North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)

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

POSTGRADUATE COURSE SYLLABUS
8:00 – 9:20 Module 1 – Endoscopy
Don’t worry, be happy: High risk patients for pediatric endoscopy
*Jenifer Lightdale MD, MPH, UMass Memorial Children’s Medical Center*

Once more unto the breach: The role of small bowel enteroscopy in pediatrics in 2018
*R. E. Kramer MD, FASGE, Children’s Hospital Colorado*

The complicated colonoscopy
*Rene Gomez-Esquível MD, University of South Florida*

Endoscopic management of pancreatic and biliary disease: ERCP and EUS
*Victor L. Fox MD, FAAP, FASGE, Boston Children’s Hospital*

9:20 – 10:40 Module 2 – Inflammatory Bowel Disease
When it just won’t stop: The management of acute severe steroid refractory colitis
*Thomas Walters MBBS, MSc, FRACP, Hospital for Sick Children*

Precision medicine approach in VEO-IBD
*Judith R. Kelsen MD, Children’s Hospital of Philadelphia*

Treat-to-target in pediatric IBD: What are the treatments and the targets?
*Eric Benchimol MD, PhD, FRCPC, Children’s Hospital of Eastern Ontario IBD Centre*

10:40 – 12:00 Module 3 – GI Potpourri
Gastrointestinal problems in autism spectrum disorders
*Kara Gross Margolis MD, Columbia University*

Weight management surgery: Indications and complications
*Rohit Kohli MBBS, MS, Children’s Hospital Los Angeles*

Screening and follow up of intestinal failure: Bringing up the grades of your intestinal failures
*Conrad R. Cole MD, MPH, MSc, Cincinnati Children’s Hospital Medical Center*

EoE: New guidelines
*Glenn Furuta MD, Children’s Hospital Colorado*

1:40 – 3:20 Module 4 – Liver/Pancreas
Immune mediated acute liver failure in childhood: Is it the real deal or fake news
*Estella M. Alonso MD, Ann and Robert H. Lurie Children’s Hospital*

New genetic discoveries in neonatal liver disease (genetic liver disease)
*Stephen L. Guthery MD, University of Utah*

Treating hepatitis B & C in children: What’s new?
*Philip Rosenthal MD, FAAP, University of California San Francisco*

Nutritional management of pediatric pancreatitis
*Veronique D. Morinville MDCM, FRCPC, Montreal Children’s Hospital, McGill University*
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Jaime Belkind-Gerson MD, Children’s Hospital Colorado

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Miranda van Tilburg PhD, Campbell University, University of North Carolina, University of Washington

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Rachel Rosen MD, Boston Children’s Hospital

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

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

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

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

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

Satisfactory Completion
For MOC credit, learners must pass the post-test with a score of 60% or higher and complete an evaluation form to receive a certificate of completion.
If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

Nurses
In support of improving patient care, this activity has been planned and implemented by Amedco LLC and NASPGHAN. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.
Amedco LLC designates this live activity for a maximum of 8 contact hours for nurses. Learners should claim only the credit commensurate with the extent of their participation in the activity.

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

8:00am – 8:20am
Don’t worry, be happy: High risk patients for pediatric endoscopy
Jennifer Lightdale MD, MPH, UMass Memorial Children’s Medical Center
Learning objectives:
1. Define high-risk pediatric patients undergoing GI procedures
2. Discuss pre-operative preparation as a means to mitigate risk
3. Identify practices which may increase safety during endoscopy in high risk patients

8:20am – 8:40am
Once more unto the breach: The role of small bowel enteroscopy in pediatrics in 2018
Robert Kramer MD, Children’s Hospital Colorado
Learning objectives:
1. Outline the various tools currently available for imaging the small bowel in children
2. Review the indications, methods and outcomes of pediatric enteroscopy
3. Discuss effective integration of videocapsule endoscopy and enteroscopy into clinical practice
4. Consider future directions in small bowel imaging

8:40am – 9:00am
The complicated colonoscopy
Rene Gomez-Esquivel MD, University of South Florida
Learning objectives:
1. Compare the different endoscopic techniques to be able to navigate difficult colons
2. Select the appropriate instrument in the management of large polyps
3. Choose the appropriate technique to manage procedural complications

9:00am – 9:20am
Endoscopic management of pancreatic and biliary disease: ERCP and EUS
Victor Fox MD Boston Children’s Hospital
Learning objectives:
1. Understand the role of ERCP in the management of biliary tract obstruction and leaks
2. Recognize the potential benefits and limitations of endoscopic therapy for chronic pancreatitis
3. Know when EUS can be used to assist or replace surgical interventions

Module 2 – Inflammatory Bowel Disease
Moderators: Maria Oliva-Hemker MD and Jeanne Tung MD

9:20am – 9:40am
When it just won’t stop: The management of acute severe steroid refractory colitis
Thomas Walters MD, Hospital for Sick Children
Learning objectives:
1. Discuss the various standard therapies currently available for treating pediatric ACS and the paradigms for their use
2. Understand the importance of pathophysiological mechanisms when making therapy choices in ACS
3. Recognize the potential risks of sequential medical therapy and the implications for surgery and surgical timing
4. Appreciate the evolving data regarding the pharmacokinetics and pharmacodynamics of anti-TNF agents and the ramifications for ACS therapy approaches
9:40am – 10:00am

Precision medicine approach in VEO-IBD

Judith Kelsen MD, Children’s Hospital of Philadelphia

Learning objectives:
1. To learn about the unique genetics of VEO-IBD and the new candidate genes that may be causative for disease
2. To review the collaborative approach used to deliver targeted therapy to patients with VEO-IBD
3. To review the how the identified genes result in the individual phenotypes of VEO-IBD through a translational approach

10:00am – 10:20am

Treat-to-target in pediatric IBD: What are the treatments and the targets?

Eric Benchimol MD, Children’s Hospital of Eastern Ontario

Learning objectives:
1. Define Treat-to-Target and our goals for therapy in pediatric IBD in 2018
2. Review the latest evidence for better outcomes using a Treat-to-Target strategy
3. Determine the best ways to achieve our targets for the treatment of children with IBD

10:20AM – 10:40am

Break

Module 3 – GI Potpourri

Moderators: Jennifer Strople MD and Elizabeth Yu MD

10:40am – 11:00am

Gastrointestinal problems in autism spectrum disorders

Kara Gross Margolis MD, Columbia University

Learning objectives:
1. Learn the prevalence and common types of presentations of GI problems in ASD
2. Recognize common presentations of GI distress in ASD
3. Answer common GI-related questions from parents of children with ASD

11:00am – 11:20am

Weight management surgery: Indications and complications

Rohit Kohli MBBS, MS, Children’s Hospital Los Angeles

Learning objectives:
1. To understand the latest data regarding impact of obesity and its related gastroenterological co-morbidities including fatty liver disease in children and adolescents
2. To understand the basic mechanisms by which surgical interventions for obesity work
3. To recognize indication and complications of common surgical weight loss procedures in use for adolescents with obesity

11:20am – 11:40am

Screening and follow up of intestinal failure: Bringing up the grades of your intestinal failures

Conrad Cole MD, MPH, MSc, Cincinnati Children’s Hospital

Learning objectives:
1. Define intestinal failure and identify associated causes
2. Design an acceptable monitoring plan for patients with intestinal failure
3. Develop management strategies to improve outcomes including prevention of nutritional deficiencies during shortages of PN components and transition to enteral autonomy

11:40am – 12:00pm

EoE: New guidelines

Glenn Furuta MD, Children’s Hospital Colorado

Learning objectives:
1. Identify diagnostic approach to patient with suspected eosinophilic esophagitis
2. Identify role of proton pump inhibitor in evaluation and treatment of esophageal eosinophilia
3. Recognize findings of AGREE (A working Group on ppi-REE) Conference

12:10pm – 1:35pm  PG Course Learning Lunches

1. The complicated endoscopy
Moderator: Marsha Kay MD
Jenifer Lightdale MD and Rene Gomez-Esquivel MD

2. Medical and psychological treatment of vomiting
Moderator: Maria Perez MD
Katja Kovacic MD and Miranda Van Tilburg PhD

3. Management of irritable bowel syndrome
Moderator: Iona Monteiro MD
Jaime Belkind-Gerson MD and Desale Yacob MD

4. Treat to target
Moderator: Jeanne Tung MD
Eric Benchimol MD and Peter Church MD

5. Severe acute colitis
Moderator: Terry Sigman MD
Thomas Walters MD and Nicholas Carman MD

6. Nutritional and medical management of complicated pancreatitis
Moderator: Gary Galante MD
Veronique Morinville MD, Victor Fox MD and Mirta Rios RDN, CSP, LDN

7. Evaluation and management of the patient with liver failure
Moderator: Henry Lin MD
Estella Alonso MD and James Squires MD

8. EoE: Complicated cases
Moderator: Emily Hon MD
Glenn Furuta MD and Amanda Muir MD

9. Weight management: Medical and surgical approaches
Moderator: Nadia Ovchinsky MD
Rohit Kohli MBBS, Jennifer Woo Baidal MD and Jennifer Crouse MS, RD, CD, CDE
Module 4 – Liver/Pancreas
Moderators: Jennifer Strople MD and Henry Lin MD

1:40pm – 2:00pm
Immune mediated acute liver failure in childhood: Is it the real deal or fake news
Estella Alonso MD, Ann and Robert H. Lurie Children’s Hospital
Learning objectives:
1. Recognize the phenotype of Pediatric Acute Liver failure with immune dysregulation and distinguish from autoimmune hepatitis with liver failure
2. Interpret immunologic biomarkers to determine level of immune activation in patients with PALF
3. Predict outcomes of patients with PALF based on the level of immune activation

2:00pm – 2:20pm
New genetic discoveries in neonatal liver disease (genetic liver disease)
Stephen Guthery MD, University of Utah
Learning objectives:
1. Review inheritance
2. Review what is in genetic lab reports
3. Review what exome sequencing is and why it is important to the clinician
4. Review new causes of liver disease

2:20pm – 2:40pm
Treating hepatitis B & C in children: What’s new?
Philip Rosenthal MD, FAAP, University of California San Francisco
Learning objectives:
1. To understand treatment options for children with chronic hepatitis B
2. To understand treatment options for children with chronic hepatitis C
3. To be aware of current treatment trials for children with chronic hepatitis B or C

2:40pm – 3:00pm
Nutritional management of pediatric pancreatitis
Veronique Morinville MD, Montreal Children’s Hospital
Learning objectives:
1. Review different feeding regimens, including supportive literature, in the management of pediatric acute pancreatitis
2. Discuss the limited evidence for dietary modifications in children with acute recurrent pancreatitis
3. Develop an approach to nutritional assessment and management of children with chronic pancreatitis

3:00pm – 3:20pm
Break

Module 5 - Functional/Motility disorders
Moderators: Maria Oliva-Hemker MD and Iona Monteiro MD

3:20pm – 3:40pm
Novel therapies for cyclic vomiting syndrome
Katica Kovacic MD, Medical College of Wisconsin
Learning objectives:
1. Know how to diagnose CVS based on NASPGHAN consensus guidelines and Rome IV criteria
2. Know the four aspects of successful CVS management
3. Learn about novel therapies
3:40pm – 4:00pm  Surgical intervention for functional disorders (top to bottom)
Jaime Belkind-Gerson MD, Children’s Hospital Colorado
Learning objectives:
1. To understand the current indications for performing a cecostomy or ACE for anterograde colonic enemas
2. To be aware of current success and complication rate of gastric and sacral electrical stimulation
3. To learn the latest evidence of sensitivity and specificity for colonic manometry in colonic dysmotility
4. To understand current status on “the very dilated rectum”. When is its resection indicated?

4:00pm – 4:20pm  Integrating hypnotherapy and CBT into medical treatment of functional disorders
Miranda van Tilburg PhD, Campbell University, University of North Carolina, University of Washington
Learning objectives:
1. Explore how physicians can integrate psychological therapies in their care for functional disorders
2. Differentiate the goals, content and efficacy of hypnotherapy and CBT for functional disorders
3. Identify and find solutions for common problems in referring for psychological treatments for functional disorders

4:20pm – 4:40pm  Reflux: New guidelines
Rachel Rosen MD, Boston Children’s Hospital
Learning objectives:
1. To understand the role and limitations of medical and surgical therapies for GERD
2. To discuss the strengths and limitations of diagnostic testing to diagnose GERD in children
3. To discuss controversies over the definition of GERD and the implications for the patient
Endoscopy in the High-Risk Patient

Jenifer R. Lightdale, MD, MPH, FAAP
Division Chief, Pediatric Gastroenterology
UMass Memorial Children’s Medical Center
Professor of Pediatrics
University of Massachusetts Medical School

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  -- Mead Johnson – Speaker/Honorarium
  -- Abbvie – Investigator/Research Grant

• I do not intend to discuss an unapproved/investigative use of a commercial product/device in this presentation.

Objectives

• Define high risk pediatric patients undergoing GI procedures
• Discuss pre-operative preparation as a means to mitigate risk
• Identify practices which may increase safety during endoscopy in high risk patients
Background

- Major adverse events during pediatric GI procedures are rare
  - Cardiopulmonary
  - Bleeding
  - Perforation
  - Infection
- High risk patients for pediatric endoscopy are children with co-morbidities that place them at increased risk for these rare events
  - Across all or a subset of procedures

Safety of Pediatric GI Procedures

- Peds-CORI data from >10,000 procedures provides overall rate of intra-procedural adverse events
  - EGDs 2.3%
  - Colonoscopy 1.1%
- Colorado Children’s Hospital reported a post-procedural AE rate 2.6%
  - Fever, abdominal pain, chest and throat pain
  - Concerns for infection and/or perforation

Cardiopulmonary

- Sedation complications account for ~60% of all AEs during pediatric GI procedures
  - i.e. Risk of hypoxia 1.5% vs. bleeding 0.3%
- Range from minor to major
  - Transient oxygen desaturation
  - Aspiration
  - Respiratory arrest
  - Shock
  - Myocardial infarction

Thakkar, GIE 2007; Thakkar, CGH 2008; Kramer, JPGN 2016

Ben-Menachem, GIE 2012
Cardiopulmonary

- Examples of pediatric populations at increased risk for cardiopulmonary events
  - Congenital Heart Disease
  - Pulmonary Hypertension
  - Cystic Fibrosis
  - Muscular Dystrophy
  - Infants < 1 year of age
  - Obesity
  - Children with URIs

- Underlying conditions
  - Compromised cardiopulmonary function
  - Decreased FEV-1

Thakkar, GIE 2007; Lightdale, GIE 2014; Gilger, Curr Gil Rep 2005

Cardiopulmonary

- Patients with difficult airways due to congenital or acquired abnormalities
  - Pierre Robin syndrome
  - Treacher Collins’ syndrome
  - Laryngeal atresia
  - Craniofacial abnormalities
- Anatomic variations
  - Large tongue
  - Highly arched or narrow palate
  - Short, thick neck
  - Prominent overbite
  - Limited ROM of neck

http://healthlineinfo.com

Cardiopulmonary

- Down Syndrome
  - Macroglossia
  - Hypotonia
  - Atlanto-occipital instability
- Acquired chronic lung diseases
  - Recurrent aspiration
  - Aerodigestive disorders
- Medications which can potentiate cardio-pulmonary risks
  - Anti-seizures
  - Psychotropic
  - Opioids
  - Benzodiazepines

http://healthlineinfo.com
Bleeding

• Rare during diagnostic procedures (0.3-0.43%)
  – Advancing the scope
  – Obtaining biopsies
• Intraluminal vs. intramural (hematomas)
  – Duodenum
  – Sigmoid Colon
• More common with therapeutic maneuvers
  – Dilation
  – Hemostasis
  – Polypectomy
• ERCP in children reported to have 1.4% rate of “serious” bleeding

[Thakkar, GIE 2007; Thakkar, CGH 2008; Enesvedt, JPGN 2013]

Bleeding

• More likely in patients with
  – Thrombocytopenia
  – Poor platelet function
  – Coagulopathy
  – Use of anti-thrombotic medications
• Examples of pediatric populations at increased risk of bleeding during GI procedures
  – Stem cell transplant recipients
  – End stage liver disease
  – Kidney failure/uremia
  – Patients being treated with anticoagulants
  – Patients with clotting disorders
  – Advanced Cystic Fibrosis

Bleeding

• Anti-thrombotic guidelines for adults (scarce pediatric data)*
  – “Higher” vs. “lower” risk for bleeding
• Elective procedures
  – Defer until therapy complete (i.e. warfarin for DVTs)
  – Vs. change to low-molecular weight heparin
• Low-risk procedures
  – OK to continue clopidogrel or ticlopidine
• All procedures
  – OK to continue Aspirin or NSAIDs

[Anderson, G IE 2009]
Perforation

- Rare during diagnostic procedures (0.06-.3%)
  - Can occur with instrumentation
- Large vs. small
  - Shaft of scope vs. tip
- Excessive air insufflation
  - Not described in children
- Immediate presentation (visualization of extraintestinal structure during endoscopy) vs. delayed (abdominal pain, tenderness after waking)

Peter B. Cotton, 1980:
“The view is decidedly odd when the instrument actually penetrates the organ…”

Photos courtesy of Boston Children’s Hospital

Perforation

- At risk patients have decreased mucosal wall thickness and/or strength
  - Inflammation
  - Connective tissue changes
- Examples of pediatric populations at increased risk
  - History of caustic ingestion
  - Esophageal atresia/tracheo-esophageal fistula
  - Severe IBD
  - Patients with intestinal strictures
  - Primary and secondary (SMA syndromes, Hirschsprung’s disease, etc) pseudo-obstruction with dilation
  - Epidermolysis bullosa
  - Ehlers-Danlos Syndrome (Vascular Type)
Ehlers-Danlos Syndrome

- Group of hereditary connective tissue diseases
  - 6 subtypes, all with defective collagen fibers
  - 1 in 5,000 live births
  - Abnormalities of joints, skin and connective tissue
- Vascular type (a.k.a. Type IV)
  - 5% of EDS
  - Autosomal Dominant vs. sporadic (COL3A1)
  - High risk of spontaneous and iatrogenic perforation and bleeding – most often in children and teens
  - Especially in the colon – contains high amount of collagen
  - GI procedures and surgery should be only performed if necessary and with extreme caution

Infection

- Result from the procedure and/or from use of contaminated instruments
  - Endogenous vs. exogenous transmission
- Minor vs. major infectious disease
  - Transient bacteremia
  - Septic shock
  - Seeding of valves, shunts and/or other devices
- Patients at higher risk
  - Neutropenic (absolute or functional)
  - Asplenics
  - Cirrhotics
  - Those on immunosuppressive medications
  - Those with medical implants
Infection

• Rates of transient bacteremia after diagnostic procedures in adults 4%
  – Vs. typical ADLs (i.e. Chewing food (7-51%), tooth brushing and flossing (20-40%)
• Rates of exogenous transmission extremely rare (1/1.8 million procedures)
  – ERCP outbreaks with New Delhi metallo-B-lactamase E. Coli and carbapenem-resistant Enterobacteriaceae

Khasab, GIE 2015; Wilson, Circ 2007; Epstein, JPGN 2014

Infection

• Patients at risk for endocarditis
  – Particularly from enterococci

Wilson, GIE 2015; Wilson, Circ 2007

Infection

• Because of low rates, AHA/ASGE no longer broadly recommend antibiotic prophylaxis prior to endoscopic procedures
• Instead, “context matters”
  – BOTH patient and procedural

Khasab, GIE 2015; Wilson, Circ 2007
Pre-procedure Assessment

- Means of mitigating risk
- Lends itself to a checklist – integrated with procedure scheduling
- Essential to planning
  - Location of procedure (i.e. Main Operating Room vs. Dedicated Procedure Unit)
  - Type of sedation (Anesthesiologist vs. Endoscopist administered)
  - Goals of procedure (Diagnostic vs. Therapeutic)
Pre-procedure Assessment

Goals of Pre-procedural Assessment

1. Identification of procedural risk factors
   - History
   - Medications
   - Labs
   - Implants
2. Consultation and communication with other specialty physicians, if necessary
3. Optimization of patient's physiologic condition prior to procedure
4. Reduction of anxiety through education
5. Personalization of informed consent
6. Formulation and communication of sedation/anesthesia plan

ASA Classification

American Society of Anesthesiologists (ASA) suggestion for non-anesthesiologist classification of patient's physical status:

<table>
<thead>
<tr>
<th>ASA Class</th>
<th>Physical Status</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Normal healthy patient</td>
</tr>
<tr>
<td>2</td>
<td>Patient with mild systemic disease</td>
</tr>
<tr>
<td>3</td>
<td>Patient with severe systemic disease</td>
</tr>
<tr>
<td>4</td>
<td>Patient with severe systemic disease that is a constant threat to life</td>
</tr>
<tr>
<td>5</td>
<td>Moribund patient not expected to survive without emergent procedure</td>
</tr>
</tbody>
</table>

- Classes 1,2 - Moderate Sedation (MS)
- Class 3 - Careful evaluation/decision
- Classes 4,5 - General Anesthesia (GA)
Caveats of ASA Classification

- Higher ASA class has been associated with increased risk of adverse events*
  - Useful in endoscopic risk stratification**
- Crude patient categories that don’t (can’t) capture complex clinical scenarios
- Should be viewed in context of other risk factors
  - Airway
  - Cardiac
  - Bleeding
  - Immune status

Anesthesiologists may label more patients as ASA II*

- Consider reflux in decision making
- Reflux NOT a systemic disease

Mallampati Airway Classification

- Mallampati, Anesth 1987

Thakkar, GIE 2007; Enestvedt, JPGN 2013

Lightdale, JPGN 2005
Mallampati Airway Classification

- Should be performed in sitting position
- Do not have pt say “Ah” (falsely improves results)
- Not entirely predictable

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Soft palate, uvula, A&amp;P tonsillar pillars visible</td>
</tr>
<tr>
<td>II</td>
<td>Soft palate, uvula visible</td>
</tr>
<tr>
<td>III</td>
<td>Soft palate, base of uvula visible</td>
</tr>
<tr>
<td>IV</td>
<td>Soft palate (and uvula) not visible at all</td>
</tr>
</tbody>
</table>

Mallampati, Anesth 1985; Agostoni, GIE 2011

Thrombocytopenia

- Minimum threshold platelet count for the performance of diagnostic GI procedures in children is not established
- Khan et al. evaluated children s/p SCT with platelets >50,000/mL
  - Risk of bleeding requiring transfusions 4%
  - Duodenal hematoma 2%
- Current recommendations*
  - EGD ok if platelets >20,000/mL
  - Biopsies ok if platelets >50,000/mL

Khan, GIE 2006; Ben-Menachem, GIE 2012

Pre-procedural Preparation for Patients at High Risk of Bleeding

- Check CBC/INR prior to procedure
  - Only in risky situations, not routinely in all patients
  - Neutropenia, elevated INR – safe for diagnostic procedures BUT proceed with caution!
  - INR 1.4-1.7 for therapeutic procedures
- Correct coagulopathy as much as possible prior to procedure
  - Reverse anti-coagulation
  - Vitamin K
- Consult hematology for patients with factor deficiencies/clotting disorders
  - Discuss with blood lab regarding specific Factors ($$$)

Giles, Endoscp 2006; Coates, J Ped Surg 2011; Baron, NEJM 2013.
### Pre-procedural Preparation for Patients at High Risk of Bleeding

- Alert and consult general surgeons
- Type and Cross for blood products
- Have in OR vs. “on-call”
  - PRBC
  - FFP
  - Platelets
  - Recombinant activated factor VII

*Coates, J Ped Surg 2011*

### Procedural Factors that Increase Risks

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Potential Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty intubating the esophagus</td>
<td>Cardiopulmonary</td>
</tr>
<tr>
<td>Prolonged procedures</td>
<td>Bleeding/Perforation</td>
</tr>
<tr>
<td>Liberal insufflation with air</td>
<td></td>
</tr>
<tr>
<td>Instrumentation</td>
<td></td>
</tr>
<tr>
<td>Blind advancing of scope or instrument</td>
<td></td>
</tr>
<tr>
<td>Creation of stomas for enteral tube placement</td>
<td>Infection</td>
</tr>
<tr>
<td>Therapeutic variceal sclerosis</td>
<td></td>
</tr>
</tbody>
</table>

*Ben-Menachem, GIE 2012*

### Perforation during Colonoscopy*

- **Shaft-induced**
  - Result from “big loops”
  - Usually larger than expected
  - Located on the anti-mesenteric wall
- **Tip-induced perforation**
  - “Sliding by” technique (a.k.a. red out – loss of lumen)
- **Excessive air pressure perforation**
  - Not described in children
  - >169 mm Hg in the sigmoid vs. >81 mm Hg in the cecum
  - Beware trying to bypass a stricture
  - Can create an intermittent obstruction, with accumulation of upstream and increased hydrostatic pressure
  - More common in left colon

*Gershman and Ament, Practical Pediatric Gastroenterology, 2007*
Decreasing Risk of Perforation

- Avoid blind intubation of the lumen
  - Colonoscopy
  - Upper endoscopy
- Avoid excessive pressure
  - Advancing forward
  - Forcefully withdrawing
  - Imbedding the tip
- Avoid excessive air insufflation
  - CO₂ may be safer in high risk situations
- Avoid premature cutting of a polyp
  - Coagulate before cutting

“Special features” of the Duodenum*

<table>
<thead>
<tr>
<th>Organ</th>
<th>Wall thickness on CT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>3 - 5</td>
</tr>
<tr>
<td>Duodenum</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Colon</td>
<td>&lt;3</td>
</tr>
</tbody>
</table>

- The third portion of the duodenum
  - relatively fixed retroperitoneal position
  - adjacent to the lumbar spine
  - particularly rich submucosal vascular plexus

Gershman and Ament, *Practical Pediatric GI Endoscopy* 2007


http://intranet.tdmu.edu.ua
Duodenum as a “Set up” for Bleeding

• More prone to shear injury when force is applied
• Extending biopsy forceps > 2-3 cm beyond the tip of the endoscope to grasp the mucosa
  – Might increase risk...
  – May tent the mucosa up to the biopsy channel
  – Can cause the mucosa to strip away from the immobile wall beneath it

Post-biopsy Duodenal Hematoma

• 18 published cases of duodenal hematoma after biopsy
  – 14 with no bleeding risk factors
  – 4 SCT patients
• Complication noted mainly in children
  – Mean age was 11.7 ± 1.2 (range 5-23) yrs
• Clinical presentation severe abdominal pain and vomiting s/p EGD with biopsy
  – Obstruction from hematoma
  – Acute pancreatitis

Photos courtesy of Boston Children’s Hospital
Decreasing Risks of Infection

• Follow recommendations of the AHA SBE Prophylaxis Guidelines
  — Consult with pediatric cardiology
• Single-dose cephalexin has been shown to decrease peristomal infection during PEG placement
• Prophylactic antibiotics recommended for cirrhotic patients admitted with GI hemorrhage

Future Directions

• Develop guidelines for pediatric populations at high risk for complications during GI procedures
  — Evidence-based
• Further identify practices which may increase safety during endoscopy

Take Home Messages

• Keep patients safe by assessing them with respect to inherent risks of endoscopy
  — Weigh goals of procedure against any medical conditions which may increase likelihood of adverse events
• Employ a standardized risk assessment as part of routine procedural scheduling
  — Communicate with all appropriate providers prior to procedure, especially anesthesiologists
• Utilize pre-procedure checklists
• Avoid performing endoscopy and/or associated instrumentation blindly or imprudently
Thank you!

“Do or do not... there is no try.”

Master Yoda
Once More Unto the Breach:
The Role of Small Bowel Enteroscopy in Pediatrics in 2018

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Director of Endoscopy
Digestive Health Institute
Children’s Hospital Colorado/ University of Colorado

FINANCIAL DISCLOSURE

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

OBJECTIVES

• Outline the current tools available for device-assisted enteroscopy (DAE) of the small bowel in children
• Review the indications, methods and outcomes of pediatric enteroscopy
• Discuss effective integration of videcapsule endoscopy and enteroscopy into clinical practice
• Consider future directions in small bowel imaging
TIMELINE

METHODS OF DEVICE-ASSISTED ENTEROSCOPY

<table>
<thead>
<tr>
<th>Method</th>
<th>OD (mm)</th>
<th>Smallest Reported Pt</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Push Enteroscopy</td>
<td>9.7</td>
<td>9.8</td>
<td>- No additional equipment needed</td>
<td>- Limited depth of insertion</td>
</tr>
<tr>
<td>(Olympus PCF PH190L/I)</td>
<td>11.7</td>
<td>11.5</td>
<td>- Uses standard instruments</td>
<td>- Shallow learning curve</td>
</tr>
<tr>
<td>(Olympus PCF H190L/I)</td>
<td>12.0</td>
<td>11.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Fuji EC 600 LS)</td>
<td>12.2</td>
<td>12.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Pentax EC 2990Li)</td>
<td>9.8</td>
<td>9.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spiral Enteroscopy</td>
<td>9.5</td>
<td>9.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo-Ease Discovery 16</td>
<td>Not reported in Peds</td>
<td>Little capital investment</td>
<td>Moderate learning curve</td>
<td>Large size, More off the market, Large size, Not as deep insertion as DBE, Need longer instruments</td>
</tr>
<tr>
<td>Single Balloon Enteroscopy (DBE)</td>
<td>Scope 9.2</td>
<td>13.5 kg</td>
<td>May not need to change endoscope system</td>
<td>Good depth of insertion</td>
</tr>
<tr>
<td>(Olympus 1290)</td>
<td>Outer: 12.2</td>
<td>12.2</td>
<td>Somewhat easier than DBE</td>
<td></td>
</tr>
<tr>
<td>(Olympus 1290)</td>
<td>Scope 8.5</td>
<td>13.5 kg</td>
<td>May need additional endoscopy system</td>
<td></td>
</tr>
<tr>
<td>(Olympus 1290)</td>
<td>Outer: 12.2</td>
<td>12.2</td>
<td>Smaller diameter balloon system</td>
<td></td>
</tr>
<tr>
<td>(Fuji EN-410PS)</td>
<td>7.92 kg</td>
<td>7.92 kg</td>
<td>May need additional endoscopy system</td>
<td></td>
</tr>
</tbody>
</table>

GENERAL PRINCIPLES/ PUSH ENTEROSCOPY

- Need to be able to straighten enteroscope to remove loop in stomach
- Maneuver often used in ERCP to put scope in “short position”
  - Once within 2nd portion of duodenum, turn L/R angulation wheel forward (look to right) and lock
  - Pull back on enteroscope and use clockwise torque to reduce scope within gastric lumen
  - Once in short position, advance scope in usual fashion
**Single Balloon Enteroscopy**

*Presenter non-published animation*

**DOUBLE BALLOON ENTEROSCOPY**

- Similar concept as single balloon but has balloon on distal end of endoscope, as well as at the end of the overtube
- Balloons anchor the bowel in place during reductions to straighten and “pleat” the bowel onto the shaft of the scope
- Using repeated cycles of advancement and reductions, able to “inchworm” through the bowel
- Can use antegrade or retrograde approach, depending on area of interest

**INDICATIONS**

Indications for DBE

- Biliary stenosis
- Occult GI bleeding
- Post-polypectomy bleeding
- Polypsis syndrome
- IBD
- Abdominal pain
- Other

Yokoyama K, et al. JPGN 2016;63;34-40. PMID 26628449
**METHODS (TIPS AND TRICKS)**

- Wear waterproof gown, shoe covers
- Ensure instruments are long enough to go through enteroscope
- Essentially a two-person procedure: scope driver and overtube driver
- Avoid deployment of balloon at level of papilla (pancreatitis risk)
  - Initial advancement, put scope into “short position”, then advance overtube, then advance scope further into duodenum/proximal jejunum
- Initial “set up” often the most difficult part of antegrade procedure

Methods (Tips and Tricks- continued)

- Keep track of cycles of advancement/reduction to help estimate depth of insertion
- Use air (preferably CO₂) as sparingly as possible
- Stop when goal achieved or arrest of forward progress
- Use fluoroscopy to help guide reductions (at least initially)
- Pulse and low dose setting more than adequate, usually < 30 seconds total fluoro time
- Fluoro images progress from pretzel-like configuration to concentric circles with reductions
"HOW DO I KNOW WHERE I AM?"

- Normal Proximal Jejunum
  - Fine velvety appearance of villi
  - Kerkring's folds thin and closely stacked together
- Normal Mild Jejunum
  - Villi more rounded and course
  - Folds thinner and less tightly packed
- Normal Distal Jejunum
  - "pearly" appearance of mucosa
  - Folds less frequent and flatter
- Normal Proximal/Mid Ileum
  - Very flat, low profile folds
  - Geographic, undulating contour of mucosa
- Normal Terminal Ileum
  - Nodular appearance of lymphoid tissue

OUTCOMES

<table>
<thead>
<tr>
<th>Study Year</th>
<th>No. procedures</th>
<th>Mean age, y (range)</th>
<th>Route of insertion, distal-to-proximal, cm</th>
<th>Diagnostic yield, %</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living 2007</td>
<td>38 (24)</td>
<td>Unknown (- -)</td>
<td>14-36</td>
<td>80.5</td>
<td>Severe ileus</td>
</tr>
<tr>
<td>Lin et al. 2009</td>
<td>10 (6)</td>
<td>18-36</td>
<td>2035</td>
<td>86.7</td>
<td>None</td>
</tr>
<tr>
<td>Heinrich et al. 2012</td>
<td>19 (14)</td>
<td>15.7 (8-16)</td>
<td>136</td>
<td>77.8</td>
<td>None</td>
</tr>
<tr>
<td>Lin et al. 2012</td>
<td>15 (11)</td>
<td>15.5 (6-20)</td>
<td>9.4</td>
<td>46.6</td>
<td>Abdominal pain, bleeding, discomfort</td>
</tr>
<tr>
<td>Dohle et al. 2013</td>
<td>11 (7)</td>
<td>15.2 (14-19)</td>
<td>49</td>
<td>82.7</td>
<td>Nodular mucosa</td>
</tr>
<tr>
<td>Lin et al. 2014</td>
<td>10 (6)</td>
<td>15.7 (10-16)</td>
<td>(10-15) (11.5)</td>
<td>70.7</td>
<td>Hypertension, pelvic abscess</td>
</tr>
<tr>
<td>Our series</td>
<td>277 (177)</td>
<td>15.2 (2-19)</td>
<td>366/91</td>
<td>61.1</td>
<td>Mesenteric ischemia, perforation</td>
</tr>
</tbody>
</table>

*Including 18 patients ages between 21 and 26 years old.
*Excluding trans-rectal approach.
*Focusing on patients suspected to have Crohn disease.
*Including laparoscopy-assisted DBE.
*Number of patients.
INTEGRATION WITH WIRELESS CAPSULE ENDOSCOPY (WCE)

- Combination of services offers best opportunity to identify lesions and intervene
  - WCE less invasive, approved in children as young as 2 (reported as young as 10 mo, 11.5 kg)
  - Need to balance in young children who need endoscopic placement
  - Specifically in IBD, Occult GI bleeding and Polyposis cases
- Review capsule images prior to enteroscopy to “know your target”
- Critical: estimate what portion of the bowel is involved to determine antegrade vs retrograde
  - Retrograde DAE much more technically challenging due to colonoscopy with more flexible scope and overtube - Pre-scope with standard colonoscope
  - Ileum= retrograde approach, would avoid antegrade and retrograde procedures at same session

CONCORDANCE OF VCE AND BALLOON ENTEROSCOPY

- Single center pediatric study* of 36 patients who underwent VCE and subsequent DBE
  - VCE with sensitivity of 95%, specificity of 20%
  - DBE with sensitivity of 67%, specificity of 65%
  - Low kappa index 0.372, overall agreement is low but varies by indication
    - Greatest for PLE (1.0) > Polyps (0.8928) > Occult GI Bleed (0.7216) > Crohns (0.6471) > Abdominal Pain (0.3919)
  - Were 5.7% normal in VCE versus 35.9% normal in DBE
  - What to do when balloon enteroscopy negative/ normal
    - Depends on indications and patient status
    - Consider placing marker (clip, tattoo) at site of deepest advancement and schedule repeat study from alternative approach
    - Consider repeat VCE study to confirm findings

*Denialifar TF, et al. JPGN 2016; 62(6);824-827. PMID 26655936
TRAINING AND COMPETENCE
• No formalized mechanism for training or certification presently exists
• NASPGHAN guidelines currently recommend 10 procedures at minimum
• Some difficulty in defining technical success
  • Can’t reliably use anatomic landmarks for antegrade procedures
  • Usually defined as achieving the desired result or goal of the procedure
• Analysis of 280 (adult) DBE procedures\(^1\) was not able to show a statistical learning curve for antegrade procedures, but threshold of 30-35 retrograde procedures to achieve 75% technical success rate
• A multicenter study with 6 centers\(^2\) showed decreased procedure duration and fluoro time after 10 procedures and recommended 20 procedures for retrograde studies
• Still a challenge to initiate a program where no experienced providers exist

FUTURE DIRECTIONS
• New Indications
  • DAE-assisted ERCP
    • Largest cohort in pediatric series out of Japan
    • Important tool for biliary access in increasing number of children with Roux anatomy (BA transplant patients, gastric bypass patients)
    • Development of shorter enteroscope that allows for use of standard ERCP catheters needed
  • DAE in difficult colonoscopy
    • Shown in adults with enlarged, redundant colons to allow for complete colon evaluation
• New Technology
  • Navi-Aid BGE
  • Navi-Aid AB
  • Olympus automated spiral enteroscopy
TAKE HOME MESSAGES

• Device-assisted enteroscopy (SBE, DBE) can be safely performed, even in children as small as 10-14 kg, and can/should be an integral part of any capsule endoscopy program to allow us to intervene when significant findings are encountered.

• Indications and applications for DAE in children continue to grow, with the opportunity to provide critical interventional procedures as an alternative to more invasive surgical approaches.

• Though challenges exist in obtaining appropriate supervision for training in pediatrics, the learning curve for DAE is relatively shallow and incorporates many of the basic endoscopy skills that experienced endoscopists already possess.

• New technology may offer the ability to incorporate DAE into clinical practice with a more reasonable capital investment and allow for “on-the-fly” conversion of standard endoscopy into small bowel enteroscopy.

REFERENCES CITED


Published Videos


Complicated Colonoscopy
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Disclosures
In the past 12 months, I have the following relevant financial relationships with the following manufacturers discussed in this CME activity:
Cook Medical: Speaker

Objectives
• Endoscopic techniques to navigate difficult colonoscopies
• Management of large polyps
• Dealing with complications during difficult colonoscopies
Difficult colonoscopies

- No standardized definition
- Prior failed colonoscopy
- Therapeutic colonoscopy
- Large polyp
- Strictures

Difficult colonoscopies

- Prior surgeries - Adhesions
- Inflammatory bowel disease
- Smaller patient
- Strictures
- Larger polyps
- Flat polyps

Pediatric colonoscopy risks

- Pediatric Endoscopy Database System–Clinical Outcomes Research Initiative (PEDS-CORI)
- Out of 7792 colonoscopy procedures
- Risk of complications 1.1%; 95% [CI], 0.9–1.3 vs 0.28% (adults)
- Bleeding 0.4 % vs 0.1-0.6% (adults)
- Hypoxia 0.28 % vs 0.23% (adults)

Pediatric colonoscopy risks

• Risk of perforation 0.01% vs 0.05-0.08% adults
• Polypectomy 2.67 (95% CI, 1.01–7.03) times increased risk for bleeding


Basics

• Adequate prep
• Polyethylene glycol-3350 1.5-4g / kg
• See Bowel Preparation guidelines by NASPGHAN Endoscopy and Procedures Committee
• No standard prep
• PEG-3350 is the most commonly used
  • <50 kg 4 g/kg day prior
  • >50 kg 238g in 1.5 liter


How to improve colonoscopic skills

• Numbers
• ASGE guidelines for credentialing to perform GI endoscopy suggest 275
• Elite athletes

How to improve colonoscopic skills

- Get your annual numbers
  - Procedures
  - Cecal intubation rate
  - Complication rates
  - Adenoma detection rate, Polyp detection rate (adults)
- Record your procedures
- Get a coach
- See your colleagues
- Get input from nurses or techs

Preventing loops

- Scope caliber
- Using mechanical devices to increase stiffness
- Scope handling
Water immersion

- Cochrane review comparing water vs air
- No difference in cecal intubation
- Less pain
- Water prolongs intubation ~1 minute (no stat diff)

No difference in cecal intubation rate

Water infusion versus air insufflation for colonoscopy - Pain
Water infusion versus air insufflation for colonoscopy - Pain

Less pain

Water infusion versus air insufflation for colonoscopy - Time

No difference in time
Air versus Carbon Dioxide (CO₂)

- Meta-analysis of 24 RCTs totaling 3996 patients
- No difference in cecal intubation rate or time
- Less pain

Air versus Carbon Dioxide (CO₂) - Pain

- A pediatric specific study
- Pain was greater on the air arm
- No difference in cecal intubation times
- Both arms had increase on end tidal CO₂, but no difference

Techniques to improve cecal intubation rate

- Water to facilitate “slide-by”
- Reduce loops early
- Suction to accordion colon
Management of large polyps

Lifting solutions

- Saline
- Epinephrine 1:10,000
- Dyes (methylene blue, indigo carmine)

- Off label
  - Hyaluronic acid, glycerol, ophthalmic solutions containing hydroxypropyl methylcellulose
  - Eleview ® not approved < 18 years old or pregnant
Lifting solutions

Management of complications

- Good prep difference between clean contaminated- contaminated
- Early recognition is a paramount
- Know your electrosurgical generator

Management of complications - Bleeding

- Snare tip soft coagulation
  - Learn specific settings
- Epinephrine injection
- Endoscopic clip

- Hemostatic powder (not approved in pediatrics)
Management of complications - Perforations

- Endoscopic clip
- Management of abdominal compartmental syndrome with needle decompression
- Medical management
- Surgical management

Take home points

- No standard definition of a “difficult colon”
- Improve your colonoscopy skills by constantly evaluating your technique using the elite athlete approach
- Use a combination of water, CO2 in complicated colonoscopies
- For large polyps learn your lifting solution and management of immediate and delayed complications
Endoscopic management of pancreatic and biliary disease: ERCP, EUS

Victor L. Fox, MD
Boston Children’s Hospital
Harvard Medical School

Disclosure

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

Potential Disease Indications

**Biliary**
- Neonatal cholestasis
- Choledocholithiasis
- Choledochal malformations
- Strictures and leaks
- Infections
- Tumors or neoplasia

**Pancreatic**
- Acute biliary pancreatitis
- Recurrent acute and chronic pancreatitis
- Trauma/leaks
- Pancreatic fluid collections
- Tumors or neoplasia
Learning Objectives

1. Understand the role of ERCP in the management of biliary tract obstruction and leaks
2. Recognize the potential benefits and limitations of endoscopic therapy for chronic pancreatitis
3. Know when EUS can be used to assist or replace surgical interventions

Special Tools

- Portable C-arm fluoroscopy
- Ultrasound processor
- Side-viewing duodenoscope
- Curved linear array echoendoscope

Accessories

- guidewires
- sphincterotomes
- dilation catheters
- balloon and basket retrieval catheters
- stents
- biopsy needles

Case (1)

- **History**
  - 10 y female admitted to hospital with RUQ abdominal pain and jaundice for 3 days
- **Past History**
  - negative
- **Family History**
  - mother had autoimmune hemolytic anemia treated with splenectomy at age 23 y
- **Exam**
  - afebrile, icteric, RUQ tenderness
- **Labs**
  - normal CBC, elevated AST, ALT and GGT, total and direct bilirubin = 4.7/2.2, rising to 9.2/5.7 on hospital day 3
Case (1)

- US showed small stones and sludge in gallbladder, dilated common bile duct (CBD) with small stone
- Surgery with laparoscopic cholecystectomy (LC) suggested

Case (1)

- Family refused surgery
- ERCP + sphincterotomy (ES) performed, stone removed without complications
- Repeat US improved but bilirubin level remained elevated

Case (1)

- Evaluation for hemolysis
  - Diagnosis = hereditary spherocytosis
- Follow-up
  - At 1 month: gallbladder stones cleared by US and direct bilirubin level returned to normal
  - At 6 months: child well, no additional interventions planned
Management Controversies for Bile Duct Stones

• How long should we wait for spontaneous passage of CBD stone?
• Should cholecystectomy be performed if cholelithiasis resolves after ERCP with ES?
• When should ERCP be performed in relation to surgery: before, after, not at all?
• Who will perform ERCP and where?
• Are some children too young or too small for ERCP?

Consider: ERCP vs LC

• ERCP
  – Pancreatitis = ~5-10%
  – Hemorrhage = ~2%
  – Does not improve outcome of biliary pancreatitis
• LC
  – Leak, infection, obstruction = < 5%
  – Retained stone = ?%

Equipment NOT designed for children

**Biliary Leaks and Strictures**

- After pediatric liver transplantation
  - Leaks 7-9%
  - Strictures 12.7-23%
- Leaks after blunt trauma and partial hepatectomy
- Endoscopic therapy is first line treatment followed by percutaneous or surgical approaches

---

**Anastomotic stricture in 9 y male after liver transplantation**

Successful treatment with endoscopic dilation and stent

---

**Grade 4 liver laceration in 15 y male with bile leak, resolved by stent**

Contrast extravasation Trans-papillary stent

---

Anderson CD et al Pediatr Transplant 2010;14:358-63
Valentino PL et al Pediatr Transplant 2016;20:647-51

Bile leak after right hepatic trisectionectomy for mesenchymal hamartoma in 2 y female, resolved by stent

PSC: Natural History

- Nearly 50% have adverse liver outcomes after 10 y
- 13% have varices after 1 y
- 16% symptomatic dominant stricture after 5 y
- 1% with cholangiocarcinoma (CCA)
- 14% children went to liver transplantation after median 4 y

Hepatology 2017;66:518-27
Indications for Endoscopy

(Adult) Guidelines for Endoscopy in PSC (adapted from ESGE/EASL guidelines)

- ERCP treatment and duct sampling (brush or bx) should be performed in patients with significant strictures (by MRC) and symptoms likely to improve with therapy (e.g., jaundice, fever, pain)
  - Cite retrospective and prospective series show short-term improvement in symptoms and liver chemistries; longer transplant-free survival compared with Mayo clinical risk model


- 96 pts treated with repeated dilation (+ stent if cholangitis)
- Mean 5.2 dilation/pt
- Liver transplant-free survival
  - 81% at 5 y
  - 52% at 10 y

Kaplan-Meier survival probability

55
Case (2)

- 16 y male with UC since age 9 y, long-term remission, presented with painless jaundice
- Exam: icteric, enlarged liver and spleen
- MRCP and ERCP showed markedly dilated CBD (18 mm)

Case (2)--Therapy

4-6 Fr/6-8Fr dilation catheter
4 mm balloon catheter
7 Fr stent

Results:
Study terminated after interim analysis
Both approaches equally effective at reducing symptoms
Serious adverse events = 17 (pancreatitis 9, cholangitis 4)
45% stent in group vs 6.7% in balloon dilation group

But should we stent after dilation for PSC?

65 patients randomized to stent for 2 wks or no stent after balloon dilation

Results:
Study terminated after interim analysis
Both approaches equally effective at reducing symptoms
Serious adverse events = 17 (pancreatitis 9, cholangitis 4)
45% stent in group vs 6.7% in balloon dilation group
Acute Recurrent Pancreatitis (ARP) and Chronic Pancreatitis (CP)

Case (3)

- **History**
  - 10 y female presents with 4 day history of progressively worsening epigastric pain associated with nausea, but no fever or change in bowel pattern
- **Past History**
  - recurrent episodes of abdominal pain due to “constipation”

Case (3)

- **Exam**
  - Appears uncomfortable, afebrile, mild tachycardia, moderate epigastric tenderness
- **Labs**
  - Normal CBC, mildly elevated lipase and amylase
- **Imaging**
  - US revealed abnormal pancreas with heterogeneous echogenicity of parenchyma and markedly dilated duct
- **Diagnosis = chronic pancreatitis (CP)**
Case (3): MRCP

- Dilated main pancreatic duct and side branches
- Stones in the main duct
- Atrophy of pancreatic parenchyma

ARP/CP: Goals for endoscopic therapy

- Relieve duct obstruction
- Improve drainage
- Treat secondary complications
  - divert leaks
  - drain fluid collections

Endoscopic Therapy

- Sphincterotomy
- Stone removal
- Stricture dilation
- Stenting
Does Endoscopic Therapy Help?

**Endoscopic Rx for ARP/CP**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Mean age, y</th>
<th>Therapy</th>
<th>Mean follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal (2014) [India]</td>
<td>172</td>
<td>13.8</td>
<td>Sphincterotomy, Dilation, Stent, ESWL</td>
<td>13 m Improved = 83%, No pain = 63%</td>
</tr>
<tr>
<td>Oracz (2014) [Poland]</td>
<td>72</td>
<td>11.5</td>
<td>Sphincterotomy, Dilation, Stent, ESWL</td>
<td>4.5 y Reduced AP episodes/y from 1.75 to 0.23</td>
</tr>
<tr>
<td>Troendle (2017) [INSPPIRE]</td>
<td>117</td>
<td>NR</td>
<td>Sphincterotomy, Stent, Stone removal</td>
<td>NR &quot;Helpful&quot; ARP = 56%, CP = 53%</td>
</tr>
</tbody>
</table>

AP = acute pancreatitis
NR = not reported
ESWL = extracorporeal shock wave lithotripsy

**Pancreatic Fluid Collections (PFC)**

(Pseudocyst and walled-off necrosis)
7 y male c/o abdominal pain, no history of trauma  
Dx = acute idiopathic pancreatitis  
elevated lipase, amylase and abnormal CT scan  
(Day 1)  
Localized segment of hypo-perfusion  

Evolving necrosis, fluid collections  
(Day 5)  

Walled-off Necrosis (WON)  
(Day 17)  
(Day 30)  
CT  
MRI
Endoscopy: extrinsic compression

Gastric lesser curve  Duodenum

EUS-Guided Cystogastrostomy
(Day 31)

Needle access  Dilation catheter

Balloon dilation  Stent placement
Efficacy of Endoscopic Drainage of PFCs

Original Article
Endoscopic drainage of pancreatic fluid collections: Long-term outcomes in children
Zeheer Nabi, Sundeep Lodhia, Rihangar Boora, Radhika Chowan, Rakesh Gupta, Mohni Ramchandani, Babash Kailapile, Priti Pat, Smitesh Loherty, Guduru Venkata Rao and D. Nagashwar Reddy
Asian Institute of Gastroenterology, Hyderabad, India
EUS-guided PFC Drainage

- Retrospective series over 3 y (2013-16)
- Etiology of pancreatitis (n = 30 pts)
  - Idiopathic = 23, trauma = 6, gallstone = 1
- Mean age = 13 y (range 5-17)
- Type of PFC: pseudocyst = 13, WON = 17
- Approach: gastric = 26, esophageal = 4
- Clinical success 28/30 (93.3%)
- Recurrence = 2, median f/u interval = 829 d (range 150-1230)

Nabi Z et al. Digestive Endoscopy 2017;29:790-7

Summary/Take Home Points

- Therapeutic ERCP is first-line therapy for management of bile duct stone, strictures, and leaks
- Endoscopic dilation of dominant strictures in PSC improves symptoms and prolongs transplant-free survival
- Endoscopic interventions that improve pancreatic duct drainage can reduce severity and frequency of pain attacks in patients with ARP/CP
- EUS-guided drainage has replaced surgery as first-line therapy for simple and complex fluid collections

Future Directions

- More frequent EUS-guided biopsies of pancreas to define spectrum of “autoimmune pancreatitis” and other chronic pancreatitis
- Development of small equipment for use in children---2018 FDA public meeting for pediatric medical device development
- ERCP and EUS training opportunities for pediatric endoscopists
**When it just won’t stop:**
The Management of Acute Severe Steroid Refractory Colitis (ASC)
Module 2, NASPGHAN Annual Post Graduate Course
25th October 2018, Hollywood, Florida
Dr Thomas D Walters, MBBS. MSc. FRACP
Assoc. Prof University Toronto (Paed)
Co-Director Paediatric IBD Program
Director, CIDsCaNN National Data Co-ordinating Centre

**Disclosures**

- In the past 12 months, I have had the following relevant financial relationships
  - Janssen Canada
    - Speaker, Consultant, Research Support
  - AbbVie Canada
    - Speaker, Consultant, Research Support
  - Ferring Canada
    - Speaker, Consultant
  - Merck Canada
    - Consultant

**Objectives**

- By the end of this session you will
  - Be able to discuss the various standard therapies currently available for treating Pediatric ASC and the paradigms for their use
  - Understand the importance of patho-physiological mechanisms when making therapy choices in ASC
  - Recognize the potential risks of sequential medical therapy and the implications for surgery and surgical timing
  - Appreciate the evolving data regarding the pharmacokinetics and pharmacodynamics of anti-tnf agents and the ramifications for ASC therapy approaches
They are on their way in...

- 12 y/o patient diagnosed with Ulcerative Colitis last week, has been on oral steroids for a few days and is 'getting worse'
  - Stooling 8 times per day, mostly blood
  - Significant abdominal pain with stooling
  - Up twice over night to poop
  - Lethargic

The Paediatric UC Activity Index (PUCAI)

Remission: <10
Mild: 10-30
Moderate: 35-60
Severe: 65-85

Tumer D, et al; Gastroenterology 2007;133:423-432

PUCAI cutoffs (n=205)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Sens/Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>99%/91%</td>
</tr>
<tr>
<td>Mod</td>
<td>98%/91%</td>
</tr>
<tr>
<td>Mild</td>
<td>99%/94%</td>
</tr>
<tr>
<td>None</td>
<td>99%/99%</td>
</tr>
</tbody>
</table>

Turner D et al; Gastroenterology 2007;133:423-432
The UC Continuum

Acute Severe Colitis

- Severe
- Completely Non-Responsive
- Relatively Refractory
- Responsive
- Mild
- Dependent

Steroid Responsiveness

ASC (Acute Severe Colitis)

- Dfn: PUCAI ≥ 65 points
  - Clinically unwell
  - Marked diarrhoea
  - Hematochezia
  - Abdominal Pain
- A medical emergency
  - It might be how they first present
  - It might happen later on

Predicting Response to Standardized Pediatric Colitis Therapy

Detailed Standardized Treatment Plan based on PUCAI
PROTECT Data

• N=400
  – 133 had PUCAI >= 65 at presentation

<table>
<thead>
<tr>
<th></th>
<th>Clinical Remission by week 4</th>
<th>Required Additional Therapy by week 12</th>
<th>5-ASA only by 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>40%</td>
<td>36%</td>
<td>32%</td>
</tr>
<tr>
<td>Colectomy</td>
<td>4 (1%)</td>
<td>8 (6%)</td>
<td>18 (14%)</td>
</tr>
</tbody>
</table>

Hyams et al. DOW 2018, Washington DC

Management of Paediatric Ulcerative Colitis, Part 2:
Acute Severe Colitis—An Evidence-based Consensus
Guideline From the European Crohn’s and Colitis
Organization and the European Society of Paediatric
Gastroenterology, Hepatology and Nutrition


New, Revised and Expanded...

• Thrombosis Prophylaxis
• Empiric use of Oral Antibiotics
• Infliximab Dosage Regimens
The Management of ASC

When to change
When to wait

Rules!

What
Why?
When

#1 Steroid

• How much SHOULD I give?
• Can I give more?

Steroids...from the guidelines

• Recommendation: *(aka ‘RULE’)*
  “1mg/kg IV (upto 40mg) of methylprednisolone once daily in the morning is recommended as initial treatment at admission”
  “Higher doses, 1.5mg/kg (upto 60mg/day) in 1-2 divided doses should be reserved for the more severe end of the spectrum”
But what about…

“Some small case series suggest a benefit to higher and even pulse doses while others did not”.

When they DO work… HOW do they work?

---

Steroids: Mechanism of Action

- Genomic:
  - Increase anti-inflam
  - Decrease pro-inflam

- Non-Genomic:
  - Interrupt Messengers

---

Why would they NOT work?

- Genetic variation
- GR receptor blockade

Inflammatory Activation > G-Receptor Activation

Genomic:
- Increase anti-inflam
- Decrease pro-inflam

Non-Genomic:
- Interrupt Messengers
But what about…

“Some small case series suggest a benefit to higher and even pulse doses while others did not”.

“…given the few anecdotal reports and the severity of ASC, it is not unreasonable to dose higher in selected patients for several days until response has been achieved”

Nagata et al. Digestion 2010;81:188-92

Steroids…from the guidelines

• Recommendation:
  “1mg/kg IV (upto 40mg) methylprednisolone once daily in the morning is recommended as initial treatment at admission”
  “Higher doses, 1.5mg/kg (upto 60mg/day) in 1-2 divided doses should be reserved for the more severe end of the spectrum”

• Practice point: (aka ‘Cooking Tip’)
  “As there is no firm evidence that a higher dose is superior, a rapid decline to 1mg/kg/d (40mg/d) should be employed once response has been observed”

**Day 3**

- **PUCAI ≤ 40**: Continue Steroids, if ≤ 30 consider change to Oral
- **PUCAI >/= 45**: Prepare for 2nd Line Therapy
  - Are they a prompt and rapid responder?
  - The PUCAI has rapidly fallen from 65+ to 40 or less
  
  **No?** → **Maybe they won’t**
  
  **Maybe they will…**

**Day 5**

- **PUCAI 70+:** Start 2nd Line Therapy
  
  - Have they had no/minimal response?
  - The PUCAI remains 70 or higher
  
  **Yes?** → **Lose the Badge!**

- **PUCAI ≤ 30**: Consider change to oral therapy
  
  - Have they had a FANTASTIC response?
  - The PUCAI is now 30 or less
  
  **Yes?** → **Start thinking ‘oral’**
Day 5

- PUCAI 70+: Start 2nd Line Therapy
- PUCAI <= 30: Consider change to oral therapy
- PUCAI 35 - 65: Keep on going
  - Are they a bit better?
    - The PUCAI remains at 35 to 65

Yes? → Maybe they will
Maybe they won’t...

Daily monitoring should confirm gradual response
Decision on 2nd Line Rx is usually made within 2-5 days

Yes? → Maybe they will
Maybe they won’t...

Antibiotics

- Should I use them?
- When?

Why? → When
Antibiotics

• Should I use them?
• When?

When

*Antibiotics in IBD: Still a Role in the Biological Era?
Oren Ledder and Dan Turner
IBD, August 2018, Vol 24(8):1676-1688

Role of **Oral** Antibiotics in ASC

Lumen

Body

Aberrant Immune Response

Ongoing Stimulus

Microbes

Pediatric Randomized trial of Antibiotics in acute Severe Colitis (PRASCO study)

Arm A

IV Methylprednisolone + PO Vancomycin

Arm B

IV Methylprednisolone + PO Vancomycin

Turner et al. ESPGHAN 51st Annual Meeting, May 2018
**PRASCO Primary endpoint**

**PUCAI score at day 5**

- IVCS+AB: 25 (16.7)
- IVCS: 40 (20.4)

\[ p = 0.037 \]

**PRASCO study clinical outcomes**

<table>
<thead>
<tr>
<th>IV Corticosteroids</th>
<th>IV Corticosteroids + antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>13 (83%) responded</td>
<td>10 (83%) responded</td>
</tr>
<tr>
<td>3 (19%) remicade</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>2 colectomy</td>
<td>1 colectomy</td>
</tr>
<tr>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>1 yr</td>
<td></td>
</tr>
<tr>
<td>1 colectomy</td>
<td>1 colectomy</td>
</tr>
</tbody>
</table>

**Most recently...**

Combination Antibiotics Improves Disease Activity and Alters Microbial Communities in Children With Ulcerative Colitis

- Marked improvement in inflammatory markers and clinical activity associated with marked alteration in gut microbiota and a substantial reduction in alpha-diversity
Antibiotics...from the guidelines

- **Textual ‘Cooking Tip’**
  “A short course of the oral antibiotic ‘cocktail’ **could** be considered in selected severe refractory cases, while preparing for colectomy. They should be discontinued if there is no significant response in 4 to 7 days.”

  *Salvage Therapy should not be delayed*

2nd Line...from the guidelines

- **Recommendations**
  - Infliximab is recommended as the second-line medical therapy in patients with ASC failing IVCS
  - Calcineurin inhibitors (cyclosporine and tacrolimus) can be considered as an alternative
  - When introducing 2nd line therapy always consider the possibility of non-response and always discuss the possible need for colectomy.

Infliximab in ASC

- How much should I give?
- How often should I give it?

  ![Why?](image1.png)  ![What](image2.png)  ![When](image3.png)
TDM with anti-TNF

It seems somewhat intuitive:
*If you ain’t there then you can’t help!*

Perpetually coming-and-going is poorly tolerated!

TDM Summary

- **Pharmaco-Kinetics (Chief Players)**
  - ‘Routine’ Clearance
    - Via the Fc Gamma receptor and the RES
    - Modifier
      - FcRN recycling system for IgG and albumin (Saturable system)
  - Disease Based Clearance (antigen sink)
    - TNF-alpha concentrations
    - Modifier
      - Intestinal ‘Leak’
  - **Immune Based Clearance**
    - Neutralizing Anti-bodies To Infliximab (ATI)

Low and Un-detectable Drug at Trough is associated with factors other than sensitization

- Intestinal ‘Leak’
- **Immune Based Clearance**
  - Neutralizing Anti-bodies To Infliximab (ATI)
Infliximab is rapidly cleared from patients with ASC

![Graph showing clearance rates of Infliximab](image)

Ungar et al. Aliment Pharmacol Ther, June 2016; 43(12):1293-9

### Intensification of Infliximab Induction Regimen Improves Response Rate in Steroid-Refractory Pediatric Ulcerative Colitis

SS Ho, P Church, A Sharma, K Frost, TD Walters, AM Griffiths

SickKids Inflammatory Bowel Disease Centre
The Hospital for Sick Children, Toronto
Department of Paediatrics, University of Toronto, Toronto
Pediatric Inflammatory Bowel Disease, Research Forum
DDW2016, San Diego, May 23rd 2016

Ho et al. Gastroenterology, April 2016; 150(4):S131-S132

### Results

<table>
<thead>
<tr>
<th>Steroid Dependent</th>
<th>Steroid Refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>Remission</td>
</tr>
<tr>
<td>Standard</td>
<td>Intensified</td>
</tr>
<tr>
<td>65%</td>
<td>57%</td>
</tr>
<tr>
<td>64%</td>
<td>50%</td>
</tr>
</tbody>
</table>

OR: 4.8, p = 0.006 (95% CI: 1.4 – 26.6)

n=37, n=24, n=38, n=38

Ho et al. Gastroenterology, April 2016; 150(4):S131-S132
Intensified induction prevented colectomy in the short term

Peter C Church, Shaun Ho, Ajay Sharma, Karen Frost, Joley Johnstone, Aleixo Muise, Thomas D Walters, Anne M Griffiths

17/74 patients underwent colectomy during follow-up
Infliximab...from the guidelines

- **Practice points:** *(aka 'Cooking Tips')*
  - Due to rapid clearance of infliximab in acute severe UC, doses up to 10 mg/kg/dose may be considered and may be given more frequently than usual (e.g. weeks 0, 1, and 4-5)
  - Drug levels obtained during induction may guide maximization of efficacy
  - Response should be judged daily by PUCAI. Significant response (PUCAI drop 20+ pts) is anticipated within 4-7 days
  - Infliximab maintenance schedule (dose and interval) may be gradually adjusted to standard regimen, ideally guided by TDM.


3rd Line...from the guidelines

- **Recommendations**
  - In general, prompt referral for urgent colectomy is recommended following failure of 1 second-line medical therapy.

Vedolizumab in ASC

- Can I?

**Why?**

**When**
Shutting Down the Party

Turn off the Bar
‘Anti-cytokine’ Approaches
• Anti-TNFα

Lock the Front Door
‘Anti-adhesion’ Approaches (Cell Trafficking)
• Vedolizumab (Mab to α4β7)

August 2013

Efficacy of Vedolizumab in Anti-TNF refractory Paediatric Ulcerative Colitis: Data from the Canadian Children Inflammatory bowel disease Network (CIDsCaNN).

Nicholas Carman, Eileen Crowley, David Mack, Hien Huynh, Eytan Wine, Wael El-Matary, Amanda Ricciuto, Valerie Arpino, Peter Church, Thomas Walters, Anne Griffiths
Clinical outcomes at 6 months based on steroid responsiveness

<table>
<thead>
<tr>
<th>Steroid Free Remission at months</th>
<th>Steroid Refractory: 4 patients</th>
<th>Steroid Ineffective: 24 patients</th>
<th>Steroid Responsive but Dependent: 12 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid Free Remission at months</td>
<td>0%</td>
<td>35%</td>
<td>67%</td>
</tr>
<tr>
<td>Colectomy</td>
<td>100%</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

N = 40

Carman N et al, PIBD, Barcelona, September 2017

Vedolizumab in ASC...from the guidelines

- **Practice points:** *(aka ‘Cooking Tips’)*
  - Calcineurin Inhibitors need to bridge to a long-term maintenance agent
    - If thiopurines have already failed then you may consider Vedolizumab


Managing ASC: Top 5

- Recognize and treat ASC promptly and aggressively
  - Use the evidence,
  - Know the physiology,
  - Make sensible patient-based decisions
- Ongoing assessment is essential, make decisions based on progress, but be patient
  - The ‘art’ is knowing when to wait and when to change
- Intensification of Infliximab therapy may be helpful, TDM during induction can be useful
  - If you are not there, then you can’t help
- The role for ‘routine’ oral antibiotics has not yet been established
- Vedolizumab is something to consider ...post-ASC
The way forward

- Identifying predictors of response to allow precision medicine should be a research, and clinical priority.
Pathogenesis and Genomic Approach to VEO-IBD

Judith R. Kelsen, MD
Director of the Very Early-Onset IBD Program
Inflammatory Bowel Disease Center
Division of Gastroenterology, Hepatology and Nutrition

Disclosures

• I have nothing to disclose

Objectives

• To review epidemiology and incidence of VEO-IBD
• To demonstrate that VEO-IBD is a different disease than older onset IBD
• To review the role of epithelial and immunoregulatory processes in VEO-IBD
• To demonstrate a collaborative approach to care for these patients
VEO-IBD: A Different Disease?
- Presentation ≤ 5 years of age
- Phenotype often different
  - However, heterogeneous population
- Frequently more severe disease
- Poor response to standard therapies
- Often misdiagnosed

Increase in Incidence
- VEO-IBD comprises 15% of pediatric IBD
  
  - Rapid rise in incidence that is even greater than other populations of IBD

Benchimol, AJG, 2017

Early Diet Affects Microbiome
Life events such as diet changes, antibiotics and fever influence microbiome structure
Distinct Phenotype

**Histologic Differences**

Colon: abundant apoptosis, scattered eosinophils, eosinophilic granules

Duodenum: severe villous atrophy and blunting
Antibiotics
Innate Immunity
Adaptive Immunity
Infection
Maternal Exposures
Mode of Delivery
Diet
Metabolites
Proteomics

Older Onset: Polygenic
VEO: Monogenic Digenic

VEO-IBD Networks

IBD Associated Immune Deficiencies
- IL-10, IL-10R
- NOD2
- Severe dyskeratotic conjunctiva
- Trichohepatic enteric syndrome
- IPEX
- Multiple intestinal atresia
- NEMO (IKBKG)
- ADAM17
- Glycogen storage dis 1b
- LAD I
- Hermansky Pudlak

- Leaky SCID
- PLCG2
- WAS
- DOCK8
- XLA

IBD often a presentation
IBD Associated Immune Deficiencies

- IL-10, IL-10R
- XIAP
- Severe dyskeratosus congenita
- Trichohepatic enteric syndrome
- IPEX
- Multiple intestinal atresia
- CGD
- NEMO (IKBKG)
- ADAM17
- Glycogen storage dis 1b
- LAD I
- Hermansky Pudlak

IBD more often occurs after the diagnosis in these conditions

How Do We Translate Genetic Findings into Clinical Care?

VEO-IBD Program

- Multidisciplinary Clinic
  - IBD evaluation and diagnostic work up
  - Immunophenotyping
  - Nutrition, Rheumatology, Surgery
  - Clues for monogenic disease
- Genetics/Bioinformatics: development of WES pipeline
Immunophenotyping

• Screen:
  • DHR
  • Immunoglobulins
  • Titers
  • Lymphocyte subsets

• Specific Defects
  • XIAP flow
  • IL-10R

Precision Medicine Approach

Cohort
• >650 Patients
• Multidisciplinary clinic: immunophenotyping performed

Analyses
• WES: >900 samples, 230 trios
• 44 Candidate genes identified
• 5 novel defects

Validation
• Functional analyses on candidate genes

Therapy
• HSCT: 10 (3 currently undergoing evaluations)
• Targeted therapies: 9

• IL-1 receptor antagonist
• Rituximab
• Abatacept
• Rapamycin
• Anti-IL-18

Patient Case
Case 1

- 17 mo old male presented with recurrent fever, constipation, intermittent blood in the stool
- Serious infections, including severe pneumonia
- PE: Hypertelorism, epicanthal folds, low set ears
- Colonoscopy: colonic ulcerations, consistent with VEO-IBD

Immunology Evaluation

<table>
<thead>
<tr>
<th>Lab</th>
<th>Value</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>30 mg/dL</td>
<td>(539-1597)</td>
</tr>
<tr>
<td>IgA</td>
<td>48 mg/dL</td>
<td>(48-336)</td>
</tr>
<tr>
<td>IgM</td>
<td>17 mg/dL</td>
<td>(50-194)</td>
</tr>
</tbody>
</table>

- No titers to diphtheria, tetanus, or pneumococcus
- No switched memory B cells
- Low T cell counts but normal function

Decreased Plasma Cells
Histopathology in VEO IBD

Healthy Control

Normal duodenum with CD79+ plasma cells

VEO-IBD

Monogenic defect in B cell development

ZBTB24

Fewer CD79+ plasma cells

Absent IgA producing plasma cells

Mildly affected duodenum with CD79+ plasma cells

Conrad et al, Inflammatory Bowel Disease. 2017, 23(12):2252-5

Homozygous Autosomal Recessive Mutation: ZBTB24

- ICF2: Immunodeficiency, centromere instability, and facial anomalies type 2
- B cell abnormalities
- Therapy: IVIG
What About the Majority of Cases Without an Identified Defect?

Red Flags for Monogenic Disease

- Pan-enteric disease
- Extreme poor growth
- Atypical pathology
- Abnormal lymphocyte subsets
  - Low NK cells/functions
  - Low switched memory B cells

Clues if the Defect is Not Identified

- Disease location
  - Small bowel, colon, panenteric
- Pathology
  - Inflammatory cell type
    - Neutrophils, lymphocytes, eosinophils
  - Plasma cells
  - Villous blunting
  - Apoptosis
Associated Autoimmune Disease – Other Locations of Inflammation

- Fevers, oral ulcers
- Arthritis
- Uveitis
- Pyoderma
- Sclerosing cholangitis
- AIH
- Diabetes
- Thyroid disease
- Psoriasis

Therapeutic Strategies

- TNF/IL-1 directed therapy: Colon has primarily neutrophils
  - Anakinra (CGD)
- If lymphocytes are prominent
  - Rapamycin (sirolimus)
  - Abatacept
  - Vedolizumab
- B cell directed therapy
  - Rituximab
  - IVIG

Conclusions

- VEO-IBD is a different disease
- WES/WGS is a powerful tool to identify disease causing mutations
- Multidisciplinary approach is needed to evaluate and treat this population
- Goal: targeted individualized therapy to identified pathways can be life-saving!
## Thank You

### VEO-IBD Team
- Maire Conrad, MD
- Kate Sullivan, MD, PhD
- Marcella Devoto, PhD
- Noor Dawany, PhD
- Kate Hamilton, PhD
- Trusha Patel, MD
- Edward Behrens, MD
- Rawan Shraim
- Audrey Merz
- Priya Vaidiwaran
- Robert Baldassano, MD
- David Piccoli, MD
- Petar Mamula, MD
- Andrew Grossman, MD
- Lindsey Albenberg, DO
- Betsy Maxwell, MD
- Ronen Stein, MD

### Collaborators:
- Nancy Spinnert, PhD
- Pierre Russo, MD
- Claudio Giraudo, PhD
- Michael Marks, PhD

### Penn
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- Kyle Bittinger, PhD
- Christopher Brown, PhD
- David Artis, PhD
- Greg Sonnenberg, PhD
- Harland Winter, MD
- Chris Moran, MD

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- NIH K23DK100461-01A1
- IBD Center Grateful Families
TREAT-TO-TARGET IN PEDIATRIC IBD:
WHAT ARE THE TREATMENTS AND THE TARGETS?

ERIC BENCHIMOL, MD, PhD, FRCP C
Associate Professor of Pediatrics and Epidemiology
University of Ottawa
CHEO Inflammatory Bowel Disease Centre
Children's Hospital of Eastern Ontario
Ottawa, Ontario, Canada

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

OBJECTIVES
• Define ‘Treat-to-Target’ and our goals for therapy in pediatric IBD in 2018
• Review the latest evidence for better outcomes using a Treat-to-Target strategy
• Determine the best ways to achieve our targets for the treatment of children with IBD
TREAT TO TARGET: WHAT DO WE MEAN?

HIGH
Risk of progression
TARGET

LOW
Unreached Target


What Are the Targets?


What Is the Optimal Target?

Optimized disease activity scores

**CLINICAL SYMPTOMS & ENDOSCOPIC SEVERITY**

![Graph showing correlation between Crohn's Disease Activity Index (CDAI) and Crohn's Disease Endoscopic Index of Severity (CDEIS)](image1)

*Images courtesy of Dr. David Rubin*

---

**wPCDAI and SES-CD: WEAK CORRELATION**

![Graph showing correlation between wPCDAI and SES-CD](image2)

*Images courtesy of Dr. David Rubin*

---

**SURROGATE MARKERS - PUCAI**

<table>
<thead>
<tr>
<th>Table 3. Validation Results of the PUCAI and PUCAI With Laboratory Tests, Compared With Lichtenber and See Indices</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PGA</strong></td>
</tr>
<tr>
<td>PUCAI</td>
</tr>
<tr>
<td>PUCAI with laboratory tests</td>
</tr>
<tr>
<td>Lichtenber index</td>
</tr>
<tr>
<td>See Index</td>
</tr>
</tbody>
</table>

NOTE: Numbers represent Pearson rho correlation coefficient.
PGA, Physician Global Assessment on a 100-mm visual analogue scale.
*P < .001.

*Images courtesy of Dr. David Rubin*
SURROGATE MARKERS - PUCAI

- At 3 months:
  - Area Under the ROC: 0.75 (95% CI 0.60-0.89)
  - PUCAI <10 for SSFR: Sens 90%, NPV 91%
  - For colectomy: Sens 82%, Spec 64%

Schechter et al, Gut 2015; 64: 580-8

PUCAI <10 (remission)
PUCAI 10-35 (mild)
PUCAI 40-60 (moderate)
PUCAI ≥65 (severe)

TREATING A PATIENT WITH CROHN’S DISEASE

Resolution of abdominal pain and normalization of bowel habit should be the target

Peyrin-Biroulet et al., Am J Gastroenterol 2015;110:1224-38
Colombel et al., Gastroenterology 2017;152:351-61

WHAT IS THE OPTIMAL TARGET?

Surrogate markers (ESR/CRP, fecal biomarkers)
Optimized disease activity scores
### SURROGATE MARKERS – CALPROTECTIN & FIT

![Graphs showing FIT and Calprotectin concentrations](image)

- **Takashima et al., Am J Gastroenterol 2015; 110: 873-80**

### CALPROTECTIN IN CHILDREN

<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>N</td>
<td>8 studies, 397 patients</td>
<td>10 studies, 867 patients</td>
</tr>
<tr>
<td>Sens</td>
<td>97.8%</td>
<td>99%</td>
</tr>
<tr>
<td>Spec</td>
<td>68.2%</td>
<td>65%</td>
</tr>
<tr>
<td>LR+</td>
<td>3.07</td>
<td>2.8</td>
</tr>
<tr>
<td>LR-</td>
<td>0.03</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### CALPROTECTIN IN CHILDREN - ImageKids

![Graphs showing disease severity and Calprotectin levels](image)

- Weinstein-Nakar et al., Clin Gastroenterol Hepatol 2018; 16: 1089-97
Resolution of abdominal pain and normalization of bowel habit should be the target.

Histological remission and biomarkers (CRP/FC) are not targets.

Failure of CRP/FC normalization should prompt further endoscopic evaluation, irrespective of symptoms.

Resolution of abdominal pain and normalization of bowel habit should be the target.

**CALM STUDY**

*Effect of tight control management on Crohn’s disease (CALM): a multicentre, randomised, controlled phase 3 trial*

Peyrin-Biroulet et al., Am J Gastroenterol 2015; 110: 1234-48

Colombel et al., Gastroenterology 2017; 152: 351-61

**CALM STUDY DESIGN**

Colombel et al, Lancet 2017; 390: 2779-89
PRIMAR Y ENDPOINT (wk 48)

Mucosal healing (CDEIS <4) and no deep ulcerations

<table>
<thead>
<tr>
<th></th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission</td>
<td>80.9 (%77/222)</td>
</tr>
<tr>
<td>Tight control</td>
<td>45.9 (%56/223)</td>
</tr>
</tbody>
</table>

Colombel et al, Lancet 2017; 390: 2779-89

SECONDARY ENDPOINT

CDAI <150 and discontinuation of steroid use for at least 8 weeks

<table>
<thead>
<tr>
<th></th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM arm (n=127)</td>
<td>23.0 (29/127)</td>
</tr>
<tr>
<td>TC arm (n=122)</td>
<td>45.1 (55/122)</td>
</tr>
<tr>
<td>CM arm (n=111)</td>
<td>42.0 (47/111)</td>
</tr>
<tr>
<td>TC arm (n=107)</td>
<td>56.2 (61/107)</td>
</tr>
</tbody>
</table>

Colombel et al, Lancet 2017; 390: 2779-89

CALM STUDY: CONCLUSIONS

• Monitor with biomarkers, not just clinical symptoms

• Abnormal biomarkers is a RED FLAG, prompt further investigations or treatment escalation

• NOTE: CALM study is not a Treat-to-Target RCT
  ▶ Biomarker remission was the target
  ▶ Tight control is a way to reach the target
WHAT IS THE OPTIMAL TARGET?

Mucosal healing by endoscopy
Imaging (MRE, capsule)
Surrogate markers (ESR/CRP, fecal biomarkers)
Optimized disease activity scores

TREATING A PATIENT WITH CROHN’S DISEASE

Resolution of abdominal pain and normalization of bowel habit should be the target

TREATING INTESTINAL INFLAMMATION

Absence of ulceration is the target
Endoscopy or cross-sectional imaging should be performed 6-9 months after treatment starts
Histological remission and biomarkers (CRP/FC) are not targets
Failure of CRP/FC normalization should prompt further endoscopic evaluation, irrespective of symptoms

STRIDE

Peyrin-Biroulet et al., Am J Gastroenterol 2010; 105: 1329-38
Colombel et al., Gastroenterology 2017; 152: 351-61
**A TREAT-TO-TARGET STRATEGY USING PAN-ENTERIC CAPSULE (PCE) ENDOSCOPY IN PAEDIATRIC CROHN’S**

**Primary Outcome**
- To assess MH and DR rates at three time points (0, 24, 52 weeks) and to guide a treat-to-target strategy

**Secondary Outcome**
- Efficacy of a “treat-to-target” strategy to MH and DR rates
- PCE vs biomarkers, MRE and SICUS

Oliva et al., Clin Gastroenterol Hepatol 2018, in press
Slides courtesy of Salvatore Oliva and Stan Cohen
DEFINITIONS

- CLINICAL REMISSION (CR): PCDAI < 10
- BIOMARKER REMISSION (BR): FCP < 100 µg/l, CRP < 5 mg/ml
- SB MUCOSAL HEALING: LEWIS SCORE < 135
- COLONIC MUCOSAL HEALING: SES-CD SCORE ≤ 1
- PARTIAL MUCOSAL HEALING: Reduction >50%
- DEEP REMISSION (DR): MH + CR + BR

CLINICAL REMISSION (CR)
BIOMARKER REMISSION (BR)
SB MUCOSAL HEALING
COLONIC MUCOSAL HEALING
PARTIAL MUCOSAL HEALING
DEEP REMISSION (DR)

HEALING IS ACHIEVABLE (n=48)

Baseline | 24 Wks | 52 Wks
--- | --- | ---
BR=18 | CR=40 | CR=42
CR=26 | BR=31 | BR=33

MUCOSAL HEALING = BETTER OUTCOMES

CLINICAL RELAPSE

PROBABILITY

TIME (MONTHS)
MUCOSAL HEALING = BETTER OUTCOMES

Oliva et al., Clin Gastroenterol Hepatol 2018, in press
Slides courtesy of Salvatore Oliva and Stan Cohen

MUCOSAL HEALING = BETTER OUTCOMES

Oliva et al., Clin Gastroenterol Hepatol 2018, in press
Slides courtesy of Salvatore Oliva and Stan Cohen

LONG-TERM OUTCOMES (n=42)

Oliva et al., DDW 2018
Slides courtesy of Salvatore Oliva and Stan Cohen
LONG-TERM OUTCOMES (n=42)

WHAT IS THE OPTIMAL TARGET?

Histologic remission
Mucosal healing by endoscopy
Imaging (MRE, capsule)
Surrogate markers (ESR/CRP, fecal biomarkers)
Optimized disease activity scores

TREATING A PATIENT WITH CROHN’S DISEASE

Resolution of abdominal pain and normalization of bowel habit should be the target
Assess outcomes at least every 3 months until resolution
After symptom resolution, outcomes should be assessed at least every 6-12 months

TREATING INTESTINAL INFLAMMATION

Absence of ulceration is the target
Endoscopy or cross-sectional imaging should be performed 6-9 months after treatment starts
Histological remission and biomarkers (CRP/FC) are not targets
Failure of CRP/FC normalization should prompt further endoscopic evaluation, irrespective of symptoms

STRIDE

Oliva et al., DDW 2018
Slides courtesy of Salvatore Oliva and Stan Cohen
UNANSWERED QUESTIONS

- Histologic remission
- What if aphthous ulcers in multiple regions?
- Mayo 0 vs Mayo 1
- What if not healed after maximizing anti-TNF?
- Cost effectiveness
- Patient preference

UNANSWERED QUESTIONS

- Correlation ≠ Causation!

Source: tylervigen.com/spurious-correlations

CONCLUSIONS

- Treat-to-target strategy requires:
  - Aggressive monitoring
  - Changing therapy
- Target is no longer clinical symptoms alone
- Mucosal healing is associated with improved long-term outcomes
ACKNOWLEDGEMENTS

Slides:
• Nick Carman
• Stan Cohen
• Salvatore Oliva
• David Rubin

Funding:
Gastrointestinal Problems in Children with Autism

Kara Gross Margolis, MD
Associate Professor of Pediatrics
Columbia University Medical Center
New York-Presbyterian Morgan Stanley Children’s Hospital

I have no disclosures to reveal

Matthew

- Chief complaint: "recent regression"
- HPI:
  - 17 year old male with history of autism
  - 6 months prior to his visit
    - Some verbal ability
    - Good eye contact
    - Avid reader, math genius
  - Gastroenteritis during trip to India
    - Diarrhea for 5-7 days
    - Resolved with course of Ciprofloxacin
    - Behaviors radically changed:
      - Catatonic:
        - Nonverbal, no eye contact
        - Stopped reading and math
Matthew-2

- Severe obsessive compulsive behaviors
  - Inhibited daily activities
  - Intensive care unit secondary to water intoxication
- GI Symptoms
  - Banging on chest
  - Excessive salivation
  - Difficult defecation
  - Self-disimpaction
- Treated for severe constipation and gastritis
- All behaviors resolved once GI conditions treated
  - Obsessive compulsive disorder
  - Catatonic-like behavior

Important Points

- Kids with autism have GI conditions
- Clinical presentations of GI distress can be dramatically different than kids without autism
- Important to understand these distinctions for diagnosis and treatment

Objectives

- History of GI conditions and autism
- GI Conditions in Autism
  - Prevalence
  - Types
  - Presentations
- Common questions from parents
- The Future
History of GI Issues in ASD

• 1943: Leo Kanner described autism in his seminal paper
  – 7/11 children described to have “feeding or dietary issues”
  • Supportive of association between ASD & GI
  – These issues all related to autistic behavior
  • A theme throughout history

https://en.wikipedia.org/wiki/Leo_Kanner

Gastrointestinal disorders are more common in children with ASD

Coury D L et al. Pediatrics 2012;130:S160-S168

Gastrointestinal Symptoms in Autism Spectrum Disorder: A Meta-analysis

• Meta-analysis confirms reason for this concern¹.
  – Overall: OR 4.42
    • 95% CI, 1.90–10.28
  – Constipation: OR 3.86
    • 95% CI, 2.23–6.71
  – Diarrhea OR 3.63
    • 95% CI, 1.82–7.23

¹McElhanon et al. Pediatrics 2014;133
GI problems are common in ASD

- Constipation
- Diarrhea
- Gastro-esophageal reflux disease (GERD)
- Gastritis, esophagitis
- IBS
- Nutrition
  - food/texture aversion
- Allergy/food sensitivity
- Small bowel bacterial overgrowth
- Inflammatory bowel disease

History: Presentation is often NOT Abdominal Pain

http://blog.listentoyourgut.com/help-my-childs-stomach-hurts/

Gastrointestinal symptoms cause difficult behaviors

- Behaviors
  - self-injury
  - aggression
  - vocal tics
  - regression
- Comorbidities
  - sleep disturbance
  - anxiety

From files of Tim Buie; Used with family permission
Medications are Important

- **Medications**
  - **Selective Serotonin Reuptake Inhibitors:**
    - Paxil, Prozac
      - Abdominal pain, nausea, gastritis, ulcers, GI bleed
      - Diarrhea → constipation
      - Decreased → increased appetite
  - **Antipsychotics:**
    - Increased appetite
    - Constipation
  - **Supplements**
    - Probiotics: bloating, nausea, cramping
    - Fish oil: nausea, abdominal cramping
    - Check for dangerous ingredients
    - NIH Dietary Supplement Label Database
    - Trial without supplements
Anticipatory Guidance

- Most caregivers of children with ASD ask GI-related questions
- Many ask the same questions!
  - A lot of data with references at the end

https://www.friendshipcircle.org/blog/2014/12/17/10-ways-to-improve-communication-with-your-pediatrician/

Should My Child Get Vaccinations? Does My Child Have Colitis?

- Andrew Wakefield
  - Lancet 1998: link between MMR vaccine, appearance of autism and an inflammatory bowel disease
    - "Autistic colitis"
  - Lancet retracted the study
    - No persistent MMR in blood or CSF
    - Lymphonodular hyperplasia
- Findings have not been reproduced
  - No difference existed in autism rates between vaccinated and unvaccinated children
    - 2014 meta-analysis in Vaccine
    - JAMA: No difference after MMR vaccine

Should My Child Get Vaccinations? Does My Child Have Colitis?

- Subgroups may have intestinal immune abnormalities
  - Altered immunologic and inflammatory gene expression pathways in blood
  - Altered transcriptome profiling in the intestine
    - Overlap with some IBD
  - Crohn's disease & ulcerative colitis may be common
    - Expert-verified IBD in a very small # of patients
Can my child eat gluten and dairy?

Wheat “Consumption” and Hospital Admissions for Schizophrenia During World War II
A Preliminary Report
F. C. Dohman, M.D.

• Opioid Peptide Theory:
  Peptides from milk and gluten cause Autism
  Gluten & casein-derived urine opioids in ASD
    - Bind neuronal receptors in test tube
  Theory
    - Kids with ASD maldigest casein & gluten
    - Leak through gut wall → brain
    - Bind brain neurons
    - Affect brain by modulating opioid levels

Flawed studies with no controls
  No human data
  Peptides are large
  No increased gut or brain permeability
  Recent study: no opioids in ASD or controls
Can my child eat gluten and dairy?

- Studies do not currently support a link between ASD and
  - Celiac disease
  - Intestinal permeability ("leaky gut")
  - Lactose intolerance
- 2 meta-analyses
  - Insufficient evidence to support GFD as treatment for autism
    - Few studies with sound scientific science
    - 5 randomized double-blind placebo-controlled studies
      - No significant changes in behavior or GI studies
- Systematic review of 6 RCTs (214 patients)
  - Little evidence GFCF is beneficial
    - Multiple open-label studies
- Health benefits of gluten
  - Protein, iron and calcium

Does My child Have Autistic Colitis and/or Leaky Gut?

- Low-grade GI inflammation in a subgroup of children with ASD matched NT controls
  - Disaccharidases, calprotectin, lactoferrin
- Pan-enteric infiltration of immune cells in GI tract
  - Wakefield senior author
- Zonulin release and gene expression increased in blood in ASD
  - Increased release in chronic inflammatory diseases
  - Release associated with gluten and microbial profiles
Can my child eat gluten and dairy?

- Some kids respond
  - Significant numbers of parents report improvements
    - Socability, anxiety, hyperactivity
- Review history +/- testing
  - Celiac disease
  - Wheat, dairy allergy
  - Gluten sensitivity
- Sub-group of patients who may benefit
  - Symptoms or profile of these individuals unclear
    - Microbiota differences
      - Increased intestinal permeability
      - Increased carbohydrate and lactose digestion
- If attempted, recommend nutritional support

Fecal Transplant At Home – DIY Instructions

- Does fecal transplant help?

Increased abundance and diversity of clostridial species

In ASD
Will fecal transplant help my child?

- Overall increase in bacterial diversity and abundance:
  - Bifidobacteria
  - Prevotella
  - Desulfovibrio

Microbe-Metabolite Correlations

- ASD
- OTU132 Lachnospiraceae
- OTU177 Cellvibacteraeae
- OTU320 Sarcina ventriculi
- OTU61 Clostridium XI
- ASD + GI
- OTU76 R. torques
- OTU265 Clostridium XI

Metabolites in pathway:
- Glutamate metabolism
- Gamma-glutamyl amino acid
- Tryptophan metabolism
- Histidine metabolism
- Endocannabinoids
- Pregnenolone steroids
- Sphingolipids/Sphingosines
- Bile acid metabolism

https://www.elegantthemes.com/blog/editorial/
Future directions

• Microbiome
  – Dietary interventions
    • Gluten, casein, food additives, refined sugar
    • Ketogenic diet, MCT
  – Fecal transplant
    • Double-blind, placebo-controlled
  – Functional studies
• Link between immune dysfunction, autism & GI
• Comorbidity cluster
  – Could inform medical evaluation, treatment & etiology
    • Seizures and GI problems
    • GI problems and sleep disorders

Is Screening Available?

• Rome IV
Are guidelines available?

Evidence-based algorithms for the assessment of abdominal pain, constipation, chronic diarrhea, and GERD should be developed.

Conclusions

- GI issues are common in children with autism
- GI conditions in autism may worsen behaviors and other co-morbidities
- GI conditions should be ruled out
- Aggression or self-injurious behaviors may require psychopharmacological or behavioral management
- Medical etiologies should also be evaluated
- Parents are usually right!
- Know the literature

Thank You!

- Columbia
  - Nane Khokhlova, MS
  - Sam Li, MD, PhD
  - Moniak Madra, PhD
  - Albert Xing, MS
  - Nij Park, MS
  - Mike Gershon, MD
  - Agnes Whissler, MD
  - Jeremy Weems-Vanderwiele, PhD
  - Mark Amore, PhD
- University of Vermont
  - Gary Maew, PhD
- Duke School of Medicine
  - Marc Canan, PhD
  - Jacob Jacobsen, PhD
- Yale School of Medicine
  - George Anderson, PhD
- Florida Atlantic University
  - Randy Blakesley, PhD
- Massachusetts General Hospital
  - Harland Winter, MD
- Children’s Hospital of Boston
  - Timothy Buie, MD
- Baylor
  - Ruth Ann Luna, PhD
  - Tar Savidge, PhD
  - James Versalovic, MD, PhD
- Research Support
  - NIH HD1
  - Department of Defense
  - NIH K08
  - Autism Research Institute
  - The Center for Discovery
  - Sederberg Family Foundation for Digestive Health

Pediatrics. 2010 Jan;125 Suppl 1:S1-18
References-1

• Slide 7
• Slide 10
  - 1CDC; Autism and Developmental Disabilities Monitoring (ADDM) Network.
  - 14Inflamm Bowel Dis. 2015 Jul 25.

References-2

• Slide 12
  - 7Son J et al.PLoS One.2015 Oct 1:10(10);e0137725.
• Slide 17

References-3

• Slide 18
• Slide 20
References

Slide 23
- 10 Fasano A et al. J Peds 2017;188 (15-17).

Slide 24
- 1 Kushak RI et al. JPGN, 62 (2016), 687-691.

References

Slide 24

Slide 25

Slide 26
- 4 Ding HT et al. JADD 2017; 47(2) 480-489.

Slide 32
- 1 Lee RWY et al. Physiol Behav 2018;188 pp 205-211.
- 2 Adams JB et al. Nutrients 2018. 10(3)8369
Weight Management Surgery: Indications And Complications

Rohit Kohli, MBBS, MS

Disclosures
- Investigator Initiated Research
  - Raptor Pharmaceuticals
  - Vision Pharmaceuticals
  - Epigen Pharma
- DSMB/Research Agreements
  - Shire
  - Galectin Therapeutics
  - Takeda Pharmaceutical Company
- Consultant/Speaking Compensation
  - Epigen
  - Intercept Pharmaceuticals
  - Alexion Pharmaceuticals

Objectives/Outline
- Part I: Therapeutic Approach to Childhood Obesity
- Part II: Indications for Surgical Intervention
- Part III: Complications from Surgical Intervention
Obesity Therapeutic Approach

Weight Loss Interventions

- Lifestyle
- Drug therapy

Weight Loss Interventions

- Lifestyle
- Drug therapy
- Bariatric surgery

Bariatric Surgery Procedures

- Roux-en-Y Gastric Bypass
- Gastric Banding
- Vertical Sleeve Gastrectomy
Sleeve Gastrectomy (VSG) in mice


VSG Reduces Hepatic Steatosis

Myronovych, Kohli et al. Obesity 2014 Feb;22(2):390-400

Indications
Indications

Clinical
Severe NASH is an indication for surgery in adolescents.

**Selection criteria for adolescent weight loss surgery**

**BMI Comorbidities**
- > 35
  - Type 2 DM
  - moderate-severe OSA (AHI ≥ 15 events/hr)
  - pseudotumor cerebri
  - severe NASH
- > 40
  - Mild OSA (AHI>5 events/hr)
  - HTN
  - Insulin resistance/IGT
  - Dyslipidemia
  - impaired QOL or ADL

Pratt, JSA et al. Obesity 2009; 17:901

The Washington Post

October 29th 2017

Fatty liver disease fastest-growing reason for transplants in young U.S. adults

NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: Recommendations from the Expert Committee on NALFD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)

(JPGN 2017;64: 319–334)
**NASPGHAN Clinical Practice Guideline**

- Bariatric surgery is **not recommended** as a specific therapy for NAFLD
- Bariatric surgery may be considered
  - ≥ BMI 35 kg/m²,
  - who have non-cirrhotic NAFLD and
  - other serious comorbidities

Strength: 1, Evidence: B.

**Pediatric obesity tripled last 4 decades**

- Approximately 1600 adolescents undergo bariatric surgery a year!

NHANES I 71-74
NHANES II 76-80
NHANES III 88-94
NHANES 03-06

Circulation 2012; 126(15) 1569-1712
JAMA Peds 2013;48 (12):2401-2407

**Complications**
Complications

Surgical

Surgical Complications

- Peri-operative
  - 7.9% major
    - VSG 4.5%
  - 14.9% minor
    - VSG 11.9%

- Post-operative
  - 5% readmission
  - 13% re-operation
    - VSG 10%


Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 Aug 3.
Complications

Medical

Nutritional Complications

• Low ferritin
  – 5% baseline increased to 57%
    • VSG 34%

• High transferrin
  – 3% baseline increased to 16%
    • VSG 5%

• Low B12
  – <1% baseline increased to 8%
    • VSG 8%

Future

Obesity/Comorbidities
Therapeutic Approach

Lifestyle  Rx/Sx  Lifestyle
FXR is a molecular target for the effects of vertical sleeve gastrectomy

Obesity/Comorbidities
Therapeutic Approach

Endoscopic Gastric Sleeve

https://youtu.be/9SGp04I1gPw?t=91

Video Credit: Vivek Kumthari, Director of Bariatric Endoscopy, Johns Hopkins School of Medicine, Baltimore, MD
**So What should One do?**

- **Screen:**
  - More children are obese and at risk for NAFLD / NASH
  - Screen for NAFLD and diagnose NASH

- **Treat:**
  - Lifestyle modification can be effective
  - Refer to a bariatric surgery program

- **Wait:**
  - On newer therapeutic agents and procedures

---

@liver4kids

George Ferry YIA / Takeda Innovation
Prof. Ken Setchell, Cincinnati Children’s
Prof. Randy Seeley, U of Michigan
Nutrition screening and follow up of intestinal failure:
Bringing up the grades of your intestinal failure

Conrad R. Cole MD, MPH, MSc
Intestinal Rehabilitation Program
Intestinal Care Center
Cincinnati Children's Hospital Medical Center
Cincinnati, OH

Disclosure

• I have no financial relationships to disclose that are relevant to my presentation

Learning Objectives

At the end of the presentation, the learner is able to:
• Define intestinal failure (IF) and identify associated causes
• Design an acceptable monitoring plan for patients with IF
• Develop management strategies to improve outcomes including prevention of nutritional deficiencies during shortages of Parenteral Nutrition (PN) components and transition to enteral autonomy
**Intestinal Failure**

- Umbrella term
- Lack of functional intestinal mass necessary
  - To adequately digest and absorb nutrients and fluids
  - To maintain protein-energy, fluids and micronutrient balance
- In children
  - Inadequate for normal growth and development
- Using parenteral support
  - Dependent on parenteral nutrition (PN) for 6 weeks

Merritt RJ et al. JPGN 2017;65: 588–596

**Function is more important than length**

**Disease Entities Leading to IF**

<table>
<thead>
<tr>
<th>Disease entity</th>
<th>NEC</th>
<th>Gastrostomy</th>
<th>Intestinal atresia</th>
<th>Veloce</th>
<th>Combination</th>
<th>Pneumonitis/thoracic disease</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvert et al.</td>
<td>50%</td>
<td>45%</td>
<td>25%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
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<tr>
<td>Dore et al.</td>
<td>40%</td>
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<td>Vela et al.</td>
<td>50%</td>
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<td>Talalay et al.</td>
<td>50%</td>
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<td>25%</td>
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<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Cohran VC, Prozialeck JD and Cole CR
Pediat Res 2017; 81:545-549
Improving Survival of IF by Era

The introduction of hepatoprotective strategies and multidisciplinary management has led to improved outcomes.


IF Patients Managed at the Intestinal Rehabilitation Program

Intestinal Rehabilitation Team

Professionals
- Pediatric surgeons
- Transplant surgeons
- Pediatric gastroenterologists
- Neonatologists
- Interventional radiologists
- Gastroenterology/pediatric nutrition nurses
- Pharmacists
- Registered dietitians
- Social workers
- Physical/occupational/speech therapists
- Child-life specialists
- Psychologists
- Medical educators

Merritt RJ et al. JPGN 2017; 65:588-594
**Nutrient Absorption in Small Bowel**

- Iron
- Folate
- Carbohydrates, protein, fats, vitamins, minerals, trace elements

The risk of developing nutrient deficiencies depends on:
- Postsurgical anatomy, amount of bowel resected and degree of malabsorption
- Increased inflammation from bacterial overgrowth
- Impaired motility

---

**Protective against vitamin deficiencies**

- After transition to 100% EN, multivariate analysis identified that the following were protective:
  - Regular use of a multivitamin supplement (P=0.004)
  - Intact ileocecal valve (P=0.02),
- Independent of bowel length, gestational age, and duration of PN.

---

**High Prevalence of Multiple Micronutrient Deficiencies in Children with Intestinal Failure: A Longitudinal Study**

- 30 children with IF
- Mean age 5 years (range 2-9 years)
- Median PN duration of 23 weeks (IQR: 13-34 wks)
- Micronutrient deficiencies identified:
  - 33% had at least 1 vitamin deficiency (Vitamin D)
  - 77% had at least 1 mineral deficiency (Iron and Zinc)

---

Yang CF et al. J Pediatr. 2011;159:39-44.e1
Multiple Micronutrient Deficiencies among Patients with Intestinal Failure during and after Transition to Enteral Nutrition


- 178 children
  - (56% boys; 74% Caucasian)
- Mean age: 5.7±4.8 years
- Mean PN duration: 20 months

Primary Diagnosis Associated with IF

Micronutrient deficiencies during transition to FEN and after successful transition

* p<0.05
Risk factors for deficiencies for patients on PN

- Primary gastrointestinal diagnoses
  - Hirschsprung disease
  - Primary Dysmotility
  - Complex Gastroschisis (i.e., gastroschisis with atresia)
    \( p = .003 \)
- Duration of PN \( (p < 0.001) \)

Micronutrient Deficiency Risk Factors after Transition to Full Enteral (FEN)

- Variables associated with deficiencies after successful transition to FEN include
  - Birth weight \( (p=0.03) \)
  - Weight percentiles \( (p=0.02) \)
  - Height percentiles \( (p=0.04) \)
  - PN duration \( (p=0.013) \)

Bone Health in Intestinal Failure

- Bone mineral density (BMD)
  - Abnormal in 12.5%
- Exclusive TPN associated with low BMD \( (p=0.03) \)
- Age (>10 years) was significantly associated with abnormal BMD z score \( (p=0.02) \)
- No association between BMD and 25(OH) vitamin D \( (p=0.31) \)
3 months old patient on TPN since birth referred for Intestinal Rehabilitation.
Who was very irritable and inconsolable
Had anemia and Neutropenia

Differential Diagnosis

- Child abuse
- Osteomyelitis
- Ricketts (Vitamin D and Ca deficiency)
- Scurvy (Vitamin C deficiency)
- Copper deficiency
  - Dietary
  - Menkes-Kinke hair syndrome
Risk factors for copper deficiency

- Removing copper in TPN of cholestasis patients
- Absence of copper in TPN during shortages

Copper Deficiency

- Neutropenia and impaired immunity
- Hypochromic anemia: low concentrations of ceruloplasmin or ferroxidase needed to incorporate iron into HB
  - Iron absorption is decreased in copper deficiency due to decreased activity of copper dependant ferroxidase in the intestine which helps with iron uptake
- Retarded growth
- Osteoporosis
- Depigmentation of hair and skin

Copper Supplementation in Parenteral Nutrition of Cholestatic Infants

Supplementation of parenteral Cu at 20µg/kg/day in cholestatic infants

- Does not lead to a significant increase in Cu toxicity or worsening of liver disease
- Prevents developing copper deficiency

JPEN 2010; 50: 650-654
Case: Worsening Intestinal Dysmotility

- 2 yrs 7 months old child presented to our clinic after being on TPN for 9 months
- He had being evaluated at 2 institutions for feeding aversion, vomiting and intolerance with worsening constipation and abdominal distention since the age of 6 months

Thyroid function test results.

Urinary iodine concentration (UIC): Normalization with enteral formula that provided iodine above RDA
Why Iodine deficiency?

• The current micronutrient mix available for use in children on PN in the US is deficient of iodine
• Absence of enteral iodine leads to deficiency
• Data is sparse to guide regarding time for development of hypothyroidism in absence of iodine in diet

Prevalence of Iodine Deficiency in 24 IF Patients on TPN> 6 months

Receiving < 50% calories from Enteral Nutrition

<table>
<thead>
<tr>
<th>Spot Urinary Iodine mcg/L</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>≥100</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>&lt;20 (severe)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td>20-50 (moderate)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>51-99 (mild)</td>
<td>2 (10.0)</td>
</tr>
</tbody>
</table>

**Prevalence of Thyroid Dysfunction**

<table>
<thead>
<tr>
<th>TSH (µIU/ml)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>≤4 (normal)</td>
<td>16 (66.7)</td>
</tr>
<tr>
<td>&gt;10 (severe)</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>≤10</td>
<td>18 (75.0)</td>
</tr>
</tbody>
</table>


**Iodine deficiency and chronic PN**

- None of the children with hypothyroidism had autoimmune thyroiditis
- There was no association between duration of PN use and development of iodine deficiency
- Children on chronic PN are at risk for developing iodine deficiency and resultant hypothyroidism; hence, these children should be screened
- Further studies are needed to define the temporal onset of iodine deficiency and timing to thyroid dysfunction related to PN.


**How Should I Monitor My Patient?**
Home PN - Monitoring I

- Weight
- Height
- Head circumference (patients < 3 years age)
- Clinical examination
- Diet assessment by a registered dietitian
- Frequency depends on
  - Clinical stability of patient
  - Duration of PN
    - Labs are initially weekly, spread out with demonstrated stability
  - Developmental assessment in younger children
  - Psychosocial functioning
  - Renal function (Ccr)

Every 1-3 months with more frequent monitoring initially

---

Home PN - Monitoring II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolytes</td>
<td>Weekly to bi-weekly</td>
<td>Monthly</td>
</tr>
<tr>
<td>BUN/creatinine</td>
<td>Weekly to bi-weekly</td>
<td>Monthly</td>
</tr>
<tr>
<td>Ca, P, Mg</td>
<td>Weekly to bi-weekly</td>
<td>Monthly</td>
</tr>
<tr>
<td>vancomycin</td>
<td>once weekly</td>
<td>monthly</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Weekly to bi-weekly</td>
<td>Monthly</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>At 2 weeks</td>
<td>3-6 months</td>
</tr>
<tr>
<td>CH50, platelets</td>
<td>Weekly to bi-weekly</td>
<td>1-3 months</td>
</tr>
<tr>
<td>Iron indices</td>
<td>As indicated</td>
<td>3-6 months</td>
</tr>
</tbody>
</table>

---

Home PN - Monitoring III

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat-soluble vitamins (A, D, K)</td>
<td>As indicated</td>
<td>6-12 months</td>
</tr>
<tr>
<td>Carnitine</td>
<td>As indicated</td>
<td>6-12 months</td>
</tr>
<tr>
<td>Riboflavin, folate/Vitamin B12</td>
<td>As indicated</td>
<td>6-12 months</td>
</tr>
<tr>
<td>Thyroid function parameters</td>
<td>As indicated</td>
<td>1-3 months</td>
</tr>
<tr>
<td>Liver &amp; Biliary tract ultrasound</td>
<td>As indicated</td>
<td>6-12 months</td>
</tr>
<tr>
<td>Bone densitometry</td>
<td>As indicated</td>
<td>12 months</td>
</tr>
<tr>
<td>Trace elements (Cu, Mn, Se, Zn)</td>
<td>As indicated</td>
<td>6-12 months</td>
</tr>
</tbody>
</table>
Preclinic Planning Sessions

• Learning session held weekly with team
• Patient care issues
• Growth (weight, length, head circumference)
• Laboratory Monitoring
  – Data from labs are downloaded into database weekly
  – Database report on individual patients reviewed
    • When were labs last done?
    • Review results
    • What labs need to be done based on monitoring recommendations?
    • What supplements or therapy are appropriate?
• Review of population measures

Management

• Regular use of multivitamin and iron supplements in patients with enteral tolerance
• Parenteral Iron in patients without any enteral tolerance
• Treat identified deficiencies

Summary

• Micronutrient deficiencies persist in patients with IF during and after transition to FEN
• Data support the need for routine monitoring and supplementation of these patients
• Frequent shortages are an emerging challenge
Greetings from the University of Colorado School of Medicine and Anschutz Medical Campus!

Eosinophilic Esophagitis Guidelines
Recommendations from the AGREE publication
NASPGHAN Annual Meeting
Postgraduate Course
October 25, 2018
Hollywood, FL

Glenn T. Furuta
University of Colorado School of Medicine
Digestive Health Institute
Gastrointestinal Eosinophilic Diseases Program
Mucosal Inflammation Program
Children’s Hospital Colorado
Aurora, CO

Disclosures
• Co-Founder of EnteroTrack
• Consultant for Shire
• Royalties from UpToDate
Objectives

• Recognize changes in diagnostic criteria for EoE

• Understand rationale for changes

Diagnostic Criteria

• Clinicians use diagnoses to manage illness, provide appropriate treatment, and predict prognosis.

• Diagnostic criteria provide guidance to clinicians on the specific signs, symptoms, or test results that indicate the presence of an illness, and classifying patients into diagnostic categories facilitates communication among clinicians and researchers.

Coggins et al 2005
Jason et al 2006

2007-Diagnostic Guidelines for clinical research

AGA INSTITUTE

Eosinophilic Esophagitis in Children and Adults: A Systematic Review and Consensus Recommendations for Diagnosis and Treatment

Sponsored by the American Gastroenterological Association (AGA) Institute and North American Society of Pediatrist Gastroenterology, Hepatology, Nutrition

2007-Diagnostic Guidelines for clinical research

**Recommendations.** Acid suppression is useful as a part of fulfilling the diagnostic criteria for EE. In addition, it may be used in lieu of esophageal pH monitoring for patients with established EE who have symptoms secondary to concomitant GERD. PPI therapy

---

**Suggested Evaluation for EoE 2007-2011**

- Symptoms suggestive
- Treat with High Dose PPI
- Histology
  - Abnormal-EoE
  - Normal-GERD

---

**What is my patient’s diagnosis?**

- Normal-not EoE?
  - How long to treat?
  - How do I follow up patients after I stop PPI?
  - What happens if symptoms recur?
    - EGD on or off of PPI

GERD, EoE, something else?
Symptom
Eos
EoE
No Eos
EGD on PPI
2 months
PPI exposure
One endoscopy
Eos
EoE
No Eos
Symptoms return, EGD off PPI
4-6 months
PPI exposure
Two endoscopies
EGD
No Eos?
Other esophagitis?
GERD?
NERD?
Functional?
4-6 months
PPI exposure
Two endoscopies

PPI treatment impact on esophageal eosinophilia
11 studies, n=311

Adults- 7 studies, n=159
PPI Response
49% (n=78)

Children-4 studies, n=152
PPI Response
32% (n=48)

2008-2011-Clinical impact of PPI

ORIGINAL ARTICLES—ALIMENTARY TRACT

Esophageal Eosinophilic Infiltration Responds to Proton Pump Inhibition in Most Adults

153
2011-Diagnostic Guideline Revision

Eosinophilic esophagitis: Updated consensus recommendations for children and adults

An emerging body of literature and clinical experience describes a subset of patients whose symptoms and histopathologic findings are responsive to PPI treatment and who might or might not have well-documented GERD. Until more is known regarding this subgroup of patients, these patients should be given diagnoses of PPI-responsive esophageal eosinophilia. Future studies should be performed to determine whether PPIs help to diminish an immune/antigen-driven response, as is known to occur in patients with EoE.

2008-2017

Ability to rule out GERD as a cause for esophageal eosinophilia was challenging and became confusing

Or

maybe, patients can have both GERD and EoE or another form of esophagitis
A working Group on ppi-REE (AGREE) Conference

May 5, 2017
Northwestern University
Chicago, IL

AGREE

- 12 month process involving 53 physicians (GI, allergy, pathology)
- 4 teams reviewed world’s literature
  - Biologic impact of PPI
  - Evidence of PPI role in children and adults
  - Assessment of GERD
- 8 hour Face to Face meeting- DDW 2017

AGREE

32 adult and 21 pediatric members

- NASPGHAN members (13) - Rachel Rosen, Sam Nurko, Sandeep Gupta, Mina Chehade, Josh Wechsler, Barry Wershil, Chris Liacouras, Phil Putnam, Amanda Muir, Calies Menard-Katcher, Vince Makkada, Carlo Di Lorenzo

- Pan Asian Member (1) - Yoshi Ohtsuka

- ESPGHAN members (5) - Rok Orel, Christoph Dupont, Neil Shah, Jorge Dias, Noam Zevit

- LASPGHAN (2) - Mario Viera, Cristina Targa

Dellon E et al Gastroenterology 2018
Why have AGREE?

• Discuss strengths of literature supporting current views and practice

• Determine clinical pathways that promote safe, impactful and cost effective approaches for evaluating and treating children and adults with esophageal eosinophilia.

• Power in a conversation!

New EoE Definition

• Symptoms of esophageal dysfunction

• AND

• At least 15 eos/hpf (or ~60 eos/mm²) on biopsy

• Competing causes of esophageal eosinophilia (GERD, achalasia, Crohn’s disease, etc) have been ruled out

Proposed Algorithm

Clinical Presentation suggestion of EoE

EOD with biopsy

Eosophageal eosinophilia > 15 eos/hpf (~60 eos/mm²)

Evaluate for non-EoE disorders that cause or potentially contribute to esophageal eosinophilia

Eosinophilic Esophagitis
17 year old male with food impaction

- Atopic
- Family history of esophageal stretching
- EREFS-5
  - Stricture-1

10 year old male with heartburn

- Regurgitation of food and episode of hematemesis
- Family history of Barrett's esophagus
- Friable mucosa
- EREFs-0

Differential Diagnosis of food impaction

- Complicated GERD
- Achalasia
- Congenital Stricture
- Hiatal hernia
- Cancer

Hirano I et al Gut 2012

Edema-1
Rings-1
Exudate-1
Furrows-1
Differential Diagnosis of heartburn and regurgitation

- GERD
- Anatomic or functional partial obstruction
- NERD / Functional
- EoE
3 year old female with feeding problems

- Feeding refusal and prolonged meals
- Atopic
- No weight gain for 3 months
- EREFs-3

Symptom
- No Eos
- GERD/other Eos EoE GERD

EGD on no treatment
- 1 week One endoscopy
- 2 months Two endoscopies
- PPI Diet TCS PPI Other
- Clinical evaluation
- Other esophagitis
- EoE
- No EoE

Evaluation for EoE 2018

Use clinical judgement

- Clinical evaluation suggestive of EoE
  - History of food impaction
  - Highly atopic patient
  - Family history of EoE
  - Negative pH monitoring
  - Endoscopic assessment suggests EoE
    - Exudates, proximal stricture, longitudinal tear
Evaluation for EoE 2018

*Use clinical judgement*

- Clinical evaluation suggestive of GERD
- Symptoms consistent with GERD
- Responsiveness to PPI
- Abnormal pH impedance monitoring
- Family history of GERD, fundoplication
- Endoscopic assessment suggestive of GERD
  - Erosions, Barretts

Just tell me what to do please?

- Evaluate patients for presenting symptoms
- When indicated, perform EGD off of PPIs
- Interpret histological findings in the context of all of the presenting features and testing
- Treat after discussion with family regarding outcomes, risks, benefits and quality of life
- Consider repeating endoscopy in future to assess for mucosal healing
- FOLLOW PATIENT during annual visit

Challenges of new diagnostic algorithm

- Institute clinical practice change
- Define clinical trial entry criteria
- Determine the durability of PPI treatment
- Identify optimal follow up of patients
- Monitor for PPI side effects
Special Cases

• “Asymptomatic inflammation”

• Other GI diseases and esophageal eosinophilia

• Eosinophilic inflammation of stomach, small intestine or colon and esophageal eosinophilia

• Immunotherapy and esophageal eosinophilia

Future needs

• Biomarkers of EoE, GERD and others-
  - Can I measure something other than tissue eosinophilia?
  - Exhaled NO
  - Peripheral eosinophilia
  - Gene
  - Functional

Future needs

• Natural history of EoE-
  • Do EoE patient require repeated EGDs?
  • Do patients outgrow EoE?
  • Do all patients develop strictures if left untreated?
  • Does EoE lead to cancer?
Future needs

• Natural history of PPI responsiveness
  • What do I do with my patient who is taking PPIs?
  • How long does PPI effect persist?
  • How long to take PPI?
  • How to follow patients on PPIs?
Immune Mediated Acute Liver Failure in Childhood

Is it the Real-Deal, or Fake News

Estella M. Alonso, M.D.
Siragusa Transplant Center
Ann and Robert H. Lurie Children’s Hospital
Feinberg School of Medicine
Northwestern University, Chicago, IL

Disclosures

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

Objectives

• Review causes of PALF secondary to immune mediated liver injury
  • Autoimmune hepatitis
• Describe the phenotype of PALF with immune dysregulation and distinguish from PALF due to autoimmune hepatitis.
• Examine immunologic biomarkers of immune activation in patients with PALF
• Discuss relationship between levels of immune activation and outcomes in PALF
Immune Mediated Hepatocyte Injury

- Autoimmune Hepatitis
- Drug induced autoimmune type injury
  - Minocycline
  - Hydralazine
- DRESS
- HLH/MAS
- Drug induced immune dysregulation
  - CTLA-4 check point inhibitors
- Indeterminate PALF

Making a Diagnosis

Indeterminate versus Undetermined

What's the Difference? Who Decides?

- Few patients receive a full diagnostic work-up
- Evaluation guided by clinical presentation and history
- Prioritization of blood samples in small children
- Death or transplantation prior to completion of work-up
- Indeterminate patients are younger and more likely to receive liver transplantation
- Investigation of metabolic and autoimmune disorders is frequently incomplete
  - Somewhat more complete in younger children
  - Utility of urine toxicology screen, lactate/pyruvate ratios
    - Very few have lactate and pyruvate levels

Table IV: Frequency of diagnostic testing for autoimmune hepatic autoantibodies

<table>
<thead>
<tr>
<th>Testing</th>
<th>Number of samples tested</th>
<th>Number of positive results</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMA</td>
<td>253 (72%)</td>
<td>197 (78%)</td>
</tr>
<tr>
<td>SMA</td>
<td>233 (70%)</td>
<td>159 (68%)</td>
</tr>
<tr>
<td>ANA</td>
<td>288 (82%)</td>
<td>170 (59%)</td>
</tr>
<tr>
<td>dsDNA</td>
<td>61 (15%)</td>
<td>32 (52%)</td>
</tr>
<tr>
<td>JCA</td>
<td>97 (27%)</td>
<td>34 (35%)</td>
</tr>
<tr>
<td>LA</td>
<td>72 (20%)</td>
<td>33 (46%)</td>
</tr>
<tr>
<td>Antistrials</td>
<td>70 (20%)</td>
<td>33 (47%)</td>
</tr>
</tbody>
</table>

≥ 7 months had k and FAO defects

[Image of a table showing frequencies]
### 21 day Outcome (N = 945)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dead (N=119)</th>
<th>Transplant (N=280)</th>
<th>Alive (N=545)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indeterminate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ANCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead (N=119)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant (N=280)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive (N=545)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### AIH Diagnostic Criteria

- Autoantibody positive or elevated IgG
  - < 1:80 definitely positive
  - 1:40 may be positive in children
  - ANA positive in up to 12% of healthy children
- Compatible histology
  - Clear interface hepatitis, with or without lobular activity
  - Plasmacytic infiltrate
  - Granulomas or significant bile duct injury may suggest alternate diagnosis or overlap with PSC
- Exclusion of other diagnosis
  - Age appropriate work-up
  - Wilson's disease can have similar histology

### AIH Histology

![Histology Image]
Immunohistochemistry of AIH

Possible pathways of autoimmune attack of hepatocytes in AIH

AIH vs Indeterminate PALF


Di Giorgio et al. JPGN 2015;60:159-64
AIH-PALF Treatment Response

- ALF Study Group experience
  - Steroids did not improve patient survival in any individual diagnostic group
  - Improved spontaneous survival in patients with the highest ALT levels (54% versus 25%, p=0.003)
- Pediatric experience
  - Most reports describe response even with fibrosis
  - Bacterial infections more common after the third week

Aplastic Anemia (AA)

- Can occur coincident or following hepatitis presentation
- Can present after liver transplantation
- May be the dominant medical problem with liver injury not resulting in synthetic failure
- PALF Study Group 4-7% cumulative risk of AA at 12 months
  - PALFSG II 7/178 (4%) Indeterminate patients
  - PALFSG III 3/44 (7%) Indeterminate patients

Indeterminate ALF with AA

Single center study of IND-ALF cases presenting over 15+ years. Aplastic Anemia developed in 9 (8%) of 110 IND cases. All were classified as aplastic after liver transplantation. Cases were matched to 47 IND-ALF survivors without AA.
Emerging Theory of Dysregulated Immune Responses

• Biomarkers of immune activation similar to HLH and MAS
• Patients with strongest evidence of immune activation have lowest spontaneous survival
• Overlapping phenotype in survivors and liver transplant recipients
• Dysregulated immune responses not exclusive to indeterminate cases

Cytokine Storm Syndromes

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLH</th>
<th>MARS/EBV-HLH</th>
<th>MAS</th>
<th>Immunodeficiency</th>
<th>Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of inflammation</td>
<td>Host</td>
<td>Environmental</td>
<td>Immune</td>
<td>Cytokine</td>
<td></td>
</tr>
<tr>
<td>Treatments</td>
<td>Bone marrow transplant</td>
<td>Cytokine inhibitors</td>
<td>Immune supplementation</td>
<td>Anti-oxidants</td>
<td></td>
</tr>
</tbody>
</table>

Courtesy of Ed Behrens, Children’s Hospital of Philadelphia

Diagnosing HLH in PALF

Table E: Diagnostic criteria for HLH according to the HLH-2004 trial

Diagnosis of HLH may be established if patient fulfills 5 or 6 of the following:
1. Fever > 38.5°C
2. Splenomegaly
3. Cytopenia: platelets < 100,000/mm³ or 60% decrease in 1 week
4. Petechiae
5. Neutropenia (< 1500/mm³)
6. Hypertriglyceridemia (fasting > 2.5 times normal or 500 mg/dl)
7. Hypoalbuminemia (serum albumin < 3.0 g/dl)
8. Hemophagocytosis in bone marrow, liver, spleen or lymph nodes
9. Low or absent NK cell activity
10. Elevated ferritin

From Behrens et al. 2004 (86)}
Biomarkers of Immune Activation in PALF

- Markers of immune activation collected within 48 hrs of study entry
  - Plasma IL2R levels, Natural Killer (NK) lytic activity, Perforin + NK cells, Perforin + CD8 cells, Perforin + NK cells, Granzyme + NK cells, Granzyme + CD8 cells
- Clinical outcome and biochemical markers of liver function
  - Excluded if steroids or biological prior to sample collection
  - 77 patients included, 35% indeterminate
- Outcome at 21 days
- Soluble IL2 Receptor α
  - Significantly higher in patients that died (p<0.02) or had LT (p<0.01)
  - Values > 5000 IU/mL
  - All 30 patients with normal levels survived

Serum Inflammatory Markers Predict Outcomes

- 49 patients with at least 3 samples within first 7 days
- Assessed 26 inflammatory mediators
  - Chemokines, cytokines and reactive nitrogen species
- Outcomes at 21 days
- Dynamic Bayesian Network Analysis
  - Differentiated survivors
  - Raw mediator levels not predictive

= Azhar, N et al PLOSone 2013;8:e78202
Relevance of Autoantibodies in PALF

- Overall 28% of PALF patient autoantibody positive
  - 94% with AIH
- Autoantibodies not significantly associated with 21 day outcomes

Prevalence and Significance of Autoantibodies in Children With Acute Liver Failure

Pediatric Transplantation Volume 18, Issue 5, pages 503-509, 14 JUN 2014 DOI: 10.1111/petr.12296

- Hypothesized that indeterminate PALF cases would exhibit a unique pattern of hepatic inflammation
- Compared archived specimens from iPALF, AIH and dPALF
  - Small prospective study of LT recipients
  - IHC staining with scoring minimal, moderate, dense
  - CD8-cytotoxic T-cells
  - Perforin
  - CD103- tissue resident memory T-cells
- TCRβ sequencing of prospective iPALF cases demonstrated increased clonality compared to dPALF and control cases

The role of CD8+ T cell hepatic infiltration in indeterminate PALF

- Hypothesized that indeterminate PALF cases would exhibit a unique pattern of hepatic inflammation
- Compared archived specimens from iPALF, AIH and dPALF
  - Small prospective study of LT recipients
  - IHC staining with scoring minimal, moderate, dense
  - CD8-cytotoxic T-cells
  - Perforin
  - CD103- tissue resident memory T-cells
- TCRβ sequencing of prospective iPALF cases demonstrated increased clonality compared to dPALF and control cases

**Results**

56 PALF cases:
- 33 iPALF
- 9 AIH
- 14 dPALF

- 6 Drug toxicity
- 5 Wilson’s
- 3 Mitochondrial

<table>
<thead>
<tr>
<th>Characteristics of Indeterminate, Autoimmune Hepatitis, and Diagnosed PALF</th>
<th>iPALF n=33</th>
<th>AIH n=9</th>
<th>dPALF n=14</th>
<th>P value all 3</th>
<th>P value iPALF vs. AIH</th>
<th>P value iPALF vs. dPALF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>4 (1-17)</td>
<td>9 (1-14)</td>
<td>15 (2-17)</td>
<td>0.004*</td>
<td>0.11**</td>
<td>0.002**</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>22 (67)</td>
<td>5 (56)</td>
<td>5 (36)</td>
<td>0.15 †</td>
<td>0.70</td>
<td>0.05 †</td>
</tr>
<tr>
<td>Sample type used for study, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explant/wedge biopsy</td>
<td>28 (85)</td>
<td>7 (78)</td>
<td>7 (54)</td>
<td>0.04</td>
<td>0.48</td>
<td>0.03</td>
</tr>
<tr>
<td>Needle biopsy</td>
<td>5 (15)</td>
<td>2 (22)</td>
<td>7 (54)</td>
<td>0.06</td>
<td>0.48</td>
<td>0.03</td>
</tr>
<tr>
<td>21-day outcome, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous recovery</td>
<td>7 (21)</td>
<td>0</td>
<td>2 (15)</td>
<td>0.09</td>
<td>1.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>26 (79)</td>
<td>7 (78)</td>
<td>7 (54)</td>
<td>0.00</td>
<td>1.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>3 (21.5)</td>
<td>0.00</td>
<td>1.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Developed aplastic anemia, n (%)</td>
<td>8 (24)</td>
<td>0</td>
<td>0</td>
<td>0.05</td>
<td>0.17</td>
<td>0.08</td>
</tr>
</tbody>
</table>

**CD8+ T cell predominant hepatic infiltration in iPALF**

8 iPALF patients had soluble interleukin-2 receptor levels measured
- Elevated for age in 6 (75%), with 4 having dense, 1 moderate, and 1 minimal CD8 staining
- All of the 8 iPALF patients that developed AA had dense (n=7) or moderate (n=1) CD8 staining
- 3 had peripheral blood flow cytometry performed which was notable for a low CD4:CD8 ratio of ≤1.0 in all cases
**CD103 Staining**

Dense IHC staining for CD103 in 16 (62%) iPALF vs 1 (12%) AIH and no dPALF cases (p<0.001)

**TCRβ Sequencing**

TCRβ sequencing of iPALF cases demonstrated increased clonality compared to dPALF and control cases (p < 0.01)

Clonality assessed by:
- Measuring % of reads that composed the top 20 clones
- Measuring % overlapping clones between duplicates of each sample (expected to be higher if specific clones dominate the specimen)

**Liver Biopsy can be safe in PALF**

- Major complications are infrequent
  - 1/26 with Hgb drop requiring PRBCs
- No hemodynamic instability
- Transjugular route in infants > 10 kg
- Biopsy results contribute to diagnosis or management in 62%

Chapin et al JPGN 2018 Jul 19. doi: 10.1097
PALFSG Immune Activation

Subjects Enrolled N= 158
Study Sample at Enrollment N= 50
Excluded N= 3
Analyzed N= 47
No Study Sample N= 108

Of those Analyzed:
Age, median (Q1, Q3): 13.0 (4.0-15.0)
Male: 51.1%

Final Diagnosis of 47

Unsupervised cluster analysis segregates PALF subjects into 3 groups based on degree of immune activation...

PALF subject immune activation state correlates with 21 day outcomes...
Establishing an Immunophenotype

- Immunedysregulation
  - Is it a disease or an complication
  - Is some level of immune activation necessary for tissue repair and regeneration

- Diagnosis
  - Measures of immune activation in peripheral circulation
  - Liver Biopsy

- Treatment
  - Would immunosuppression interrupt harmful inflammatory cascades or dampen regeneration
  - Would translational studies lead to targeted biological therapy

Summary

- A significant subset of patients with indeterminate PALF may have immune dysregulation as the etiology of their ongoing hepatic injury
- PALF with immune dysregulation is characterized by a dense CD8+ T-cell hepatic infiltrate consistent with expansion of a tissue resident memory T-cell phenotype
  - Liver biopsy can be performed safely in PALF
- Patients who meet criteria for AIH may have immune activation status that is intermediate between iPALF and dPALF
- Peripheral markers of immune activation may identify phenotype and predict outcomes
  - sIL2-r
  - Reversal of CD4/CD8 ratio
Innovations in the Genomics of Neonatal Cholestasis

Stephen L. Guthery, MD
Professor, Pediatrics
Professor, Human Genetics (Adjunct)
Pediatric Gastroenterology, Hepatology and Nutrition
University of Utah
Intermountain Primary Children's Hospital

Disclosure

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

I will discuss clinical sequencing laboratories from which I receive no funding.

Cholestasis in infants
Adapted from Gottesman et al, 2015
17 Studies, 12 countries, 1692 patients
Objectives

1. Understand the consequences of next generation sequencing.
2. Rekindle your interest in Mendelian inheritance.
3. Review the "clinical significance" nomenclature for genetic variants.
4. Become familiar with four new cholestatic liver diseases and their clinical relevance.

"Next Generation Sequencing"

- Human Genome Project
- Sequencing chemistry
- File compression methodology
- Computational power
- Analytical tools
- Next generation sequencing
  - Rapid
  - Inexpensive
  - Accurate
  - Massive amounts of data
Accessibility is the consequence of next generation sequencing

1. We have the ability to clinically sequence a gene panel or the entire “exome”.
2. Gene panels and exomes are routine for suspected Mendelian disorders.
3. Rapid innovations in how tests are ordered.
4. Rapid advances in disease discovery.

An “exome” is all protein coding regions in a genome

- All exons = “exome”
- 1% of the genome
- Main assumption: most Mendelian diseases are due to mutations in protein coding regions

~20,800 Genes
~200,000 exons

United Healthcare Community Plan Medical Policy

- “Whole Exome Sequencing (WES) is proven and/or medically necessary and covered…”
- “Comparator (e.g., parents or siblings) WES is proven and/or medically necessary for evaluating a genetic disorder when the above criteria have been met and WES is performed concurrently or has been previously performed on the individual…”

A gene panel: subset of genes of interest known to cause a phenotype

Emory Genetics Laboratory Adult and Neonatal Cholestasis Panel
66 genes

Invitae Primary Immunodeficiency Panel
207 genes

King’s College cholestasis panel: 27 genes

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Disorders</th>
<th>Bile acid synthesis disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRPS8</td>
<td>Dubin-Chanarin syndrome</td>
<td>Δ(4)-3-oxosteroid 5-β-reductase</td>
</tr>
<tr>
<td>FIC1</td>
<td>Naranjo-Sickel disease type C</td>
<td>3-β-hydroxy-Δ-5-C27-steroid oxidoreductase</td>
</tr>
<tr>
<td>TJP2</td>
<td>ABC syndrome</td>
<td>Dehydro-7 α-hydroxylase</td>
</tr>
<tr>
<td>MKK6</td>
<td>Neonatal suffering cholangitis</td>
<td>Bile acid CoA ligase</td>
</tr>
<tr>
<td>FMR1</td>
<td>GRACIE syndrome</td>
<td>Bile acid-CoA:amino acid N-acyltransferase</td>
</tr>
<tr>
<td>Citrin</td>
<td>Engleman-Najjar syndrome</td>
<td>Cholesterol 7-α-hydroxylase</td>
</tr>
<tr>
<td>BSEP</td>
<td>Neonatal ichthyosis-cholangitis syndrome</td>
<td>α-methylacyl-CoA racemase</td>
</tr>
<tr>
<td>G5l</td>
<td>Giant syndrome</td>
<td>Sterol 27-hydroxylase</td>
</tr>
</tbody>
</table>

Improved access for patients: Invitae

- Provides out-of-pocket cost estimates
- Ease of ordering for clinicians
  - Prior authorization
  - Automatically generated letter of medical necessity
  - Collection kits sent directly to patients
- "Invitae now offers testing for all diagnostic and proactive panels to first-degree family members at no additional charge to help inform and empower more families"
Spectrum of genetic contribution to disease


Environment

Alcohol related liver disease
Viral hepatitis
Crohn disease (~14%*)

Genetic

PFIC
Niemann-Pick
Alagille syndrome
Citrin deficiency
Bile acid synthetic disorders

Autosomal recessive disorder I: both copies of gene contain the same pathogenic mutation.

Autosomal recessive disorder II: each copy of gene contains different pathogenic mutations. Compound heterozygosity.
Autosomal dominant: single mutation in a gene is sufficient to cause disease

Autosomal dominant with *de novo* mutation

Nomenclature to describe clinical significance of identified variants

Pathogenic/likely pathogenic

Variant of uncertain significance

Benign/likely benign

Variant of uncertain significance = non-diagnostic result (probably)

“The p.M3642I mutation in PKHD1 variant has been reported in individuals with autosomal polycystic kidney disease... however, there was not sufficient information in the reports to conclude this variant as causative of disease... Together, the data is insufficient to determine the clinical significance and p.M3642I is classified as a VOUS”

Assigning causality in a genetic test result

Must follow Mendelian inheritance.
- Autosomal recessive disorders require mutations on both chromosomes
- Autosomal dominant disorders require a single mutation
- Compound heterozygosity may require parental sequencing to define causality
  Caveat: sometimes assays miss the other variant

Must be clinically significant to be disease causing
- Must be pathogenic or likely pathogenic.
  Caveat: Variants of uncertain significance may be disease causing in the future, but not at the time you receive the report.

Compound heterozygosity can only be identified by testing parents
**Bile acid transport disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFIC1</td>
<td>ATP8B1</td>
</tr>
<tr>
<td>PFIC2</td>
<td>ABCC10</td>
</tr>
<tr>
<td>PFIC3</td>
<td>ABCC8</td>
</tr>
<tr>
<td>Dubin-Johnson syndrome</td>
<td>ABCC9</td>
</tr>
</tbody>
</table>

**Bile acid synthesis disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBAS 1</td>
<td>HSD3B7</td>
</tr>
<tr>
<td>CBAS 2</td>
<td>AKR1D1</td>
</tr>
<tr>
<td>CBAS 3</td>
<td>CYP7B1</td>
</tr>
<tr>
<td>CBAS 4</td>
<td>AMACR</td>
</tr>
</tbody>
</table>

**Cholesterol and/or triglyceride synthesis disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolemia</td>
<td>LDLR</td>
</tr>
<tr>
<td>Familial hypertriglyceridemia</td>
<td>LPL</td>
</tr>
</tbody>
</table>

**Tight junction disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFIC4</td>
<td>TJP2</td>
</tr>
</tbody>
</table>

**Mutations in TJP2 cause progressive cholestatic liver disease**

- Mutations in TJP2:
  - Normal GGT cholestasis
  - Nine out twelve required transplantation
  - Designated PFIC4 by OMIM
  - Zhou et al reported two patients with HCC
  - Autosomal recessive

- Abnormalities in cholangiocyte-cholangiocyte light junctions leads to cholestasis
  - TJP2 is necessary for claudin-1 localization in cholangiocytes
  - Mutations in CLDN1 gene cause ILVASC syndrome

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

- Mutations in NR2H4:
  - Normal GGT cholestasis
  - Severe coagulopathy
  - Rapid progression
  - Designated as PPICs by OMIM
  - Autosomal recessive

- FXR is a master regulator of bile acid production
- FXR activation leads to decreased intracellular bile acid levels
- FXR agonists are in clinical trials for treatment of cholestatic liver disease

**FXR**

Adapted cholic acid image courtesy of Mcstrother: https://commons.wikimedia.org/wiki/File:Cholic_Acid_vs_Other_Bile_Acids.svg

**Mutations in NR2H4**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolemia</td>
<td>LDLR</td>
</tr>
<tr>
<td>Familial hypertriglyceridemia</td>
<td>LPL</td>
</tr>
</tbody>
</table>

**Disorders of bilirubin metabolism**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbert’s syndrome</td>
<td>UGT1A1</td>
</tr>
<tr>
<td>Crigler-Najjar syndrome type I</td>
<td>UGT1A1</td>
</tr>
<tr>
<td>Crigler-Najjar syndrome type II</td>
<td>UGT1A1</td>
</tr>
</tbody>
</table>

**FXR**

Adapted cholic acid image courtesy of Mcstrother: https://commons.wikimedia.org/wiki/File:Cholic_Acid_vs_Other_Bile_Acids.svg

**FXR**

183
Mutations in **DCDC2**:  
- Neonatal sclerosing cholangitis  
- High GGT cholestasis  
- Milery omentum  
- Giant cell changes not prominent  
- Ductular reaction with bile duct plugs  
- Autosomal recessive

Mutations in **MYO5B**:  
- Normal GGT cholestasis  
- Phenotypically similar to PFIC1 & PFIC2  
- Age of presentation was 7-15 months  
- One patient with normal duodenal biopsy  
- Autosomal recessive

**Summary**  
1. Innovations in genomics improves access to genetic testing for Mendelian disorders.  
2. When interpreting genetic test reports, consider what is known about Mendelian inheritance and "clinical significance" of genetic variants.  
   1. Autosomal recessive disorders require mutations on both chromosomes  
   2. Autosomal dominant disorders require a single mutation  
   3. Consider compound heterozygosity in "sporadic" Mendelian disease and it may require parental sequencing to define causality  
   4. Variants must be classified as pathogenic or likely pathogenic to be disease causing*

3. New genetic discoveries are providing insight into mechanisms of cholestasis:  
   1. Tight junction disorders- TJP2  
   2. Cholangiociliopathies- DCDC2  
   3. Bile acid receptor defects- NR1H4  
   4. Phenotype expansion- MYO5B

*Variants of uncertain significance may be disease causing in the future
A few references


Treatting Hepatitis B & C in Children: What’s New?

Philip Rosenthal, M.D.
Professor of Pediatrics & Surgery
University of California, San Francisco

Disclosure

- I have the following financial relationships with the manufacturers of any commercial product(s) and/or provider of commercial services discussed in this CME activity:
- Research Support from: Roche/Genentech, BMS, Gilead, Abbvie, NIH
- Consultant for: Roche, Gilead, Intercept, Alexion, Retrophan, Alibreo, Audentes
- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

Objective

- To understand new treatment options for children with chronic hepatitis B viral infection
- To understand new treatment options for children with chronic hepatitis C viral infection
HBV Genotypes

- 8 Genotypes identified: A-H
- Based on ≥ 8% divergence of HBV complete sequence
- Sub-genotypes: Differ in complete genomic sequence by between 4% and 8%
- Disease outcome appears to be strongly associated with HBV genotype
Epidemiology of HBV in Children

- In much of the world, the lifetime risk of contracting HBV is >60%
- In the US, universal infant vaccination was instituted in 1991
  - The incidence of acute hepatitis B has declined significantly
  - Chronic hepatitis B remains a substantial problem due to:
    - Vertical transmission
    - Immigration from areas of endemicity
    - Infection by HBsAg+ household contacts
- Chronic HBV infection develops in
  - 90% of infants infected as neonates
  - 25-50% of children aged 1-5 years who are acutely infected

Treatment of Chronic Hepatitis B

- What is the evidence that treatment improves outcome?
- Who should be treated?
- When should treatment be initiated?
- How long should antiviral treatment be given?
- How do we deal with antiviral resistance?

Chronic Hepatitis B in Children

- The largest proportion of children and young adults are in the immune tolerant phase of the natural history of infection
  - They have very high viral loads and normal ALT levels
  - Level of viremia at this stage is probably not predictive of risk of liver disease or hepatocellular carcinoma (HCC)
  - Therapies are ineffective (and probably not needed) at this stage of infection
- Children with consistently elevated ALT or those with a family history of HCC should be referred for further evaluation and consideration of treatment
Therapeutic Options for the Child Chronically Infected with HBV

- **PEG-IFN alfa 2a** for >3 yo and **entecavir** >2 yo are the preferred therapies for children 2-12 years of age.
- Both **adefovir** and **tenofovir** are approved for children 12 years of age and older.
  - Adefovir is rarely used, since virologic responses were less robust.
  - Tenofovir is currently being tested in children less than 12 years of age.
- **Lamivudine**, while labeled for ages 3 and older, is the least favored nucleos(t)ide analogue option.
  - There is a high risk of developing antiviral resistance.

### HBV Response to Therapy in Children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age Indication (years)</th>
<th>Primary Endpoint</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN alfa-2b</td>
<td>&gt;1</td>
<td>Loss of HBV DNA and HBeAg after 24 weeks of treatment.</td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>&gt;3</td>
<td>Loss of HBV DNA and HBeAg reversion at wk 48</td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td>&gt;12</td>
<td>HBV DNA &lt; 100 c/ml and normal ALT at wk 48</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>&gt;12</td>
<td>HBV DNA &lt; 400 c/ml at wk 72 and HBeAg seroconversion and HBV DNA &lt; 50 IU/ml.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% Reached Endpoint</th>
<th>Treated/placebo</th>
<th>% HBeAg Seroconversion</th>
<th>Treated/placebo</th>
<th>% HBsAg Loss or Seroconversion</th>
<th>Treated/placebo</th>
<th>% Viral Resistance at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of HBV DNA</td>
<td>26/11*</td>
<td>25/13*</td>
<td>19/2*</td>
<td>860*</td>
<td>24/24*</td>
<td></td>
</tr>
<tr>
<td>Loss of HBeAg</td>
<td>22/15</td>
<td>165</td>
<td>21/15</td>
<td>24/4/12.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg Seroconversion</td>
<td>Not reported</td>
<td>2/0</td>
<td>1/subject</td>
<td>3/1 subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg Loss or Seroconversion</td>
<td>10/1.2</td>
<td>2/0</td>
<td>1/subject</td>
<td>3/1 subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral resistance at 1 year</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Approved Antiviral Therapies in Children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use in Children</th>
<th>Treatment Category</th>
<th>Common Side Effects</th>
<th>Monitoring for Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN alfa 2a</td>
<td>&gt;3y 180 mcg/1.73 m^2 SC qwk</td>
<td>C</td>
<td>Flu-like symptoms, fatigue, mood disturbances, hypotension, asthenia, diarrhea, arrhythmias and weight loss in children</td>
<td>CBC (monthly to every 3 months) TSH (every 3 months) Clinical monitoring for autoimmune, hepatic, neuropsychiatric, and infectious complications</td>
</tr>
<tr>
<td>IFN alfa 2b</td>
<td>&gt;3y 6 million IU/m^2 SC x 2wk</td>
<td>C</td>
<td>Flu-like symptoms, fatigue, mood disturbances, hypotension, asthenia, diarrhea, arrhythmias and weight loss in children</td>
<td>CBC (monthly to every 3 months) TSH (every 3 months) Clinical monitoring for autoimmune, hepatic, neuropsychiatric, and infectious complications</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>&gt;2y 3 mg/kg daily to max 100 mg</td>
<td>C</td>
<td>Pancreatitis, Lactic acidosis</td>
<td>Amostras if symptoms, Lactic acid levels if clinical concern</td>
</tr>
</tbody>
</table>
Approved Antiviral Therapies in Children

Drug | Use in Children | Pregnancy Category | Potential Side Effects | Monitoring on Treatment
---|---|---|---|---
Entecavir | <2 y weight-based to 10 kg, above 10 kg 0.5 mg daily | C | Lactic acidosis | Creatinine clearance at baseline. If at risk for renal impairment, measure baseline creatinine, serum phosphate, calcium, and parathyroid hormone and protein at least annually. Consider bone density study at baseline and during treatment, especially in children with history of fracture or risk for osteopenia. Lactic acid levels if clinical concern.
Adefovir | >12 years 10 mg daily | C | Acute renal failure, Fanconi syndrome, Nephrogenic diabetes insipidus, Lactic acidosis | Creatinine clearance at baseline. If at risk for renal impairment, measure baseline creatinine, serum phosphate, calcium, and parathyroid hormone and protein at least annually. Consider bone density study at baseline and during treatment, especially in children with history of fracture or risk for osteopenia. Lactic acid levels if clinical concern.
Tenofovir disoproxil fumarate | >12 years 300 mg daily | B | Nephropathy, Fanconi syndrome, Osteomalacia, Lactic acidosis | Creatinine clearance at baseline. If at risk for renal impairment, measure baseline creatinine, serum phosphate, calcium, and parathyroid hormone and protein at least annually. Consider bone density study at baseline and during treatment, especially in children with history of fracture or risk for osteopenia. Lactic acid levels if clinical concern.

Chronic Hepatitis B in Children:
Therapeutic Challenges

- The minority of children require treatment
- Therapeutic options are limited compared to those available in adults
- Inappropriate treatment confers the potential for viral resistance to current and future therapies
- Patient selection and timing are the most critical challenges
Long-Term Goals of Antiviral Therapy

- Decrease risk of development of cirrhosis
- If cirrhosis is present, decrease risk of decompensation
- If decompensated cirrhosis present, treat to revert patient to compensated cirrhosis
- Decrease risk of development of hepatocellular carcinoma

Goals of therapy: HBeAg-Positive

- HBeAg-positive
  - Best response if ALT > 2 times upper limit of normal (80 U/L)
  - HBeAg loss and seroconversion to anti-HBe
  - Durable suppression of HBV DNA to low or undetectable levels
  - Normalization of ALT
  - Durability of HBeAg seroconversion ≈70–90%

Goals of therapy: HBeAg-Negative

- HBeAg-negative
  - Treat persons with at least moderate hepatitis or fibrosis (Ishak, Metavir stage 2/4)
  - HBeAg seroconversion not an endpoint
  - Durable suppression of HBV DNA to low or undetectable levels
  - Normalization of ALT
  - Long-term therapy the rule with oral agents
**Duration of Treatment**

- **HBeAg-positive:**
  - Until at least 6 months after loss of HBeAg and appearance of anti-HBe
- **HBeAg-negative (anti-HBe positive):**
  - Interferon: 1 year
  - Nucleoside analogues: Indefinitely

**Hepatitis C Virus**

- Capsid
- Envelope protein
- Protease/helicase
- RNA-dependent RNA polymerase

- **Epidemiology of HCV in Children**
  - An estimated 13.2 million children between the ages of 1 and 15 years are infected worldwide. This represents 10% of the WHO estimate for global HCV prevalence.
  - U.S.: 0.4-0.6% of asymptomatic children are positive for anti-HCV (NHANES III)
  - Higher rates associated with homeless children, street youth, maternal HCV
  - ~23,000 to 46,000 children in the US with active infection
  - Globally, ~50,000 newborns each year acquire HCV from maternal-neonatal transmission
To Treat or Not to Treat?

- Treatment of children under 3 years of age
  - No FDA approval
- Cirrhosis and hepatocellular carcinoma are rare in childhood
- Liver transplantation is rare in children with HCV
- Interferon-based therapies have unfavorable side-effects
- Treatment of children ≥ 3 years of age
  - To prevent stigma and prevent future cirrhosis and HCC

Pediatric HCV Treatment Regimens with PEG-IFN

- PEG-IFN alpha 2a plus ribavirin
  - Approved for ages 5-18 years
  - Response rates higher for PEG/ribavirin vs. PEG/placebo
- PEG-IFN alpha 2b plus ribavirin
  - Approved for ages 3-18 years
  - 48 weeks for Genotype 1 and Genotype 4; 24 weeks for Genotype 2 and Genotype 3
- Highest SVR in Genotype 2 and Genotype 3 or HCV RNA <600,000 IU/ml

Recommendations for Monitoring During Therapy

<table>
<thead>
<tr>
<th>Laboratory test to be monitored</th>
<th>Obtain on following week of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with diff; Absolute Neutrophil Count</td>
<td>0, 1, 2, 4, 8, 12 and every 4-8 wks. thereafter</td>
</tr>
<tr>
<td>Hepatic panel, glucose</td>
<td>0, 1, 2, 4, 8, 12 and every 4-8 wks. thereafter</td>
</tr>
<tr>
<td>TMBtotal T4</td>
<td>0, 12, 24, 36, 48</td>
</tr>
<tr>
<td>Urine HCG (for females ≥13 years old)</td>
<td>0, 24</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>0, only repeat if clinically indicated</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>0, only repeat if clinically indicated</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>0, 24, 48, 72</td>
</tr>
</tbody>
</table>
PEG-IFN/Ribavirin is Better than PEG-IFN/Placebo in Children with HCV

Genotype Non-1 Is Best Predictor of Sustained Virologic Response to PEG-IFN/Ribavirin in Children with HCV

IFN Treatment Side Effects

- Constitutional
  - Fever, abdominal pain, myalgias in most
- Growth and development
  - Weight z scores fall off during treatment and recover
  - Height z scores fall off during treatment and may take longer to recover off therapy
  - Neutropenia in up to one third may require dose reduction, which does not result in reduced response to treatment or increased infections
5 Year Follow-up in the PEDS-C Study

- Durability - 100% of the children who cleared HCV 5 years ago are still HCV RNA negative

Hepatitis C virus (HCV) genome and drug targets

Sofosbuvir Based Therapies for Adolescents 12-<18 Years of Age or WT >35 kg

- Sofosbuvir 400 mg plus ledipasvir 90 mg orally once daily for 12 weeks for Genotype 1,4,5 or 6 infection without cirrhosis or with mild cirrhosis
- Sofosbuvir 400 mg orally daily plus weight based ribavirin 15 mg/kg/d (see next slide) up to 1200 mg orally in two divided doses for 12 weeks for genotype 2 and 24 weeks for Genotype 3
Weight-based Ribavirin Dosing

- Recommended dosing for Ribavirin in Combination Therapy with Sofosbuvir in Adolescents 12 years of age and older or weighing >35 kg
- Body Weight in Kg  Ribavirin Daily Dosing
  - < 47  15 mg/kg/d
  - 47-49  600 mg/d
  - 50-65  800 mg/d
  - 66-80  1000 mg/d
  - >80  1200 mg/d

Adverse Effects of Sofosbuvir + Ribavirin

- Fatigue and headache most common
- All contradictions to ribavirin also apply to combination therapy
- HBV reactivation has been reported in HBV/HCV co-infected adult patients who were undergoing or had completed treatment with HCV Direct Acting Antivirals, not receiving HBV antiviral therapy
  - HBV reactivation resulted in serious liver problems or death
  - Adolescents should be screened for HBV before starting sofosbuvir therapy

Ledipasvir-Sofosbuvir in Adolescents

- Phase 2 open-label study in 100 adolescents 12-17 years of age with HCV Genotype 1
- 90 mg ledipasvir and 400 mg sofosbuvir once daily for 12 weeks
- 98% SVR 12
- No patients with virologic failure
- Headache 27%, diarrhea 14%, fatigue 13%
- No SAE’s

Balistreri et al Hepatology 2017;66:371-8
Sofosbuvir + Ribavirin in Adolescents

- Phase 2 open label study in 52 adolescents 12-17 years of age with HCV genotypes 2 (25%) and 3 (75%)
- Sofosbuvir 400 mg once daily and weight-based ribavirin twice daily for 12 weeks (Genotype 2) or 24 weeks (Genotype 3)
- 98% SVR 12; 100% Genotype 2; 97% Genotype 3
- Nausea 27%, headache 23%
- No SAE’s

Wirth et al Hepatology 2017;66;1102-10

Current Pediatric Trials with Direct Acting Antivirals

- Ledipasvir/Sofosbuvir for genotype 1,4,5 or 6: 3-11 yo
- Sofosbuvir/Ribavirin for genotype 2 or 3: 3-11 yo
- Sofosbuvir/Velpatasvir for genotypes 1-6: 3-18 yo
- Ombitasvir-paritapavir-ritonavir +/- dasabuvir +/- ribavirin for genotype 1 or 4: 3-11 yo
- Glecaprevir/Pibrentasvir for genotypes 1-6: 3-<18 yo

Practice Guidelines- HBV

Practice Guidelines- HCV

• NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents.

AASLD Practice Guidelines- HBV

• AASLD guidelines for treatment of chronic hepatitis B
• Norah A. Terrault, Natalie H. Bzowej, Kyong-Mi Chang, Jessica P. Hwang, Maureen M. Jonas, M. Hassan Murad
• First published: 13 November 2015
• https://doi.org/10.1002/hep.28156

Practice Guidelines- HCV

• HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C
• https://www.hcvguidelines.org
• HCV Guidance Published in HEPATOLOGY
• Download: http://onlinelibrary.wiley.com/doi/10.1002/hep.27950/pdf (link is external) [PDF]
• AASLD/IDSA HCV Guidance Panel
• Accepted manuscript online: 25 JUN 2015
Nutritional Management in Pediatric Pancreatitis

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I have no financial relationships with a commercial entity to disclose

Objectives of Presentation

1. Review different feeding regimens, including supportive literature, in the management of pediatric acute pancreatitis (AP)
2. Discuss the limited evidence for dietary modifications in children with acute recurrent pancreatitis (ARP)
3. Develop an approach to nutritional assessment and management of children with chronic pancreatitis (CP)
Background: Definitions of Pancreatitis
(= Similar Pediatric/Adult)

- **AP**: ≥2 of 3: (1) Amylase and/or Lipase > 3x ULN, (2) Pain compatible with pancreatic origin, (3) Imaging features
- **ARP**: At least 2 separate attacks AP
- **CP**: Components of Chronicity, Irreversibility of damage
  - "Continuing inflammatory disease... irreversible morphological change...causing pain and/or permanent loss of function" (Pain, EPI, DM)
  - Mechanistic—"Pathologic fibro-inflammatory syndrome... in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress"

Background: Why Important in Children?
1. Pancreatitis not rare in Pediatrics/Incidence Increasing
2. 20-30% of children with AP will have a recurrence (INSPIRE cohort 2012-2016: 359 children with ARP/CP)
3. Children’s Growth/Development/QOL: Different considerations than adults

Incidence estimates:
- United States (Morinville 2010)
- Australia (Nydegger 2007)

OBJECTIVE 1
Review different feeding regimens in the management of pediatric acute pancreatitis (AP)

**EN**= Enteral Nutrition

**PN**= Parenteral Nutrition

"Mild" AP = most common; no organ dysfunction, no local or systemic complications

"Severe" AP (SAP) = AP with organ dysfunction > 48h
Historical Perspective:
Nutritional Treatment of Pancreatitis (Adults)

• 1960s: TPN ↑ ability to sustain critically ill patients
• 1990s: Recognition TPN Risks
• 1997: ↓ complications EN vs PN in severe AP publication
• 2010s: Meta-analyses supporting EN > TPN: EN as “standard of care” for AP patients requiring nutritional support -- ↓ mortality rates, shorter hospitalizations, ↓ risk infections, ↓ organ failure, ↓ surgical interventions

Timing of Enteral Feeds in AP (Adults)

• “Early” EN (within 48h or 72h)
• Early vs delayed EN with respect to prevention of infected necrosis, mortality in AP
• NJ within 24h vs PO within 96h: No benefit to early (all were fed within 96h)
• Early NJ within 24h vs NPO x 72h: no significant differences (all began oral clear fluids at 72h)
• Early oral in mild AP: safe, ↓ Length of stay (LOS)
• Early oral vs PN in moderate/severe AP: ↓ LOS

Location of Feeds in AP? Composition of Feeds in AP? (Adults)

• Severe AP: no significant differences NG vs NJ; NG/ND/NJ
• Low-fat solid diet (vs clear liquids) as initial meal mild AP: Safe, More calories
• Full solid diet (vs soft diet vs clear fluids) mild AP: ↓ LOS, No ↑ in pain
• Elemental formula (vs not: semi-elemental or polymeric), started within 3d, in mild AP or severe AP: No Differences in outcomes
### Literature in Pediatrics? Oral/Enteral Feeds

- **Early EN (within 48h) + aggressive IV (within 24h) versus 3 other groups:**
  - ↓ LOS, ↓ ICU, ↓ Severe AP
  - Retrospective, single-center
  - 201 children total

- **Oral within 24h vs NPO in mild AP:**
  - No increased pain severity (even if more fat): Similar LOS
  - Retrospective, single-center
  - 38 admissions reviewed

### Literature in Pediatrics? Oral/Enteral

- **Early patient-directed (PDN) oral nutrition (low fat) in mild AP versus team-directed nutrition (TTDN):**
  - Early PO tolerated, ↓ LOS
  - NPO 14h vs 34h; LOS 48.5h vs 93h
  - Prospective study of 30 children vs historical cohort (92 encounters/ 87 children), single site

- **Non-AP literature:**
  - PICU NPO (+/- EN) x 7d is clinically superior to early TPN: ↓ infection, ↓ LOS, ↓ ventilation ➔ Withholding TPN suggested
  - Multicenter, Randomized
  - 1440 children (723 early PN; 717 late PN)

### Pediatric Guidelines: Management of Acute Pancreatitis in Children*

- **NASPGHAN Pancreas Committee**
  - Mild AP: early oral/ EN (within 48-72h)
  - PN if EN not possible for prolonged period of time (> 5-7d)
  - Combo EN and PN superior to PN
  - Unclear role of EN in cases involving pancreatic laceration or duct disruption

- **EPC/ HPSG (European Pancreatic Club/ Hungarian Pancreatic Study Group)**
  - Oral feeding as soon as tolerated
  - If cannot feed oral by 72h, start EN
  - EN via NG or NJ
  - Elemental or polymeric
  - Complete PN as second line when EN not tolerated

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*Primarily expert panels with voting on recommendations*

**Background/ Methods:**
NASPGHAN/ ESPGHAN Position Paper JPGN 2018

- 13-member International Working Group: NASPGHAN Pancreas Committee (Chair VM) + ESPGHAN Cystic Fibrosis/ Pancreas Working Group (Chair MW) + expert nutritionists (2015)
- Review adult + pediatric literature (to Aug 2016) AP, ARP, CP
- Modified version of GRADE recommendations (A: high quality; B: moderate quality; C: low quality evidence) and 1= strong recommendation and 2=weak recommendation
- All recommendations but one were Grade 1C

**Nutritional Recommendations for Pediatric AP**

1.1 Children with mild AP should be started on a general (regular) diet and advanced as tolerated. *Grade 1B*

1.1aa Children with mild AP should be nourished preferably via mouth as compared to nasogastric route

1.1b Enteral nutrition (oral, NG or NJ as tolerated) should be attempted in children with SAP within 72 hours from presentation to medical care, once deemed hemodynamically stable
Nutritional Recommendations for Pediatric AP

• 1.4a Jejunal tube feedings should be reserved for those unable to tolerate oral or nasogastric tube feedings in mild AP
• 1.4b Based on the limited data from the adult literature, the use of oral or NG tube feeding in children with SAP is likely to be safe and provide benefit
• 1.4c Even in severe AP, jejunal tube feeding should be reserved for those unable to tolerate oral or NG tube feeding
• 1.5a The use of specialized formulas or immunonutrition is not necessary in the management of pediatric AP

NASPGHAN / ESPGHAN Position Paper 2018

Nutritional Recommendations for Pediatric AP

• 1.3a EN is favored over PN when possible in AP (* Trauma)
• 1.3c Parenteral mode of nutrition should be used when oral/NG/NJ feeds are not tolerated (* Timing)
• 1.3b Combination of EN and PN, rather than PN alone, should be used in children who do not meet caloric goals with EN alone and have not received full calories for a week into hospitalization

NASPGHAN / ESPGHAN Position Paper 2018

OBJECTIVE 2
Discuss the limited evidence for dietary modification in children with acute recurrent pancreatitis (ARP)

Fat content/Composition?
Micronutrients/Antioxidants?
Pancreatic Enzyme Replacement Therapy (PERT)
Exocrine Pancreatic Insufficiency (EPI)
Nutrition in Adult and Pediatric ARP: Literature

- Historically: prolonged NPO → prolonged low-fat diet post AP
- AP literature supports early return to normal nutrition (within 1w)
- Variations in definitions fat content “low fat” vs “normal fat”
- No studies/evidence supporting indication for diet differing from normal (*exception: hypertriglyceridemia)
- Use of anti-oxidants Adult literature AP/CP: +/- benefit; small series children CP: ? benefit
- PERT to “rest” pancreas?
  - Use of PERT during recovery from AP (transient EPI)?
  - No studies in adults or children with ARP

Nutritional Recommendations for Children with ARP

- 2.1a When tolerated, children should receive a regular-fat diet in between episodes of ARP
- 2.1b A regular-fat diet can safely be started within one week after the onset of illness in AP as tolerated for cases other than caused by hypertriglyceridemia (triglycerides > 1000mg/dL or > 10mmol/L)
- 2.2a PERT should not be routinely used in children diagnosed with ARP, who do not have exocrine pancreatic insufficiency
- 2.3a There is insufficient evidence to support supplementing children with ARP with antioxidants

OBJECTIVE 3

Develop an approach to nutritional assessment and management in children with chronic pancreatitis (CP)

Pancreas-Sufficient CP (PS-CP)
Exocrine Pancreas Insufficient CP (EPI-CP)
+/- with Type 3c Diabetes Mellitus (T3cDM)
Nutritional Assessment/Therapy in CP: Adults

• Main concerns EPI, Type 3cDM; deficiencies vitamins (ADEK), micronutrients (zinc, selenium, etc), pain limiting intakes
• Assessments: Anthropometry, clinical symptoms, biochemistry, bone/muscle (sarcopenia) health, exocrine function
• Nutritional measures: weight, height, BMI, mid-arm circumference, triceps skin fold, handgrip strength, bio-impedance
• Adults CP nutritional screening Q3-6m suggested
• T3cDM: Risk of hypo- and hyper-glycemias, malnutrition; +/- increased risks micronutrient deficiencies
• Vitamin A deficiency correlates with malnutrition in CP adults
• 65% CP low bone mineral density (BMD) vs 10% controls; worse if EtOH and EPI

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Nutritional Assessment/Therapy in CP: Adults

• Lower handgrip strength, fat and muscle stores CP vs controls
• PS-CP: sufficient nutrition status on regular food but Q. increased caloric requirements?
• CP males higher energy expenditure vs controls
• Estimates that CP resting energy expenditure (REE) increased 30-50%, basal energy expenditure increased 1.5-1.8x
• ↓Fat, ↑MCT, + hydrolyzed formulas to decrease pain in CP
• No clear PERT dosing recommendations in CP, EPI
• CP-T3cDM: may need altered CHO and MCTs to prevent ketoacidosis

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Nutrition in CP- Limited Literature in Pediatrics Can one Extrapolate Adult Data? CF Data?

• 25% CP children with malnutrition (Poland 2014)
• 1/3 CP children with EPI (INSPIRE 2015)
• Comparison CF vs CP +/- EPI: Starting point? Shared concerns: increased REE, +/- EPI, fat-soluble vitamin and micronutrient deficiencies, DM, bone health (+frequent CFTR mutations in CP)
• CF nutritional screening Q3m, vit. D screening Q1y in spring (if supplement, recheck in 3m); follow vitamins A/E/PT
• CF diet recommendations: 35-40% fat, 20% protein, 40-45% CHO

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Nutrition in CP: Limited Literature in Pediatrics
Extrapolation of Adult Data/ CF Data

- No clear recommendations for routine monitoring zinc, selenium in CP (1996 series 7 children with hereditary pancreatitis: lower selenium); unclear whether vitamin B12, vitamin C levels lower in CP
- Bone health: CF BMD testing based on age (B yr), other criteria
- Dosing PERT in CF: Age-based recommendations; aim < 10,000 IU lipase/kg/d
  - Use of CF – EPI guidelines for PERT dosing
  - PERT to be considered when growth and/or weight gain unsatisfactory or symptoms EPI
  - Acid-suppressive drug when severe malabsorption despite appropriate PERT

Mathew 1996; Bowrey 1999; Rasmussen 2013; Kolodziejczyk 2014; Schwarzenberg 2015; Abu-El-Haija 2018; Parniczky 2018

Nutritional Recommendations for Children with CP

- 3.1a Children with CP should undergo routine surveillance to screen for signs of impaired growth and/or malnutrition utilizing validated measures of nutrition including weight, height and body mass index
- 3.1b The frequency of evaluation of children with CP for signs of impaired growth/ malnutrition should be every 3-6 months
- 3.2a Children with CP, with or without EPI, should receive a regular diet
- 3.2b Children who have both CP and T3cDM require specialized diabetic nutritional evaluation

NASPGHAN / ESPGHAN Position Paper; JPGN 2018

Nutritional Recommendations for Children with CP

- 3.3a Children with CP should have fat-soluble vitamin levels measured every 6-12 months
- 3.3b If supplemental vitamins are provided in CP, levels should be repeated 3 months after dose adjustment
- 3.3c There is no evidence to recommend routine monitoring of other vitamins, minerals or trace elements in CP unless their deficiencies are suspected clinically

NASPGHAN / ESPGHAN Position Paper; JPGN 2018
Nutritional Recommendations for Children with CP

3.4a Bone mineral density should be measured in children with CP and malnutrition, persistently low vitamin D or history of fractures, specifically in vertebrae, hip, or wrist

3.5a Children with CP should be screened for pancreatic exocrine insufficiency every 6 to 12 months utilizing fecal elastase or 72h fecal fat collection

3.5b In children with CP and EPI, PERT dosing should be similar to recommendations established for treating exocrine pancreatic insufficiency in CF

3.5c Dosing of PERT should be followed clinically and via repeating tests of fat maldigestion/malabsorption as necessary

3.5d In patients with T3cDM, strict adherence to glucose control should be maintained to prevent hypoglycemia, malnutrition and hyperglycemia-associated weight loss

3.5e Children with CP who develop EPI and/or T3cDM require more frequent follow-up for malnutrition, growth delay and vitamin deficiencies than the general CP population

Future Directions/Research in Children?

In General: Pediatric prospective studies to support (expert) recommendations

AP: Early vs Late; Site of feeding especially in SAP; Type of feeding/Additional components (Glu, Arg, Omega-3)

ARP: Is low-fat beneficial? Any role for PERT? Anti-oxidants?

CP: Better understanding REE in CP children; Optimal nutritional measures to monitor; Effect of macronutrient composition; Prevalence of deficiencies; Bone health risk factors and natural history; Better defining effects of EPI and T3cDM on nutritional outcomes
SUMMARY/ TAKE-HOME POINTS: NUTRITION IN ACUTE PANCREATITIS

1. AP: EN superior to TPN
2. AP: PO/ NG/ NJ appear equivalent
3. AP: Early gut nutrition not harmful, may reduce LOS
4. Mild AP: Can provide complex calories early
5. Severe AP: EN likely can wait 48-72h
6. Severe AP: If cannot institute early EN, NPO may be better than early TPN

SUMMARY/ TAKE-HOME POINTS: NUTRITION IN ACUTE RECURRENT AND CHRONIC PANCREATITIS

1. ARP: Little data to support any dietary interventions
2. CP: Screen for EPI, T3cDM, fat-soluble vitamins, bone health, growth parameters
3. CP-EPI: Dosing of PERT similar to CF
4. CP-T3cDM: closer follow-up/ more potential complications

Recent Publications/ Resources for Recommendations
References - 3

• Shintakuya R et al. Sarcopenia is closely associated with pancreatic exocrine insufficiency in patients with pancreatic disease. Pancreatology 2017; 17: 70-75.
• Xu Y. Pancreatic exocrine function and morphology following an episode of acute pancreatitis. Pancreas 2012; 41:922-7.

References for Pictures in slide set

• http://www.srcs.k12.ca.us/District/HR/PublishingImages/Pages/Work-Year-Calendars/Calendar.jpg (slide 8)
• https://www.sporcle.com/blog/2016/11/stopwatch-on-sporcle/ (slide 8)
• http://epmonthly.com/wp-content/uploads/2016/04/NGTube703-703x437.png (slide 9)
• https://www.slideshare.net/IlanaKovach/collin-college-nursing-abbreviation-1128 (slide 19)
• https://www.livealittlelonger.com/what-you-must-know-about-osteopenia (slide 22)
• http://vitamin.laguost.us/vitamins-ade-and-k/ (slide 22)
• https://www.25doctors.com/learn/fat-in-stool (slide 22)
• https://www.pancan.org/news/6-things-know-pancreatic-enzymes/ (slide 24)
• https://www.everydayhealth.com/adhd/adhd-research.aspx (slide 29)
Cyclic Vomiting Syndrome

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Disclosures

- No financial disclosures
- Therapies discussed are off-label

Objectives

- Prevalence & burden of disease
- Diagnosis
- Mechanisms → targeted treatment options
  - Behavioral
  - Pharmacological
  - Alternative
ANS
Imbalance
Migraine
VOMITING
Brainstem
Stomach
relaxants
Antiemetics
Antihistamines
Prokinetics

Neuromodulators
CBT
Lifestyle changes
Antimigraine
Brainstem targets
Neuromodulators
CBT
Lifestyle changes

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>CVS</td>
<td>1.9-2.3%</td>
<td>3.2 per 100,000 (IR)</td>
</tr>
<tr>
<td>Celiac</td>
<td>0.75%</td>
<td>2-7 per 100,000</td>
</tr>
<tr>
<td>Crohn’s</td>
<td>0.043%</td>
<td>4.56 per 100,000 (WI)</td>
</tr>
</tbody>
</table>

2% of U.S. adults!

Burden of CVS

- 131 ED visits in one year
- $200 million spent annually
- 24 school days/year missed
- Quality of life is poor
  - Anxiety is a predictor
- Comorbidities common
  - Fatigue, POTS, sleep disturbance

Aziz et al. Clin Gastroenterol Hepatol 2018
Venkataraman et al. BMC Emergency Medicine 2010
Tarbell et al. The Journal of Pediatrics 2013

Why are episodes so disabling??

Autonomic dysfunction

- Children with CVS: sympathetic & parasympathetic nervous system imbalance
- High baseline anxiety (83%) & low vagal tone prior to stress test
- Adults: 90% sympathetic & 83% system abnormalities
- Symptoms: sweating, agitation, lethargy, dizziness, hypersensitivity

Tarbell et al. Autonomic neuroscience; 2017
To et al. Journal of Pediatrics 1999
Venkataraman et al. Neurogastroenterology & Motility 2010
4 Phases

1) Prodromal: min-hrs $\rightarrow$ time to intervene!
2) Emetic: hrs-days $\rightarrow$ rapid fire vomiting, unrelenting nausea
3) Recovery: sleep
4) Inter-episodic: baseline health
Diagnosis

- ≥5 attacks in any interval/3 attacks in 6 months
- Episodic attacks of intense nausea and vomiting lasting 1 h-10 days, occurring at least 1 week apart
- Stereotypical pattern and symptoms in the individual patient
- Vomiting ≥ 4 times/h for ≥ 1 hr
- Return to baseline health between episodes

Workup

- Electrolytes
- UGI: malrotation
- Renal U/S: hydronephrosis
- EGD??

Fasting triggered → metabolic workup

Treating CVS: Several Avenues

- Lifestyle changes
- Mitochondrial
- Prophylactic
- Abortive
- Rescue

Help your patients (and yourself): COMPOSE ED PROTOCOL
Lifestyle changes

- Trigger identification & avoidance
  - Stress/excitement, sleep, infections, MSG, aged cheese
- Sleep hygiene
- Diet (avoid fasting) & fluids
- Regular exercise
- Stress management
- Formulate hospital rescue plan

Mitochondrial supplements

- Co-enzyme Q10: 10mg/kg/d div BID
- Ubiquinol
- Epic4health.com
- L-carnitine: 50-100mg/kg/d div BID
- Riboflavin: 200 mg BID

Spectrum Needs (33 ingredients)
Prophylactic Therapies

• CBT
• Pharmacological neuromodulation

Cognitive Behavioral Therapy

Reversing negative thoughts and emotions → restructuring thinking

We focus on the GI symptoms

Hypnotherapy

• Long lasting effects in pediatric functional pain
• No data in CVS

Huertas-Caballos et al. Cochrane database; 2008
Rutten et al. Arch Dis Child 2013
Benninga et al. Am J Gastroenterology 2012
Neuromodulation: Brain Targeted Drug Therapy

**Tricyclic Antidepressants (TCAs) (>5yrs):** Amitriptyline, Nortriptyline, Doxepin, Imipramine
- Titrate to 1mg/kg QHS
- Blood level (goal 100-200) & P450 gene testing
- ECG: baseline and with dose increases (Qtc interval prolongation)

**Cyproheptadine (<5 yrs):** antimigraine, stomach relaxant
- 0.25mg/kg/day QHS

**Propranolol (2nd line):**
- 0.25-1mg/kg/day div BID or TID

---

Neuromodulator Drugs in Functional N&V

- Adults with Functional Nausea & Vomiting disorders
- TCAs, Tetracyclic (Mirtazapine), SSRIs, Antiepileptics (Keppra, Depakote), Anxiolytics (Wellbutrin, Buspar)
- 72% moderate improvement (22% remission)
- Non-TCA comparable effects to TCAs

*Consider alternate neuromodulators when TCAs fail!*

Patel et al. Postgrad Med J 2013

---

**Topamax:** anti-migraine, anti-seizure
- 1.5–2.0 mg/kg/day PO div BID (25-50mg 2xD)
- Titrating up slowly
- Warn about: cognitive dysfunction, renal calculi

**Mirtazapine:** anti-anxiety, stomach emptying
- 7.5-30mg QHS

**Levetiracetam, Zonisamide, Valproate, Phenobarbital**

Malamood et al. Drug Des Devel Ther 2017
Autonomic dysfunction & CVS

Treatment: Autonomic Dysfunction

- **Water, salt, exercise**
- **Fludrocortisone:** 0.05-0.1mg daily
- **Side effects:** fluid retention, neurological, kidney problems in higher doses
- **Fludrocortisone study:** 71% of adolescents with chronic nausea had some improvement (4 weeks)
- **Midodrine:** 5-10mg as needed
  - Orthostatic hypotension (blood pressure drops)

Prokinetics?

**Erythromycin**
- Loss of response, drug interactions

Combination of erythromycin and propranolol for treatment of childhood cyclic vomiting syndrome: a novel regimen

**Gastric Electrical Stimulation**
- Small study: vomiting episodes reduced by 69%


**ANS Imbalance**

**Migraine**

**VOMITING**

**Neuromodulators**

- Cyproheptadine
- Mirtazapine
- Prokinetics

**Antimigraine Brainstem targets**

**Abortive**

**5-HT3 antagonists**

- Topical Ondansetron (8mg/ml): inner wrist
- Sublingual ondansetron
- Granisetron

**Triptans**

- Sumatriptan 20mg nasally/6mg s.c (can repeat in 1 hr)
- Zolmitriptan 5mg nasally
- Rizatriptan 5-10mg tab
- Frovatriptan 2.5mg tab: longer acting
**NK1-R antagonist: Aprepitant (Emend)**

- Effective in CVS and chemotherapy-induced N&V
  - Acute (3-day) vs prophylactic (40-125mg twice weekly)
  - 81% complete or partial response (prophylactic)

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**Abortive: other aspects**

<table>
<thead>
<tr>
<th>Sedation</th>
<th>Pain</th>
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<tbody>
<tr>
<td>Benadryl</td>
<td>Tylenol</td>
</tr>
<tr>
<td>Diastat PR</td>
<td>Motrin</td>
</tr>
<tr>
<td>Ativan/Chlorpromazine</td>
<td>Toradol</td>
</tr>
<tr>
<td></td>
<td>Tramadol</td>
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</tbody>
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**Alternative**

- Capsaicin: topical
- Ginger
- Acupuncture: P6 acupoint
- CBD
**Pyridoxine/Doxylamine (Diclegis)**

- Pyridoxine (B6) + Doxylamine (antihistamine): 10-20mg QHS
- Nausea/vomiting of pregnancy
- Delayed release
- Morning nausea and insomnia

**ED Therapy**

- Darkened, quiet room, vitals q. 4-6
- IV: If dehydrated 10mL/kg NS + D10 0.45 NS + KCl at 1.5X maintenance
- ANTIEMETIC: ondansetron 0.2-0.3 mg/kg q. 6h
- SEDATION: lorazepam 0.05 mg/kg q. 6h
- ANALGESIA: ketorolac 1.0 mg/kg ≤ 30 mg
- Admit: if > 5% dry, no urine X 12h, Na⁺ < 130 mEq/L, AG > 18 mEq/L, intractable emesis

**Novel therapies: Neuromodulation**

Percutaneous Electrical Nerve Field Stimulation
Novel therapies: what about CGRP?

- CGRP increased during acute migraine attacks
- Expressed in trigeminal ganglion
- Triggering of trigeminovascular reflex in migraine → pain
- Antibodies against CGRP
- Erenumab: FDA-approved (adults)

Conclusion

- CVS is common and disabling
- Individualize therapy
- Neuromodulation is key
- Consider alternate neuromodulators when TCAs fail
- Aprepitant is effective both as abortive and prophylactic
- Lifestyle modifications, CBT, & alternative therapies may be equally effective
- Consider targeting ANS dysfunction
- Auricular neurostimulation and CGRP antagonist hold promise as novel therapeutic agents
Questions

1. The 2008 Cyclic Vomiting Syndrome (CVS) NASPGHAN consensus guidelines recommends that all patients with symptoms of CVS should have a screening endoscopy. True vs False

2. The most common specific clinical feature of CVS is:
   a) Vomiting for several days
   b) At least 6 emeses/hour during an episode
   c) Stereotypical episodes in the individual patient
   d) ≥5 attacks in a 6 month period

3. The abortive agent Aprepitant should be dosed as follows during the CVS prodrome:
   a) 20mg intranasally
   b) 125mg PO x 1
   c) Day 1: 125mg PO, Days 2-3: 80mg PO 1xO
   d) 6 mg s.c. x 1
Surgical intervention for functional GI disorders

Jaime Belkind-Gerson, MD, MSc
Director Neurogastroenterology and Motility Program
Digestive Health Institute
Children's Hospital Colorado
Associate Professor of Pediatrics
University of Colorado School of Medicine

Enteric Nervous System

- Network of neurons in gut wall
- Largest division of autonomic nervous system
- Capable of autonomous activity without CNS input
- 650 nerve cell bodies per mm
- 500 million neurons
- >20 functional classes
- Controls motility, absorption, secretion, blood flow, immune function, microbiome composition

ENS = The Second Brain

Enteric Neuropathies

- Anatomical or functional
- Congenital or acquired
- Cause of GI dysmotility in up to 30% of the population

- Esophageal Achalasia
- Intestinal Pseudoobstruction
- Hirschsprung's Disease
- Anal Achalasia
- Gastroparesis
- Pyloric Stenosis
- Irritable Bowel Syndrome
- Slow transit constipation
Gut motility

Treatments for ENS Disorders

- Motor problems
  - Medication
  - Decompression and mechanical irrigation
  - PT/Biofeedback
  - Botox
  - Electrical stimulation
- Sensory problems
  - Medication
  - Behavioral techniques
  - Electrical Modulation
- Immune regulation and Others
  - Medication
  - Microbiome modification

Colonic Manometry

(normal) segmental

(total colonic)
Result of Surgical Mapping

Current Surgical Management of Pediatric Idiopathic Constipation: A Systematic Review of Published Studies

\textit{Longo} S. (2015)

\textit{Author Information}

Abstract

\textbf{OBJECTIVE:} Surgeons for pediatric idiopathic constipation (IC) often undergo after failure of bowel management programs. Outcomes are determined by patient demographics, severity of illness, complications, and symptoms.

\textbf{METHODS:} A systematic review of 30 published studies identified outcomes of IC surgery.

\textbf{RESULTS:} The anterograde continence enema (ACE) has been used for many years and has also been called Malone Anterograde Continence Enema (MACE). The ACE has been popularized by surgeon, with the first published cases in 1990.

\textbf{CONCLUSIONS:} Surgical management of IC is based on case studies and expert opinion. No single operation has been associated with the most effective treatment.
Severe Colonic Dysmotility

Candidates for ACE

- Children with severe fecal incontinence
- Severe constipation that has not responded adequately to medical therapy
- Ano-rectal abnormalities (imperforate anus, Hirschsprung's dx)
- Spinal cord problems
- Neuro-muscular disorders
### Types of ACE
- Cecostomy: Chait/Button/Cecostomy tube
- Appendectomy (Malone)

### Procedures for ACE
- Interventional Radiology
- Surgical (Laparoscopy, open)
- Laparoscopy/colonoscopy

### Colonic manometry as predictor of cecostomy success

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number</th>
<th>Percentage</th>
<th>Success Rate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecostomy</td>
<td>21</td>
<td>62%</td>
<td>78%</td>
<td>0.001</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>15</td>
<td>50%</td>
<td>60%</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*P* values (chi square, confidence interval)

*Fig. 1. The presence of good colonic function with MANP after 2 months is related to successful clinical outcome (Van de Berg et al., 2006).*

### Artregrade colonic anemias and intestinal diversion are highly effective in the management of children with intractable constipation

- 44 patients (1-26 mean 9yo)
- 16 ACE
- 1 year post op, all normalized their colonic manometry
- 19 diversion (5 ileostomy / 14 colostomy)
- 14 had continuity reestablished (mean 27 mo)
- All did well (58 mo FU)

*From systematic review based on prospective clinical manometry studies. Of those undergoing ACE procedures, age younger than 12 years was a predictor of success. When prior enema/bowel manometry was not predictive of success. Second manometry 1 year post-ACE showed improvement in all patients while the nonoperated colon, prior manometry completed in M.U. Nurses.*
Contemporary short- and long-term outcomes in patients with unremitting constipation and fecal incontinence treated with an antegrade continence enema

Scott C. Daley, John K. Smith Jr., Justin Sheiklak, Joseph M. Orefe, Frederik J. Rozenblatt

- 93 patients
- Aged 10 +/- 4 yo
- F/U of 26 to 41 mo

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Short and Long Term Efficacy of ACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>No (%)</td>
</tr>
<tr>
<td>No accidents at 1 month</td>
<td>67 (72.0)</td>
</tr>
<tr>
<td>Improvement at 1 month</td>
<td>92 (98.9)</td>
</tr>
<tr>
<td>No accidents at 3 months</td>
<td>69 (93.1)</td>
</tr>
<tr>
<td>Improvement at 3 months</td>
<td>80 (96.4)</td>
</tr>
<tr>
<td>No accidents at end of follow-up</td>
<td>80 (90.0)</td>
</tr>
<tr>
<td>Improvement at end of follow-up</td>
<td>88 (94.4)</td>
</tr>
<tr>
<td>Normalization of bowel function at end of follow-up</td>
<td>77 (82.8)</td>
</tr>
</tbody>
</table>

Probability of independence from ACE over time

Why does the ACE help?

- Decompression
- Microbiome changes

References:

Why does the ACE help?

• Recovery of muscular function
  - Chae et al. Smooth muscle adaptation and recovery of contractility after mesenteric ischemia bowel resection in rats. 2013.

• Recovery of ICC
  - Chae et al. Smooth muscle adaptation and recovery of contractility after mesenteric ischemia bowel resection in rats. 2013.

References:

Why does the ACE help?

• Recovery of ENS
  - Post injury neurogenesis

References:

Irrigations may also be done trans-anally (retrograde)


References:
A word of Caution

Spastic left colon: ? complication
Pelvic Outlet Problems

Radiopaque Marker Colonic Transit Study

HR Anorectal Manometry

- Position of sensors
- Resting pressure
  - High
  - Normal
  - Low
- Squeeze (3 brief, one extended)
  - Higher than baseline?
  - Can it be maintained?
- Bear down (3 brief, one extended)
  - Does the perineum descend?
  - Does the sphincter relax?
- Sensory balloon inflation tests
Newer methods of therapy involve muscle strengthening and external biofeedback stimulation, improving comfort and decreasing anxiety.
Chemical Denervation IAS

• 73 children (30HD, 43 IAS achalasia)
• F/U 32.1 +/- 2.9 months
• Mean 2.7 +/- injections per child
• Initial improvement in 89%
• 53.4% excellent or good long-term outcome
• Maintained for 17.1 +/- 3.1 months
• 9.5% developed transitory fecal incontinence

CONCLUSIONS: Anal sphincter BoTox may be an effective and safe long-term therapy for children with nonrelaxing IAS

Results - Demographics

• 164 charts reviewed → 22 patients were excluded due to lack of follow up visit → 142 charts examined
• 8mo-19 yrs (mean 7.4yo)
• Botulinum injection
  – 99 received one time
  – 26 received twice
  – 17 received 3 or more times,
  – Total of 203 separate BoTox treatments analyzed
• 123 completed an ARM prior to BT injection
  – 35 Normal resting pressure
  – 88 High resting pressure
Results: Response

- Ninety eight (70%) had a positive response.
- Twenty two (22%) able to wean down/off medications for an extended period of time after the Botox injections.

Gastric Electrical Stimulation

- Used in experimental trials for Gastroparesis
- high-frequency / low energy stimulation is currently the only type in clinical setting
- Does not improve gastric emptying
- In adults seems to improve quality of life mostly by decreasing nausea
Gastric Electrical Stimulation in Children

- 24 patients (median 24 mo of symptoms)
- 46% tube feeds, 25% TPN
- 60% had dx gastroparesis
- PedsQL module pre & post in 18/24 (median 8mo)
- Improvement in pain, PO, nausea, reflux, bloating, constipation (P<0.05)
- Improvement for both, gastroparesis and non-gastroparesis
- 13% needed tube feeds and 13% after GES
- 65% reported improvement, 15% same or worse
- 5 had complications (most abdominal discomfort)

Conclusions & Inferences:
In the largest series to date of pediatric patients who have undergone GES for FD, we found significant improvements in upper gastrointestinal symptoms, quality of life, and perception of global health. Patients were less dependent on tube feeding or parenteral nutrition.

Gastric Electrical Stimulation in Children

- 97 patients (majority teenage caucasian girls)
- 96 temporary GES & 66 improved
- 67 permanent GES: significant reduction in all individual symptoms (p<0.001) & total symptom score TSS (p<0.0001) at 1, 6, 12 and >12 mo.
- Recurrence of symptoms and device removal in 7 cases
- 41 continued improvement after 12 mo (mean F/U 3.5 y)

Conclusions: This study represents the largest experience of systematic application of GES in children. GES is a safe and effective therapy for selected children with intractable GI symptoms with continued symptomatic improvement at 1 year and beyond.

Islam et al., 2015

Sacral Electrical Stimulation (SNS)

- Several articles on its use for bladder/micturition problems
- Has showed good results in adult fecal incontinence and it’s use growing
- Intractable constipation?
• 2006: Humphreys et al. 23 children with functional urinary incontinence, constipation and soiling - 80% positive response stool. *(J Urol, 2006)*

• 2010: Guys et al. multi-centric prospective randomized, cross over study in 33 children with urinary and fecal incontinence of neurological origin - 78% positive response for bowel function. *(J Urol, 2010)*

---

**Sacral Electrical Stimulation**

Proposed mechanism:

- □ rectal compliance
- □ External anal sphincter tone
- □ right colonic peristaltic activity
- □ left colonic peristaltic activity

---

**SNS for Constipation in adults**

- 36 patients Age 45 +/- 14: nerve evaluation
- 20 responded: permanent nerve stimulator
- Positive response: 12/20 (active) 11/20 (sham)
- Pain related to device: 5
- Infection/hematoma: 3
- Definitive removal of device: 2
- At 1 year: 11 of 20 continued to respond
- Stimulation had no effect on colon transit time

*CONCLUSION: These results do not support the use of sacral nerve stimulation to treat intractable refractory constipation in adults who initially responded to temporary nerve stimulation. Registered number: NCT00505626 (http://www.clinicaltrials.gov).*
SNS for Constipation in children

- 13 patients aged 10-18 yo (all girls)
- Functional constipation (Rome 3)
- Not responding adequately to laxative therapy
- All but 2 presented spontaneous defecation >2 x/week (without meds)
- Cleveland Clinic constipation score: 20.9 – 8.4
- One lead revision and 2 pacemaker relocations

CONCLUSION: Sacral neuromodulation appears to be a promising new treatment option in adolescents with refractory functional constipation who are not responding to intensive conservative therapies. Larger randomized studies with long-term follow-up are needed.

SNS for Constipation in children

- 22 patients
- Median age 12 yo
- Median ACE frequency decreased 7/week to 1/week At 12 months (p<0.0001)
- 10 (45%) cecostomy/appendicostomy closed
- 6 (25%) complications needing further surgery

CONCLUSION: In patients with severe constipation (1 > 4 weeks) and in patients who had a median decrease in ACE of 66%, 10 (45%) had cecostomy/appendicostomy closed, and 6 (25%) complications requiring further surgery.

The “Fight or Flight” response and the ENS

Tyrosine hydroxylase = Sympathetic innervation

The “Fight or Flight” response and the ENS

Inhibition Of motility

Constricting the sphincters

Inhibition Of secretion
The “Fight or Flight” response and the ENS

Conclusions

• We ARE getting better clinically
• We need more tools, but novel opportunities are now available: irrigation/decompression techniques, electrical stimulation, PT/biofeedback, microbiome manipulation, regenerative medicine
• We can not do this alone
• Multidisciplinary (basic and clinical) work is sorely needed.
• Bench-to-bedside, careful research and evidence-based approach will triumph!

The Future is Bright!

THANK YOU
Integrating hypnotherapy and CBT into medical treatment of functional disorders

Miranda A.L. van Tilburg, PhD
Campbell University
University of North Carolina
University of Washington

Conflict of Interest
- Consultant for Mahana Therapeutics

Learning objectives
- Explore how physicians can integrate psychological therapies in their care for functional disorders
- Differentiate the goals, content and efficacy of hypnotherapy and CBT for functional disorders
- Identify and find solutions for common problems in referring for psychological treatments for functional disorders
I: Integrate psychological therapies in care for functional disorders

Psychological factors
- Onset of symptoms
- Exacerbation of symptoms
- Maintenance of symptoms
- Disability related to symptoms

Anxiety and Depression?

Catastrophizing
Dwelling on the worst outcome and feeling helpless

Somatization
Dwelling on physical symptoms

"My child's condition is terrible; I feel it is never going to get better"
"I can't stand it anymore; nothing will make it better"

Catastrophizing=
Dwelling on the worst outcome and feeling helpless

"My child's condition is terrible; I feel it is never going to get better"
"I can't stand it anymore; nothing will make it better"

van Tilburg et al J Psychosom Res 2013
Lavigne et al J Pediatr Psychol 2014
Hollier et al DDW 2018
Newton et al 2018 Neurogastroenterol Motil
(provisionally accepted for publication)
Psychological therapies in FGID

- Evidence for CBT
  - IBS/FAP
  - Functional Dyspepsia
  - Fecal Incontinence
- Evidence for hypnotherapy
  - FAP/IBS
- Unavailable to majority of patients
  - Lack of trained therapists
  - Lack of integrative care
  - Poor insurance coverage

Medical and psychological care

<table>
<thead>
<tr>
<th>Treatment visits</th>
<th>Jointly</th>
<th>Separately</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jointly Integrative Care</td>
<td>Integrative Care</td>
<td></td>
</tr>
<tr>
<td>Separately Multidisciplinary Care</td>
<td>Sequential Care</td>
<td></td>
</tr>
</tbody>
</table>

Evidence for integrative care

- Improved access to psychological care
- Improved collaboration among providers
- Improved patient satisfaction and QoL
- Decreased healthcare costs
Which patients should receive integrative care?

- Treatment resistant
- Comorbid psychiatric condition
- High disability
- Willing to accept BioPsychosocial model
- All patients

II: Goals, content and efficacy of hypnotherapy and CBT for functional disorders

Oh Freud is too darn hard to read. I switched to Dr Phil years ago
Cognitive Behavioral Therapy

- **Cognitive therapy**
  - Replace incorrect cognitions
  - Fear of Disease
  - Catastrophizing

- **Behavioral therapy**
  - Facing fears
  - Bathrooms outside of house
  - School avoidance
  - Eating
  - Replace unhelpful behaviors
  - Wellness rather than pain behaviors
  - Parental protectiveness
  - Relaxation
  - Guided imagery
  - Progressive muscle relaxation
  - Deep breathing

Efficacy of CBT

- **Functional Constipation**
  - Cognitive -> Parents
  - Behavioral -> Child
  - One study found no evidence of efficacy

- **Fecal Incontinence**
  - Education parents
  - Teaching defecation skills
  - Reducing fear of BM
  - Parent-child conflict
  - Limited evidence of efficacy

- **FAP/IBS**
  - Child alone, Child/Parent, Parent only
  - Reducing maladaptive pain thoughts/coping
  - Exposure therapy
  - Several trials report reductions in pain and disability
  - Effects persist for at least 1 year
  - Phone and internet delivery

Hypnosis

- **Definition:**
  "A state of consciousness involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion."

- **Hypnosis components:**
  - Induce light trance
  - Deepening if needed
  - Suggestions for well-being, relaxation and symptom reduction
  - Transition to normal consciousness
### Hypnosis myths

<table>
<thead>
<tr>
<th>Myth</th>
<th>Truth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slavishly obey therapist</td>
<td>Free will</td>
</tr>
<tr>
<td>Passively under influence of therapist</td>
<td>Patient actively engages in imagery and makes own changes</td>
</tr>
<tr>
<td>Semi sleep state</td>
<td>Hyper attentive</td>
</tr>
<tr>
<td>Special state that few have experienced</td>
<td>Common state equal to day dreaming or losing oneself in movie/book</td>
</tr>
<tr>
<td>Quackery</td>
<td>Officially endorsed by AMA and AHA</td>
</tr>
<tr>
<td>Antireligious or non-Christian</td>
<td>Hypnosis is not a belief/religion</td>
</tr>
</tbody>
</table>

### Efficacy of Hypnosis

- **FAP/IBS**
  - Three RCT
  - Improved pain, reduced disability
  - Can reduce somatization
  - Larger effect sizes than CBT
  - Effects persist for at least 5 years
  - Audio-delivery

Rutten et al. Arch Dis Child 2013

### III: Common problems in referring for psychological treatments
Reluctance to referral for psychological txt

“It is all in your head”
Stigma
Been there, done that

Quick fix

**Biology-only**

---

Solutions:

- Establish rapport
- Agree on treatment goals
- Explain BioPsychoSocial Model
  - Hurt ≠ harm
- Explain role of psychological therapy
  - Learning to cope
- Collaborate with psychologist
  - Shared treatment goals
  - Train psychologist in GI
  - Work with health psychologists only
- Remain available – do not dump patient

---

Where to find a therapist?

- Rome PsychoGastro group
  - https://theromefoundation.org/working-teams-and-committees/rome-psychogastroenterology-committee/
- APA, Div 54: pediatric gastro
  - special interest group
  - https://www.societyofpediatricpsychology.org/gastroenterology
- NASPCHAN website
  - Education ->
  - Motility Resources ->
  - Psychological and Behavioral treatment providers
- Hypnosis:
  - ASCH.net
  - Ibshypnosis.com
  - Esh_hypnosis.edu (Europe)
- CBT
  - abct.org
  - www.abct.eu (Europe)
  - Academyofct.org
  - www.abpp.org
How to pay for psychologist in your practice?

- Cost money initially but over time usually neutral
- Can reduce cost of calls, follow up appointments
- Health and behavioral vs mental health codes
- Split salary across divisions
- Consider research/donations
- Talk to business manager and consider creative solutions
- Keep main goal in mind: To give best treatment to patients.

Take home messages

- Psychological factors are important
  - Focus on catastrophizing & somatization
  - Psych Tx efficacious treatments
- CBT
  - Addresses unhelpful cognitions and behaviors
- Hypnosis
  - Focused attention \(\rightarrow\) increased suggestibility

- Integrative care
  - Improves access to Psych care
  - Increased QoL; decreased costs
- Challenges of Integrative care:
  - Costs
  - Finding a therapist
  - Patient reluctance

DO NOT DROP YOUR PATIENT AT PSYCHOLOGISTS DOOR AND ASSUME THAT TAKES CARE OF IT
GERD Guidelines

Rachel Rosen, MD, MPH
Associate Professor of Pediatrics
Boston Children’s Hospital

Disclosures

• Consultant:
  • Janssen Pharmaceuticals
  • Reckitt Benckiser

• I am thankful for the following funding:
  • NIH R01DK097112
  • Translational Research Program

Learning Objectives

• To understand the role and limitations of medical and surgical therapies for GERD
• To discuss the strengths and limitations of diagnostic testing to diagnose GERD in children
• To discuss controversies over the definition of GERD and the implications for the patient
First, understanding the guidelines....

- GER versus GERD
  - When symptoms become bothersome, it becomes GERD
  - Bothersome for who-parent or patient? Bothersome how?
- The guideline evaluated papers based on the outcome of symptom improvement, not improvement of reflux by testing.
  - Most studies do not assess symptoms.
  - There are very few validated symptom questionnaires.
- Therefore, expert opinion important in the guidelines

Case 1

- 3 month old infant referred to you for fussiness, spitting up 3x/day
- PMD has started the infant on BID zantac with no improvement
- Family is requesting PPI, told they have intractable reflux by the lactation consultant
- Infant initially breast fed but 2 days ago switched to a “gentle” formula because the family was desperate
- Patient taking 6 ounces every 3-4 hours, with each bottle taking an hour to feed. Patient’s best feeds are during sleep when sleeping

Diagnosis? Next steps?

- GER versus GERD? Does the diagnosis matter?
- Why aren’t the medicines helping?
- What are the next steps from a management perspective?
• Is it overfeeding?
• Is it mixed correctly?
• Is it hyperconcentrated?
• Is it a cow’s milk allergy?
• Have you modified the feeds (volume, frequency, composition, thickening)?

What’s the evidence?
Does giving the GERD diagnosis matter?
Scherer et al Pediatrics 2013

Parental interest in medication—higher numbers=more interest in medications

Parental appreciation of medication offer—higher numbers=more parental appreciation

Seeing a consultant who diagnoses reflux affects prescribing of PPIs to infants
Duncan et al Submitted for Publication

Why are medicines ineffective?
Does Positioning Matter?
Omari et al. J Peds 2007

Increased cows milk intolerance in infants with GERD
Hua et al. J Paeds Child Health 2015

| Table 16 Association between GOR and non-lgE-mediated cows milk allergy (n = 4674) |
|---------------------------------|-----------------|-----------------|-----------------|
| No CMA                          | non-lgE-mediated CMA† |
| r (%)                           | r (%)            | aOR (95% CI)   | P |
| Parent-reported GOR             |                  |                |
| No                              | 3392             | 94 (2.7%)      | 1.0 0.015       |
| Yes                             | 951              | 41 (4.11)      | 1.60 (1.10-2.33)|
| Anti-reflux medication          |                  |                |
| No                              | 594              | 21 (3.48)      | 1.0 0.15        |
| Yes                             | 330              | 19 (5.41)      | 1.60 (0.84-3.04)|

Impact of Cow’s Milk on Reflux
Borrelli et al. J Peds 2012

<table>
<thead>
<tr>
<th>Amino Acid Formula</th>
<th>Cow’s Milk</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Events</td>
<td>65 (39-87)</td>
<td>105 (58-127)</td>
</tr>
<tr>
<td>Total Proximal Events</td>
<td>50 (24-61)</td>
<td>72 (47-94)</td>
</tr>
</tbody>
</table>

257
Thickening helps with regurgitation and vomiting
Horwath, Dziechciarz, Szajewska Pediatrics 2008

| Study or Subgroup | Treatment | Control | Weight | MD | RD
|-------------------|-----------|---------|--------|----|----
|                   |           |         |        |    |    |
|                   |           |         |        |    |    |
|                   |           |         |        |    |    |

But keep in mind...Osmolarity changes with fortification and may impact gastric emptying

And what about those PPIs?
RCT of Lansoprazole in Infants
Orenstein et al J Peds 2009

<table>
<thead>
<tr>
<th>Lansoprazole (4.4 mg/5 mL, n = 81)*</th>
<th>Placebo (4.4 mg/5 mL, n = 111)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy: Responder rate, n (%)</td>
<td>44 (54%)</td>
<td>44 (49%)</td>
</tr>
<tr>
<td>Discontinued due to inefficacy, n (%)</td>
<td>28 (35%)</td>
<td>29 (36%)</td>
</tr>
<tr>
<td>Induced symptoms:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cry. % of feedings (Composite 2)</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>• Regurgitation, % of feedings</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>• Spitting up, % of feedings</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>• wheezing, % of feedings</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>• Total, Global severity assessment</td>
<td>41 (51%)</td>
<td>41 (49%)</td>
</tr>
<tr>
<td>Physician: Improved at week 4</td>
<td>44 (54%)</td>
<td>40 (46%)</td>
</tr>
</tbody>
</table>

RCT of Omeprazole for Crying
Moore et al J Peds 2003

Table III. Cry fuss data in response to treatment with omeprazole or placebo

<table>
<thead>
<tr>
<th>Cry fuss time in min/24 h (mean ± SD)</th>
<th>Baseline</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Combined*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Omeprazole</strong> (n = 15)</td>
<td>246 ± 105</td>
<td>203 ± 113</td>
<td>197 ± 129</td>
<td><strong>194 ± 125</strong></td>
</tr>
<tr>
<td><strong>Placebo</strong> (n = 15)</td>
<td>287 ± 132</td>
<td>204 ± 87</td>
<td>199 ± 115</td>
<td><strong>201 ± 105</strong></td>
</tr>
<tr>
<td><strong>Total</strong> (n = 30)</td>
<td>267 ± 119</td>
<td>203 ± 99</td>
<td>196 ± 121</td>
<td><strong>194 ± 121</strong></td>
</tr>
</tbody>
</table>

*Mean of the combined data from Period 1 and Period 2 (n = 30).
| Baseline versus Period 1, P = .846 |
| Baseline versus Period 2, P = .988 |

Summary

- Reflux in infants is largely nonacidic—antacids don’t help this.
- Thickening will help with regurgitations—unclear if it helps with pain
- Osmolarity, overfeeding, and type of feeds matter
- Symptoms of cow’s milk protein allergy overlap with reflux—formula change is higher up than PPI in the algorithm

* really need to do something about this early reflux.
Case 2

• 15 year old with heart burn and regurgitation 5-10x per day
• Pain occurs during and after meals and is significant enough that it prevents her from finishing meals or eating out
• Patient has been trialed on 4 weeks of a QD PPI with no improvement in symptoms
• Patient undergoes endoscopy which is grossly normal with biopsies negative for any inflammation

What is the diagnosis? Is this GERD? Next steps?

Algorithm for Typical Symptoms
Take home points from the algorithm:
- Early impedance/pH testing
- Short courses of PPI
- Symptom correlation matters

NERD in Pediatrics
Mahoney et al / Peds 2017

N=58
18% with histologic inflammation

34% Hypersensitive Esophagus
36% True NERD
27% Functional Heartburn
31% More likely NERD
34% More likely Functional

Remember: Adult data with 40% true NERD, 35% hypersensitive esophagus, 25% functional heartburn

Can symptoms predict who will have what Rome IV diagnosis?
Savarino et al Gut 2009

But no studies in children
There is an imperfect correlation between microscopic esophagitis and diagnosis.

Savarino et al. J Gastro 2014

And remember, if you scope someone on PPI and there is no esophagitis, you may falsely label someone as functional or NERD.

Do I care about these new diagnoses? Is it just semantics?
SSRI for hypersensitive esophagus
Viazis et al. Am J Gastro 2012

219 Patients recorded symptoms during the study day.

Positive St 165 (47.2%)
75 (71.4%) Hypersensitive esophagus

39 Patients Clomipram 50 mg = 1
36 Patients Placebo = 1
24 Patients (61.5%)
No symptoms
12 Patients (33.3%)

P=0.021

SSRI for functional heartburn
Ostovaneh et al. NGM 2014

Percentage of Heartburn Free Days
Baseline
End of Treatment

Omeprazole
Fluoxetine
Placebo

Imipramine for functional heartburn and hypersensitive esophagus
Summary

• Early testing is important to provide the correct diagnosis
• PPIs are not always the answer, even in patients who seem like they are having classic reflux
• The presence of microscopic esophagitis does not always give you the cause for pain
• Remember that treating with acid suppression prior to your scope effects your ultimate diagnosis

Case 3

• 1 year old with wheezing and cough
• Patient seen by otolaryngology and pulmonology
• Diagnosed with “red airways” during a bedside endoscopy
• CXR showed signs of chronic inflammation
• Pulmonology and Otolaryngology refer to gastroenterology for reflux treatment

Extraesophageal symptom algorithm
Why no algorithm?

• There is no study that has shown, in children, that reflux burden respiratory outcomes—this includes O2 requirement, bronchiectasis, ALTE/BRUEs, asthma flares, pneumonias, hospitalization risk
• There is no study to show that treatment of reflux with medication or surgery improves respiratory/airway outcomes
• Therefore, there is no algorithm for the diagnosis or treatment of respiratory symptoms
• Based on expert opinion, the working group suggests not to use H2RAs or PPIs in patients with extraesophageal symptoms except in the presence of typical GERD symptoms and/or diagnostic testing suggestive of GERD.

Summary

• Non-medicine options are first line therapy for infant reflux
• PPI should be used at the lowest doses and for the shortest time possible
• Making an affirmative diagnosis using pH/MII testing and endoscopy is important in children with persistent typical symptoms to avoid unnecessary long term reflux therapies
• There is no evidence to support PPI use for the treatment of reflux in infants or in children with respiratory symptoms

Thank you