximin), two new treatments, manufactured by two different companies, for irritable bowel syndrome with diarrhea (IBS-D) in adult men and women.

According to the National Institutes of Health, collectively with irritable bowel syndrome (IBS) experience a number of signs and symptoms, including pain or discomfort in the abdomen and changes in bowel movement patterns. Studies estimate that IBS affects 10 to 20 percent of adults in the United States, affecting a population...
How does food cause GI symptoms?

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

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?

RDBC trial of 103 children (13±3 y) with IBS.

8 day diet excluding carbohydrates thought to cause symptoms of IBS.

Children with less than 75% improvement in abdominal pain continued in the study (n=85).

Randomly assigned to groups given psyllium (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.

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."

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)

\[ p<0.01 \] for SLCBT


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


Gastrointestinal Microbiome Signatures of Pediatric Patients With Irritable Bowel Syndrome

Using 16S 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?


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?