**NASPGHAN POSTGRADUATE COURSE**  
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Some of the slides reproduced in this syllabus contain animation in the power point version. This cannot be seen in the printed version.
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NASPGHAN CME Mission Statement
The education mission of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition is to:

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

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

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

AMA PRA Statement
NASPGHAN designates this educational activity for a maximum of 8.5 AMA PRA Category 1 Credit(s)™
Physicians should only claim credit commensurate with the extent of their participation in the activity.
Postgraduate Course
Thursday, October 10, 2013
Practice of a Pediatric Gastroenterologist: Updates on Management

Course Aims:
1. Learn updated clinical and cutting edge information
2. Identify newer treatments
3. Able to manage complicated cases

7:55–8:00 AM
Introduction
Sandeep Gupta MD

8:00–9:15 AM
Module 1 – A,B,C: Updates in Hepatitis
Moderators: Melanie Greifer MD and Pinar Bulut MD

Autoimmune Hepatitis: The when, ifs and how
Vicky Ng MD, Hospital for Sick Children

Learning objectives:
1. Know what to do when standard therapy with steroids/immunomodulators fails
2. Learn if and when to stop therapy
3. Understand how to monitor for complications of disease and therapy

Updates on Hepatitis B: 2013 and beyond
Jean Molleston MD, Riley Hospital for Children

Learning objectives:
1. Know the newer therapies in Hepatitis B in children
2. Discuss whether to treat now or wait
3. Outline the role of genotyping and resistance panels

Treating children with Hepatitis C: 2013 and beyond
Regino Gonzalez - Peralta MD, University of Florida, Gainesville

Learning objectives:
1. Understand the newer adult Hepatitis C therapies and their impact on children
2. Know who to treat and how
3. Learn monitoring of patients with Hepatitis C

9:15–10:30 AM
Module 2 – Updates in Pancreatic Diseases
Moderators: Sandeep Gupta MD and Anupama Chawla MD

When and how to assess pancreatic function: An update for clinicians
Sohail Husain MD, Children’s Hospital of Pittsburgh of UPM

Learning objectives:
1. Know the newer evidence for pancreatic insufficiency assessment
2. Discuss the interpretation of pancreatic function tests
3. List evaluation for non-CF causes of pancreatic insufficiency such as mitochondrial and metabolic disorders
Managing nutrition in Cystic Fibrosis (CF): Role of the pediatric gastroenterologist Sarah Jane Schwarzenberg MD, University of Minnesota Amplatz Children’s Hospital

Learning objectives:
1. Know impact of nutritional status on lung function in CF
2. Outline factors confounding good nutrition in CF
3. Discuss options to facilitate nutrition beyond enzymatic supplements in CF

Beyond the basics in management of pancreatitis
Aliye Uc, University of Iowa

Learning objectives:
1. Know updates in fluid therapy and monitoring in acute pancreatitis
2. Learn the newer genetic tools for chronic pancreatitis
3. Understand the role of enzyme supplementation in pancreatitis

10:30 - 10:50 AM Break

10:50 AM - 12:25 PM Module 3: Updates in Endoscopy
Moderators: Sandeep Gupta MD and Victor Fox MD

Endoscopy in the high-risk patient: Keeping your patient safe
Jenifer Lightdale MD, Boston Children’s Hospital

Learning objectives:
1. Identify high risk patients including Ehlers-Danlos, GVHD, multiple co-morbidities, special medications
2. Discuss pre-operative check list and preparation in high-risk patients
3. Recognize safer practices during endoscopy in high-risk patients

Advances in hemostasis in upper gastrointestinal bleeding
Bradley Barth MD, Children’s Medical Center of Dallas

Learning objectives:
1. Learn about updates on hemostasis techniques for upper GI bleed
2. Discuss what to do with clots: keep ‘em or remove?
3. Recognize the effects of transfusion on outcome

Surveillance endoscopies: The established, the debated and the unknown
Mitchell Shub MD, Phoenix Children’s Hospital

Learning objectives:
1. Recognize who to perform surveillance in including polyps, IBD, Barrett
2. Learn when to perform surveillance endoscopies
3. Know how to conduct surveillance procedures
Expanding the view: Update on upper GI strictures  
Mark Gilger MD, Children’s Hospital of San Antonio

Learning objectives:
1. Learn the various ways to dilate strictures and the pros and cons
2. Discuss frequency of dilations
3. Know techniques to sustain dilation

12:25 - 1:50 PM  
**Learning Luncheons** (separate registration and ticket required)

1. **Controversies in management of EoE** – Glenn Furuta MD and Edaire Cheng MD  
Moderator: Ed Hoffenberg MD
2. **Crohn disease: Challenging cases**: Robert Baldassano MD and Barbara Kirschner MD  
Moderator: Jennifer Strople MD
3. **Pancreatitis: Acute and long-term management** – Sohail Husain MD and Aliye Uc MD  
Moderator: Henry Lin MD
4. **GI Bleeding** – Bradley Barth MD and George Zacur MD  
Moderator: Victor Fox MD
5. **Ulcerative Colitis – Challenging cases**: Wallace Crandall MD and Andrew Grossman MD  
Moderator: Diana Riera MD
6. **Autoimmune Hepatitis** – Vicky Ng MD and Mark Deneau MD  
Moderator: Jyoti Ramakrishna MD
7. **Hepatitis B and C** – Jean Molleston MD and Regino Gonzales-Peralta MD  
Moderator: Stanley Fisher MD
8. **Functional upper GI disorders** – Carlo Di Lorenzo MD and Alfred Yeung MD  
Moderator: John Stutts MD
9. **Updates on parenteral and enteral nutrition** – Praveen Goday MD and Sarah Schwarzenberg MD  
Moderator: Christine Waasdorp-Hurtado MD

1:50 - 3:05 PM
**Module 4: Updates in Pediatric Nutrition**  
Moderators: Sandeep Gupta MD and Christine Waasdorp-Hurtado MD

**Clinical issues in parenteral nutrition**  
Praveen Goday MD, Medical College of Wisconsin

Learning objectives:
1. Learn updates on lipids including restrictions, modifications, and types of lipids
2. Discern how to manage the various shortages and impact on patients
3. Recognize the use of ethanol locks and clinical application

**Enteral nutrition in Crohn disease: Where should this be in our treatment algorithm?**  
Robert Baldassano MD, Children’s Hospital of Philadelphia

Learning objectives:
1. Be able to respond to a common patient question: “Is our Western diet killing us?”
2. Know the use of defined formula diets in the treatment of IBD
3. Learn the importance of the gut microbiota in enteral nutrition in Crohn disease

Severe obesity in your clinic: The disconnect between the epidemic and the interventions
Sarah Barlow MD, Texas Children’s Hospital

Learning objectives:
1. Learn assessment and socio-economic epidemiology of severe obesity
2. Understand the additional medical risks conferred by severe obesity
3. Know tertiary interventions including meal replacement, new medications in adults, and surgical procedures in adolescents

3:05 - 3:25 PM  Break

3:25 - 5:00 PM  Module 5: Updates on Luminal Disease
Moderators: Melanie Greifer MD and Judith Kelsen MD

Decision making in ulcerative colitis: Escalate medical therapy or call the surgeon?
Wallace Crandall MD, Nationwide Children’s Hospital

Learning objectives:
1. Review treatment for steroid refractory UC
2. Know long term risks of medications used for refractory UC
3. Learn post-operative complications and management

Post-surgical management of Crohn Disease: Have things changed?
Barbara Kirschner MD, University of Chicago, Comer Children’s Hospital

Learning objectives:
1. Be able to prepare patients for surgery including optimizing pre-operative medications
2. Learn how surgery impacts maintenance medical therapy
3. Recognize use of medications for post-operative recurrence

Gastroparesis: Paralysis for the patient and provider?
Carlo Di Lorenzo MD, Nationwide Children’s Hospital

Learning objectives:
1. Discern when to suspect gastroparesis
2. Learn updates on gastric function testing
3. Know newer therapies for gastroparesis

Eosinophilia beyond the esophagus
Glenn Furuta MD, Children’s Hospital of Colorado

Learning objectives:
1. Know clinical implications of GI eosinophilia
2. Learn newer managements of GI eosinophilic diseases
3. Recognize systemic causes of GI eosinophilia
Autoimmune Hepatitis
(The “when”, “ifs”, and “buts”)

Vicky Lee Ng, MD, FRCPC
Hospital for Sick Children
University of Toronto

NASPGHAN 2013 Post-Graduate Course
Chicago, Illinois – Thursday, October 10, 2013

Disclosure

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

Learning Objectives

• To highlight key pearls on diagnostic criteria for AIH in children
• To review what to do when “standard” therapy fails
• To review “if” and “when” to stop therapy
• To understand how to monitor for complications of disease and therapy
Introduction – 1

• Consider AIH in all patients with acute/chronic hepatitis of undetermined causes - including acute severe hepatitis and pediatric acute liver failure
• Diagnosis of AIH
  – presence of compatible clinical signs and symptoms, lab abnormalities, serological [ANA and SMA (type 1); anti-LKM 1 or anti-LC1 (type 2)], histological findings; AND
  – exclusion of other etiologic conditions

Typical Histopathology of AIH

Kindness of J. R. Wanless, Dalhousie University

Introduction – 2

• All children with AIH should undergo cholangiographic studies to exclude PSC
• Diagnostically challenging cases – other serological markers (anti-SLA, atypical pANCA), scoring systems may help
• In patients with multiple endocrine disorders, remember APECED = autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
### Standard Therapy – AIH in Children

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Regimen</strong></td>
<td>Prednisone 1-2 mg/kg (max 40-60 mg)/day x 2 weeks ± Azathioprine 1-2 mg/kg/day</td>
</tr>
</tbody>
</table>
| **Maintenance**  | Prednisone taper over 6-8 weeks to 5 mg/day (or 0.1-0.2 mg/kg/day)  
switch to alternate day Prednisone adjusted to response ± Azathioprine |
| **Endpoint**     | Normal liver tests for 1-2 years during treatment  
Liver biopsy histopathology discloses no inflammation ± Azathioprine |


### Introduction – 3

- No randomized treatment trials have reflected disease diversity in a large number of pts
- Goal of treatment in children is to achieve full remission = normal serum AST or ALT levels and IgG levels with negative or low-titre autoantibodies – may take several months
- Long-term monotherapy with azathioprine is generally well tolerated – strategy to suppress inflammatory activity and d/c corticosteroids


### Learning Objective #1

- To highlight key pearls on diagnostic criteria for AIH in children
- To review what to do when “standard” therapy fails
- To review “if” and “when” to stop therapy
- To understand how to monitor for complications of disease and therapy
Difficult to Treat Patients

• ~80% of patients with AIH respond very well to "standard" treatment
• Potential contributors to those (~20%) AIH patients with management challenges include:
  – Non-response
  – Drug intolerance
  – Non-compliance
  – Overlap syndromes
  – Comorbidities

Endpoints of Standard Therapy

<table>
<thead>
<tr>
<th>Px Endpoint</th>
<th>Criteria/Definition</th>
<th>Courses of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>Disappearance of Sx, normal LFTs and Ig levels, LBix no inflammation</td>
<td>Discussion of withdrawal and monitoring schedule</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>Worsening clinical, lab, and histological features despite compliance with Px, Dx of jaundice, ascites, HE</td>
<td>Ensure adherence Re↑ Pred, continue Aza Consider alternate agents</td>
</tr>
<tr>
<td>Incomplete Response</td>
<td>Some or no improvement in clinical, lab, and histological features despite Px compliance</td>
<td>Attempt to taper Pred to lowest level possible (&lt;10 mg QD) to prevent worsening AST, ALT, and indefinite Aza Px</td>
</tr>
<tr>
<td>Drug Toxicity</td>
<td>Development of intolerable AEs: cosmetic, symptomatic osteopenia, HT, brittle diabetes, progressive cytopenias</td>
<td>Reduction in dose or dc offending agent; maintenance on tolerated drug</td>
</tr>
</tbody>
</table>

Alternative Treatment Considerations

• Strategies for non-adherence → particularly adolescents
• Mycophenolate mofetil (MMF)
• Calcineurin inhibitors
  – Cyclosporine (CyA)
  – Tacrolimus (FK)
• Budesonide
• Others – 6-MP, methotrexate, cyclophosphamide, rituximab, rapamycin
• Liver transplantation
N = 11 (adults)
Indications for MMF
- Azathioprine intolerance – 9
- Steroid refractory – 4
- Recurrent relapses following steroid taper - 2
- TPMT deficiency – 1
- ≥ 6 mos duration

• Retrospective Single Center
• N = 21
  - refractory to conventional therapy (12)
  - intolerance to medication (9)
• MMF dosage 500 mg - 1 g po BID
• MMF did not induce remission in those patients refractory to conventional Px
• BUT - significant ↓ steroid use

N=26 “difficult to treat” pediatric AIH pts
MMF dose – initially 20 and ↑'ing to 40 mg/kg/day
Positive response - 18/26 (69%)
  - 14/18 normal AST in 2 months
  - S/E in 50% - neutropenia, abdominal pain, diarrhea, nausea, hair loss & anemia
  - discontinued due to S/E in 15%
Short-term cyclosporine induces a remission of autoimmune hepatitis in children

- Rapid initial control of hepatitis
  - 25/32 (78%) normal AST/ALT by 6 mos → transition to Aza/Prednisone
- Dose of 4 mg/kg/day (÷TID)
  - ↑ q2-3 d targeting C0 level = 250 ng/ml
- No change in growth velocity
- Avoidance of steroid-associated adverse effect
- CyA side effects – hypertrichosis (55%), gingival hyperplasia (39%), nephrotoxicity (HT, elevated serum Cr)

Liver Transplantation for AIH

- Liver transplantation is indicated in:
  - Pts presenting in fulminant liver failure (with encephalopathy)
  - Pts with chronic disease progressing to end-stage liver disease despite treatment (10-20%)
    - established cirrhosis at diagnosis, long history before start of Px
- Risk of recurrent AIH post-LT
Summary

• Remember non-adherence particularly in adolescents and young adults

• Literature to-date for the treatment of resistant cases with calcineurin inhibitors and MMF is limited
  – Viewed as rescue and not as primary treatment – more toxic and more expensive than prednisone and azathioprine
  – MMF – currently (probably) the most promising current agent

• No data are available on the effectiveness of budesonide or ursodeoxycholic acid in childhood AIH

Learning Objective #2

• To highlight key pearls on diagnostic criteria for AIH in children
• To review what to do when “standard” therapy fails
• To review “if” and “when” to stop therapy
• To understand how to monitor for complications of disease and therapy

Autoimmune Hepatitis in Childhood: A 20-Year Experience

Hepatology 1997;25:541-547

• N=52 consecutive patients over 20 years
  – Type 1 – 32
  – Type 2 – 20

• Treatment discontinued in 19%
  – Only Type 1 AIH

• Development of end-stage liver disease requiring LT (8-14 years after diagnosis) in 8.5%
  – despite treatment
• N=30
• Treatment discontinued in 6/30 (21%)
• Remission maintained for a minimum of 2 years, with normal clinical and biochemical, and histology from liver biopsy stable

• N=131, multi-center study in Netherlands – retrospective
• Px tapered >2 years of clinical & biochemical response
  ◦ Relapse – 61/131 (47%)
  ◦ Loss of remission - 56/131 (42%)

• “These findings indicate a reluctant attitude towards discontinuation of immunosuppressive treatment in AIH patients”

Duration of Treatment and Prognosis

• Optimal duration – unknown

• “Cessation of treatment should (could) be considered if LBx shows minimal or no inflammatory changes after 1-2 years of normal LFTs + normal IgG levels + negative or low-titre autoantibodies...however, advisable not to attempt Px withdrawal within 3 years of Dx or during or immediately before puberty - when relapses are more common.”
Learning Objective #3

1. To highlight key pearls on diagnostic criteria for AIH in children
2. To review what to do when “standard” therapy fails
3. To review “if” and “when” to stop therapy
4. To understand how to monitor for complications of disease and therapy

### Prednisone-Related Side Effects

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosmetic (usually mild)</td>
<td></td>
</tr>
<tr>
<td>• Facial rounding, weight gain, dorsal hump striae</td>
<td>80% (after 2 years)</td>
</tr>
<tr>
<td>• Hirsutism, Alopecia</td>
<td></td>
</tr>
<tr>
<td>Somatic (usually mild)</td>
<td>80% (after 2 years)</td>
</tr>
<tr>
<td>• Emotional instability</td>
<td></td>
</tr>
<tr>
<td>• Glucose intolerance</td>
<td></td>
</tr>
<tr>
<td>• Cataracts</td>
<td></td>
</tr>
<tr>
<td>Somatic (severe)</td>
<td>13% (treatment ending)</td>
</tr>
<tr>
<td>• Osteopenia, vertebral compression</td>
<td></td>
</tr>
<tr>
<td>• Diabetes (brittle)</td>
<td></td>
</tr>
<tr>
<td>• Psychosis</td>
<td></td>
</tr>
<tr>
<td>• Hypertension (labile)</td>
<td></td>
</tr>
<tr>
<td>Inflammatory/neoplastic</td>
<td>Rare</td>
</tr>
<tr>
<td>• Pancreatitis, Opportunistic infection, Malignancy</td>
<td></td>
</tr>
</tbody>
</table>

Table 8, AASLD Practice Guidelines, Hepatology 2010;51(6):13

### Azathioprine-Related Side Effects

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic (mild)</td>
<td>46% (esp with cirrhosis)</td>
</tr>
<tr>
<td>• cytopenia</td>
<td></td>
</tr>
<tr>
<td>Hematologic (severe)</td>
<td>6% (treatment ending)</td>
</tr>
<tr>
<td>• Leukopenia</td>
<td></td>
</tr>
<tr>
<td>• Neutropenia, Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Somatic (usually mild)</td>
<td>5%</td>
</tr>
<tr>
<td>• Nausea, Emetia, Rash, Fever, Arthralgia</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>3% (after 10 years)</td>
</tr>
<tr>
<td>• Nonhepatic cell types</td>
<td></td>
</tr>
<tr>
<td>Hematologic/Enteric</td>
<td>Rare (treatment ending)</td>
</tr>
<tr>
<td>• Bone marrow failure</td>
<td></td>
</tr>
<tr>
<td>• Vileus atrophy</td>
<td></td>
</tr>
<tr>
<td>• Malabsorption</td>
<td></td>
</tr>
<tr>
<td>Teratogenic during pregnancy</td>
<td>Rare (Theoretical)</td>
</tr>
</tbody>
</table>

Table 8, AASLD Practice Guidelines, Hepatology 2010;51(6):13
Monitoring for Complications of Disease

- Hepatocellular carcinoma
  - U/S screening for the development of neoplastic foci
  - Challenges – DDx include macronodular cirrhosis, regenerative nodule
  - Serum AFP levels (?)q6-12 monthly
- Attention to associated autoimmune disorders
  - Celiac disease, thyroiditis, vitiligo, type 1 diabetes, IBD, nephrotic syndrome

Teufel et al; World J Gastroenterol 2009;15:578-582

Monitoring for: Complications of Treatment

- Counseling - nature and frequency of side effects associated with each treatment regimen
- Pretreatment HAV and HBV vaccination if no previous vaccination
- Long-term steroid therapy:
  - monitor for bone disease at baseline and then annually.
- Azathiopurine therapy:
  - Measure Aza metabolites (6-thioguanine and 6-methylmercaptopurine) – although ideal therapeutic level has not been determined
  - Erythrocyte thiopurine methyltransferase activity

“Bone Protection Regimen”

- Chronic liver disease, with or without chronic corticosteroid Rx, associated with osteoporosis
- Conservative regimen:
  - Increase calcium in diet
  - Vitamin D supplementation
  - Discourage foods containing caffeine
  - Regular weight-bearing exercise
- Monitor bone density (DXA scan)
- Bone-building therapies - controversial in children, may be suitable for adults
Future Directions

- Peptides which block autoantigen presentation competitively
- Agents which inhibit secondary signals and lead to activation of immunocytes
  - Example: cytotoxic T lymphocyte antigen-4
- T cell vaccination
- Oral tolerance therapy
- Monoclonal antibodies and other recombinant proteins which affect cytokine expression or action

Take-Home Messages

- Non-responders to standard therapy require alternate agents (MMF, CNIs) - despite which they may still progress to LT-requiring ESLD
- Long term Fx is required for the majority of pts
- D/ C of therapy COULD be considered after 1-2 yrs of complete remission if LBx shows no evidence of inflammation
- Adjunctive therapies for bone disease include a regular weight bearing exercise program, supplementation with vitamin D & calcium, and consideration re: bone active agents.

Thank you for your attention!
I have the following financial relations to disclose

- Schering-Plough
- Roche
- Vertex Pharmaceuticals, Inc.

- Products or services produced by these companies are relevant to my presentation

Objectives

- Know the newer therapies in hepatitis B in children
- Discuss whether to treat now or wait
- Outline the role of genotyping and resistance panels
Natural History of Hepatitis B

- Immunotolerant Hepatitis B
  - 4-5% HBeAg seroconversion/year
- Active disease
  - 2-20% HBeAg+ reactivation
  - 10-30% cont active disease
  - 10-20% HBeAg-reactivations

- Cirrhosis 2-3%/year
- HCC 1-15%/15 years

Immunotolerant

-active disease:
  - HBeAg+ (> 6 months)
  - HBV DNA > 20,000 IU/ml
  - ALT > 1.5 x normal or > 60 IU/L
  - Moderate/severe inflammation/fibrosis

Reactivated Hepatitis B with active disease:
  - HBeAg+ (> 12 months)
  - HBV DNA > 2000 IU/ml
  - ALT > 1.5 x normal or > 60 IU/L
  - Moderate/severe inflammation/fibrosis

Hepatitis B: Who to Treat

Hepatitis B: Who to Not Treat

- Immunotolerant Hepatitis B:
  - HBeAg+
  - HBV DNA > 20,000 IU/ml
  - Normal ALT
- Inactive carrier:
  - HBeAg-
  - HBV DNA < 2000 IU/ml
  - Normal ALT

Lok A. Hepatology 2009.
Jonas M. Hepatology 2010.

Special Circumstances that May Promote Treatment

- Cirrhosis or advancing disease
- Kidney disease related to Hepatitis B
- Post-liver transplant
- On chemotherapy or immunosuppression
- Co-infection

Jonas M. Hepatology 2010.

Adult Treatment Options for Hepatitis B

<table>
<thead>
<tr>
<th></th>
<th>IFN Alpha</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>SubQ</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Duration</td>
<td>4-12 Months</td>
<td>≥ 1 year</td>
<td>≥ 1 year</td>
<td>≥ 1 year</td>
<td>≥ 1 year</td>
</tr>
<tr>
<td>Side effects</td>
<td>Many</td>
<td>Minimal</td>
<td>Renal</td>
<td>Minimal</td>
<td>Renal, bone</td>
</tr>
<tr>
<td>Resistance</td>
<td>0</td>
<td>20-70%</td>
<td>0-29%</td>
<td>1%</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from Lok. Hepatology 2009.
### Adult Hepatitis B Responses to Anti-Viral Therapy

<table>
<thead>
<tr>
<th>Loss of DNA</th>
<th>Controls</th>
<th>IFN</th>
<th>LAM</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Tenofovir</th>
<th>PegIFN</th>
<th>PegIFN+ LAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-17%</td>
<td>37%</td>
<td>40-44%</td>
<td>21%</td>
<td>67%</td>
<td>76%</td>
<td>25%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>HBeAg-/Ab+</td>
<td>4-6%</td>
<td>+18%*</td>
<td>16-21%</td>
<td>12%</td>
<td>21%</td>
<td>27%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>HBeAg+</td>
<td>0-1%</td>
<td>8%</td>
<td>1%</td>
<td>0</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Normal ALT</td>
<td>7-24%</td>
<td>+23%</td>
<td>41-75%</td>
<td>48%</td>
<td>68%</td>
<td>68%</td>
<td>39%</td>
<td>46%</td>
</tr>
<tr>
<td>Histology improves</td>
<td>49-56%</td>
<td>53%</td>
<td>53%</td>
<td>72%</td>
<td>74%</td>
<td>38%</td>
<td>41%</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Lok: Hepatology 2009.

### Treatment of Hepatitis B in Children: Interferon


### Treatment of Hepatitis B in Children: Lamivudine

- 288 children, RCT 52 weeks of Rx then extension study
- HBeAg-/DNA- in 23% on LAM vs 13% placebo
- 64% resistance at 3 years
- 54% virologic response at 3 years if no resistance
- 3% HBsAg loss

Treatment of Hepatitis B in Children: Adefovir

- RCT 173 children, adefovir vs placebo
- Children 12-17 years: Adefovir 23% DNA-/ALT nl
  Placebo 0% DNA-/ALT nl
- Children < 12 years: No significant difference
- No mutations
- Little toxicity


Treatment of Hepatitis B in Children: Tenofovir

- 23 children with hepatitis B, mostly Asian, normal ALT
- Lamivudine 8 weeks then lamivudine/IFN 10 months
- 22% HBeAg seroconversion
- 17% HBsAg seroconversion
- Response durable at 3 years; no YMDD mutations


A Tantalizing Pilot Study: Combination Therapy in Pediatric Hepatitis B

- 23 children with hepatitis B, mostly Asian, normal ALT
- Lamivudine 8 weeks then lamivudine/IFN 10 months
- 22% HBeAg seroconversion
- 17% HBsAg seroconversion
- Response durable at 3 years; no YMDD mutations

Take-Home Points: What to Use to Treat Children with Hepatitis B and When

- Only children with active disease should be treated
- Many would suggest IFN as a first line drug, especially for younger children
- Nucleoside analogues can now be considered in older children:
  - Tenofovir is licensed for over age 12
  - Entecavir is licensed for over age 16
  - (Lamivudine and adefovir have disadvantages)

Epidemiology of Most Common HBV Genotypes (Prevalence in US)

- A (35%): Europe/North America (African-Americans and Caucasians)
- B (22%): Asia
- C (31%): Asia
- D (10%): India, Mediterranean, Middle East
- E-G (2%)


Hepatitis B Genotype and Natural History

- Genotypes B&C: More vertical transmission
- Genotypes A&D: More chronicity
- Genotypes C&D: Higher histologic activity
- Genotype C: ↓ Rate of HBeAg seroconversion
- Genotype C: Higher rate of HCC
- Genotype B: Younger age of HCC (often not in setting of cirrhosis)

Hepatitis B Genotype and Response to Rx

- Genotypes A and B are more responsive to Interferon
- Response to nucleoside analogues is not different among Hepatitis B genotypes
- Genotype B may be more associated with LAM resistance

Hepatitis B Genotype and Response to Peg-IFN Therapy

Take-Home Points about Genotype

- Genotypes B and C are worse
- Genotypes A and B respond better to IFN
- Genotype not useful to predict response to nucleosides
- Future studies should have stratification by genotype
- Genotyping is not widely recommended for clinical use now
HBV Mutations

- **Pre-S mutants** affect surface antigen expression-immunologic role
- **Pre-core mutants and basal core promoter (BCP) mutants** enhance replication and result in increased disease severity and HCC
- **Drug resistance mutants** in viral polymerase cause resistance to lamivudine or other drugs


How Mutations, Genotyping and Viral Resistance Panels Might Be Used

- Limited clinical role for genotyping now
- Mutations such as pre-core or BCP may contribute to virus's behavior but testing unlikely to change management
- Adult guidelines suggest checking viral resistance when viral breakthrough occurs
- Future potential: Panels that help us predict which patients will benefit from Rx

What's Exciting?

- NCT01519960 Peg-IFN monotherapy for children with chronic active hepatitis B
- NCT01368497 Peg-IFN and Entecavir for treatment of Hepatitis B in immunotolerant children
- New drugs
- New ways to predict who will have worse disease and who will respond
Acknowledgements

• Thanks to the course directors for inviting me to speak
• Thanks to Vicki Haviland-Wilhite for expert secretarial assistance
Treating HCV: 2013 and Beyond...

Regino P. González-Peralta, M.D.
University of Florida College of Medicine
UF Health Shands Children’s Hospital
Gainesville, Florida

Financial Disclosures

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- Abbott
- Gilead
- Bristol Myers Squibb
- Merck (Schering-Plough)

Products produced by ALL of these companies are relevant to my presentation.

Objectives

TREATMENT
Who should be Rx?
Monitoring
**Standard of Care HCV Therapy: Children**

**IFN/PEG-IFN-α-2a (PEG-2a)**
- "Branched" 40-kDa PEG moiety
- Dose: 104 μg/m² SQ once weekly
- Available: prefilled syringes or as vials

+ Ribavirin (15 mg/kg/day)

**PEG-IFN-α-2b (PEG-2b)**
- "Linear" 12-kDa PEG
- Dose: 60 μg/m² SQ once weekly
- Available: Measured vials/ready-use pens

**Childhood HCV: PEG+Ribavirin**

Sustained Virologic Response (SVR) (%)

<table>
<thead>
<tr>
<th></th>
<th>Wirth (n=61)</th>
<th>Jara (n=30)</th>
<th>Wirth (n=107)</th>
<th>Schwarz (n=55)</th>
<th>Sokal (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG2b</td>
<td>193/318 (61%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Impact of HCV Genotype**

SVR (%)

- Genotype 1
- Genotype 2/3

<table>
<thead>
<tr>
<th></th>
<th>Christensson (n=11)</th>
<th>Wirth (n=107)</th>
<th>Gonzalez-Peralta (n=118)</th>
<th>Wirth (n=40)</th>
<th>Schwarz (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG+Ribavirin</td>
<td>IFN+Ribavirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IL28B Single-Nucleotide Polymorphism

SVR (%)  SVR (%)  

rs12979860

NO pediatric data with respect to IL28B and response to therapy

PEG-RBV: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Adults (n=511)</th>
<th>Children (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Flu-like' symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid Abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia (Hgb &lt;10 g/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia (Grade 3/4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN-related toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose reductions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-adherence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Manns et al. Lancet 2001; Wirth et al. J Hepatol 2010

PEG-RBV: On-Treatment Monitoring

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>When to Check (Rx week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC (ANC)</td>
<td>0, 1, 2, 4, 8, 12 and Q 4-8 after</td>
</tr>
<tr>
<td>Liver tests-Glucose</td>
<td>0, 1, 2, 4, 8, 12 and Q 4-8 after</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>0, then only if clinically needed</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>0, 24, 48, 72</td>
</tr>
</tbody>
</table>

Mack CL, et al. JPGN 2012
**PEG+Ribavirin: Growth**  
*Peds C*

- **Weight**
- **Height**
- **BMI**

**Mechanism?**
- Cytokine effect?
- Not related to poor caloric intake

---

**Direct Acting Antivirals**  
**Protease Inhibitors: HCV Genotype 1**

- **Treatment Naive Adults**

<table>
<thead>
<tr>
<th></th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>69</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>75</td>
</tr>
</tbody>
</table>

- FDA-approved for adults in May 2011
- Trials actively enrolling children

**SVR (%)**
- Telaprevir-Boceprevir + PEG-RBV

- **P<0.001**
- **P<0.001**

---

**Telaprevir-Boceprevir + PEG-RBV**

- **'Room for Improvement'**

  - Complex regimens
  - High 'pill burden'
  - Food requirement
  - Suboptimal efficacy: cirrhosis, non-responders
  - 'Real-world' experience: toxicity
  - Anemia, rash, GI
  - Premature discontinuation

---


**Chung, R ClinicalOptions.com/hepatitis**
'Warp-Speed' Evolution of HCV therapy
'The Pipeline'

<table>
<thead>
<tr>
<th>1 DAA+PEG/RBV</th>
<th>New IFNs</th>
<th>IFN-Free Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sofosbuvir (NS5B)</td>
<td>Sofosbuvir (SOF)+RBV</td>
</tr>
<tr>
<td></td>
<td>Simeprevir (PI)</td>
<td>SOF+Ladispavir±RBV</td>
</tr>
<tr>
<td></td>
<td>Faldaprevir (PI)</td>
<td>Asunaprevir+daclastavir</td>
</tr>
<tr>
<td></td>
<td>Vaniprevir (PI)</td>
<td>ABT-450/r+ABT-267+ABT-333+RBV</td>
</tr>
<tr>
<td></td>
<td>Daclastavir (NS5A)</td>
<td>Faldaprevir+BI207127+RBV</td>
</tr>
</tbody>
</table>

New IFN's

- Sofosbuvir (NS5B)
- Simeprevir (PI)
- Faldaprevir (PI)
- Vaniprevir (PI)
- Daclastavir (NS5A)

IFN-Free Regimens

- Sofosbuvir (SOF)+RBV
- SOF+Ladispavir±RBV
- Asunaprevir+daclastavir
- ABT-450/r+ABT-267+ABT-333+RBV
- Faldaprevir+BI207127+RBV

IFN-Free Regimens
1 DAA+PEG/RBV

'SAll Oral' Regimens for HCV Genotype 1

Phase II

<table>
<thead>
<tr>
<th>Electron Study</th>
<th>LDV (n=34)</th>
<th>GS9669 (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AE</td>
<td>2 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (15%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (3%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Pre-D/C *</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

SOF+RBV
Ledispavir
GS9669

Who Should be Treated?

- Package insert: "...compensated liver disease..."
- AASLD Practice Guidelines 2009
  - Bridging fibrosis → Cirrhosis

Treating Children with Chronic HCV

**IN FAVOR...**
- Avoid disease progression
- Remove social stigma
- Decrease HCV burden
- Children 'better' candidates

**AGAINST**
- Benign disease
- Efficacy
- Toxicity
- Direct Acting Antivirals


Monitoring children with HCV infection

- Evaluated yearly
- Education
- Assess liver disease
  - CBC, liver tests, HCV RNA and PT/INR (cirrhosis)

Mack CL, et al. JPGN 2012

Treating HCV: 2013 and Beyond...

"An approach"

- Genotype 1
- Genotype 2/3
- Assess 'Rx profile'
- Liver biopsy?
- Motivated
- No Contraindications
- Treat

Abnormal ALT
Exclude other causes
Treating HCV: 2013 and Beyond...

Conclusions & Take Home Messages

- PEG-RBV is SOC for children
- Suboptimal efficacy
- Toxicity

Whether to Treat or Not? ...Difficult
Monitoring remains an important practice

- 'All ORAL' regimen on HORIZON
- Simple-short
- BRIGHT FUTURE

Gracias
When and how to assess pancreatic function: an update for clinicians

Sohail Z. Husain, MD
Children’s Hospital of Pittsburgh of UPMC
and the University of Pittsburgh

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

Patient case
• 5 yo boy with mild, chronic diarrhea
• Greasy stools
• Started at 1 yr of age
• Poor weight gain and linear growth
• Negative stool studies
• Normal intestinal biopsies
• Does our patient have pancreatic insufficiency (PI)?
• How can we diagnose PI?
• If PI, what’s the cause?
Objectives

- Pancreatic insufficiency (PI)
- Pancreatic function testing (PFT)
- Updates on the causes of pancreatic insufficiency

Pancreatic insufficiency (PI)

- An inability to properly digest food due to a lack of digestive enzymes made by the pancreas

![Enzyme Distribution Pie Chart](image)

- Proteases: 90%
- Amylase: 7%
- Lipases: 2%
- Nucleases: <1%

(Scwerek G. Gastroenterology 1981)

Pancreatic function tests (PFTs)

- Indications
  - Evaluate chronic diarrhea, steatorrhea, failure to thrive
  - Define pancreatic function in pts with cystic fibrosis (CF)
  - Assess efficacy of pancreatic enzyme replacement therapy
  - Rule out chronic pancreatitis; child with chronic abdominal pain

<table>
<thead>
<tr>
<th>Indirect (non-stimulatory)</th>
<th>Stool</th>
<th>Serum</th>
<th>Breath</th>
</tr>
</thead>
</table>

| Direct (stimulatory) | Dreiling tube | Endoscopic pancreatic function testing (ePFT) | Secretin-enhanced MRCP (sMRCP) |
### Stool assessment for PI: Fecal fat
- Detects steatorrhea
- Coefficient of fat absorption (CFA)
  \[
  \text{CFA} = \frac{\text{fat intake} - \text{fat in stool} / \text{fat intake}}{} \times 100
  \]
  - Normal > 93% (> 85% in less than 6 mo. old)
  - 72 hr collection gold standard
- Fat intake
  - Adolescent or adult: High fat diet; 100 gm fat per day
  - Younger child: Ascertain 72 hr intake
- **Our patient**
  - Intake 167.3 gm fat; stool fat 20.3 gm; 88% CFA (low)

### Challenges with fecal fat
- Laborious, unpleasant
- Test for fat malabsorption, not just PI
- Consider non-pancreatic sources
  - Mucosal (celiac), cholestasis
- Steatorrhea due to PI occurs when lipase output dips below 10%
- Detects only severe PI

### Stool assessment for PI: Elastase-1
- Stable, specific for human pancreas
- Normal > 200 µg elastase/g stool
- Particularly good for monitoring the development of PI in patients with CF
- Low levels (false-positive) with diarrhea
- Only detects severe PI
- **Other tests**
  - Chymotrypsin: less sensitive; requires discontinuation of enzymes
  - Steatocrit: cheap; has low sensitivity
- **Our patient**: Fecal elastase-1 80 µg elastase/g stool (low)
Serum assessment for PI

- Fat soluble vitamins (A,D,E,K)
- Immunoreactive trypsinogen (IRT)
- Low in infants with CF
- Amylase
  - IRT and amylase low in Shwachman-Diamond Syndrome (SDS)

Control
IRT
Amylase
SDS

Breath assessment for PI:
13C-mixed triglyceride meal

Pro
- Can assess efficacy of PERT
- Non-invasive
- Sensitive

Con
- Availability of substrate
- Tachypneic infants
- CF pt.s with chronic lung disease and CO2 retention
- Expensive, time-consuming
- Influenced by PERT
- Test for fat maldigestion, not just PI

Direct assessment of PI

Pancreatic enzymes (CCK)
Fluid and bicarbonate (secretin)

- Pancreatic secretions can be selectively stimulated by CCK, secretin, or both.
The ideal scenario: The Dreiling tube

CCK
40 ng/kg/hr
Secretin
0.2 ug/kg over 1 min
Collections every 15 min for 1 hr

Measure
• Volume
• [Peak bicarbonate]
• [Total protein]
• Pancreatic enzyme activity

The dreaded Dreiling tube

Pro
• Surrogate “gold standard”
• Can detect mild PI

Con
• Invasive, cumbersome
• Impractical
• Not available

The practical scenario: Endoscopic pancreatic function testing (ePFT)

Pro
• Direct test
• Can potentially detect mild PI
• Concomitant histology

Con
• Lack standards in children (protocol and reference values)
• General anesthesia may inhibit pancreatic secretions
• Duodenal intubation
• Time-consuming; reimbursement?
Endoscopic pancreatic function testing (ePFT)

Our patient's ePFT: (in nm/ml.min)
- Trypsin 44 (>55)
- Lipase 90 (>146)
- Amylase 10 (>32)

What is the cause of PI in our patient?

Updates on the causes of PI in children

Cystic fibrosis (CF)
- 85% of patients with classic CF have PI
  - 65% of infants at birth have PI
  - 15-20% will have progressive loss of pancreatic function by 3 years of age
- Pancreas-sufficient CF patients have improved survival
- Improving PI might improve survival
- Stool elastase-1 useful to
  - Define pancreatic function
  - Need for PERT
**Shwachman-Diamond Syndrome (SDS)**

- **Triad**
  - PI
  - Bone marrow dysfunction
  - Short stature
- Mutation in SBDS, found in ~90% of SDS patients
- PI affects almost all SDS patients
- Replacement of acinar cells by fat
- Serum pancreatic enzymes are low in SDS patients

(Dror, AnnNYAcadSci, 2011)

**Johanson-Blizzard syndrome (JBS)**

- **Key findings**
  - PI
  - Severe developmental delay
  - Hypoplasia or aplasia of the nasal wings
- Loss of function mutations in the UBR1 gene (Zenker, NatGen, 2005)
- PI
  - Most consistent feature
  - Replacement of the pancreas by fat and connective tissue
- Endocrine insufficiency develops in adulthood

(Arabshahi N, WJGastro, 2011)

**Mitochondrial cause for PI:**

- **Pearson marrow pancreas syndrome**
- **Key findings**
  - Severe hypoplastic, macrocytic anemia
  - PI (pancreatic fibrosis)
- Diagnosed during infancy
- Multisystem
  - Liver, kidneys, muscle, neurologic
- Mutation/deletion of mitochondrial DNA (mtDNA)
- Diagnosis
  - Clinical picture
  - High serum lactate/pyruvate
  - Southern blot for mtDNA rearrangements
Other causes of PI
- Chronic pancreatitis
- Pancreatic obliteration after severe, acute pancreatitis
- Pancreatic tumors
- Celiac disease
- Diabetes
- IBD

Summary of our patient’s data
- PI
  - Fecal fat: CFA low
  - Stool elastase-1: Low
  - ePFT: Low pancreatic enzyme activity
- Gene testing for SBDS: Positive
- Diagnosis: SDS
  (also had unexplained anemia)

Summary
- Indirect PFTs detect severe PI, but miss mild cases
- The stool elastase-1 is the most convenient PFT

<table>
<thead>
<tr>
<th>Indication</th>
<th>PFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen for PI (pt. with steatorrhea)</td>
<td>Fecal elastase-1</td>
</tr>
<tr>
<td>Define pancreatic function in CF</td>
<td>Fecal elastase-1</td>
</tr>
<tr>
<td>Define pancreatic function in SDS</td>
<td>Serum IRT &amp; amylase</td>
</tr>
<tr>
<td>Assess fat malabsorption on PERT</td>
<td>Fecal fat</td>
</tr>
<tr>
<td>Assess for mild PI</td>
<td>13C-mixed triglyceride test</td>
</tr>
<tr>
<td>Rule out CP</td>
<td>ePFT</td>
</tr>
<tr>
<td></td>
<td>+MRCP</td>
</tr>
</tbody>
</table>
Future Directions

- Develop a better, non-invasive PFT that can detect even mild PI in children

- Determine whether a combination of the available PFTs, along with additional biochemical and imaging data, has optimal sensitivity and specificity in children, or in select ages or disease subsets

- (1) Validate a standardized protocol for endoscopic PFT in children and (2) establish reference values

- Examine whether PFT in children is of value in diagnosing chronic pancreatitis in children

INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure)
Managing nutrition in cystic fibrosis: the role of the pediatric gastroenterologist

Sarah Jane Schwarzenberg, M.D.
University of Minnesota Amplatz
Children’s Hospital
October

I have the following financial relationships to disclose:

BristolMeyerSquibb
Spark Healthcare Consultants

No Products or services produced by this (these) company (companies) are relevant to my presentation.

Objectives

• Know the impact of nutritional status on lung function in CF
• Outline some (non-pancreatic) factors confounding good nutrition in CF
• Outline some options to facilitate nutrition beyond enzyme supplements in CF
Cystic fibrosis
• Autosomal recessively inherited defect in the cystic fibrosis transmembrane conductance regulator (CFTR)
• Reduced transport of chloride across cell membranes results in thickened mucosal secretions and decreased bicarbonate flow in pancreas, liver, and intestine.
• Most deaths are associated with inexorable decline in pulmonary function

Genetic variation
• Hundreds of CFTR mutations described
• Function-impairing mutations classified into 5 categories
• ~85% of individuals with CF have very early pancreatic insufficiency (PI)

Nutrition and lung function in CF
• Prospective, observational study using data from the CFF Registry, 1989-1992
• 3142 patients with CF stratified by peak weight-for-age percentile (WAP) at age 4-5 years into 4 groups:
  – Less than 10th percentile
  – 10th to less than 25th percentile
  – 25th to less than 50th percentile
  – 50th percentile or greater
Question
What is the impact of nutritional status in early life on the timing and velocity of height growth, lung function, complications of CF, and survival through age 18 years?

Results
- Patients with a WAP >50% at age 4 years reached a much higher height-for-age early in life and maintained this advantage into adulthood
- Pulmonary function (FEV₁%predicted) was much lower in CF patients with WAP<10% at age 4 years. This finding tracked through age 18 years.

Survival highest in patients with better WAP at age 4 years
Conclusions

• In CF, better early childhood nutrition is associated with better height growth, better lung function, and improved survival into adulthood
• Better childhood nutrition is associated with more normal glucose metabolism

Factors confounding nutrition in CF

More Calories expended
- Increased pulmonary effort
- Chronic/recurrent inflammation
- CFTR mutations

Fewer Calories in
- Poor appetite/intake
- Gastroparesis
- Prolonged small bowel transit
- Diminished sense of smell
- Abdominal pain
- Depression
- Poorly social chaos
- Behavioral problems
- Malabsorption
- Pancreatic insufficiency
- Poor adherence to enzyme therapy
- Impaired micelle formation
- Small bowel overgrowth
- Cystic fibrosis related diabetes
- Cystic fibrosis liver disease

Other genetic factors

Malnutrition

Small intestine pH in CF

• 10 adults with CF and PI matched with 10 healthy subjects
• Smartpill measured pH and pressure every 5-20s for 72 hours
Intestinal pH in CF v. control

Implications

- Absence of bicarbonate secretion has profound impact on intestinal pH in CF
- Acidic pH
  - Impairs dissolution of pancreatic enzyme capsule
  - Reduces intestinal solubility
  - Reduces mixed micelle formation
- Acidic intestinal milieu may be another factor impairing nutrition in CF

Small bowel overgrowth is common in CF

Fridge JL, et al. JPGN 2007

- Estimates of about 50% in studies that exclude subjects with dysmotility
- Risk factors include
  - Stasis from slow motility
  - Previous intestinal surgery
  - Gastric acid suppression
  - Thick intestinal mucus
Impact of SBO on patients

- Abdominal pain, bloating, flatulence
- Malabsorption, anemia
- Diarrhea
- Nausea, dyspepsia

Small bowel bacterial overgrowth contributes to poor nutritional intake and increased nutrient losses

Small bowel transit in CF

- 16 PI CF children mean age 16.7 ± 3.6 years
- 12 healthy adult controls, mean age 28.6 ± 9.2 years
- Liquid test meal labeled with 99m technetium sulfur colloid, with assessment of gastric emptying and small bowel transit


Results

- No differences in two groups with respect to gastric emptying
- At 6 hours, 37% tracer beyond terminal ileum in CF patients compared to 69% in controls.
- Subjects with CF had significantly prolonged small bowel transit times
Options to improve nutrition in CF

- Review and optimize enzyme dose and adherence
- Review patient's diet with an experienced CF dietician
- Consider adding a PPI to improve intestinal pH

Consider confounding disease

- Evaluate for signs and symptoms of small bowel overgrowth and consider trial of metronidazole or rifaximin
- Ask patient about abdominal pain
  - Evaluate for gastroparesis
  - Evaluate for DIOS
  - Consider non-CF gastrointestinal disease
- Consider oral glucose tolerance test

Therapy to improve nutrition

- Time-limited interventions
- Behavior therapy to improve intake
- Offer oral supplements
- Consider cyproheptadine as an appetite stimulant
- Consider a G-tube for nocturnal feeds
- Consider Endocrinology consult
Behavioral therapy in CF
Stark LJ et al, Pediatr Pulmonol 2011

• 79 children with CF in multicenter study received nutrition education and/or behavioral therapy
  – Mean age: 7.64 years
  – Gender balanced
• Comparison
  – Age and gender matched patients from CFF Registry (Comparison Sample)
  – Matched 5:1, registry:treatment group

Results

• Children in Clinical Trial Group demonstrated less decline in BMI z-score over 2 years, compared to Comparison Sample
  – CTG -0.05; CS -0.21, p<0.00001
• No statistically significant difference in decline of FEV1 between the two groups

Conclusion

• Short-term, intensive nutrition education and behavior therapy can improve weight gain in CF
• Results are durable over at least 2 years, and, in some studies, over 5 years
Gastrostomy feeds in CF
Best C, et al. JPGN 2011

• Retrospective study of large CF database
• 46 patients with CF with GT (adults and children)
• Weight, height, and PFT data from 2 years before GT placement and up to 4 years after GT placement

Results
• No evidence of an adverse consequence of GT placement at any FEV₁
• Significant improvement in BMI within 1 year
• Improvement in BMI less for adult females
• Rate of decline of ppFEV₁% predicted improved after GT placement and was durable out to 4 years

Summary
• Adequate, even robust nutrition improves survival in CF
• Many complications of this multi-system disease impact nutrition in CF
• Pediatric gastroenterologists can improve patient care and prolong life in CF by addressing the GI confounders of good nutrition
Take-home messages

• Optimal enzyme therapy is not the only factor insuring good nutrition in CF
• Weight loss or failure to gain is an urgent medical issue in a patient with CF
• Improving nutrition can have a positive impact on pulmonary function

Future Directions

• What does “optimal nutrition” mean in CF? What is the role of muscle vs fat accretion in CF?
• How do intestinal pH, small intestinal overgrowth, and abnormal transit interact to create malnutrition in CF?
Objectives

- Know updates on fluid therapy and monitoring in acute pancreatitis.
- Learn the newer genetic tools for chronic pancreatitis.
- Understand the role of pancreatic enzyme supplementation in pancreatitis.
“Golden Hours” of Management in Acute Pancreatitis

- Increased cytokines
- Increased other proinflammatory mediators
- Vasodilation
- Intravascular volume depletion
- End-organ hypoperfusion

Under-resuscitation is associated with morbidity (SIRS, necrotizing pancreatitis, organ failure) and mortality.

Fluid resuscitation improves pancreas perfusion, prevents intestinal ischemia, bacterial translocation, secondary pancreatic infection.

Lactated Ringer vs. Normal Saline

Fluid and Electrolytes

- Adequate fluid resuscitation to maintain urine output ≥ 0.5 mL/kg/hour without renal failure.
- Avoid electrolyte disturbances and fluid overload.
- Lactated Ringer may be superior to normal saline.

How to predict severity of acute pancreatitis?

- Modified Glasgow
- Ranson
- APACHE II
- Lipase score
- PAPS

Pediatric Data

- Conducted a survey of current practices
- 16 different institutions
- 75% in the US.
### Pediatric Data

#### Criteria to start feedings

<table>
<thead>
<tr>
<th>Number of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>12</td>
</tr>
</tbody>
</table>

### Diet

- **When to start feeds?**
  - depends on the severity of AP, OK to start early
  - correlate with clinical readiness, abd pain
- **What mode of nutrition?**
  - prefer enteral over TPN
  - NG vs. NJ
- **What to feed?**
  - recent studies in adults with mild AP support full diet
    (Moraes JM et al. J Clin Gastroenterol 2010 44:517)
  - no evidence that low-fat diet is helpful

### Pain Control

- Narcotic analgesics are preferred, but there are no extensive studies in peds or adults.
- No clinical evidence to suggest that meperidine is superior to morphine.
- Morphine or related opioid drugs were used in 94% of children with AP (INSPPIRE survey, JPGN 2012;55: 261–265).
**Surgery**

- Necrosectomy (rare in peds)
- Cholecystectomy (optimal timing of cholecystectomy after hospital admission for gallstone pancreatitis may be within 48 h for mild disease and > 2 weeks later for more severe disease) (Scand J Surg 2010;99:81).

**ERCP (AGA recommendations)**

- ERCP within 24 h for patients with gallstone pancreatitis with cholangitis.
- ERCP within 72 h if high suspicion of persistent common bile duct stone.
- Endoscopic sphincterotomy in the absence of choledocholithiasis at the time of the procedure is a reasonable therapeutic option, but data supporting this practice are lacking.

**NG Suction**

- Not shown to decrease symptoms, mortality or hospital stay.
- May be useful if:
  - severe gastric distention
  - refractory nausea and vomiting
  - obstruction seen on abdominal x-ray
**Chronic Pancreatitis**

- A chronic inflammatory process.
- Irreversible morphologic changes.
- Pain and/or permanent loss of function.
- Exocrine pancreatic insufficiency.
- Diabetes.

---

**Acute Recurrent Pancreatitis and Chronic Pancreatitis in Children**

50 papers in the literature
0 clinical trials

* Case reports, small cohorts looking into etiologies, a few reviews

---

**Pediatric Data**

INSPPIRE Survey

JPGW 2012;55: 261–265
INSPIRE To Study Acute Recurrent and Chronic Pancreatitis in Children-180 children from 14 centers enrolled to study the etiologies, epidemiology, natural history and outcome.
Pediatric Acute Recurrent and Chronic Pancreatitis—etiologies

- Genetic (49%) (61 of 91 tested)
  - PRSS1-30%
  - CFTR-22%
  - SPINK1-14%
  - CTRC-3%
- Obstructive (34%)
- Idiopathic (20%)
- Toxic-Metabolic (17%)
- Autoimmune (3%)

Genetics of Pancreatitis

- PRSS1 (cationic trypsinogen)
  - Autosomal dominant
  - 80% penetrance
  - Mutations are due to increased activation or decreased inactivation of trypsin (i.e. R122H, N29I).
- SPINK1 (trypsin inhibitor)
  - Autosomal recessive/complex inheritance
  - 2% have mutation, <1% have pancreatitis (i.e. N34S)
  - Pancreatitis is dose-related (homozygous>>>het)
  - Associated with other mutations (CFTR)

CASR = Ca-sensing receptor
CTRC = Chymotrypsinogen C
CFTR = Cystic fibrosis transmembrane generator
PRSS1 = Cationic trypsinogen
SPINK1 = Pancreatic secretory trypsin inhibitor
Genetics of Pancreatitis

- **CFTR (>1700 mutations)**
  - 2 Severe mutations = Cystic Fibrosis
  - 1 severe, 1 mild mutation = mild or atypical CF, ARP, CP
  - CF carriers = 3-4 fold increase risk in pancreatitis.
  - 1 any +SPINK1 = CFTR-associated pancreatitis
  - 1 any +divisum = CFTR-associated pancreatitis

New Modifier Genes in ARP and CP

- **CTRC** (trypsin degrading enzyme)
- **CASR** (a calcium-sensing receptor)
- **CLDN2** (tight junction protein on X chromosome)

Treatment of Pain in Chronic Pancreatitis

- Both tramadol (840 mg) and morphine (238 mg) are effective in controlling pain in CP. (Dig Dis Sci 1999; 44:1107).

- Pregabalin (gradual increase to 300 mg BID for 3 wks) reduces pain in CP compared to placebo. (Gastroenterology 2011;141:536).
Treatment in Chronic Pancreatitis

- Daily antioxidants may be associated with decrease in painful days for patients with CP (selenium 600 mcg, ascorbic acid 0.54 g, beta-carotene 9,000 units, alpha-tocopherol 270 units and methionine 2 g):
  - no painful days in 32% vs. 13% (p=0.009)
  - painful days reduced by 7.4 vs. 3.2 days (p < 0.001)
  - monthly analgesics reduced by 10.5 vs. 4.4 tab (p=0.001)

Gastroenterology 2009;136:149

Pancreatic Enzymes in Chronic Pancreatitis

Cochrane Review 2009

Objectives were to compare the following:
1) pancreatic enzyme versus placebo;
2) different pancreatic enzyme preparations;
3) different dosage schedules of the enzyme preparations.

Evaluated the following outcomes: change in frequency of abdominal pain, duration of pain episodes, intensity of pain, weight loss, steatorrhea, fecal fat and quality of life.
Pancreatic Enzymes in Chronic Pancreatitis

• 10 trials, involving 361 participants, satisfied the inclusion criteria.
• Although some individual studies reported a beneficial effect of pancreatic enzyme over placebo in improving pain, incidence of steatorrhea and analgesic consumption, the results of the studies could not be pooled for these outcomes.
• There was a significant reduction in fecal fat.
• Conclusion: The role of pancreatic enzymes in CP is equivocal.

Summary-Take Home Points

• Most of our information on pancreatitis is from adult studies.
• Children get pancreatitis.
• New information on pediatric pancreatitis confirm that: Children are not “little adults”.

Future Directions-Unmet Needs

• A better understanding of epidemiology, etiologies, pathogenesis, natural history and outcome.
• Predictors of disease severity in acute pancreatitis.
• Better diagnostic modalities.
• New therapeutic approaches.
INSPPIRE Members

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- Mark Lowe
- Sohail Husain
- Peter Durie
- Doug Fehman
- Brad Barth
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- Soma Kumar
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- Tom Lin
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- Tha Pugatch
- Roxanne Strachan
- Margaret Bruce
- Vanessa Bonett
Endoscopy in the high-risk patient: Keeping your patient safe

Jenifer R. Lightdale, MD, MPH
Boston Children’s Hospital
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I have no financial relationship with any commercial entity to disclose.

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 at increased risk for these rare events

Safety of Pediatric GI Procedures

• Peds-CORI data from >10,000 procedures*
  – Overall rate of complications 2.3%
  – Risk of hypoxia 1.5%
    • Sedation related
    – Risk of bleeding 0.3%

  *Thakkar, 2007

Cardiopulmonary

• Generally relate to sedation/anesthesia
  – Account for ~60% of all AEs that occur*

• Range from minor to major
  – Transient oxygen desaturation
  – Aspiration
  – Respiratory arrest
  – Shock
  – Myocardial infarction

  *Ben-Menachem, 2012
Cardiopulmonary

• Examples of pediatric populations at increased risk for cardiopulmonary events
  – Infants < 1 year of age
  – Congenital Heart Disease
  – Pulmonary Hypertension
  – Cystic Fibrosis
  – Muscular Dystrophy
• Sedation/anesthesia must take into account
  – Compromised cardiopulmonary function
  – Decreased FEV-1

Bleeding

• Rare in diagnostic procedures
  – Advancing the scope
  – Obtaining biopsies
• Commonly associated with therapeutic maneuvers
  – Dilation
  – ERCP
  – PEG placement
  – Hemostasis
  – Polypectomy
• Intraluminal vs. intramural (hematomas)
  – Duodenum
  – Sigmoid Colon

Bleeding

• Examples of pediatric populations at increased risk of bleeding during GI procedures
  – Stem cell transplant recipients
  – End stage liver disease
  – Patients being treated with anticoagulants
  – Patients with clotting disorders
• More likely in patients with
  – Thrombocytopenia
  – Coagulopathy
Perforation

- Rare during diagnostic procedures
  - Can be associated with instrumentation
- Large vs. small
  - Shaft of scope vs. tip
  - Immediate presentation (visualization of extraintestinal structure during endoscopy) vs. delayed (abdominal pain, tenderness after waking)
- Occurrence suggests decreased mucosal wall strength*
  - Inflammation
  - Connective tissue changes

*Ben-Menachem, 2012

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

Photos courtesy of Boston Children’s Hospital

Perforation

- Examples of pediatric populations at increased risk for perforation
  - History of caustic ingestion
  - Esophageal atresia/tracheo-esophageal fistula
  - Severe duodenitis
  - Severe ulcerative colitis
  - Patients with multiple co-morbidities (i.e. Type I diabetes, cerebrovascular disease, peripheral vascular disease, renal insufficiency, liver disease)
  - Ehlers-Danlos Syndrome (Vascular Type)
Ehlers-Danlos Syndrome

- Group of hereditary connective tissue diseases
  - 6 subtypes, all with defective collagen fibers
  - 1:5,000 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

*Burcharth, 2012

Infection

- Result from the procedure and/or from use of contaminated instruments
- Minor vs. major infectious disease
  - Transient bacteremia
  - Septic shock
  - Seeding of valves, shunts and/or other devices
- Patients at higher risk
  - Immunosuppressed
  - Asplenics
  - Cirrhotics
  - Those with medical implants
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

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 patients’ physical status:

<table>
<thead>
<tr>
<th>ASA Class</th>
<th>Physical Status</th>
</tr>
</thead>
<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
  - Immunocompromised

* Thakkar, 2007; ** Enestvedt, 2013

Anesthesiologists may label more patients as ASA II*

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

* Lightdale, 2005
Risk Factors for Difficult Airways

- Congenital 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

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

*Agostoni, 2011.*
Medications

• Cardiopulmonary effects
  – Can potentiate sedation/anesthesia
• Anti-seizure medications
• Psychotropic medications
• Pain medications
  – Benzodiazepines
  – Opioids


Antithrombotic Therapy

• New guidelines for adults (scarce pediatric data)*
  – Elective vs. urgent/emergent procedures
    – “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

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Procedure</th>
<th>Low-Molecular Weight Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polypectomy</td>
<td>Diagnostic procedures with biopsies</td>
<td>*Anderson, 2009; Kamath, 2012</td>
</tr>
<tr>
<td>Biopsy or pre-op sphincterotomy</td>
<td>EUS without FNA</td>
<td></td>
</tr>
<tr>
<td>ERCP</td>
<td>Capsule endoscopy</td>
<td></td>
</tr>
<tr>
<td>PSC placement</td>
<td>Stent deployment (without dilation)</td>
<td></td>
</tr>
<tr>
<td>ESL with FNA</td>
<td>EUS with FNA</td>
<td></td>
</tr>
<tr>
<td>Endoscopic hemostasis</td>
<td>Diagnostic procedures with biopsies</td>
<td></td>
</tr>
<tr>
<td>Treatment of varices</td>
<td>*Anderson, 2009; Kamath, 2012</td>
<td></td>
</tr>
</tbody>
</table>

Thrombocytopenia

• Minimum threshold platelet count for the performance of diagnostic GI procedures 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, 1999; Samama, 2003; BSG, 2011
Pre-procedural Preparation for Patients at High Risk of Bleeding

- Check CBC/INR prior to procedure
  - Important if patients at risk for bleeding, but no role for obtaining labs 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 2006; **Kamath 2012; ***Coates, 2011.

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, 2011.

Procedural Factors that Increase Risks

- Difficulty intubating the esophagus
- Prolonged procedures
- Liberal insufflation with air

Cardiopulmonary

- Instrumentation
- Blind advancing of scope or instrument

Bleeding/Perforation

- Creation of stomas for enteral tube placement
- Therapeutic variceal sclerosis

Infection

*Ben-Menachem, 2012
Perforation during Colonoscopy*

- Shaft-induced
  - Result from "big loops"
  - Usually larger than expected and 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
  - Attempts to bypass strictures can create an intermittent obstruction, as well as accumulation of upstream and increased hydrostatic pressure
  - More common in left colon

*Gershman and Ament, 2007.

Decreasing Risk of Perforation

- Avoiding excessive pressure*
  - Advancing forward
  - Forcefully withdrawing
  - Imbedding the tip
  - Insufflating with air
- Avoiding premature cutting of a polyp
  - Coagulate before cutting
- Avoiding blind intubation of the lumen
  - Colonoscopy
  - Upper endoscopy

*Gershman and Ament, 2007.

“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
- Lack of well developed serosal layer in the retroperitoneum BUT WITH rich submucosal vascular plexus

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
  – 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

Post-biopsy Duodenal Hematoma

Photos courtesy of Boston Children’s Hospital

Duodenal Hematoma and Pancreatitis

- Well associated scenario
  - Iatrogenic from biopsy-related hematomas
  - Trauma
- Secondary to ampullary obstruction
  - Pancreatitis will rapidly resolve after surgical evacuation
- May be advisable to sample duodenum as far away from papilla as possible

*Guzman, Bousvaros, Buonomo, Nurko, 1998.

Decreasing Risks of Infection

- SBE Prophylaxis
  - AHA/ASGE 2007 Guidelines – generally NOT indicated in diagnostic procedures*
  - Congenital heart disease is complex
  - Recommend case-by-case basis
- 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!
Advances in Hemostasis for Upper GI Bleeding

Brad Barth, MD, MPH
Children’s Medical Center Dallas
University of Texas Southwestern

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

Objectives

• Provide an update on hemostatic techniques for UGI bleeding
• Discuss what to do with clots: keep them or remove them
• Recognize the effects of transfusion on outcome
ASGE Recommendations

• Recommend antisecretory therapy with PPIs

Standards of Practice Committee. The role of endoscopy in the management of acute non-variceal UGI bleeding. GIE 73(5) 2012

Upper GI Bleeding

The Effect of Acid and Pepsin on Blood Coagulation and Platelet Aggregation


Upper GI Bleeding

• Effect of IV PPI on patients with UGI bleeding PRIOR to EGD
  – 6 trials including 2223 patients
  – No significant difference in mortality, rebleeding or need for surgery compared to controls
  – DID significantly reduce rates of high risk stigmata identified on EGD
  – DID significantly decrease the need for endoscopic therapy

Upper GI Bleeding

- Omeprazole 1 mg/kg q 12 hours

- Proposed PPI drip dose: 1 mg/kg bolus followed by 0.1 mg/kg/hour infusion

ASGE Recommendations

• Recommend antisecretory therapy with PPIs
• Suggest prokinetic agents in patients with high probability of fresh blood or clot

Standards of Practice Committee. The role of endoscopy in the management of acute non-variceal UGI bleeding. GIE 75(5):2012.

Upper GI Bleeding

• Prokinetic
  – IV erythromycin or metoclopramide
  – Infuse 20-120 minutes prior to endoscopy in patients with acute UGIB
  – Decreased need for repeat endoscopy to determine cause and site of bleeding.
  – Did NOT affect transfusion requirements, duration of stay, need for surgery

ASGE Recommendations

• Recommend antisecretory therapy with PPIs
• Suggest prokinetic agents in patients with high probability of fresh blood or clot
• Recommend AGAINST epinephrine alone for peptic ulcer bleeding

Standards of Practice Committee. The role of endoscopy in the management of acute non-variceal UGI bleeding. GIE 75(6):2012.

Upper GI Bleeding

• Combination therapy
  – Thermal devices, injectable agents (sclerosants, thrombin/fibrin glue) and clips are all equally effective for achieving hemostasis in PUD
  – IF EPINEPHRINE IS USED, should be used in conjunction with another method to reduce risk of rebleeding, surgery and death

Standards of Practice Committee. The role of endoscopy in the management of acute non-variceal UGI bleeding. GIE 75(6):2012.
Remove the Clot?

<table>
<thead>
<tr>
<th>Signs of active hemorrhage</th>
<th>Risk of recurrent bleeding without endoscopic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active arterial bleeding (spurting)</td>
<td>Approx 90%</td>
</tr>
<tr>
<td>Non-bleeding visible vessel</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Hemorrhaging ulcerating site</td>
<td>15%</td>
</tr>
<tr>
<td>Ulcer healing without other signs</td>
<td>15%</td>
</tr>
<tr>
<td>Flat spots</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Clean-based ulcers</td>
<td>&lt;2%</td>
</tr>
</tbody>
</table>

Standards of Practice Committee. The role of endoscopy in the management of acute non-variceal UGI bleeding. GIE. 75(5):2012.

Effects of Transfusion on Outcome in UGI Bleeding

- Is early blood transfusion harmful in GI bleeding?
  - 25 patients with severe UGI bleeding
    - Hemorrhage → HYPERcoagulable response
    - PRBC → partial reversal of above response
  - 50 patients randomized to receive 2 units or nothing
    - Transfusion group = 9 rebled
    - No transfusion group = 1 rebled (p<.01)

Effects of Transfusion on Outcome in UGI Bleeding

• What is an appropriate transfusion threshold?
  – 921 patients with UGI bleeding
    • 461 to restrictive strategy (Hgb below 7)
    • 460 to liberal strategy (Hgb below 9)
    – Less patients transfused (p<0.001)
    – Higher probability of survival (p=0.02)
    – Less chance of rebleeding (p=0.01)
    – Less chance of adverse events (p=0.02)

Villanueva, et al. NEJM 2013;368:11-21

New Technology

• Hemostatic spray
  – Mineral based hemostatic granules that concentrate clotting factors at bleeding site

New Technology

• Stents for emergent variceal tamponade
  – Fully covered, self-expanding metal stents with a balloon on the distal tip of the delivery device to aid in positioning
  – Allows for oral nutrition
  – Does NOT mandate ongoing intubation
  – Does NOT impair patient mobility
  – Can remain in place as long as 2 weeks
New Technology

- Devices for mechanical closure
  - Over the scope clip

Wright, et al. GIE 2010; 71:71-78

http://i.ytimg.com/vi/HeACJnR9t0o/hqdefault.jpg

Iacopini et al., World J Gastro, 2010
Take-Home Messages

- Use the scope with the largest suction channel possible, and CLEAN
- PPI and prokinetic therapy PRIOR to endoscopy may be helpful
- Epinephrine alone is RARELY enough
- Non bleeding adherent clot has 8-35% chance of rebleeding in adults. Consider removing it CAREFULLY!
- A conservative transfusion strategy is usually appropriate

Useful References

  - http://www.asge.org/assets/0/71542/71544/b4349a10-9b72-463e-ac7b-
  794c7aa29b4.pdf
  - http://www.asge.org/assets/0/71312/71314/c1df0d0e-4d9d-4f7f-acdb-
  be4e20f98075.pdf
Surveillance Endoscopies: The established, the debated, and the unknown

Mitchell Shub, M.D.
Phoenix Children’s Hospital
Professor and Vice-chairman
Department of Child Health
University of Arizona College of Medicine-Phoenix

I have no financial relationship with any commercial entity to disclose

Learning Objectives

- Recognize who requires endoscopic surveillance: Polyposis syndromes, IBD, and Barrett’s esophagus
- Learn when to perform surveillance endoscopies
- Know how to conduct surveillance procedures
“Beware of false knowledge; it is more dangerous than ignorance.”

George Bernard Shaw

### Polyposis Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Incidence</th>
<th>Gene(s)</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Adenomatous Polyposis</td>
<td>1 in 10,000</td>
<td>APC</td>
<td>Multiple including Gardner and Turcot</td>
</tr>
<tr>
<td>Peutz-Jeghers (PJS)</td>
<td>1 in 200,000</td>
<td>LKB1 (STK11)</td>
<td>• Mucocutaneous pigmented macules</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hamartomatous polyps (multiple)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Intussusception risk</td>
</tr>
<tr>
<td>Juvenile Polyposis (JPS)</td>
<td>1 in 100,000</td>
<td>SMAD4 or BMPR1A (in 50-60%)</td>
<td>• &gt;5 JP (usually 50 to 100) in colorectum or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mult JP throughout GI tract or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ≥1 JP and Fam Hx JPS</td>
</tr>
</tbody>
</table>

Barnard J. JPGN 2009; 48:S75-S78

### Familial Adenomatous Polyposis

- Risk of colorectal cancer >90% by age 50
- Adenomas: average age of onset 16 (case reports of younger onset)
- Colorectal cancer: average age 39 (earliest reported case age 5)
- Lifetime risk:
  - Gastric fundic adenocarcinoma ≈ 0.6%
  - Duodenal/ periampullary cancer ≈ 5% (rare under age 20)
### Surveillance Endoscopies:
#### Familial Adenomatous Polyposis

<table>
<thead>
<tr>
<th>Surveillance protocol</th>
<th>Age of initial evaluation</th>
<th>Type of procedure</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>10 – 12 y of age (Sooner: family h/o aggressive disease)</td>
<td>Flex sig or colonoscopy</td>
<td>1 – 2 y</td>
</tr>
<tr>
<td>Upper GI tract</td>
<td>20 – 25 y or at initial colonoscopy</td>
<td>EGD and side viewing scope</td>
<td>1 – 3 y</td>
</tr>
<tr>
<td>Small bowel</td>
<td>If symptomatic</td>
<td>Capsule vs. MR imaging vs. enteroclysis?</td>
<td>Unknown</td>
</tr>
<tr>
<td>Post-colectomy (pouch)</td>
<td>6 – 12 mo. after surgery</td>
<td>Flex sig</td>
<td>1 y (6 mo. if retained rectum)</td>
</tr>
</tbody>
</table>

Barnard J, JPGN 2009; 48: S75-S78

### Peutz-Jeghers Syndrome

Mucocutaneous pigmented macules

Small bowel polyps
Peutz-Jeghers Syndrome

<table>
<thead>
<tr>
<th>Surveillance protocol (Lifetime CA risk)</th>
<th>Age of initial evaluation</th>
<th>Type of procedure</th>
<th>Frequency *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon (39%)</td>
<td>8 y</td>
<td>Colonoscopy</td>
<td>2 – 3 y or repeat at 18 y if no polyps detected</td>
</tr>
<tr>
<td>Stomach (29%)</td>
<td>8 y</td>
<td>EGD</td>
<td>2 – 3 y</td>
</tr>
<tr>
<td>Small bowel (13%)</td>
<td>8 y</td>
<td>Video capsule vs. MR imaging vs. double-balloon enteroscopy?</td>
<td>2 – 3 y</td>
</tr>
</tbody>
</table>

* Based on limited evidence

Jasperson K, Cancer J 2012; 18: 328-33

Juvenile Polyposis Syndrome

Surveillance Endoscopies: Juvenile Polyposis Syndrome

<table>
<thead>
<tr>
<th>Surveillance protocol (Lifetime CA risk)</th>
<th>Age of initial evaluation</th>
<th>Type of procedure</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon (50% but rare in childhood)</td>
<td>10 - 15 y *</td>
<td>Colonoscopy</td>
<td>1 – 3 y *</td>
</tr>
<tr>
<td>Stomach (21% if gastric polyps present)</td>
<td>10 - 15 y *</td>
<td>EGD</td>
<td>1 – 3 y *</td>
</tr>
<tr>
<td>Small bowel (?)</td>
<td>?</td>
<td>Video capsule vs. MR imaging vs. double-balloon enteroscopy (not defined)</td>
<td>?</td>
</tr>
</tbody>
</table>

* Based on limited evidence

Jasperson K, Cancer J 2012; 18: 328-33
Barnard J, JPGN 2009; 48: S75-8
Surveillance Endoscopy
Polyposis syndromes

Practical guidelines for surveillance endoscopy:
• Remove all polyps when technically feasible
• If unable to remove all polyps remove as many as possible especially larger ones

Colorectal Cancer in IBD

• UC - Pancolitis
  – Meta-analysis cumulative risk:
    • 2% after 10 yrs, 8% after 20 yrs, 18% after 30 yrs
  – 30 year surveillance study in UK:
    • 7.7% at 20 yrs and 15.8% at 30 yrs
• CD - Colonic (> 50% involvement)
  – Cumulative risk:
    • 2.9% (1.5 - 5.3%) after 10 yrs.
    • Lifetime relative risk of CRC is increased 4.5 fold
  – CD involving only small bowel does not confer increased risk for CRC

Surveillance Endoscopies:
Colorectal cancer in IBD

Established risk factors:
• Longer disease duration
• Younger age at onset
• Extensive disease (Pancolitis)
• Greater disease severity
• Primary sclerosing cholangitis
• Family history of CRC

References:
Surveillance Endoscopies: Colorectal cancer in IBD

Current guidelines: consensus panel¹

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Years after onset of symptoms not diagnosis</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC (excluding proctitis)</td>
<td>8 – 10 yrs</td>
<td>1 – 2 y when normal and if normal X 2, then every 1 - 3 y</td>
</tr>
<tr>
<td>CD (involving &gt; ⅓ -⅖ of colon)</td>
<td>8 – 10 yrs</td>
<td>1 – 2 y when normal and if normal X 2, then every 1 - 3 y</td>
</tr>
<tr>
<td>Coexisting PSC</td>
<td>As soon as both diagnoses established</td>
<td>Annually</td>
</tr>
</tbody>
</table>


Surveillance Endoscopies: Colorectal cancer in IBD

Suggested approach to Surveillance colonoscopy:
- 4 quadrant biopsies every 10 cm and every 5 cm in rectosigmoid
- Sample all suspicious lesions: dysplasia-associated lesion or mass (DALM)
- Biopsy flat mucosa around base of suspicious lesion (separate specimen container)
- Treat active colitis prior to surveillance

Itzkowitz S, Present, D, Inflamm Bowel Dis 2005; 11:314-21

Surveillance Endoscopies: Colorectal cancer in IBD

Limitations of current guidelines:
- Requires minimum 32 biopsies with jumbo forceps to have 90% sensitivity rate
- Multifocal, flat, subtle neoplastic lesions are easy to miss and can rapidly progress
- Costly to process a large number of biopsies
Surveillance Endoscopies:
Colorectal cancer in IBD
New strategies for targeted biopsies:
• **High-definition endoscopy** – superior resolution (1 study showed 3 fold benefit)
• **Chromoendoscopy** – dye spray technique, methylene blue or indigo carmine (several studies suggest significant improvement in pick-up rate)
• **Miniaturized confocal** microscopy – allows for localized histologic evaluation


Flat lesion highlighted by indigo carmine chromoendoscopy

DALMs accentuated by methylene blue
Barrett’s Esophagus

- Replacement of normal esophageal mucosa by specialized intestinal metaplasia
- GERD major predisposing factor
- Premalignant condition for adenocarcinoma (AC)
- Annual progression rate to AC ≈ 0.5%
- Data regarding frequency of AC in children lacking (limited to few case reports)¹


Barrett’s Esophagus
Risk factors

**Adults** - Prevalence ≤ 6.8%
- White male > 50 y
- GERD symptoms > 5 y
- Obesity
- Hiatal hernia
- Nocturnal reflux
- Tobacco use

**Pediatrics** - Prevalence < 0.25%
- Neurologic impairment
- Congenital esophageal abnormalities
- Hiatal hernia
- Chronic lung disease (CF)
- Family h/o severe GERD or BE
- Long-term survivors of solid tumors

Nguyen, D et al. Gastrointest Endosc 2011;73:877-80

Barrett’s Esophagus
Dysplasia Documentation*

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>Documentation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2 EGD’s within 1 year 4 quadrant bx every 2 cm Tongues – Every 2 cm on each tongue</td>
<td>3 - 5 y</td>
</tr>
<tr>
<td>Low grade</td>
<td>Highest grade on repeat EGD within 6 mo Expert pathologist to confirm 1 y</td>
<td></td>
</tr>
<tr>
<td>High grade</td>
<td>Mucosal irregularity - endoscopic resection Multiple jumbo forceps bx every 1 cm Expert pathologist to confirm no adenocarcinoma Every 3 months or intervention</td>
<td></td>
</tr>
</tbody>
</table>

* Based on adult data – May not substantially reduce mortality

Wang K. Sampiner R Am J Gastroenterol 2008;103:788-87
Surveillance Endoscopies: Barrett’s esophagus

New strategies for targeted biopsies:

- **High-definition endoscopy** – superior resolution
- **Chromoendoscopy** – dye spray technique, methylene blue or indigo carmine
- **Miniaturized confocal microscopy** – allows for localized histologic evaluation
- **Biomarker assay** – from brush cytology

Gaddam S, Sharma P / J Dig Dis 2010;11:323-33
Jankowski J, Satsangi / Gastroenterology 2013;144:667-9

Barrett’s Esophagus

- Tongue of metaplastic epithelium (high resolution endoscopy)
- Circumferential with nodules of high grade dysplasia

Barrett’s Esophagus

New endoscopy technology

- High resolution endoscopy
- Indigo carmine chromoendoscopy
Take Home Message

- Surveillance in polyposis syndromes should start in childhood
- Lifetime CRC risks are similar in UC and colonic CD
- Barrett’s esophagus in children
  - Adenocarcinoma very rare
  - Evidence lacking to develop surveillance schedule

Future Directions

- Newer diagnostic techniques are needed to improve sensitivity and specificity of colonoscopy and EGD surveillance
- Training in new techniques will be required
- Multicenter pediatric studies are needed to identify costs and benefits of surveillance
Expanding the view: Update on Upper GI Strictures
October 10, 2013

Mark A. Gilger, M.D.
Pediatrician-in-Chief
Children’s Hospital of San Antonio
Professor & Vice Chair
Baylor College of Medicine

Disclosures

• Research support
  – RedHill Biopharma
  – QOL Medical

Questions

• Has anyone in the audience performed a dilation of an upper esophageal stricture?
• What type of dilators do you use?
  – Bougie vs. balloon
• How did you learn how to do it?
  – Textbook
  – Publications
  – Colleague
  • “Therapeutic endoscopy requires a hands-on apprenticeship”
Learning Objectives

1. Learn methods of stricture dilation
2. Discuss the frequency of dilations
3. Review techniques to sustain dilation
4. Explore future therapies

Our Case: Epidermolysis bullosa - The really narrowed esophagus

• 11 y/o female referred by the chief of surgery, unable to swallow with moderate malnutrition
• Diagnosis: recessive, dystrophic EB
• UGI shows complete obstruction

Considerations

• Would you agree to take this case?
• Why?
  – The child needs to eat
  – Unable to perform interposition surgery
• Why not?
  – Complete obstruction on UGI, the child needs a gastrostomy
Considerations

- Is the obstruction “really” complete?
  - Need for diagnostic upper endoscopy
  - Prepared for stricture dilation
    - What are your options?
      - Bougie dilation
      - Through-the-scope balloon dilation

Our case

- Repeat UGI with delayed films revealed incomplete obstruction & multiple strictures

Goals of dilation

- Relief of dysphagia
  - Simple strictures
    - Once may be enough
  - Refractory strictures
    - Repeated to maintain swallowing
    - Most common in children

- Prevent recurrence
  - Acid reduction
  - Esophageal anomalies
    - TE fistula

Prevent recurrence
Pediatric esophageal strictures

- **Responsive (simple)**
  - GERD

- **Refractory (complex)**
  - Irreducible
    - Caustic
    - Radiation
    - Dermatologic
    - Sclerotherapy
  - Congenital
    - Usually surgical (esophageal anomaly)
  - Eosinophilic
  - Malignant
  - Rare

Symptoms

- Dysphagia
  - r/o dysmotility
  - r/o infection
  - r/o web / ring
  - r/o malignancy

Diagnostics

- Barium swallow (UGI)
  - Establish
    - Location
    - Length
    - # of strictures
    - Lumen diameter
    - Associated pathology
      - Diverticula
      - Tracheal remnant
  - Upper endoscopy
    - At time of dilation
Contraindications

- Known esophageal perforation
- Known malignant stricture
- Bleeding disorder
- Unstable patient
- Anatomic deformity
- Eosinophilic esophagitis

Dilators

- Mechanical (bougie)
  - Radial and longitudinal shearing force
    - Maloney
    - Hurst
    - Savary-Gilliard
      - Over the wire
- Balloon
  - Uniform, radial force, less shear
    - Over the guidewire
    - Over the wire

Bougie vs. Balloon

- Why balloons for kids?
  - You can see what you’re doing
    - Blind pouches
    - Abnormal mucosa
      - Caustic injury
      - Epidermolysis bullosa
  - Ability to wire through narrow strictures
  - Ability to use radiographic assistance
Our Case - Pre-dilation

- Family discussion
  - May not work, may be true obstruction
  - Very high risk of esophageal perforation
  - Very high risk of post-procedure pain & swelling
  - If successful, will require long-term, repeat dilations
  - Requires general anesthesia

How to do balloon dilation

- Select endoscope with largest biopsy port
- Use trained endoscopy assistants
- Lubricate balloon & biopsy channel
  - Vegetable spray lubricant
- Advance balloon into the stricture & note location
  - Distance from incisors (in centimeters)
- Advance under direct visualization placing balloon in "hour glass" position

How to do balloon dilation

- Inflate balloon to ½ desired initial atmospheres & re-check placement
- Hold catheter tightly
  - Esophageal motility will pull balloon in
- Begin dilation at to 1-2 mm more than initial estimated stricture diameter
- Hold for 1 minute/dilation
- Move balloon catheter in and out during dilation
  - If balloon moves freely, increase diameter by 1mm
  - If stricture moves with the balloon, hold x 1 minute, then done
How to do balloon dilation

- Oh, oh, there’s blood!
  - Good! No blood, no dilation.
- After dilation, carefully advance endoscope through the stricture
  - If resistance stop, can try cork-screw maneuver
- Document everything
  - Especially stricture location (CM from incisors)
  - Dilation diameters (to help you next time)

---

EB case - First “EGD” with dilation

- Unable to enter upper esophagus secondary to high location of upper stricture & limited opening of mouth
- Retrograde esophageal dilation
  - Entered distal esophagus via g-button site with 5 mm endoscope
  - Placed guide wire retrograde and advanced out of mouth
  - Placed 6,7,8 mm balloon over guide wire and dilated upper and lower stricture using contrast and fluoroscopy
**EB Case**

- Balloons are the most logical choice
- Repeat dilations required
  - Life long
- General anesthesia required
  - Exquisite patient handling by anesthesia staff
    - No "tape" placed on skin surface
  - Nasal trumpet, no tracheal intubation

---

**EB Case - Post dilation**

- Gastrografin swallow
  - PRN per risk of perforation
- Pain control
  - Generally narcotics
- High dose intravenous corticosteroids
  - Decrease post-procedure edema

---

**Adjunct therapy for recalcitrant strictures**

- Oral & intravenous corticosteroids
- Injectable corticosteroids
  - Thins the mucosa
    - OK 1-2 times, but not repeated
- Mitomycin C
- Acid reduction
- Stents
  - Liben, J. et al. - Endoscopy 2006
  - Broth, S. et al. - JPGN 2003

---
Future Considerations -
• Polydioxanone stent
  – Biogradable (absorbable)

Review
• Most pediatric esophageal strictures are refractory
  – Repeated dilations are the rule
• Balloon dilators are usually the best
• Adjunct therapy to sustain dilation needs further study

Conclusions
• Know your own limits
• Get help when needed
• Know the data
• Most important, “Primun non nocere”
Clinical issues in parenteral nutrition

Praveen S. Goday, MBBS, CNSC
Associate Professor
Pediatric Gastroenterology and Nutrition
Medical College of Wisconsin
Milwaukee, WI

Disclosures

• Expert Reviewer for Best Doctors, Inc.

Objectives

• Learn updates on lipids including restrictions, modifications, and types of lipids
• Recognize the use of ethanol locks and clinical applications of these locks
• Discern how to manage the various parenteral nutrition shortages and impact on patients
Lipid emulsions

Fish-oil vs soybean oil-based lipid emulsions

<table>
<thead>
<tr>
<th>Fish oil-based emulsion</th>
<th>Soybean oil-based emulsion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 gm/kg per day</td>
<td>Up to 3.4 gm/kg per day</td>
</tr>
<tr>
<td>Lack of phytosterols</td>
<td>High concentrations of phytosterols</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Pro-inflammatory</td>
</tr>
<tr>
<td>omega-3 fatty acids</td>
<td>omega-6 fatty acids</td>
</tr>
<tr>
<td>Higher dose of vitamin E</td>
<td>Lower dose of vitamin E</td>
</tr>
<tr>
<td>Alpha tocopherol</td>
<td>Gamma tocopherol</td>
</tr>
</tbody>
</table>

- Phytosterols reduce biliary flow by antagonizing the farnesoid X receptor, a bile acid nuclear receptor
- Compared to γ-tocopherol, α-tocopherol is more efficient at counteracting free radical damage from lipid peroxidation

Goulet et al. JPEN J Parenter Enteral Nutr 2010;34:485-95

Decreasing Intralipid provision

Decline in PNALD from 43% to 22%

Sanchez et al. http://dx.doi.org/10.1016/j.jpedsurg.2012.08.016
Decreasing Intralipid provision

<table>
<thead>
<tr>
<th></th>
<th>2-3 gm / kg per day</th>
<th>1 gm / kg per day</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of cholestasis</td>
<td>43.8%</td>
<td>51.7%</td>
<td>0.61</td>
</tr>
<tr>
<td>Time to cholestasis</td>
<td>27.7 ± 10.6 days</td>
<td>32.6 ± 24.1 days</td>
<td>0.48</td>
</tr>
</tbody>
</table>


Soybean oil + Fish oil lipid provision

• Provided a combination of fish oil emulsion and soy emulsion, each dosed at 1 g/kg per day
  – 9 out 12 patients demonstrated resolution of cholestasis, defined as a conjugated direct bilirubin of 0 μmol/L, at a median time of 24 weeks
  – 5 patients were transitioned to fish oil monotherapy due to lack of response


Inconclusive RCT

• Double-blind randomized controlled trial
  – Nineteen neonates were enrolled (10 soy; 9 fish oil)
• Incidence of cholestasis significantly lower than expected
  – early study termination
  – inability to assess for differences in the incidence of cholestasis

Nehra et al. JPEN DOI: 10.1177/0148607113492549
Persistence of fibrosis

- Hepatic fibrosis persisted in two infants with intestinal failure on Omegaven, despite improvements in cholestasis
- In 6 patients with resolved hyperbilirubinemia
  - fibrosis was persistent in 2
  - progressive in 3
  - regressed in 1
  - remained severe (grade 2 or higher) in 5 of 6


Catheter-related bloodstream infections (CRBSI)

- Infection rates in patients with intestinal failure
  - 8–26.5 CRBSI per 1000 catheter days
- Each CRBSI episode
  - estimated hospital cost ~$56,000
  - additional hospital stay of 6.5 days


Ethanol

- Disinfectant
  - bactericidal and fungicidal by nonspecifically denaturing cell membrane proteins
  - less likely than antibiotics to promote resistance
- 40% ethanol can inhibit bacterial growth in existing biofilms
- 70% ethanol can kill biofilm-forming microbes
  - Staph aureus, Strep pyogenes, and E coli after 1 hour
  - Pseud aeruginosa, Klebsiella pneumoniae, and Candida albicans after 4 hours

Chambers ST et al J Hosp Infect. 2006;63:193-19
### Pediatric studies with ETOH locks

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Pre-lock infection rate</th>
<th>Post-lock infection rate</th>
<th>No of days/week</th>
<th>Dwell time, hrs</th>
<th>Concentration, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouw et al</td>
<td>2008</td>
<td>5</td>
<td>11.5</td>
<td>2.1</td>
<td>7</td>
<td>4-14</td>
<td>70</td>
</tr>
<tr>
<td>Jones et al</td>
<td>2010</td>
<td>23</td>
<td>9.9</td>
<td>2.1</td>
<td>7</td>
<td>≥4</td>
<td>70</td>
</tr>
<tr>
<td>Cober et al</td>
<td>2011</td>
<td>15</td>
<td>8</td>
<td>1.3</td>
<td>3</td>
<td>≥2</td>
<td>70</td>
</tr>
<tr>
<td>Wales et al</td>
<td>2011</td>
<td>10</td>
<td>10.2</td>
<td>0.9</td>
<td>7</td>
<td>≥4</td>
<td>70</td>
</tr>
<tr>
<td>Pieroni et al</td>
<td>2013</td>
<td>14</td>
<td>9.8</td>
<td>2.7</td>
<td>1</td>
<td>2</td>
<td>70</td>
</tr>
</tbody>
</table>

### Complications

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouw et al</td>
<td>2008</td>
<td>5</td>
<td>1/10 CVC related thrombus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1/10 loss of CVL integrity</td>
</tr>
<tr>
<td>Jones et al</td>
<td>2010</td>
<td>23</td>
<td>No adverse events</td>
</tr>
<tr>
<td>Cober et al</td>
<td>2011</td>
<td>15</td>
<td>1/15 DVT in same limb as CVC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1/15 temporary difficulty in withdrawing ETOH</td>
</tr>
<tr>
<td>Wales et al</td>
<td>2011</td>
<td>10</td>
<td>2/10 CVC related thrombus</td>
</tr>
<tr>
<td>Pieroni et al</td>
<td>2013</td>
<td>14</td>
<td>No adverse events</td>
</tr>
</tbody>
</table>

### Meta-analysis

- In comparison with heparin locks, ETOH locks reduced
  - CRBSI-rate per 1000 catheter days by 7.67 events (81% ↓)
  - catheter replacements by 5.07 (72% ↓)
- 108-150 catheter days of ETOH lock exposure were necessary to prevent 1 CRBSI
- Adverse events
  - rare and included thrombotic events

### Less-than daily ETOH lock increases CRBSI

<table>
<thead>
<tr>
<th></th>
<th>Pre-ELT</th>
<th>Daily ELT (historical)</th>
<th>Daily ELT (current)</th>
<th>Less than daily ELT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily ELT (historical) vs Daily ELT (current)</td>
<td>8.0 ± 5.4</td>
<td>1.3 ± 3.0</td>
<td>0.68 ± 1.27</td>
<td>6.16 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>Daily ELT (historical) vs less than daily ELT</td>
<td>1.3 ± 3.0</td>
<td>0.68 ± 1.27</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
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<td>&lt;0.001</td>
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<td>6.16 ± 2.5</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ralls et al. Pediatrics 2012;130:e1369–e1373

---

### Drug shortages

- 89% of hospitals have experienced nutrition product shortages
- All PN products except dextrose and water have been in short supply at some point since spring 2010


---

### Why?

- Quality/manufacturing issues
- Production delays and delays companies have experienced receiving raw materials and components
- Discontinuations
- Few firms making older sterile injectable drugs
- Limited supply of raw materials
- Vulnerabilities in the system
  - small number of manufacturers, limited production capacity, long lead times and complexity of the manufacturing

http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm060796.htm#q1
Macronutrient shortages

- Fat
  - Neonates and infants should receive the highest priority
- Amino Acids
  - Use infant-specific amino acids ONLY for neonates
  - Consider the use of a standardized, commercial PN product ("premix" PN)

 Premix parenteral nutrition

- Dextrose + amino acids ± electrolytes
  - Na, K, Ca, PO₄, Mg, Cl, and acetate
- More expensive
  - Home care pharmacies can be reluctant to use
- Useful in amino acid, calcium and phosphate shortages
- May need to balance out electrolytes or choose a compromise concentration

Other shortages

- Multivitamins
  - Reserve multivitamins for children <2.5 kg or <36 weeks gestational age
  - Consider switching to enterally administered multivitamins when enteral intake > 50% of needs
  - Choose multivitamin carefully
  - Consider use of adult intravenous multivitamins for children (NOT neonates) during shortage
- Cysteine
  - Normal needs are estimated to be 30-40 mg/g of protein provided
  - Providing 20 mg/g of protein is adequate
Other shortages

• Calcium
  – Use calcium chloride with some caution
  – Alternate day calcium and phosphorus does not lead to bone accretion in neonates
• Phosphate
  – Consider provision of daily IV fat emulsion which contain 15 mmol/L of phosphate as egg phospholipids
  – Consider using the alternate salt IV phosphate and balance Na and K accordingly

Trace Element Shortages

• Ration IV multi-trace element products
  – reducing the dose by 50% or administering one dose three times a week.
• Consider withholding trace elements for first month of therapy to newly-initiated adolescent and adult PN patients who are NOT critically ill nor have pre-existing deficits

Trace Element Shortages

• Zinc, selenium, and copper shortages
  – Use oral / enteral supplementation if possible.
• Manganese and chromium shortages
  – No need to supplement (during shortage) unless signs and symptoms of clinical deficiency
Imported components from Europe

- Peditrace™
  - zinc, copper, manganese, selenium, fluoride, and iodine
- Addamel N™
  - zinc, copper, manganese, selenium, fluoride, and iodine, molybdenum, iron, and chromium
- Glyophos
  - Na glycerophosphate

Summary / Take-home points

- Reduction in soybean oil emulsion or provision of fish oil emulsion results in improvement in cholestasis
- Ethanol lock therapy decreases CRBSI in children on home PN
- Significant PN shortages have affected our ability to care for our PN patients
  - Vigilance
  - Good communication between physician, dietitian and pharmacist

Future directions

- Intravenous lipid
  - Optimal lipid composition to prevent/treat PNALD while promoting growth
- Ethanol locks
  - Optimal dosing of ethanol locks
  - Other locks
- PN shortages
  - Need to find a way to eliminate them
Enteral nutrition in Crohn disease: Where should this be in our treatment algorithm?

Robert N. Baldassano, MD
Colman Professor of Pediatrics
University of Pennsylvania, Perelman School of Medicine
Director, Center for Pediatric IBD
The Children’s Hospital of Philadelphia

I have the following financial relationships to disclose

• Janssen Pharmaceutical
• Nutricia
• Pfizer
• AbbVie, Inc.

Products or services produced by this company are relevant to my presentation

Objectives

• Modern lifestyle effects on the gut microbiome
• Effects of enteral nutrition on the gut microbiome
• Evidence of efficacy of enteral nutrition for:
  – Induction of remission
  – Maintenance of remission
  – Preventing post-op recurrences
What have we learned about IBD?
Identification of Disease Associated Pathways

Hypothesis: IBD arises from inappropriate handling of intestinal bacteria

Should we be Immunosuppressing our Patients?

Elements of Modern Lifestyle Lead to Changes in Gut Microbiota

- Improved sanitation
- Less crowded living conditions
- Decline in parasites
- Vaccinations
- Increased antibiotic use
- Caesarean section
- Refrigeration
- Food processing
- Diet changes
Diet is associated with new onset IBD

- High dietary intakes of total fats, PUFAs, omega-6 and meat were associated with an increased risk of CD and UC
- High fiber and fruit intakes were associated with decreased CD risk
- High vegetable intake was associated with decreased UC risk.


Clustering of gut microbiome into enterotypes is associated with long-term diet

The Bacteroides enterotype, highly associated with animal protein and saturated fats which suggests meat consumption as in a Western diet

The Prevotella enterotype, high values for carbohydrates and simple sugars, indicating association with a carbohydrate-based diet, more typical of agrarian societies


Diet and the Gut Microbiome

- Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

De Filippo C, et al. PNAS 2010: 14691-96
Is There a Relationship Between Diet, the Gut Microbiota, and IBD?

Nutritional Therapy Protocols

- 4 prospective randomized clinical trials comparing different Enteral Nutrition protocols
  - Peptamen™ (low fat) vs Vital HN™ (high fat)
  - Glutamine rich vs standard
  - Elemental vs polymeric

- 50% vs 100% of total caloric needs for induction with elemental formula (PCDAI < 10 at 6 weeks)
  - 50% of total caloric needs: 15% remission
  - 100% of total caloric needs: 42% remission
  - Labs improved only in the 100% group
  - Weight gain similar in the 2 groups

Pediatric Longitudinal Study of Semi-Elemental Diet and Stool Microbiome

- Prospective cohort study of children with Crohn disease from Philadelphia (used Peptamen), Toronto (used Modulen) and Halifax (used Osmolite); (n=90)
  - Enteral therapy with defined formula diet (38) vs. anti-TNFα therapy (52)

- PCDAI measured at baseline and 8 weeks

- Fecal calprotectin (FCP) measured at baseline, 1 week, 4 weeks, and 8 weeks
### PCDAI over time

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>S.D.</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-TNF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>35.6</td>
<td>13.9</td>
<td>17.5</td>
<td>60</td>
</tr>
<tr>
<td>8 weeks</td>
<td>9.9</td>
<td>15</td>
<td>0</td>
<td>52.5</td>
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<tr>
<td><strong>Enteral therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>38.0</td>
<td>16.1</td>
<td>15</td>
<td>62.5</td>
</tr>
<tr>
<td>8 weeks</td>
<td>11.2</td>
<td>11</td>
<td>0</td>
<td>45</td>
</tr>
</tbody>
</table>

*P<.0001 compared to baseline

### Calprotectin over time

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>S.D.</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-TNF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>948</td>
<td>795</td>
<td>44</td>
<td>2500</td>
</tr>
<tr>
<td>1 week</td>
<td>508</td>
<td>492</td>
<td>23</td>
<td>2500</td>
</tr>
<tr>
<td>4 weeks</td>
<td>428</td>
<td>635</td>
<td>17</td>
<td>2500</td>
</tr>
<tr>
<td>8 weeks*</td>
<td>307</td>
<td>494</td>
<td>16</td>
<td>2284</td>
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<tr>
<td><strong>Enteral therapy</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1015</td>
<td>699</td>
<td>47</td>
<td>2500</td>
</tr>
<tr>
<td>1 week</td>
<td>820</td>
<td>603</td>
<td>70</td>
<td>2295</td>
</tr>
<tr>
<td>4 weeks</td>
<td>608</td>
<td>499</td>
<td>43</td>
<td>2500</td>
</tr>
<tr>
<td>8 weeks*</td>
<td>405</td>
<td>335</td>
<td>35</td>
<td>1210</td>
</tr>
</tbody>
</table>

*P<.0001 compared to baseline by Wilcoxon Sum Rank Test

### Bacterial populations in pediatric IBD subjects on semi-elemental diet (16S rDNA sequencing)

**Conclusion:** Rapid change in gut bacterial populations upon initiating diet
Microbiome Composition before and after Nutritional Therapy

Ileum Microbiome

Shannon Diversity Score


Polymeric Diet Alone vs. Steroids for Active Pediatric CD (Induction Therapy)

• Methods (n=37)
  – Prospective 10 week randomized controlled open-label trial
  – Newly diagnosed children receive:
    • polymeric formula (n=18) or steroids (n=19)
  – Primary outcomes at 10 weeks
    • Clinical remission (PCDAI≤10)
    • Mucosal healing
      – Decrease in both endoscopic and histologic scores
        by > 50% when compared to baseline


Polymeric Diet Alone vs. Steroids for Active Pediatric CD (Induction Therapy)

Enteral nutrition n=19
Corticosteroids n=18

Maintenance Therapy with Enteral Nutrition for CD

- **Inclusion**
  - Adult patients in remission at the beginning of trial (CDAI<150)

- **Methods** (prospective study)
  - 50% of caloric needs from an elemental diet (Elental®) by overnight NG feed for 1 year (n=20)
  - Normal diet (n=20)

Yamamoto T et al. Inflamm Bowel Dis 2007;13:1493

Can remission be maintained with Partial Enteral Therapy?

- Proportion in remission was higher in the Enteral Nutrition group (P=0.01)

Yamamoto T et al. Inflamm Bowel Dis 2007;13:1493

Maintenance Therapy with Enteral Nutrition for CD

Severity of mucosal inflammation was graded 0-3

Conclusion: Endoscopic inflammation was significantly higher in the normal diet group at 12 months*

Nutritional therapy vs. 6-MP as maintenance therapy in CD

- Prospective 24 month randomized controlled open-label trial (n=95)
  - Inclusion: CDAI ≤ 150
    - Randomly assigned to:
      - 6-MP (0.5-1.5 mg/kg/day n=30)
      - ED (elemental diet ≥ 900 kcal/day n=32)
      - Control (5-aminosalicylic acid n=33)
  - Relapse: ≥ 200 CDAI

Results:
At 24 months, patients who maintained remission were 60%, 46.9% and 27% for 6-MP, ED and Controls.
No significant difference between 6-MP and ED.
Prevention of Post-op Recurrence with Enteral Nutrition for CD

![Graph showing clinical and endoscopic recurrence rates over 6 months and 1 year.]


Nutrition Therapy
“European” Protocol

- Induction:
  - Exclusive enteral nutrition with an elemental, semi-elemental, or polymeric formula
    - Duration: 4 – 12 weeks

- Maintenance Therapy: (either)
  - Nutritional therapy:
    - Repeat 4 week cycle of exclusive enteral nutrition every 3 – 4 months
      OR
  - Medical therapy:
    - 6-MP/AZA/MTX after induction with nutritional therapy

CHOP EN Experience
What if >80% of calories is from Enteral Nutrition?

- Methods
  - Semi-elemental formula
  - 80%-90% of patient’s caloric needs from formula
  - Nocturnal NG feeds (outpatient teaching program)
  - Normal diet as tolerated during the day

- Duration
  - 7 days per week for 8-12 weeks (induction)
  - 5 days per week (maintenance)

CHOP EN Experience

- Induction of remission: 65% (at 8 weeks)
- Response: 87% (at 8 weeks)
- Significant improvement in weight and linear growth
- Protocol is well tolerated
  -- no serious adverse events


Enteral Nutrition Therapy for Crohn’s Disease
(Summary/Take-Home Points)

- Induction of remission: Yes
- Maintenance of remission: Yes
- Prevent Post-op recurrence: Yes
- Mucosal healing: Yes
- Improvement in growth: Yes
- Tolerability: ????
- Serious adverse events: No
- Immunosuppressant: No!!

Enteral Nutritional Therapy:
Where should this be in our treatment algorithm?
(Future Direction)

- Should be offered to all newly diagnosed Crohn’s patients who can tolerate Nutritional Therapy
  -- Special groups
    - Malnourished patients
    - Younger patients
    - Growth failure
    - History of Cancer
    - Family history of Lymphoma?
- Consider when failing other therapies
Severe Obesity in Your Clinic: The disconnect between the epidemic and the intervention

Sarah E. Barlow, MD, MPH
Baylor College of Medicine
Texas Children’s Hospital

I have the following financial relationship to disclose:
Dyax Corporation

No products or services produced by this company is relevant to my presentation.

Objectives

1. Learn assessment and socio-economic epidemiology of severe obesity
2. Understand the additional medical risks conferred by severe obesity
3. Know tertiary interventions including meal replacement, new medications in adults, and surgical procedures in adolescents
Where are we? The epidemic

In 2009-2010, 16.9% of children 2-19 years were obese

http://jama.ama-assn.org/cgi/content/full/2009.2012v1

Higher prevalence among Hispanic youth and among Black non-Hispanic female youth

MMWR / October 15, 2010 / Vol. 59 / No. 40

What about the severely obese child?

Gubeli Pediatrics 2012;130:1136
Definitions of severe obesity

Definitions come from pre-1980’s NHANES data
• Overweight = BMI ≥ 85th %ile
• Obesity = BMI ≥ 95th %ile

Severe obesity options
1. BMI 97th percentile
2. BMI = 35 kg/m²
3. BMI 99th percentile
4. BMI 20% above 95th %ile

Limitations of definitions

1. Most obese youth (71%) have BMI ≥ 97th percentile
2. Absolute BMI of 35 is too high a bar for young children
3. 99th %ile has limited data points to support it, and CDC warns against using the percentile equations for BMIs above the 97th percentile, or related z-scores

Severe obesity definition:
20% above 95th percentile
Prevalence of severe obesity: Overall about 4%

<table>
<thead>
<tr>
<th>NHANES, by age</th>
<th>99th %ile 1999-2004</th>
<th>20% above 95th %ile 1999-2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-5 y</td>
<td>4.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>6-11 y</td>
<td>4.0%</td>
<td>4.6%</td>
</tr>
<tr>
<td>12-19 y</td>
<td>3.4%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic 2-19 y</td>
<td>5.2%</td>
<td>5.1% F, 6.9% M</td>
</tr>
<tr>
<td>Black non-Hispanic 2-19 y</td>
<td>5.8%</td>
<td>9.1% F, 7.1% M</td>
</tr>
<tr>
<td>White non-Hispanic 2-19 y</td>
<td>3.1%</td>
<td>3.5% F, 4.0% M</td>
</tr>
</tbody>
</table>

As weight increases, clustering of cardiovascular risk factors increases

Severe obesity increases risks of other severe co-morbidities

1. OSA occurs in > 50% of extremely obese adolescents.
2. NAFLD occurs in ~ 80% of extremely obese adolescents, and 20% have NASH
3. Prediabetes is 3 to 5 times more likely among severely obese adolescents compared with obese adolescents
What to do

- Behavior modification
- Pharmacotherapy (and behavior modification)
- Surgery (and behavior modification)
- Meal replacement (and behavior modification)

Evidence for comprehensive behavior-based programs for childhood obesity

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive, medium to high intensity</td>
<td></td>
</tr>
<tr>
<td>Comprehensive, low intensity</td>
<td></td>
</tr>
<tr>
<td>Comprehensive, very low intensity</td>
<td></td>
</tr>
<tr>
<td>Focused, very low intensity</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion:
“…available research supports at least short term benefits of comprehensive medium to high intensity behavior interventions in obese children and adolescents”

Whitlock. Systematic Review for USPSTF Pediatrics 2010;125:e396

Bright Bodies:
12 month program for 8 to 16 year olds

209 ethnically diverse and low income, randomized
Mean BMI 35 kg/m²
Nutrition education, motivational interviewing, behavior modification, physical activity
Twice weekly for 6 months, then twice monthly for 6 months

12 month outcome
- Intervention: - 1.6 kg/m²
  Control: + 1.7 kg/m²

Follow-up at 24 months (45% of 12-month completers)
- Intervention: - 0.9 kg/m²
  Control: + 1.9 kg/m²

Savoie M. JAMA 2007;297:2697; Savoie M. Pediatr 2011; 3: 402
Pharmacotherapy

Weight control medications currently in use in youth

1. Sibutramine (Meridia)
   Seratonin and norepinephrine reuptake inhibitor
   FDA approved starting at age 16 years

2. Orlistat (Xenical, Alli)
   Enteric lipase inhibitor
   FDA approved starting at age 12 years
   (OTC ~$200 per month)

Orlistat for adolescent obesity

54 week double-blind RCT
539 subjects: 12 to 16 years of age, BMI 36 ± 4 kg/m²

<table>
<thead>
<tr>
<th>BMI change</th>
<th>Treat</th>
<th>Control</th>
<th>Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>kg/m² (mean)</td>
<td>- .55</td>
<td>+ 0.31</td>
<td>-0.86</td>
</tr>
</tbody>
</table>

| Fecal urgency (%) | 20.7 | 11.0 |
| Flatulence (%)    | 9.1  | 4.4  |
| Fecal incontinence (%) | 8.8  | 0.6  |

Chandine et al. JAMA 2005;293:2873

Meta-analysis among adults :
-2.87 kg [95CI -3.21, -2.53] = placebo-subtracted change at 1 year

Rucker D. BMJ 2007;225:1194
Approved for adults: Lorcanerin (Belviq): 5-HT2C agonist

- Action: 5-HT2C agonist, acting on anorexigenic neurons in hypothalamus
- Side effects: fatigue, mild GI sx, hypoglycemia in diabetics, elevation in prolactin. No valve problems to date.

<table>
<thead>
<tr>
<th>Drug, Study, and Treatment</th>
<th>Mean Percentage Change in Body Weight (Mean Efficacy Criteria)</th>
<th>Proportion of Patients Losing ≥ 5% of Body Weight (Categorical Efficacy Criteria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belviq</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1 and 2 combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg BID</td>
<td>-5.1</td>
<td>47</td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.5</td>
<td>23</td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg BID</td>
<td>-4.6</td>
<td>31</td>
</tr>
<tr>
<td>Placebo</td>
<td>-1.6</td>
<td>14</td>
</tr>
</tbody>
</table>

Colman NEJM 2012;376:1577

Approved for adults: Phentermine and topirimate (Qsymia)

- Action: phentermine is a sympathomimetic. Action of topirimate is not well understood
- Side effects: teratogenicity and elevated resting HR

<table>
<thead>
<tr>
<th>Drug, Study, and Treatment</th>
<th>Mean Percentage Change in Body Weight (Mean Efficacy Criteria)</th>
<th>Proportion of Patients Losing ≥ 5% of Body Weight (Categorical Efficacy Criteria)</th>
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<tbody>
<tr>
<td>Qsymia</td>
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<tr>
<td>Study 1</td>
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<tr>
<td>15 mg/32 mg</td>
<td>-10.9</td>
<td>67</td>
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<tr>
<td>Placebo</td>
<td>-1.6</td>
<td>27</td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5 mg/44 mg</td>
<td>-7.3</td>
<td>42</td>
</tr>
<tr>
<td>15 mg/52 mg</td>
<td>-5.8</td>
<td>70</td>
</tr>
<tr>
<td>Placebo</td>
<td>-1.3</td>
<td>11</td>
</tr>
</tbody>
</table>

Colman NEJM 2012;376:1577

Combination of pharmacologic treatment and lifestyle modification is superior to drug alone

From: Benefits of Lifestyle Modification in the Pharmacologic Treatment of Obesity: A Randomized Trial

Other (potential) medications

Metformin
- 28-9-18 old, possible insulin resistance, no DM.
- Blinded, placebo controlled, crossover: - 4.35 kg
- Contrave: APPROVAL DELAYED pending further study.
- Combination of bupropion and naltrexone
- Rimonabant: cannabinoid receptor-1 antagonist
- Exenatide: synthetic glucagon-like peptide; enhances insulin secretion, insulin synthesis, and possibly satiety
- Pramlintide: synthetic amylin; secreted with insulin and inhibits post-prandial glucagon secretion

1. Srinivasan et al. J Clin Endocrinol Metab 2006;91:2074

Surgery

Lap Band Gastric bypass

Brandt M. Nat Rev Endocrinol 2010;6:637

Lap band is adjustable

Selection criteria for adolescent bariatric surgery

Tanner stage IV or V
BMI ≥ 35 kg/m² with severe comorbidity or BMI ≥ 40 kg/m² with comorbidity
"Have failed" 6 month of organized attempts at weight loss
Committed to pre and post medical and psychological care
Supportive family
Able to give informed assent

Frequent barriers
- Distance from center
- Insurance
- Age
- Reluctance

Pratt Obesely 2009;17:901
Outcomes from adolescent bariatric surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Study type</th>
<th>Sample</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjustable band</td>
<td>Meta-analysis¹</td>
<td>271</td>
<td>−10.5 kg/m²</td>
</tr>
<tr>
<td>Sleeve gastrectomy</td>
<td>Meta-analysis¹</td>
<td>90</td>
<td>−14.7 kg/m²</td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>Meta-analysis¹</td>
<td>256</td>
<td>−17.2 kg/m²</td>
</tr>
<tr>
<td>Gastric bypass NIH study²</td>
<td>~ 200 (preliminary)</td>
<td>50-60% of excess weight at year 1</td>
<td></td>
</tr>
</tbody>
</table>

1. Black Obesity Rev 2013;14:634

Complications
For all procedures: nutritional deficiencies, especially iron, vitamins B12, D, and thiamine
For gastric bypass: postprandial hypoglycemia in adults
For lap band: need for re-operation for slippage or erosion in adults and small adolescent study. Also pouch dilatation
For sleeve gastrectomy: leak or bleeding along suture site

Meal Replacement
113 adolescents, 15.0 ± 1.3 y, 37.1 ± 5.1 kg/m²
- Conventional diet (CD)
  - 1300-1500 kcal/day, self selected
- Meal replacement (MR)
  - 3 protein shakes, 1 prepackaged meal, 5 fruit and vegetables
  - At 4 mon, continued MR or CD

Berkowitz Obesity 2011;19:1199
Summary
1. 4% of children 6 to 19 are severely obese
2. Severe obesity leads to high levels of cardiovascular disease risk factors, NAFLD, OSA, and pre-diabetes
3. Behavior modification has modest efficacy, is a partner in all other intensive interventions, but is not readily available
4. Orlistat is the only medication currently available for adolescents.

Take home
Despite the many severely obese children, treatment is inadequate
• the tools are limited
  – What if the options for treating staph cellulitis were either a bandaid or amputation?
• behavior modification is underutilized
  – it is time-intensive and resource-intensive
  – it is necessary even though it is not sufficient

What is the one thing you can do in the office?
1. Stop looking for “the one thing”
2. Be prepared:
  – Know what is available and how to access Programs, therapists, dietitians, physical therapy
  – Get help from social work
3. Communicate to family that best success comes from intensive support
4. Start with the basic lifestyle changes.
5 2 1 0

• 5 servings of fruits and vegetables a day
• 2 hours or less of screen time
• 1 hour (60 minutes) or more of physical activity
• 0 sugar-sweetened beverages

Future Directions
1. Evaluation of newer medications in children
2. Non-pharmacologic but intensive interventions for pre-adolescent children
   – family-based
   – potentially home-based or residential, like in-patient feeding interventions
   – meal replacement
3. Understanding and influencing parent motivation to change home environment
Decision Making in Ulcerative Colitis: Escalate Medical Therapy or Call the Surgeon?

Wallace Crandall, MD
Director, The Center for Pediatric and Adolescent IBD
Associate Medical Director for QI
Nationwide Children’s Hospital
Professor of Clinical Pediatrics
The Ohio State University College of Medicine

Disclosures
I have the following potential conflicts:
Abbott- Speaking/Consulting
Boehringer Ingelheim Pharma GmbH & Co. KG- Consulting
Glaxo Smith Kline- Consulting
Abbvie- Research support
Mead Johnson- Sponsored Visiting Professor

Additional Disclosures
I broke house windows (including those in our home and the homes of 2 neighbors) at least 4 different times growing up. All were accidents.
As a child, I hit a kid in the back with a rock. That wasn’t an accident.
I once shot a bottle rocket into the chest of another kid. It was a tough shot; I was quite proud of myself.

Given that I am both horribly conflicted and have the unseemly past described above, you will have to decide on my trustworthiness.
Objectives

- Review treatments for steroid refractory UC
- Know long term risks of medications used for refractory UC
- Learn post-operative complications

Case

14 yo male with 2 year h/o UC (pancolitis)
- Initial treatment with mesalamine
- Clinical remission for 22 months
- Moderate flare of UC
- Negative for C. diff and stool culture
- Treated with rectal mesalamine, then oral steroids
- Worsened symptoms and admitted for IV steroids

**Admission**

- Mild abd pain
- 8 BM per day, watery
- Large blood most stools
- Nocturnal awakening
- Not attending school
- AF, VSS
- Mild to moderate tenderness BLQ
- Non-toxic
- PUCAI-75 (severe)

**Day 3**

- Mild abd pain
- 8 BM per day, watery
- Large blood most stools
- Nocturnal awakening
- Not attending school
- AF, VSS
- Mild to moderate tenderness BLQ
- Non-toxic
- PUCAI-75 (severe)

**Day 5**

- Mild abd pain
- 8 BM per day, watery
- Large blood most stools
- Nocturnal awakening
- Not attending school
- AF, VSS
- Mild to moderate tenderness BLQ
- Non-toxic
- PUCAI-75 (severe)

**By Day 10**

- Mild abd pain
- 8 BM per day, watery
- Large blood most stools
- Nocturnal awakening
- Not attending school
- AF, VSS
- Mild to moderate tenderness BLQ
- Non-toxic
- PUCAI-75 (severe)
PUCAI Components

Abdominal Pain (0, 5, 10)
Rectal Bleeding (0, 10, 20, 30)
Stool Consistency of Most Stools (0, 5, 10)
Number of Stools Per Day (0, 5, 10, 15)
Nocturnal Stools (0, 10)
Activity Level (0, 5, 10)

Maximum Score- 85

Initial Evaluation and Management

Corticosteroids
No dose ranging studies in children
In adults: 60 mg no more effective than 40 mg daily
Continuous infusion or divided doses no better than once daily dosing
In children: 1-1.5 mg/kg/day up to 40-60 mg showed anticipated 71% response rate with no dose-response


Initial Evaluation and Management

C. difficile
Increasing frequency and severity in IBD
Most common pathogen in adults with IBD flare (up to 19%)
Present in 4-25% of pediatric IBD admissions

Must test for both A and B toxins
Single stool sample for both toxins identifies only 50% of infected adults
Endoscopic appearance is often misleading, as pseudo membranes often absent in IBD patients

### Admission

**Day 3**
- Mild abd pain
- 8 BM per day, watery
- Large blood most stools
- Nocturnal awakening
- Not attending school
- AF, VSS
- Mild to moderate tenderness BLQ
- Non-toxic
- PUCAI-75 (severe)

**Day 5**
- Soluncedrol 40 mg IV qd
- Lab Evaluation
  - CBC (Hb 9.3)
  - ESR/CRP (12)
  - Hepatic panel
  - Lytes

- AAS (No free air/toxic megacolon)
- Repeat C diff
- Daily PUCAI
- Regular diet

**By Day 10**
- Not eating well
- Denies abd pain
- 5 BM per day, watery
- Nocturnal stooling
- Large blood, slightly improved
- Confining to room
- AF, VSS
- Mild BLQ tenderness
- Non-toxic
- Hb-8.4
- PUCAI-60 (moderate)

---

### Prepare for Second Line Therapy

- **PUCAI < 35**
  - Consider
  - Oral steroids
  - TPMT
  - Discharge

- **PUCAI 35-45**
  - Continue current therapy

- **PUCAI > 45**
  - Screen for second line therapy
  - Surgery consult
  - Flex sig (CMV)
  - Treat for CMV as indicated

---

*Turner Am J Gastroenterol 2011;106:574–88*
Prepare for Second Line Therapy

TB screening: IGRA vs. TST
Meta-analysis of 9 studies, 1,309 patients
-85% agreement overall
-IGRA-/TST+ 4-25%; IGRA+/TST- 1-6%
-IGRA indeterminate in 5%
-IST impairs both IGRA and TST results


Prepare for Second Line Therapy

Hepatitis B Screening
Test for HBV (HBsAg, anti-HBs, and-HBcAb)
-Seronegative: Hepatitis B vaccination
-HBsAg carriers: Pre-emptive therapy
-Chronic active HBV: Standard antiviral therapy
-Acute HBV: Delay immunosuppressive therapy


Prepare for Second Line Therapy

Testing for CMV
CMV infection- virus detectable in blood or tissue
CMV disease (colitis)- virus detectable in target organ
-should only test in refractory disease
Sero prevalence in UC- 70%

Testing for CMV colitis
H and E- sensitivity 10%-87%; specificity 92%-100%
IHC- sensitivity 73%-93%
Tissue PCR- prevalence > 30% in IBD
- poor correlation with HE/IHC
- sensitivity 100%; specificity 66% (> 250 copies/mg for this study)

Prepare for Second Line Therapy

Cause of disease vs. “innocent bystander”
- Absence of viremia/PCR does not exclude CMV colitis
- Positive PCR in asymptomatic patients (may be latency)
  - Colon PCR > 250 associated with treatment resistance
- Some studies do not show worse outcomes in CMV positive pts
- Unclear if + tissue PCR but negative histology is meaningful


Testing and Treating CMV

Our Approach (Histopathology remains gold standard)
In steroid refractory patients, do rectal biopsy for IHC (or PCR)
If positive, and viral cytopathic effect:
  - Consider holding immunosuppression in severe, systemic disease
  - Check blood PCR (to monitor treatment)
  - Initial IV Ganciclovir

The real answer: There are numerous possible scenarios to be considered; make friends with your ID colleagues!

Admission
Day 3
- Not eating well
- Denies abd pain
  - 5 BM per day, watery
- Nocturnal stooling
- Large blood, slightly improved
- Confined to room
- AF, VSS
- Mild BLQ tenderness
  - Non-toxic
- Hb 8.4
- PUCAI 60 (moderate)

Day 5
- Surgery consult
- TB screening
- Hep B screening
- Plasma CMV PCR
- Additional labs/radiology as indicated
- Flex sig
- IHC for CMV

By Day 10

Initiate Second Line Therapy

**PUCAI $<$ 35**
- Consider
  - Oral steroids
  - TPMT
  - Discharge

**PUCAI 35-65**
- Continue current therapy for 2-5 days and re-evaluate

**PUCAI $>$ 65**
- Start second line therapy or proceed with surgery

Turner Ann J Gastroenterol 2011;106:574–88

**Initiate Second Line Therapy**

**Infliximab vs. CsA**

115 adult patients with severe UC, failing 5 days IV steroids
1:1 randomization to infliximab (5mg/kg) or CsA (dose adjusted)

No difference in outcome for:
- Early clinical response (84% vs. 86%) at day 7
- Mucosal healing (45% vs. 47%) at day 98
- Treatment failure (54% vs. 60%) at day 98
- Colectomy (21% vs. 17%) at day 98
- SAE (25% vs. 16%) or serious infections (7% vs. 9%)

Initiate Second Line Therapy

Infliximab vs. CsA (Additional Considerations)
Study was designed as a superiority trial of CsA
- Non-inferiority design may have detected small differences
- Non-blinded
CsA was maximized but infliximab was not
Although similar short term SAE profile, infliximab may have better long term safety profile and can be used for maintenance

Singh. Gastroenterol. 2012; 144:1136-1140

Initiate Second Line Therapy

Surgery
Indications:
- toxic megacolon
- perforation
- uncontrolled bleeding
- acute severe colitis not responsive to medical therapy (first line or rescue?)
IPAA
- Do not delay surgery to enhance nutrition or taper steroids
- In ASC, colectomy with end ileostomy as first stage with subsequent pouch


Initiate Second Line Therapy

Surgery
Selected complications
- Pouchitis (45%-60%)
- Pouch failure (5%-15% at 10 years, newer studies suggest 2.5%)
- Incontinence (7%-55%)
- Decreased fecundity (25%-30%)

Initiate Second Line Therapy

Surgery
Increased complications with pre-operative steroids, malnutrition and hypoalbuminemia

Conflicting data regarding complications and anti-TNF
Meta-analysis of post-operative complications in UC (n=1427)
-no difference in overall complications, infectious complications, or non-infectious complications


<table>
<thead>
<tr>
<th>Admission</th>
<th>Day 3</th>
<th>Day 5</th>
<th>By Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eating fair</td>
<td>Denies abd pain</td>
<td>7 BM per day, watery</td>
<td>Transfuse PRBCs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nocturnal stooling</td>
<td>Give Infliximab 5 mg/kg IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large blood</td>
<td>Additional labs/radiology as indicated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Confined to room</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AF, VSS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild BLQ tenderness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-toxic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hb-6.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PUCAI-60 (moderate)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Admission</th>
<th>Day 3</th>
<th>Day 5</th>
<th>By Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eating better</td>
<td>Denies abd pain</td>
<td>4-5 BM per day, loose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nocturnal stooling</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small blood</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AF, VSS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimal tenderness</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-toxic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hb-11.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PUCAI-45 (moderate)</td>
<td></td>
</tr>
</tbody>
</table>
Continue Medical Therapy vs. Surgery

Factors Affecting Desirable Anti-TNF Dosing

- Highest infliximab levels associated with remission/mucosal healing
- Increased TNF levels associated with severe inflammation
- Severe inflammation associated with increased clearance
- Severe inflammation associated with increased intestinal losses?
- Low albumin associated with decreased drug half-life

Singh, Gastrointest. 2012;144:1136-1140; Ordas, Clin Pharm Ther 2012; 91:635-646

Continue Medical Therapy vs. Surgery

- Initial dosing of 10 mg/kg
- Give 5 mg/kg; repeat 5 mg/kg dose if no immediate response
- Repeat doses frequently based on CRP, albumin and/or drug levels

Turner Am J Gastroenterol 2011;106:574–88
Initiate Second Line Therapy

Sequential therapy
Tacrolimus followed by infliximab (24 pts/12 pts)
- 16% steroid free remission/50% remission
- 58% colectomy/42% colectomy
- 0/2 SAE (8%) leading to discontinuation


Initiate Second Line Therapy

Sequential therapy
CsA followed by infliximab (16 pts/47 pts)
- 0-60% remission depending on number of doses
- 38% colectomy/30% 1 yr. colectomy
- 1 SAE/4 SAE 1 Death (pneumonia)


Initiate Second Line Therapy

Sequential therapy
Successive CsA and Infliximab (19 pts/86 pts)
- 33%-40% remission/22 % steroid free remission (3 months)
- 59% 1 yr. colectomy/42% 1 yr. colectomy
- 3 SAE, 1 Death (sepsis)/10% serious infections, 1 Death (PE)

Admission

Day 3
Eating fair
Denies abd pain
4-5 BM per day, loose
Nocturnal stooling
Small blood
AF, VSS
Minimal tenderness
Non-toxic
Hb-11.8
PUCAI-45 (moderate)

Day 5
Repeat Infliximab 5 mg/kg IV

By Day 10

Take Home Points (According To Me)
Follow PUCAI (day 3 and 5) to determine need to move to second line therapy
Involve your surgeon early
Exclude infectious confounders (C. diff, CMV)
Move to second line therapy in a timely fashion (Day 5)
-I favor anti-TNF over CsA
-Consider more aggressive anti-TNF dosing paradigms
-Avoid sequential therapy
Surgery is not a failure

Future Directions: Personalized Medicine

Determine:
1. presence and relevance of CMV for a given patient
2. which patients are likely to respond to a given therapy
3. best dosing paradigms for anti-TNFs (and other therapies) in severe refractory colitis for a given patient
Objectives

• Learn about the effect of preoperative therapy on postoperative outcome

• Know methods for assessing recurrence

• Be familiar with the natural history of Crohn’s following an intestinal resection

• Learn about medical therapies which reduce post-operative recurrence
Pre-Operative Management to Reduce Postoperative Complications

• Determine if preoperative antibiotics indicated for intra-abdominal fistula/abscess to improve likelihood of primary anastomosis

• Reduce level of immunosuppression to decrease risk of complications (taper steroids, hold AZA/6MP, MTX, anti-TNF biologics)

Influence of Preoperative Immunosuppression on Readmission after Surgery for Crohn’s Disease

• 338 consecutive pts received steroids, immunomodulators and/or biologics within 3 months of abdominal surgery for Crohn’s disease

• Outcome studied: rate of unplanned readmission (within 30 days of surgery)
  Steroids 13% Immunomodulators 9% Biologics 12%

• Increased readmission with combined medication classes
  0: (3%) 1: (7%) 2: (11%) 3: (16%)

Defining Postoperative Recurrence

Clinical: PCDAI; PGA. Symptoms plus objective measure: endoscopic, radiologic, histologic to distinguish IBD activity from IBS

Endoscopic: Rutgeerts score (i0-i4)

Histologic Score: d’Haens (inflammation on biopsy)

Radiologic: MRE score or SBFT if indicated
Rutgeerts Endoscopic Recurrence Score


Remission: Endoscopic score i0 or i1
- i0 No lesions
- i1 ≤ 5 aphthous lesions

Recurrence: Endoscopic score i2-i4
- i2 > 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions, or lesions confined to the ileocolic anastomosis (< 1 cm in length)
- i3 Diffuse aphthous ileitis, diffuse inflammation
- i4 Diffuse inflammation, large ulcers, nodules, and/or narrowing

Clinical Recurrence Rate 79 Pediatric Patients (CHOP)
After Resective Surgery for Crohn’s Disease:
17% at 1 yr, 38% at 3 yrs, 60% at 5 years

Pediatric Crohn’s Disease: Risk Factors for Postoperative Recurrence

Recurrence free interval (RFI) reduced:
- Preoperative 6MP v none 1.0 v 4.4 yrs
- Colonic < diffuse SB and colon < ileocecal/SB 1.2 yrs 2.9 yrs 4.4 yrs
- Disease activity at surgery (PCDAI) > 20

Not associated with recurrence:
- Disease duration, CS, 5’ASA, h/o stricture/perf. granulomas, age at surgery, gender, race
Postoperative recurrence, comparing 6MP, mesalamine or placebo: a 2 year trial
(Hanauer SB et al. Gastroenterology 2004;127:723-9)

5 centers, randomized 131 pts two weeks following intestinal resection for Crohn’s disease to: 6MP 50 mg, mesalamine (3 g) or placebo

Clinical assessments 7 weeks then q 3 months
Colonoscopy 6, 12 and 24 months
SB x-ray series 24 months

Recurrence comparing 6MP, mesalamine or placebo at 24 months:

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>6MP</th>
<th>S'ASA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>50%</td>
<td>58%</td>
<td>77%</td>
</tr>
<tr>
<td>Endoscopic</td>
<td>43%</td>
<td>63%</td>
<td>64%</td>
</tr>
<tr>
<td>Radiologic</td>
<td>33%</td>
<td>46%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Conclusion: 6MP more effective than mesalamine in preventing recurrence at 2 years.

Cochrane Database review of interventions to prevent postoperative recurrence of Crohn’s disease
(Doherty G et al. Cochrane Database Syst Rev 2009;Oct 7)

Randomized controlled trials: medical therapy v placebo or other medical agents (23 studies met the criteria)

• 1. Probiotics v placebo: NS
• 2. Nitromidazole: decreased clinical and endoscopic (RR 0.23-0.44) but higher SAE (RR 2.39)
• 3. AZA/6MP: significantly reduced clinical & endoscopic recurrence (RR 0.53-0.64), SAE=Placebo
• 4. Mesalamine when compared to AZA/6MP: higher endoscopic recurrence risk (RR 1.45)

Insufficient data: infliximab, budesonide
Cochrane Analysis of Probiotics Versus Placebo
Outcome: Severe Endoscopic Recurrence

Cochrane Analysis of Antibiotic Versus Placebo
Outcome: Severe Endoscopic Recurrence (3 months)

Cochrane Analysis of Budesonide Versus Placebo
Outcome: Severe Endoscopic Recurrence (12 months)
Cochrane “Authors’ Recommendations”
[Doherty G et al. The Cochrane Library 2009;pp1-69]

- Antibiotic therapy (metronidazole) in the immediate post-operative course to patients with risk factors for early recurrence (where tolerated)
- Risk of recurrence with mesalamine < placebo
- No evidence that budesonide or probiotics better than placebo
- Endoscopic reevaluation in 3-6 months. Discuss risks & benefits of 5’ASA v immunosuppressive or anti-TNF therapy based on endoscopic findings

Infliximab prevents Crohn’s disease recurrence after ileal resection.

Randomly assigned 24 pts. s/p ileocolonic resection within 4 weeks of surgery to receive infliximab 5 mg.kg (mean 20 days) v placebo

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence 1 yr</td>
<td>9.1%</td>
<td>84.6%</td>
<td>.0006</td>
</tr>
<tr>
<td>Endoscopic</td>
<td>9.1%</td>
<td>84.6%</td>
<td>.0006</td>
</tr>
<tr>
<td>Histologic</td>
<td>27.3%</td>
<td>84.6%</td>
<td>.01</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>80.0%</td>
<td>53.8%</td>
<td>.38</td>
</tr>
</tbody>
</table>

S.S. for endoscopic and histologic recurrence
No difference in adverse events [Dig Dis 2011;56:3610-5]
Scheduled Infliximab Monotherapy to Prevent Recurrence of Crohn's Disease

[Yoshida K et al. Inflamm Bowel Dis 2012;18:1617-23]

- 31 pts ileocecal resection
- Randomized to IFX 5 mg/kg every 8 wks or no IFX, steroid or IM within 4 weeks of surgery
- Followed 36 months
- Outcome: Endoscopic recurrence at 12 & 36 mos

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>IFX Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clin. Rem 12 mos</td>
<td>100% 68%</td>
</tr>
<tr>
<td>Clin. Rem 36 mos</td>
<td>93% 56%</td>
</tr>
<tr>
<td>Endos. Rem 12 mos</td>
<td>78% 19%</td>
</tr>
</tbody>
</table>

Early Diagnosis and Treatment of Postoperative Endoscopic Recurrence of Crohn’s with Infliximab


Outcome Measure: whether infliximab could induce endoscopic remission (Rutgeerts score <2) at 54 weeks after demonstrating postoperative endoscopic recurrence

Study: 43 patients ileocolonic resection underwent colonoscopy 6 mos post surgery

Recurrence: 24/43 pts (56%). Randomized to:
- Inflix 5 mg/kg (n=13) v Mesalamine 800 mg tid (n=11)
Early Diagnosis and Treatment of Postoperative Endoscopic Recurrence of Crohn’s with Infliximab


Results: Endoscopic Remission rate at 54 weeks
- Mesalamine 0/11 (0%)
- Infliximab 7/13 (54%)

Endoscopic Improvement: 69% of infliximab

Conclusion: treatment of endoscopic lesions with infliximab is superior to mesalamine but a sizeable proportion did not benefit.

Adalimumab in Prevention of Postoperative Recurrence of Crohn’s Disease


- Multicenter prospective study ileal/ileocecal resection (high risk: penetrating disease, previous surgery, smoker). N = 29 patients. Started 2 weeks after surgery: 160/80/40 mg
- At 1 yr: ileo-colonoscopy and/or MRE
  - Endoscopic recurrence (Rutgeerts score >2)
  - Morphologic recurrence (MR score ≥1)

Recurrence results:
- Clinical recurrence 13.7%
- Endoscopic recurrence 20.7%
- Morphologic recurrence 36.8%
- Dose escalation required: 17.2% (40 mg/wk) at a mean of 8 months (5-11 months)

Conclusion: ADA seems safe and effective in a selected group of patients s/p intestinal resection
Fecal calprotectin (FC) may predict postoperative recurrence in Crohn’s disease
[Labaton T et al. J Crohns Colitis 2013;S1873]

- 115 ileo-colonoscopies included 29 with ileocolonic resection
- Postoperative recurrence using Rutgeerts score compared with fecal calprotectin
- Correlation best in ileocolonic disease ($r=0.88$) than the colon ($r=0.725$) or ileum ($r=0.437$).

Rutgeerts i0-i1 asso with FC 98 mcg/g (30-306)

i2-i4 asso with FC 234 mcg/g (100-612)

Summary Slide

- Recurrent disease occurs frequently s/p resection for Crohn’s and increases with the length of follow-up.

- AZA/6MP and infliximab currently are the most effective therapies but a significant number of patients still have recurrent disease

Conclusions/Take Home Points

- Biologic agents most effective in reducing disease recurrence.
- Thiopurines less effective than anti-TNF. Whether long-term methotrexate with the anti-TNF biologics will increase malignancy risks in CD similar to AZA/6MP is unknown
- Mesalamine is less effective than 6MP but better than placebo
- Metronidazole also better than placebo
- Probiotics and budesonide not shown to reduce recurrence
- Fecal calprotectin may be useful in detecting early recurrence
Future Directions

- Determine whether adjustment of dose based on blood levels for AZA/6MP reduces postoperative recurrence
- Assess whether the risk of malignancy is increased with concommitent methotrexate and anti-TNF biologics
- Address the problem of loss of effect with the anti-TNFs and who should receive post-operative biologics.
- Study surrogate biomarkers (such as calprotectin) to identify patients for earlier more aggressive medical intervention
- Investigate genotype correlations with recurrence

Thank You for Your Attention
Gastroparesis: Paralysis for the patient and provider?

Carlo Di Lorenzo, M.D.

I have no financial relationship with any commercial entity to disclose

Learning objectives

• Learn when to suspect gastroparesis
• Recognize how to best test for gastric motor function
• Become familiar with newer therapies for gastroparesis
Spectrum of Gastroparesis in Children

JPEN 2012;55: 166–172
Yumiko Takeuchi, Ute Heintz, Ira Gelernter, Baharak Mohrbe, and Nicholas J. Talley

Retrospective analysis of 239 patients (0-21 y/o)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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<td>Psychiatric disorders</td>
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</table>

60% improved within 24 months

Clinical Presentation, Response to Therapy, and Outcome of Gastroparesis in Children

JPEN 2012;55:185-90
Leonel Rodriguez, Satyajit Trivedi, Hongyu Jiang, and Allan M. Goldstein

- Retrospective review of 230 children with gastroparesis
- Postviral gastroparesis in 18% and mitochondrial dysfunction (MD) in 8%
- Symptom resolution: 22% at 6 months, 53% at 18 months, and 61% at 36 months, with median time to resolution of 14 months
- Favorable prognosis: younger age, male sex, postviral gastroparesis, shorter duration of symptoms, response to prokinetics, and absence of mitochondrial disease

Impaired Gastric Emptying and Small Bowel Transit in Children With Mitochondrial Disorders

JPEN 2012;55:194-9
26 subjects, 3-18 y/o with MD and GI symptoms
Diagnosis

If your patient vomits within seconds or minutes from eating, the diagnosis is NOT gastroparesis

Dogma

If your patient vomits within seconds or minutes from eating, the diagnosis is NOT gastroparesis

Adolescent rumination syndrome

Rome III criteria:
- Repeated painless regurgitation with re-chewing or emesis
  - Begins within minutes of eating- often during the meal
  - Does not occur during sleep
  - Does not respond to GER therapy
  - No retching (effortless)
  - No evidence of inflammatory, anatomic, metabolic, or neoplastic process to explain symptoms

Rasquin A et al. Gastroenterology 2006;130:1527-37
Tests

Manometry not a great test for gastroparesis

Decreased Relative Diagnostic Yield of Esophagogastroduodenoscopy in Children With Gastroparesis

Gregory K. Wong, MD,*† Robert J. Shulman, MD,*‡ Eric R. Chua, MBBS,*† and Bruce P. Chappuis, MD, MPH*†

(J Clin Gastroenterol 2012;46:55-60)
Pediatric normal values?


- Depends from the meal
- Use adult data for a solid meal (2 large eggs, 2 slides of bread, jam, water, 345 KCal):
  Abnormal >10% left in the stomach after 4 hours, >60% after 2 hours
- No pediatric data available, but look for extremes

Gastroparesis in Children: The Benefit of Conducting 4-hour Scintigraphic Gastric-Emptying Studies

JPQN 2013;56: 439–442

- 71 patients (32 boys, average age 10.8 years)
- 62% children had abnormal GES; 23% who had normal values at 2 h had abnormal GES at 4 h (P<0.0001)
- Survey: Only 5 of the top 20 pediatric GI centers in the US conducted 4-h GES
- Transitioning from 2 h to 4 h did not result in limitation in the number of scheduled patients
- Conclusions: Extending GES to 4 hours results in a considerable increase in diagnosis of gastroparesis
SmartPill pH.p Capsule

- 26mm x 13mm
- 5+ day battery life
- Senses and records pH, pressure and temperature data from within the GI tract
- Wirelessly transmits data to the SmartPill Data Receiver

Wireless Motility Capsule Tracing
Whole Gut Transit & Motility

Measurement of gastrointestinal pH profiles in normal ambulant human subjects

Gut 1988; 29:1035-41

D F EVANS, G FVE, R BRAMLEY, A G CLARK, T J DYSON, AND J D HARDCASTLE
Conclusion: In symptomatic pediatric patients, the wireless motility capsule test is highly sensitive compared with scintigraphic gastric emptying studies in detecting gastroparesis, and seems to be more sensitive than ADM in detecting motor abnormalities.

Electrogastrography: Noninvasive Recording of Gastric Antral Electrical Activity
Tachygastria and Bradygastria Are Dysrhythmias Detected by Electrogastrography

Ultrasonography

24 adolescents

Octanoate Breath Test

$^{13}$C octanoate liquid/solid meal

Manini ML, et al., JPGN 2009;48: 287-93

Octanoate Breath Test

$^{13}$CO2
Treatment

Erythromycin

Curry JI, Lander TD, Stringer MD.

Erythromycin as a prokinetic agent in infants and children.

Aliment Pharmacol Ther 2001;15:595-603

Only one randomized placebo-controlled trial has been conducted. All except one of these studies have shown a beneficial effect of erythromycin in either promoting tolerance of enteral feeds or enhancing a measured index of gastrointestinal motility. Erythromycin appears to be equally effective when given orally (as ethylsuccinate or estolate) or intravenously (as lactobionate).
Erythromycin

In patients with poor motility:
use high (abx) doses

Comparison of the Effect of Azithromycin Versus Erythromycin on Antral and Duodenal Pressure Profiles of Patients with Chronic Functional Gastrointestinal Pain and Gastroparesis

Wei Ho • Phillip P. Tekes

Multicenter, Double-Blind, Placebo-Controlled Crossover Study to Assess the Acute Prokinetic Efficacy of Nizatidine-Controlled Release (150 and 300 mg) in Patients With Gastroesophageal Reflux Disease

Richard W. McCollum, MD; Edwin J. Pesing, MS; Allen C. Grieve, MD; Carl Griffin, MD; Jerry Sams, MD; Bette A. Harrel, MD; Ralph T. Dods, RA, and Karen Rosenberg, PhD
Conclusions: Domperidone was significantly more effective than cisapride in reducing the gastric emptying time, normalizing gastric electrical activity and decreasing the prevalence of episodes of gastric dysrhythmia. Domperidone was also more effective than cisapride in improving diabetic metabolic control.

IND needed to prescribe domperidone in the USA
Randomized Controlled Phase Ib Study of Ghrelin Agonist, RM-131, in Type 2 Diabetic Women With Delayed Gastric Emptying

What else can we do?
Botulinum Toxin:
100-200 Units divided in 4 quadrants

Gastric Electrical Stimulation (GES)
Temporary Stimulation

- Cardiac electrode
- Endoscopic clips
- Wire comes out of mouth or gastrostomy
- 5-7 days “testing” before proceeding with permanent placement

Done in children of any age

Temporary percutaneous and permanent gastric electrical stimulation in children younger than 3 years with chronic vomiting Journal of Pediatric Surgery (2011) 46, 655–661

Efficacy of permanent gastric electrical stimulation for the treatment of gastroparesis and functional dyspepsia in children and adolescents

Steven Teich, Hayat M. M. M., Juju Panati, Carlo Di Lorenzo

Neurogastroenterology & Motility

Improvement of quality of life and symptoms after gastric electrical stimulation in children with functional dyspepsia

26 children, age 4-21 year

Symptom Severity

Route of Nutrition

- Improved total score (p<0.0001)
- Nausea, Fullness, Early Satiety, Bloating, Epigastric Pain, Vomiting, Bumning
- Pro-GES, Post-GES
- p<0.0001, p<0.001, p<0.002, p<0.003, p<0.004

- 26 children, age 4-21 year
- p=0.02, p=0.04

Gastric or Jejunal Feeding, Parenteral Nutrition

- Pro-GES, Post-GES

173
Summary

• Post-viral forms of gastroparesis carry best prognosis
• Multiple tests can be used to diagnose gastroparesis, but Nuclear Medicine remains the gold standard
• Multiple medical and nonmedical interventions have the potential to improve symptoms associated with gastroparesis

Future directions

• Better correlation between symptoms and underlying pathophysiological mechanisms
• Understanding role of noninvasive testing
• Development of improved pharmacological treatments

Extra slides
Other treatments in pediatrics for “gastroparesis symptoms”?  

Cyproheptadine  

is a first-generation antihistamine with additional anticholinergic, antiserotonergic, and local anesthetic properties.

Safety and Efficacy of Cyproheptadine for Treating Dyspeptic Symptoms in Children  
J Pediatr 2013 (in press)  
Lauren Rodriguez, MD, MS; Juan Diaz, MD, PhD2; and Samuel Honko, MD, MPh2

80 children (mean age 10 y)

Fludrocortisone improves nausea in children with orthostatic intolerance (OI)

John E. Fortunato, MD; Hosanna A. Shafroat, 
Nigar M. Jafria; Peter K. Rowe, 
Debra J. Ellis, MD; Kenneth L. Kerk

17 pts with chronic idiopathic nausea, with orthostatic intolerance by abnormal tilt table tests (68%), or gastric dysrhythmias (71%)

Fludrocortisone: 0.1-0.2 mg/day for 4 weeks
Iberogast in Functional Dyspepsia

Gastrointestinal Symptom score during 8 wk of treatment with STW 5 (Iberogast) or placebo

The NCH experience:
• 31 adolescents (16 girls) admitted for the inpatient rumination rehabilitation
• 63% had nausea
• Multidisciplinary treatment, starting with very minimal po
• Average length of stay: 11.5 days
• 27 “successful” rehabs, left on oral feedings, with no overt emesis

Severe Pediatric Rumination Syndrome: Successful Interdisciplinary Inpatient Management
"Aleix D. Green, Anthony Almeida, Hayat Mousa, and Carlo Di Lorenzo"
Eosinophilia beyond the esophagus

Glenn T. Furuta
University of Colorado School of Medicine
Children’s Hospital Colorado
National Jewish Health

I have the following financial relationships to disclose:

Meritage Pharma
Knopp
Pfizer
UpToDate

No Products or services produced by this (these) company (companies) are relevant to my presentation.

Contributions from

Seema Aceves
Peter Bonis
Margaret Collins
Evan Dellon
Ikuo Hirano
Chris Liacouras
Phil Putnam
Alex Straumann
Objectives

- Know clinical implications of GI eosinophilia normal and abnormal
- Recognize systemic causes of GI eosinophilia
- Learn newer managements of GI eosinophilia diseases
"Normal" number of eosinophils in GI tract

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<td>Duodenum</td>
<td>Mean: 15</td>
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<td>Mean: 20</td>
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<td>Upper Limit: 32</td>
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Eosinophil Counts in Upper Digestive Mucosa of Western European Children: Variations With Age, Organs, Symptoms, Helicobacter pylori Status, and Pathological Findings

*N: Kalisch, 1E: Haverne, 2P: Ginzet, 3L: Papadopoulos, 4E: Dineen, 5A: Deuster,
6C: Crety, and 7C: Dupont

TABLE 1: Eosinophil counts (units/mmc) in the upper digestive tract of children with H. pylori positivity

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Objectives

• Know clinical implications of GI eosinophilia normal and abnormal
• Recognize systemic causes of GI eosinophilia
• Learn newer managements of GI eosinophilia diseases

Definition

“Eosinophilic Enteropathies = idiopathic, predominant and persistent”
Alex Straumann 2013

Traditional view-
“mucosal, muscular and serosal”
Rolf Kaijser 1936

Symptoms associated with EGIDs

• Stomach-nausea, vomiting, pain, hematemesis,
• Intestine-diarrhea, edema, pain, bleeding (occult)
• Colon-tenesmus, urgency, pain, diarrhea, bleeding
• Other organ-gallbladder, liver, pancreas
"Abnormal" number of eosinophils in GI tract?

<table>
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<tr>
<td>Duodenum</td>
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<td>Jejunum</td>
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<td>Terminal ileum</td>
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<tr>
<td>Ileum</td>
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<tr>
<td>Cecum</td>
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<tr>
<td>Asc. Colon</td>
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<td>50</td>
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<tr>
<td>Trans. Colon</td>
<td>18</td>
<td>42</td>
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<tr>
<td>Desc. Colon</td>
<td>14</td>
<td>25</td>
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<tr>
<td>Sigmoid Colon</td>
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<td>15</td>
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<tr>
<td>Rectum</td>
<td>9</td>
<td>18</td>
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</tbody>
</table>

Patterns of injury

- Mucosal disruption-erosions, ulcers
- Remodeling-wound repair, hypertrophy
- Mucosal, muscular and serosal
**Associated cells**

- Epithelium
- Inflammatory cells—neutrophils, macrophages, lymphocytes, mast cells
- Myocytes, nerves, fibroblasts

**Additional evaluations**

- Imaging—determine extent of disease
  - CT / UGI-SBFT / MRI / capsule / US
- Laboratory—identify co-morbid problems
  - Anemia
  - Hypoalbuminemia
  - Nutritional deficiencies

**Must match symptoms with histology!**
Why so important to make proper diagnosis?

- "Idiopathic"-unknown pathogenesis so using non-targeted treatments
- "Predominant"-ensure that other causes are not present
- "Persistent"-chronic treatment / evaluations will be suggested

**Diagram:**

- Initial evaluation of presenting symptoms
- "Idiopathic"-unknown pathogenesis so using non-targeted treatments
- "Predominant"-ensure that other causes are not present
- "Persistent"-chronic treatment / evaluations will be suggested

**Additional Information:**

- Lee et al. Dig Dis Sci 2011

**Chart:**

- **Original Articles—Alimentary Tract**
- Natural History of Eosinophilic Gastroenteritis
- Courses of EGE

- **A**
- **B**
- **C**

- Time

---

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Objectives

- Know clinical implications of GI eosinophilia normal and abnormal
- Recognize systemic causes of GI eosinophilia
- Learn newer managements of GI eosinophilia diseases

Systemic causes of GI eosinophilia

- No data on degree of eosinophilia
  - number, distribution, other
- Important to consider associated histological features
- Is it pathologic or protective?

Is this idiopathic, allergic, clonal or systemic?

- Evidence of clonal expansion?
- Systemic eosinophilic disease?
- Allergic response to food or drug
Systemic causes of GI eosinophilia

- Inflammatory bowel diseases
- s/p organ transplant?
- Infections
- Allergies
- Churg Strauss syndrome
- Lymphoma
- Hypereosinophilic Syndrome
- Graft vs. Host disease
- Immunodeficiency

Objectives

- Know clinical implications of GI eosinophilia normal and abnormal
- Recognize systemic causes of GI eosinophilia
- Learn newer managements of GI eosinophilia diseases

Principles of treatment

- Exclude other causes and make sure there is a match of symptoms with histology
- Maximize impact of treatment on growth and development
- Balance risks of treatment with severity of illness
Principles of treatment

- Consider quality of life, patient and family preferences
- Engage other expertise when necessary
  - Behavioral health-chronic disease
  - Nutrition-insure growth and development
  - Allergy, ENT, feeding others-co-morbid diseases
- Revisit diagnosis if treatments not effective

Old / New Treatments

- Induction- Systemic prednisone
  - with rapid weaning
- Maintenance-Topical budesonide
  - Identify minimal dose to maintain a remission
- If the dose is too high / steroid side effects
  - Azathioprine / 6-mercaptopurine

Old / New Treatments

- Surgery-perforation, obstruction, dilation
- Others?
  - Mast cell stabilizers
  - Leukotriene receptor antagonists
  - Anti-histamines
- Diet?
  - Proximal disease may be more responsive
- Biologicals?
Follow up

- Side effects of treatments
  - labs, DEXA, eye exam
- Weight / height
- Impact of treatment on QOL
- Histology

Take-Home Messages

- Make sure the symptoms match with the histological finding
- "Abnormal" intestinal eosinophilia has a differential diagnosis
- Visit with your pathologist to determine an appropriate threshold for pathological eosinophilia

Future Directions

- Define eosinophilia "south of the diaphragm"
- Determine mechanisms that eosinophils help and harm the intestinal tract to foster the development of novel therapeutic strategies
- Identify and validate biomarkers to make diagnosis and track inflammation
- Determine natural history of EGIDs
## Module 1: A,B,C: Updates in Hepatitis

<table>
<thead>
<tr>
<th>Session Description</th>
<th>Quality of Content Delivered (1 = Poor and 10 = Excellent)</th>
<th>Met Objectives (1 = Poor and 10 = Excellent)</th>
<th>Invite Speaker Back?</th>
<th>Free from Commercial Bias?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune Hepatitis: The when, ifs and how - Vicky Ng</td>
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<tr>
<td>Updates on Hepatitis B – Jean Molleyton MD</td>
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<tr>
<td>Treating children with Hepatitis C – Regino Gonzalez Peralta</td>
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## Module 2: Updates in Pancreatic Diseases

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<tbody>
<tr>
<td>When and how to assess pancreatic function – Sohail Husain MD</td>
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<tr>
<td>Managing nutrition in CF – Sarah Jane Schwarzenberg MD</td>
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<tr>
<td>Beyond the basics in management of pancreatitis – Aliye Uc MD</td>
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## MODULE C: Updates in Endoscopy

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<tr>
<td>Endoscopy in high risk patients – Jenifer Lightdale MD</td>
<td>Yes</td>
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<td>Advances in hemostasis – Bradley Barth MD</td>
<td>Yes</td>
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<td>Surveillance endoscopies – Mitchell Shub MD</td>
<td>Yes</td>
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<td>Upper GI Strictures – Mark Gilger MD</td>
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## MODULE 4: Updates in Pediatric Nutrition

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<tbody>
<tr>
<td>Clinical Issues in parenteral nutrition – Praveen Goday MD</td>
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<tr>
<td>Enteral nutrition in Crohn disease – Robert Baldassano MD</td>
<td>Yes</td>
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<td>Severe obesity in your clinic – Sarah Barlow MD</td>
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## MODULE 5: Updates on Luminal Disease

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<tbody>
<tr>
<td>Decision making in ulcerative colitis – Wallace Crandall MD</td>
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<td>Post-surgical management of Crohn disease – Barbara Kirschner MD</td>
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<tr>
<td>Gastroparesis – Carlo Di Lorenzo MD</td>
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<tr>
<td>Eosinophilia beyond the esophagus – Glenn Furuta MD</td>
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<td>Yes</td>
<td>No</td>
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</tbody>
</table>
Learning Lunches – Please select the session you attended

1. **Controversies in management of EoE** – Glenn Furuta MD and Edaire Cheng MD
   Moderator: Ed Hoffenberg MD
2. **Crohn disease: Challenging cases** – Robert Baldassano MD and Barbara Kirschner MD
   Moderator: Jennifer Strople MD
3. **Pancreatitis: Acute and long-term management** – Sohail Husain MD and Aliye Uc MD
   Moderator: Henry Lin MD
4. **GI Bleeding** – Bradley Barth MD and George Zacur MD
   Moderator: Victor Fox MD
5. **Ulcerative Colitis – Challenging cases** – Wallace Crandall MD and Andrew Grossman MD
   Moderator: Diana Riera MD
6. **Autoimmune Hepatitis** – Vicky Ng MD and Mark Deneau MD
   Moderator: Jyoti Ramakrishna MD
7. **Hepatitis B and C** – Jean Molleston MD and Regino Gonzalez-Peralta MD
   Moderator: Stanley Fisher MD
8. **Functional upper GI disorders** – Carlo Di Lorenzo MD and Alfred Yeung MD
   Moderator: John Stutts MD
9. **Nutrition-Update on enteral nutrition** – Praveen Goday MD and Sarah Schwarzenberg MD
   Moderator: Christine Waasdorp-Hurtado MD

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<td>No</td>
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</tbody>
</table>
What topics would you like to have at the next meeting?

Clinical Practice/GI Endoscopy:

Esophageal, Gastric and Duodenal Disorders:

Gastrointestinal Oncology:

Growth and Development of the GI tract:

Hepatobiliary Disorders:

Hormones, Transmitters, Growth Factors and Their Receptors:

Immunology, Microbiology & Inflammatory Diseases:

Intestinal Disorders:

Motility & Nerve-Gut Interactions:

Nutrition & Obesity:

Pancreatic Disorders:

Other:

Please list any recommended speakers:

Please offer constructive comments, criticisms and suggestions for future postgraduate courses:
1. The postgraduate course improved my knowledge base in topic areas covered.
   1  2  3  4  5  Not Applicable

2. The postgraduate course topics were relevant to my clinical practice.
   1  2  3  4  5  Not Applicable

3. The information presented accurately reflects current evidence in pediatric gastroenterology, hepatology and nutrition.
   1  2  3  4  5  Not Applicable

4. The information presented will improve the quality of my patient care.
   1  2  3  4  5  Not Applicable

5. The “rapid-fire” question format was an effective technique to address questions from the audience.
   1  2  3  4  5  Not Applicable

For future NASPGHAN postgraduate courses, would you prefer a comprehensive treatment of a single issue in pediatric gastroenterology (single topic conference), or continue the modular format as presented this year?
   _____ Comprehensive       _____ Modular