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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 8.25 AMA PRA Category 1 Credit(s)™ Physicians should only claim credit commensurate with the extent of their participation in the activity.
7:55 AM - 8:00 AM  WELCOME AND INTRODUCTION

8:00 AM – 9:15 AM  MODULE 1: LIVER
  Moderators: Henry Lin MD and Jennifer Strople MD

PRIMARY SCLEROSING CHOLANGITIS
  Dennis Black MD, Le Bonheur Children’s Hospital
  Learning objectives:
  • Learn the etiology and progression of the condition
  • Understand how to appropriately screen
  • Review the treatment controversies, including ursodiol and vancomycin

THE JAUNDICED INFANT
  Saul J Karpen MD, PhD, Emory University School of Medicine
  Learning objectives:
  • Learn the differential diagnosis and most common etiologies
  • Understand the impact of genetic testing and other diagnostic modalities
  • Know the available treatments and what is being developed

ACUTE LIVER FAILURE
  Estella Alonso MD, Ann and Robert H Lurie Children’s Hospital of Chicago
  Learning objectives:
  • Learn the differential diagnosis and most common etiologies
  • Know the treatment options and algorithms
  • Understand the time frame of referral for transplantation

9:00 AM – 9:15 AM  RAPID FIRE Q&A

9:15 AM – 10:30 AM  MODULE 2: ENDOSCOPY
  Moderators: Jyoti Ramakrishna MD and Melanie Greifer MD

THE DREADED WAKE-UP CALL (PART A)
"WE’VE GOT A BLEEDER": EMERGENCY TECHNIQUES FOR VARICEAL BLEEDING—ESOPHAGEAL AND GASTRIC
  Mercedes Martinez MD, New York Presbyterian Hospital
  Learning objectives:
  • Know the appropriate timing and preparation for emergency interventions in this group of patients
  • Learn the newest emergency interventional techniques for esophageal and gastric variceal bleeding
  • Understand the risks and outcomes as well as alternatives for these techniques

THE DREADED WAKE-UP CALL (PART B)
"WE’VE GOT ANOTHER BLEEDER": EMERGENCY TECHNIQUES FOR NON–VARICEAL UPPER GI BLEEDING
  Lee Bass MD, Ann and Robert H. Lurie Children’s Hospital of Chicago
  Learning objectives:
  • Know the appropriate differential diagnosis and causes of non-variceal upper GI bleeding
  • Know the appropriate timing and preparation for emergency interventions in this group of patients
  • Learn the newest emergency interventional techniques for non-variceal bleeding (injection, clips, heat, hemospray, EUS-guided, endoluminal suturing)
ENDOSCOPIC INTERVENTIONS FOR BILIARY TRACT DISEASE  
Victor Fox MD, Boston Children’s Hospital  
Learning objectives:  
- Learn the indications and techniques for endoscopic therapy of choledocholithiasis  
- Recognize different types of biliary strictures and approaches to endoscopic treatment  
- Understand the role of endoscopy in the management of accidental and surgical hepatobiliary injury

10:15 AM—10:30 AM  RAPID–FIRE Q&A

10:30 AM – 10:50 AM  BREAK

10:50 AM – 12:25 PM  MODULE 3: GI POTPOURRI  
Moderators: Dinesh Pashankar MD and Melanie Greifer MD

EXTRAESOPHAGEAL MANIFESTATIONS OF GASTROESOPHAGEAL REFLUX (GER): FACT VS. FICTION  
Benjamin Gold MD, Children’s Center for Digestive Healthcare  
Learning objectives:  
- Learn the extent of extraesophageal manifestations of GER  
- Know the diagnostic testing modalities  
- Understand the treatment options

EoE: PPI, EGD AND WHAT TO EAT: ALPHABET DISTRESS  
Sandeep Gupta MD, Riley Hospital for Children  
Learning objectives:  
- Understand the role of PPIs in EoE  
- Update on steroid based EoE therapies  
- Review role of diet in EoE

“GOTTA KEEP ON MOVIN”—NEW TRICKS AND TREATMENTS FOR MOTILITY DISORDERS  
Carlo Di Lorenzo MD, Nationwide Children’s Hospital  
Learning objectives:  
- Discuss pathophysiologic mechanisms contributing to functional and motility disorders  
- Present evidence supporting the use of novel medical and nonmedical treatments for motility disorders  
- Integrate these modalities in the treatment of the child presenting with a possible motility disorder

WHAT’S NEW IN THE DIAGNOSIS AND MANAGEMENT OF CONSTIPATION  
Manu Sood MD, Medical College of Wisconsin  
Learning objectives:  
- Understand when additional testing is indicated in the constipated child, including blood work and anorectal manometry  
- Review the data regarding biofeedback for treatment of dyssynergic defecation  
- Learn about new treatments for constipation

12:10 PM – 12:25 PM  RAPID FIRE Q&A
12:25 PM – 1:50 PM  LEARNING LUNCHES (See ticket for room assignment)

1. **JAUNDICE IN THE NICU**  
   Saul Karpen MD and Ezequiel Neimark MD  
   Moderator: Vicky Ng MD

2. **LIVER FAILURE**  
   Estella Alonso MD and Henry Lin MD  
   Moderator: Pinut Bulut MD

3. **GI BLEEDING EMERGENCIES—CHALLENGING CASES**  
   Mercedes Martinez MD and Lee Bass MD  
   Moderator: Anu Chawla MD

4. **EXCITING CASES IN ESOPHAGEAL DISORDERS**  
   Sandeep Gupta MD and Benjamin Gold MD  
   Moderator: Dinesh Pashankar MD

5. **ERCP, MRCP : CHOOSING THE BEST MODALITY FOR BILIARY IMAGING**  
   Victor Fox MD and Amber Spofford MD  
   Moderator: Raza Patel MD

6. **FAD OR FICTION: CASE BASED DISCUSSION OF ALTERNATIVE DIETS**  
   Robert Baldassano MD and Dale Lee MD  
   Moderator: Diana Riera MD

7. **CHALLENGING CASES IN CONSTIPATION**  
   Manu Sood MD and Katja Kovacic MD  
   Moderator: John Stutts MD

8. **THE TODDLER WITH IBD**  
   Scott Snapper MD and Abdul Elkadri MD  
   Moderator: Judith Kelsen MD

9. **INTRAABDOMINAL ABCESS: THE VIEW FROM BOTH SIDES**  
   Robbyn Sockolow MD and Jason Frischer MD  
   Moderator: Maria Oliva-Hemker MD
MODULE 4: NUTRITION
Moderators: Kelly Thomsen MD and Melanie Greifer MD

DIET AND THE MICROBIOME
Robert Baldassano MD, Children’s Hospital of Philadelphia
Learning objectives:
• Understand how diet influences the human microbiome
• Learn how the microbiome influences the response to diet and dietary components
• Become familiar with the potential ways to modify the microbiome to reduce risk and prevent or modify disease

FODMAP: NAVIGATING THIS NOVEL DIET
Bruno Chumpitazi MD, MPH, Texas Children’s Hospital, Baylor College of Medicine
Learning objectives:
• Describe the common characteristics of FODMAP carbohydrates and mechanisms of action in triggering GI symptoms
• Review the evidence to support their use in patients
• Learn to identify and appropriately counsel patients in the use of the FODMAP diet

NUTRITION IN THE CHILD WITH NEUROLOGICAL DISABILITIES
Kathleen J Motil MD, PhD, Baylor College of Medicine
Learning objectives:
• Be able to identify and address issues of malnutrition
• Understand the management of refeeding syndrome and who is at risk
• Learn appropriate tube feeding schedules and possible transition to oral feedings

2:50 PM – 3:05 PM
RAPID FIRE Q&A

3:05 PM – 3:25 PM
BREAK

3:25 PM – 5:00 PM
MODULE 5: INTESTINAL INFLAMMATION
Moderators: Maria Oliva-Hemker MD and Jennifer Strople MD

EARLY ONSET INFLAMMATORY BOWEL DISEASE
Scott Snapper MD, Boston Children’s Hospital
Learning objectives:
• Review immunodeficiencies that may present with intestinal inflammation
• Understand the phenotype, genetics and prognosis for idiopathic IBD under 5 years
• Learn an appropriate immunological evaluation of a child with early IBD

“LUMINITIS”: WHEN INFLAMMATION IS NOT IBD (MICROSCOPIC COLITIDES)
Robbyn Sockolow MD, New York–Presbyterian Hospital, Weill Cornell Medical Center
Learning objectives:
• Understand the diagnostic criteria and differential diagnosis for microscopic colitis
• Review the treatment of lymphocytic and collagenous colitis
• Discuss the diagnostic criteria and treatment of eosinophilic colitis, including approach in transplant patients

SURGERY IN CROHN’S DISEASE
Jason Frischer MD, Cincinnati Children’s Hospital and Medical Center
Learning objectives:
• Learn pre-surgical optimization of medical treatment (IFX vs non IFX)
• Understand decision making of stricturoplasty vs resection
• Know the outcomes and morbidities post operatively

BEYOND ANTI-TNF THERAPY: NEW MEDICATIONS IN THE PIPELINE
Athos Bousvaros MD, Boston Children’s Hospital
Learning objectives:
• Review the mechanism of action of emerging biologic therapies
• Review the available data on the efficacy of these medications
• Understand the risks of these therapies
• Review currently available rescue therapies for anti-TNF nonresponders in Crohn’s disease (natalizumab, thalidomide)

4:45 PM – 5:00 PM RAPID FIRE Q&A
Primary Sclerosing Cholangitis

Dennis D. Black, M.D.
Children’s Foundation Research Institute
Le Bonheur Children's Hospital
Department Pediatrics, University of Tennessee Health Science Center, Memphis, TN, USA

Disclosure

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

Objectives

- Learn the etiology and progression of PSC.
- Understand how to appropriately screen.
- Review the treatment controversies, including ursodiol and vancomycin.
Autoimmune Liver Disease

- Autoimmune hepatitis (AIH)
- Primary Sclerosing Cholangitis (PSC)
  - Large duct
  - Small duct
- AIH/PSC overlap
- Autoimmune cholangitis
- IgG4-associated cholangitis/pancreatitis

Primary Sclerosing Cholangitis

- Chronic inflammation and obliterative fibrosis of the intra- and/or extrahepatic biliary tree, leading to bile stasis, biliary stricturing, hepatic fibrosis and ultimately to cirrhosis and end-stage liver disease

Alexopoulou et al, JPGN 55:308, 2012
Pathogenesis of PSC

- Unknown, but features of immune-mediated disease
- Theories
  - "Leaky" gut
  - Gut dysbiosis
  - Aberrant "homing" of gut T cells to cholangiocytes
  - Bile acid toxicity
  - Immune dysregulation
  - Genetic predisposition

Tabibian et al, BioMed Res Int Epub 2013
**PSC Genetics**

- GWAS studies have identified 16 significant risk loci
  - Adaptive and innate immunity
  - Function known but association with PSC unknown
- These 16 loci account for 7.3% of overall risk
- Many interact with environmental factors
- Needed
  - Mechanistic studies to tie loci to disease pathogenesis
  - Matching genetic data to more detailed phenotypic data

*Henriksen et al, Curr Opin Gastroenterol 30:310, 2014*

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**IBD and PSC Genetic Overlap**

*Karlsen and Boberg, J Hepatol 59:571, 2013*

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**Pediatric PSC Series**

- Debray et al, J Pediatr 124:49, 1994 (Bicetre) 56
- Wilschanski et al, Hepatology 22:1415, 1995 (Toronto) 32
- Gregorio et al, Hepatology 33:544, 2001 (King’s College) 27
- Feldstein et al, Hepatology 38:210, 2003 (Mayo) 52
- Batres et al, Pediatr Dev Pathol 8:568, 2005 (CHOP) 20
- Chavhan et al, Pediatr Radiol 38:868, 2008 (Toronto) 19
- Miloh et al, Clin Gastroenterol Hepatol 7:239, 2009 (Mt. Sinai) 47
- Rojas et al, Fetal Pediatr Path 33:202, 2014 (Miami) 34
- **Total patients** 287
Adult and Pediatric PSC: A Continuum?

![Diagram showing the continuum from children to adults with active autoimmune-mediated bile duct injury to "burned out" autoimmune activity, progressive damage from fibrosis, architectural distortion, nutrient deficiency/hypoxia, recurrent bacterial cholangitis.]

Features of PSC in Children
- Incidence in children less than that of adults (0.23/100,000 versus 1.1/100,000)
- Overall male predominance (59%) with female predominance in teen age group in some series
- Mean age at diagnosis 13 years
- IBD in 60%, 2/3 UC, 10% asymptomatic IBD
- Jaundice at presentation in 30%
- Non-specific symptoms, such as fatigue, weight loss, abdominal pain, and pruritus
- Asymptomatic with abnormal liver tests in 20%

Autoimmunity in Childhood PSC
- 30% have PSC/AIH overlap (5-10% in adults)
  - Autoantibodies (ANA, ASMA, pANCA, rarely LKM)
  - Increased serum IgG
  - Liver histology with AIH features plus bile duct injury
  - Abnormal biliary imaging
- 30% have no overlap by histology but have autoantibodies
- "Autoimmune cholangitis" described by Gregorio et al (2001)
  - Need for biliary imaging in childhood AIH
  - Response to immunosuppression
**PSC in Pediatric IBD**

- PediIBD registry, 1736 patients
- 54% male, 81% Caucasian
- Mean age at diagnosis 11.2 years
- 61% CD, 29% UC, 10% indeterminate colitis
- 24% developed extraintestinal manifestations
  - 33% musculoskeletal
  - 7.5% dermatologic
  - 7% ophthalmologic
  - 7.8% hepatobiliary (PSC 4.8%, N=24; AIH 1.2%, N=6; gallstones 1.8%, N=9)
  - 13.7% oral
  - 13.4% iatrogenic

Jose et al, Inflamm Bowel Dis 15:63, 2009

**PSC in IBD**

- PSC occurs in 55% (range 37% to 81%) of patients with IBD, most often ulcerative colitis
- Up to 5% of children with IBD may develop PSC
- PSC increases with increased colonic involvement
- PSC rare in Crohn’s disease with isolated small bowel involvement
- Earlier adult studies suggested rectal sparing, more severe right colon disease and backwash ileitis in UC associated with PSC
- Recent adult case control study suggests more extensive, but less active disease without significant rectal sparing in UC in PSC patients


**Colitis and PSC**

- 97 adult PSC patients
- 89 UC, 10 CD
- Stratified by initial disease at presentation
- Colonoscopies and biopsy analysis

PSC Diagnosis

- High index of suspicion, especially with IBD
  - Elevation of both ALT and GGT within 90 days of diagnosis of IBD associated with high likelihood of PSC and/or AIH
- Clinical features
  - Biochemical evaluation
  - Rule out other causes of liver disease
  - Biliary imaging
  - Liver biopsy

Diseases Causing Sclerosing Cholangitis in Children

- Cystic fibrosis (CFTR mutations)
- Primary and secondary immunodeficiency
- Langerhans cell histiocytosis
- Neonatal sclerosing cholangitis
- Biliary atresia
- Ichthyosis and sclerosing cholangitis (claudin-1 mutation with defective tight junctions)
- IgG4 cholangitis/pancreatitis
- Sickle cell (Hgb SS) disease

Diseases Causing Sclerosing Cholangitis in Children

- Congenital bile duct abnormalities (Caroli’s disease, congenital hepatic fibrosis, ductal plate anomalies)
- Ischemic bile duct strictures secondary to arterial injury (radiation, transplantation)
- Prior biliary surgery or bile duct trauma
- PFIC type 3 (ABCB4, phospholipid flippase, mutations)
- *C. parvum* infection and immunodeficiency
- Primary sclerosing cholangitis

Goyal and PBDCRG, JPGN 59:321, 2014
## Diagnostic Tests

- **Laboratory tests**
  - GGT more reliable than AP as marker for cholestasis in children due to growing bone
  - Transaminases, T/D bilirubin, albumin, IgG, INR, PT, PTT
  - IgG4 to rule out IgG4 cholangiopathy
  - Autoantibodies
- **Biliary imaging studies**
  - ERCP less commonly used in children
  - MRCP now commonly used
- **Liver biopsy**

## Treatment of Childhood PSC

- Comprehensive supportive treatment for progressive cholestatic liver disease and IBD
- Monitor/treat complications
  - Cirrhosis/portal hypertension
  - Bacterial cholangitis
  - Dominant strictures
  - Cholangiocarcinoma (rare)
  - Timing/support for transplantation
- The AIH component of PSC/AIH overlap often responds to immunosuppression (corticosteroids/azathioprine), but bile duct injury may progress

## Treatment of Childhood PSC

- Over 14 drugs tested to date
  - Antibiotic, probiotic, anti-fibrotic, immunosuppressive, anti-TNF, etc.
  - Primarily in adults
  - A few with biochemical and/or symptomatic improvement
  - All without proven positive impact on long-term outcome
- **Focus today**
  - Ursodeoxycholic acid (UDCA) widely used and controversial
  - Vancomycin shows promise
UDCA

- Hydrophilic bile acid ("bear bile")
- Oral dosing enriches bile acid pool up to 40-50%
- Potential therapeutic mechanisms
  - Increases hydrophilicity index of bile acid pool
  - Stimulation of bile secretion
  - Cytoprotection
  - Immunomodulatory and anti-inflammatory effects
- FDA approved for use in PBC and gallstone dissolution in adults
- Widely used in adults and children for other liver diseases

UDCA in PSC

- Widespread use and well-tolerated
- More prompt and striking biochemical improvement in children than in adults
- NIH-funded adult high-dose UDCA RCT suggested increased adverse outcomes resulting in AASLD recommendation against use in adults
- Follow-up analysis suggested the UDCA group with earlier stage disease on biopsy did worse
- Recent 3-month withdrawal trial in adults demonstrated worsening liver tests and pruritus

UDCA in Children

- Reluctance of pediatric hepatologists to discontinue UDCA based on adult data
- Should UDCA therapy be stopped in pediatric PSC patients to avoid possible long-term adverse outcomes at the risk of losing a possible beneficial effect on early disease progression?
- Multicenter prospective trial underway sponsored by FDA OOPD to study effects of UDCA withdrawal and reinstitution in children with PSC and PSC/AIH overlap (WUP PSC, ClinicalTrials.gov NCT01088607)
Vancomycin in Adults

- Recent randomized, double-blind trial of vancomycin or metronidazole
- 35 adult patients with PSC
- Two dose levels of vancomycin or metronidazole
- No control arm
- Both drugs demonstrated efficacy
  - PSC risk score reduced in both low-dose groups
  - Less pruritus in the high dose metronidazole group
- Both vancomycin dose groups reached primary endpoint of ALP reduction with less adverse effects


Vancomycin in Children

- Prospective, uncontrolled trial in 14 pediatric patients with PSC and IBD
  - Follow-up 4–56 months
  - All showed biochemical and clinical improvement
  - Worsening with discontinuation and improvement with retreatment
  - Less improvement in patients with cirrhosis
  - Subsequent study suggested immunomodulatory effect on PSC and IBD via regulation of levels of Treg cells
  - Case report of successful treatment of recurrent PSC after OLT with oral vancomycin

Davies et al, JPGN 47:61, 2008
Davies et al, Case Rep Transplant epub 2013

Course of PSC in Children

- Outcomes: Small duct PSC > large duct PSC > PSC/AIH overlap
- Dominant strictures and recurrent bacterial cholangitis are uncommon
- One-third may need transplantation by early adulthood
- Cholangiocarcinoma is rare, but reported
- In adults, ALP normalization after diagnosis associated with better prognosis

Stanich et al, Dig Liver Dis 43:309, 2011
Outcome of PSC in Children

Patient survival and graft survival are shown over time, with a graph indicating survival rates for different periods.

PSC 2.6% of total transplants
IBD associated with worse outcomes
Recurrence rate 9.8%

Major Issues in Pediatric PSC

- No prospective, randomized, controlled trials in children
- Caution in generalizing adult treatment data to children
- Use of “hard” endpoints (portal hypertension, death and transplant) not practical in children
- Need shorter term, reliable biomarkers of disease progression
- Large multicenter consortium needed for pediatric PSC trials
On the Horizon

- New drugs
  - C-23 UDCA analogue nor-UDCA
  - Nuclear receptor agonists
- Better biomarkers
  - miRNAs
  - Fibrosis
  - Inflammation
- “Useful” genetic data
  - Insight into disease mechanisms
  - Individualize therapy
- Impact of NAFLD on PSC?

Thank you!
The Jaundiced Infant

Saul J. Karpen, M.D., Ph.D.
Raymond F. Schinazi Distinguished Biomedical Chair
Professor of Pediatrics
Emory University School of Medicine
Children’s Healthcare of Atlanta
NASPGHAN PG Course, Atlanta
October 23, 2014  No disclosures

Topics

• Bilirubin Primer
• DDx of Jaundice with & Common Etiologies
• Impact of Genetic Testing & Other Diagnostic Modalities
• Available & Future Treatments

Bilirubin

RBCs + muscles + liver
• Become old or damaged
Hemoglobin → heme
Heme → unconjugated bilirubin
in the spleen

Unc conjugated bilirubin
Bilirubin Conjugation: UGT1A1

Unconjugated Bilirubin
Not Water Soluble

Mono-glucuronidated Bilirubin

Di-glucuronidated Bilirubin

Conjugated Bilirubin
Excellent Water Solubility

Hepatic Bilirubin Transport & Metabolism

Conjugation in the ER
UGT1A1

Disorders of Bilirubin Transport & Metabolism

Orphanet, GeneReviews (50 cases...)

Distinct Mechanisms for Bilirubin & Bile Acid Transport

Blood

- Na+
- Organic anions

Bile

- BSEP
- MRP2
- OATPs

Conjugated Bilirubin & other conjugates

Bile acids

Adapted from Karpen, in Liver Diseases in Children, 2012

Risk of Hyperbilirubinemia in Breast-Fed Infants

- 59 of 252 Breast-fed infants (23%) → Hyperbilirubinemia (defined as > 15 mg/dl on DOL #3)
- Genotyping:
  - UGT1A1: 32/59 had at least 1 UGT1A1 variant (54%); as did 41% of controls!
  - SLC25A1: Not significant
  - G6PD (X-linked) 3

Complex contributions of genes & breast-feeding → Jaundice

"...GT1R mutation is a risk factor for neonatal hyperbilirubinemia only in infants with inadequate breastfeeding ..."

THE GENETIC BASIS OF THE REDUCED EXPRESSION OF UGT1A1 IN GILBERT'S SYNDROME

Peter J. Bossel, Ph.D., Sibylle Roche, M.D., Guine Bréda, and M. G. Gantza, Ph.D., and the Gilbert's Syndrome Collaborative Group.

Topics

- Bilirubin Primer
- DDx of Jaundice with & Common Etiologies
- Impact of Genetic Testing & Other Diagnostic Modalities
- Available & Future Treatments

AAP guidelines 2004

Risk Factors for Hyperbilirubinemia

- Maternal factors
  - Race or ethnic group
  - Prematurity
  - Genetic factors
    - Familial hemolytic anemia
    - Thalassemia
    - Cerebral palsy
    - Down's syndrome
  - Comorbidities during pregnancy
    - Diabetes mellitus
    - Renal insufficiency
- Perinatal factors
  - Birth trauma
  - Birth asphyxia
  - Hemolytic disease
  - Infection
  - Jaundice
  - Necrotic enterocolitis
  - Perinatal

Dennery. Acad Med 2001
AAP Practice 2004
Gourley JPGN 2005
• 122 infants @ ~ 2 days of life

Poor Inter-observer correlation

Poor bilirubin guess-timates

"The dermal zone method of estimating serum bilirubin concentration described in this report is not meant to replace laboratory determinations of serum bilirubin."

Studies of jaundice do not accurately reflect current US birth diversity
• **Q:** *What is in breast milk that leads to jaundice?*

**Brest milk jaundice: How long is too long?**

*Archives of Disease in Childhood, 1978, 53, 506–516*

*Winfield & Macfaul*

**Short reports**

Clinical study of prolonged jaundice in breast- and bottle-fed babies

• 893 infants (Aldershot, England)
• 55% BF
• 12 were jaundiced > 3 weeks (~ 2 %)
Eluates from TLC plates

Irwin M. Arias, MD

Irwin M. Arias, MD

Production of Unconjugated Hyperbilirubinemia
in Full-term Newborn Infants
following Administration of pregnane-3α,20β-diol

Ariz & Gartner Nature 1964

TABLE 5. Laboratory Evaluation of the Jaundiced Infant of 31 or More Weeks Gestation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic data</td>
<td>Blood smear, red cell indices, platelet count</td>
</tr>
<tr>
<td>Liver function</td>
<td>Serum bilirubin, alkaline phosphatase, transaminases, PT, APTT, fibrinogen</td>
</tr>
<tr>
<td>TPN concentrations</td>
<td>Blood glucose, ammonia, electrolytes, BUN, creatinine</td>
</tr>
<tr>
<td>Circulating volume</td>
<td>Blood pressure, central venous pressure, pulmonary artery wedge pressure</td>
</tr>
</tbody>
</table>

AMERICAN ACADEMY OF PEDIATRICS

Management of Hyperbilirubinemia in the Newborn Infant
Pediatrics 2004
Burden of pediatric liver disease

- Incidence of liver disease in newborns → 1:2,500
  - Mainly cholestatic & metabolic liver diseases
- No effective medical treatments for cholestasis
- ~ 10% of adults have liver disease → starts during childhood
  - Genetic predisposition & contribution from obesity
- Biliary atresia 1:10,000 newborns
  - Early recognition is key
  - ~ 60% will require liver transplantation; average age ~ 2½ y
- Donor shortage

Causes of Neonatal Cholestasis: 82 Infants in Essen Germany

- Extrahepatic bile ducts & Gall Bladder
- Intrahepatic bile ducts
- Hepatocytes

Think anatomic

Arya & Balistreri, J Gastroenterology, 2002

Neonatal Cholestasis

**Extrahepatic Bile Duct**

- Biliary atresia
- Choledochal cyst
- Bile duct hypoplasia
- Bile duct duplication
- Agenesia of the extrahepatic ducts
- Choledocholithiasis
- Agammaglobulinemia
- TPN-associated cholestasis

**Intrahepatic Bile Duct**

- Bile duct paucity:
  - Alagille Syndrome (JAG1 & Notch2)
  - Non-syndromic
- Ductal Plate Malformation:
  - Congenital Hepatic Fibrosis
  - Caroli disease
  - ARPKD & ADPKD
  - von Meyenburg complexes
- Cystic Fibrosis
- Neonatal sclerosing cholangitis
- Indeterminate ("Neonatal Hepatitis")

**Hepatocytes**

- Viral infection:
  - CMV, HSV, Parvovirus B19, HAV, HBV, Adenovirus, Enterovirus
- Bacterial/Parasitic infection:
  - Gram negative sepsis, Syphillis, TB, Listeria
- Metabolic/Storage diseases:
  - aa metabolism—tyrosinemia
  - CHO metabolism—galactosemia
  - Lipid metabolism—Niemann-Pick
  - Bile acid synthesis
  - Peroxisomal—Zellweger’s
  - Mitochondrial enzymopathies
  - Urea cycle—OTC deficiency
  - 1-antitrypsin deficiency
- Drug toxicity

**More Genes Coming in the Near Future**

- Transporter & other genes:
  - PFIC1 (ATPB1) TJP2
  - PFIC2 (ABCB11) BAAT
  - PFIC3 (ABCB4)

**Bile Formation & Adaptation 2014**

- **Hepatocyte**
- **Bile duct**

- **Transporter gene variants**
- **Altered susceptibilities to cholestasis**

**Biliary Atresia**

- Fibro-obliterrative cholangiopathy with obstruction of the common bile duct as a central component.
- No clear genetics—monozygotic twins are usually discordant
- Laterality defects in 5-10%:
  - Asplenia/polysplenia
  - Cardiac defects
  - Situs abnormalities
### Best means to diagnose BA

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sens.</th>
<th>Spec.</th>
<th>PPV</th>
<th>NPV</th>
<th>Diagnostic Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Biopsy</td>
<td>34/34</td>
<td>100%</td>
<td>94%</td>
<td>94%</td>
<td>97%</td>
</tr>
<tr>
<td>Hepatobiliary Scintigraphy</td>
<td>30/34</td>
<td>88%</td>
<td>45%</td>
<td>30/49</td>
<td>61%</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>17/34</td>
<td>50%</td>
<td>82%</td>
<td>17/23</td>
<td>74%</td>
</tr>
<tr>
<td>MRCP</td>
<td>29/34</td>
<td>89%</td>
<td>57%</td>
<td>29/44</td>
<td>66%</td>
</tr>
</tbody>
</table>

THE LIVER BIOPSY

- Readily available
- One day turn-around
- Can identify many other etiologies
- 76% Specific
- 100% Sensitive

**Entry criteria:** Direct hyperbilirubinemia: ALL subjects underwent Liver bx

**Design set:**

<table>
<thead>
<tr>
<th>Category Parameter</th>
<th>BA (30)</th>
<th>Non-BA (30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artich stools</td>
<td>28 (93%)</td>
<td>13 (43%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td>411 +/- 204</td>
<td>204 +/- 270</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triangular Cord</td>
<td>59 (19)</td>
<td>11 (12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GB Length (mm)</td>
<td>27 +/- 19</td>
<td>14 +/- 11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HA Diameter (mm)</td>
<td>2.5 +/- 2</td>
<td>1.9 +/- 2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Liver bx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duct Proliferation</td>
<td>29 (96%)</td>
<td>11 (36%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multi-nucleated cells</td>
<td>1 (3%)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Not significant:

- Liver or Spleen Enlargement
- Labs: ALT & AST, AP, WBC, Hgb, Total & Direct Bili
- MRCP: "Abnormal Car"
- Biopsy: Grade of Fibrosis

---

**Reference**

Validation set: 75 Infants: 32 with BA: Cut-OFF 23.9

Only 1 patient underwent IOC & did not have BA

Design and validation of a diagnostic score for biliary atresia:
Mohamed Abdel-Fattah, El-Kordy, Mousa Mohamed, Saeed, Ahmed Mohamed Saeed, Tahany Abdel-Fattah, Sakhra, Diana Hafez, El-Abd, Hata, Abd-Sattar Kessova, Dias, Chadour, El-Kordy, Afd, Abd-Sattar Kessova

Take home points

High utility of:
- Stool pigment visualization
- U/S, esp. Flow parameters
- Liver biopsy

No evaluation of:
HIDA, MRCP, ERCP, DNA

Tool for BA: 100% sensitivity, 97% specificity, Diagnostic accuracy 98%

Age at Kasai & Survival with Native Liver

Maksoud J Ped Surg 1998

% 5 y SNL

Age at Kasai (Days)
Q: When does BA start?

Direct Bili in ALL BA subjects within 24-48 h of life → early cholestasis is a cardinal feature of BA

Opportunity for Newborn Screening?

Mechanism of low GGT cholestasis

Retention of bile acids within hepatocytes

Absence of bile acids within bile ducts
Mechanism of high GGT cholestasis

Retention of bile acids within hepatocytes

Presence of bile acids within bile ducts

PFIC2 (ABCB11): A Deficiency of Bile Acid Transport

Solute composition of human bile

PFIC3 (ABCB4): A Deficiency of Phospholipid Transport

Solute composition of human bile

### Key Clinical Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>PFIC1</th>
<th>PFIC2</th>
<th>PFIC3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feature ATP8B1</td>
<td>ABCB11</td>
<td>ABCB4</td>
<td></td>
</tr>
<tr>
<td>Direct HyperBili</td>
<td>Birth-6m</td>
<td>Birth-6m</td>
<td>Birth – 20+ years</td>
</tr>
<tr>
<td>GGT LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>HIGH</td>
</tr>
<tr>
<td>Earliest time to cirrhosis</td>
<td>2+ y</td>
<td>6 m</td>
<td>5 m</td>
</tr>
<tr>
<td>Extrahepatic Sx</td>
<td>Diarrhea, Hearing Loss, Pancreatitis, Pneumonia</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Pruritus</td>
<td>YES</td>
<td>YES</td>
<td>YES/NO</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>NO</td>
<td>YES</td>
<td>YES (Intrahepatic)</td>
</tr>
<tr>
<td>Cancer</td>
<td>?</td>
<td>HCC (13 m)</td>
<td>HCC &amp; CCA (teens +)</td>
</tr>
</tbody>
</table>

### Key Clinical Confounders & Rule-Outs

**PFIC1**
- Bile Acid Synthesis & Conjugation Defects
- Diarrheal diseases
- Neonatal Sclerosing Cholangitis

**PFIC2**
- Bile Acid Synthesis & Conjugation Defects
- BA

**PFIC3**
- BA

**Low GGT**
- PFIC2
- PFIC1

**High GGT**
- PFIC3
- BA

**Sepsis** → ABCB11 & ABCC2 → Jaundice & Cholestasis

- ABCB11
- ABCC2
- BA
- PL
- FXR
- RXRα
- CDCA

Relative gene expression

BA

Sepsis → ↓ ABCB11 & ABCC2 → Jaundice & Cholestasis
Topics

- Bilirubin Primer
- DDx of Jaundice with & Common Etiologies
- Impact of Genetic Testing & Other Diagnostic Modalities
- Available & Future Treatments

2014 & Beyond: Genotype or Phenotype First?


Neonatal Cholestasis: Select Genetic Diagnoses: 2014

- Extra- & Intrahepatic Bile Ducts
- Hepatocytes

- Caroli disease (APK2D)
- Alagille Syndrome (JAG1 & Notch2)
- Cystic Fibrosis (CFTR)
- Niemann-Pick C (NPC1, 2)
- Tyrosinemia (FAH)
- Galactosemia (GALT, GALE)
- HIF1 (ALDOB)
- Bile acid synthesis (HSD3B7, CYP7B1)
- Peroxisomal (PEX's)
- α1-AT (SERPINA1)
The Emory Cholestasis 56 gene Panel

Many more to come, including whole exome sequencing

<table>
<thead>
<tr>
<th>Test Code</th>
<th>Test Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM30</td>
<td>Neonatal and Adult Cholestasis Gene Sequencing Panel</td>
</tr>
</tbody>
</table>

| GPP Code(s) | | |
|-------------|-------------|

BA pts CNV Chr 2q37.3
→ 1 gene → Glypican1

Two new studies support this rationale.


Whole exome sequencing

~ $4,000 – $7,000

~ 25% yield of diagnoses

Evidence From Human and Zebrafish That GPC1 Is a Biliary Atresia Susceptibility Gene

Human Zebrafish
Topics

- Bilirubin Primer
- DDx of Jaundice with & Common Etiologies
- Impact of Genetic Testing & Other Diagnostic Modalities
- Available & Future Treatments

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

Emmanuel Consens,*,†, Brigitte Geron,*, Denis Caen*, Anne Davids-Spreafico*, Monique Fabre*, Catherine Lecannet**

10 yo F homozygous ABCB11 T1210P
Failed UDCA, RIF, Diversion

Pre-Rx 3 m of 4-PB

<table>
<thead>
<tr>
<th>Pre</th>
<th>1 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>1-3</td>
</tr>
<tr>
<td>ALT</td>
<td>125</td>
</tr>
<tr>
<td>BA</td>
<td>493</td>
</tr>
<tr>
<td>Bili</td>
<td>200</td>
</tr>
</tbody>
</table>

**Bile acid opportunities for therapies**

Halihalaz A, Aydogan Y 2013
### Bile acid based therapeutic trials (~ 200 in clinicaltrials.gov)

<table>
<thead>
<tr>
<th>Glycocholic Acid: BA Synthesis Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>FXR agonists: Obeticholic Acid</td>
</tr>
<tr>
<td>NorUDCA:</td>
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<tr>
<td>TGR5 agonists: Satiety</td>
</tr>
<tr>
<td>ASBT inhibitors: Pruritus in cholestasis (ALGS, PFIC’s)</td>
</tr>
<tr>
<td>BA Sequestrant: Colesevelam</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NASH</th>
<th>PBC</th>
<th>BA diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td>PSC</td>
<td></td>
<td>Fibrosis</td>
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<td>PSC</td>
<td></td>
<td>Fibrosis</td>
</tr>
</tbody>
</table>

### Take home points: Jaundiced infants

- **New molecular understandings of conjugated & unconjugated hyperbilirubinemia.**
- **Transporter genes drive bile formation, & their dysfunction → cholestasis**
  - ATP8B1 PL Flippase PFIC1 BRIC1
  - ABCB11 BA Exporter PFIC2 BRIC2
  - ABCB4 PL Floppase PFIC3 LPAC, ICP...
- **Biliary atresia: Open for discovery & intervention**
  - **BA starts early—obtain fractionated bili’s early.**
- **New easier, comprehensive, cost-effective ways to make diagnoses involving genetic panels/exomes.**
- **New Chaperones & Bile acid based therapeutics**
Acute Liver Failure

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

Disclosures

Nothing to Disclose

Objectives

• Learn the differential diagnosis and most common etiologies
  – Review emerging approaches to improve establish etiologies of PALF
  – Detail evidence that acetaminophen toxicity contributes to PALF
• Know the treatment options and algorithms
  – Outline approaches to monitoring and treating neurological injury including cerebral edema in PALF patients
• Understand the time frame of referral for transplantation
Etiology of PALF (N = 945)

Making a Diagnosis

- Few patients receive a full diagnostic work-up
  - Prioritization of blood samples in small children
  - Death or transplantation prior to completion of work-up
  - Indeterminate patients are younger and more likely to receive liver transplantation
- Investigation of metabolic and autoimmune disorders is frequently incomplete
  - Somewhat more complete in younger children
  - Very few have lactate and pyruvate levels

Role of Liver Biopsy

- May confirm suspected treatable etiology
- Histology may not be uniform
  - >50-75% necrosis proposed as poor prognosis
- Unreliable to determine need for LT
  - Newer approaches using staining for regeneration markers may change this
- Limitations
  - Bleeding risk
  - Sampling error
  - Transjugular sampling may reduce complications
**Immunophenotyping**

- Analyzed markers of inflammation in 77 PALF patients
- SIL2Rα
  - Significantly higher in patients that died (p<0.02) or had LT (p<0.01)
  - Values > 5000 IU/mL
  - All 30 patients with normal levels survived
- Immunedysregulation
  - Should we treat with steroids

Bucuvalas, J PGGN 2013;56: 311–315

---

**APAP induced Liver Injury**

---

**Chronic APAP Exposure in PALF**

**Chronic exposure (CE; n=83), Single exposure, (SE; n=85), No exposure (NE; n=498), Not meeting either criteria (n=229)**

- **CE vs SE**
  - CE patient
    - Younger (3.5 vs 15.2 yrs., p<0.0001)
    - More males (82% vs 46%, p<0.0001)
    - More Hispanic (25% vs 7%, p=0.001)
  - Spontaneous survival lower for CE vs SE
    - 68% vs 92%, p=0.0004

- **CE vs NE**
  - Bilirubin lower (3.2 vs 13.1 mg/dL, p<0.001)
  - ALT higher (2384 vs 855, p<0.001), but lower than SE (5140, p<0.0001)
  - Spontaneous survival higher for CE vs NE
    - 68% vs 49%, p=0.008

Leonis et al, Pediatrics 2013;131:e740
APAP Adducts in PALF

- Serum from 104 patients
  - Indeterminate (n=64)
  - Acetaminophen toxicity (n=10)
  - Other diagnoses (n=30)
- 12.5% indeterminate cases adducts positive
  - Therapeutic APAP exposure in 5
  - Detectable APAP level in 3 (range 3.1-18.8 mg/L)
- 393 patients (40% of PALF)
- Adducts positive
  - 88% know APAP overdose
  - 11% indeterminate
  - 6% other diagnoses
- Outcomes
  - Indeterminate group, adduct positive patients
  75% (15/20) spontaneous survival versus 75/169
  44% (75/169) in adduct negative patients (p=0.03)

Pediatrics 2006;118(3):e676-81
Unpublished PALF Data

How Many Survive?

- Overall Prognosis
  - 33% - 53% survival with native liver
  - Including LT
    - 61% survival including LT
    - 70%-80% after LT
- Determinants of Liver Transplantation
  - Individual patient characteristics
    - Experience and bias of provider
  - Regional organ availability

Lee et al. JPGN 2005;40:575-81
Baliga et al. Liver Transpl 2004;10:1364-71
Causes of Death

- **MSOF in over 50% of non-survivors**
  - Some with presumed global metabolic disease
  - Cardiovascular collapse
  - ARDS
- **Bacterial infection**
  - Common, but primary cause of death in few
- **Bleeding complications**
  - Direct cause of death in less than 10%
- **Cerebral edema**
  - May cause death even after LT

Alterations in Coagulation

- **Defects in coagulation and fibrinolysis**
  - "rebalanced hemostasis"
- **Impaired platelet function**
  - Decreased number of platelets
  - Increased adhesion
  - Decreased aggregation
- **Microparticles**
  - Platelet, monocyte and other cell fragments
  - Procoagulant activity
  - Associated with SIRS and adverse outcomes
- **Low grade DIC**
  - 50% of cases
  - Microcirculatory thrombi in areas of necrosis

Management of Coagulopathy

- **Assessment**
  - Prothrombin Time
  - Factor levels
  - Thrombelastograph (TEG) better predictor of bleeding risk

- **Prevention of GI Bleeding**
  - Nasogastric drainage, H2 blockers

- **What is the Role of Therapy?**
  - FFP infusions
  - aFVII
  - Plasmapheresis or exchange transfusion

Hyperdynamic Cardiovascular Collapse

- **Hypotension**
  - Warm shock, low systemic vascular resistance
  - Increased cardiac output
  - First line pressor-Norepinephrine

- **Role of Adrenal Insufficiency**
  - Approximately 35% of adults with ALF
    - Low cortisol levels at baseline and following ACTH stimulation
    - Correlates with severity of illness
  - Treatment with hydrocortisone 50-100 mg/m²


Serum Inflammatory Markers Predict Outcomes

- **49 patients with at least 3 samples within first 7 days**
  - Assessed 26 inflammatory mediators
    - Chemokines, cytokines and reactive nitrogen species
  - Outcomes at 21 days

- **Dynamic Bayesian Network Analysis**
  - Differentiated survivors
  - Raw mediator levels not predictive

  Azhar, N et al PLOSone 2013;8:e78202
**Pediatric NAC Trial**

- RCT with minimization scheme to maintain balance
  - Age: less than 2 years vs. at least 2 years
  - Coma score: 0-I vs. II-IV
- Non-APAP PALF patients received a continuous IV infusion of NAC (150 mg/kg/d) or D5W for up to 7 days
- Estimate that a sample size of 184 patients (92 in each arm) to provide 80% power using a two-sided log-rank test


---

**Pediatric NAC Trial**

**Primary Outcome One Year Survival**

- Placebo: 82%
- NAC: 73%
- *P*=0.20

---
Percent survival with native liver:
Age at Randomization

Hepatic Encephalopathy
Outcomes by Peak Coma Grade
(Non-APAP Group)

Blood Brain Barrier
Cerebral Edema

- Alteration of brain organic osmolytes
  - Ammonia metabolized to glutamine in astrocytes
- Impairment in cerebrovascular autoregulation resulting in cerebral hyperemia
  - ↑ cerebral blood volume
  - ↑ pressure on brain capillaries and NH₄ delivery
- Abnormalities in brain glucose metabolism
  - Decreased glucose and O₂ consumption and increased lactate concentrations
- Inflammation
  - Pro-inflammatory cytokine levels parallel ICP

Blei AT, Journal of Hepatology 2007;46:553-582

Ammonia and Prevention of Cerebral Edema

- Ammonia
  - Brain-blood NH₄ ratio increased 4 to 8 fold in ALF
  - Arterial levels > 200 µg/dL associated with higher risk of cerebral herniation
- Decrease NH₄⁺ Production
  - Non-absorbable antibiotics and lactulose not very effective
  - Protein restriction not advised
- Increase NH₄⁺ Removal
  - Phenylacetate
    - Forms Phenylacetylglutamine which is excreted in urine
    - Reduces glutamine also

Bernal et al, Hepatology 2007;46:1844-52

Neurocrit. Care 2006;04:179–189
Pilot Study for Early Detection of HE in PALF

- Neurologic complications of PALF major determinant of outcome
  - HE difficult to assess in infants and toddlers
  - Early recognition of HE can guide therapy and transplant decisions
- Retrospective review of Standardized Care Pathway
  - 18 patients received cEEG within 1-2 days of admit
  - Mean age 6.8±1.5 yrs.
  - 74% indeterminate etiology
  - Median score HE 2 on admission
  - 53% spontaneous survival, 26% LT, 21% died
- 72% had EEG abnormalities
  - Ictal abnormalities 18%
  - Clinical seizures in 2 patients

Hussain et al, JPGN 2014;58:449-56

EEG Compliments Clinical HE Scores

<table>
<thead>
<tr>
<th>EEG Findings</th>
<th>Spontaneous Survival</th>
<th>LT or Death</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients (n=18)</td>
<td></td>
<td></td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Normal to mildly</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately or severely</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with</td>
<td></td>
<td></td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Admission HE Score ≤2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal or mildly</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>abnormal EEG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately or severely</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td></td>
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</tbody>
</table>

EEG Compliments Clinical HE Scores

<table>
<thead>
<tr>
<th>EEG Findings</th>
<th>Spontaneous Survival</th>
<th>LT or Death</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients (n=18)</td>
<td></td>
<td></td>
<td>p&lt;0.05</td>
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<tr>
<td>Normal to mildly</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately or severely</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>abnormal</td>
<td></td>
<td></td>
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<tr>
<td>Patients with</td>
<td></td>
<td></td>
<td>p&lt;0.05</td>
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<tr>
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<td>(n=16)</td>
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<td></td>
</tr>
<tr>
<td>abnormal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hypertonic Saline

- May restore osmotic gradient across astrocyte membrane
  - May also improve microvascular blood flow by reducing endothelial swelling
- May be more effective than Mannitol
- Maintain serum sodium 145-155mmol/L
- Reduced ICP, but no survival advantage observed in preliminary trial

Hypothermia

• Whole body cooling to 32°-35°C
• Supporting evidence in animal models
  – Reduces CBF
  – Reduces concentration of NH₄ in CSF
  – May improve brain oxidative metabolism of glucose
  – Decreases arterial IL-1β, TNF-α and IL-6
• Successful uncontrolled trials
• May increase infection risk and decrease regeneration


Putative Mechanisms of Hypothermia
Adapted from Crit Care Med 2009;37:S258-64

<table>
<thead>
<tr>
<th>Target</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>Arterial and brain concentrations</td>
</tr>
<tr>
<td></td>
<td>Production of intestinal bacteria</td>
</tr>
<tr>
<td>Brain Osmolarity</td>
<td>Prevents brain lactate and alanine accumulation</td>
</tr>
<tr>
<td>Brain extracellular space</td>
<td>Accumulation of glutamate and glutamate</td>
</tr>
<tr>
<td></td>
<td>induced astrocyte swelling</td>
</tr>
<tr>
<td>Cerebral Hemodynamics</td>
<td>Improved cerebral blood flow, cerebral toxin</td>
</tr>
<tr>
<td>Brain Glucose Metabolism</td>
<td>Cerebral metabolic rate of glucose and oxygen</td>
</tr>
<tr>
<td></td>
<td>De novo synthesis of lactate and alanine</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Production of cytokines</td>
</tr>
<tr>
<td></td>
<td>Shifts from pro to anti-inflammatory milieu</td>
</tr>
</tbody>
</table>

Management of Intracranial Hypertension in ALF

Timing of Transplantation

- **Contraindications**
  - High ventilatory requirements
  - High dose pressors
  - Irreversible neurological injury

- **Listing**
  - 1A criteria
    - Onset of HE within 8 weeks
    - Level of HE not specified
  - Ventilator dependent
  - Dialysis/CVVH
  - INR > 2.0
  - PELD not validated for ALF

Summary

- Difficult to predict spontaneous survival
- New diagnostic tools to understand the role of untethered inflammation and screen for early brain injury
- Treatment options support and preserve brain function
- Bleeding is a rare cause of mortality and less common than previously thought
Portal hypertensive variceal bleeding.

When **RED** is not attractive

Mercedes Martinez, MD
Center for Liver Disease and Organ Transplantation Columbia Presbyterian
Columbia University, NY

NASPGHAN Post graduate course 2014

Conflict of interest

- The author has no conflict of interest with any organization regarding the material discussed here.

Objectives

- Know the appropriate timing and preparation for emergency interventions in this group of patients
- Learn the newest emergency interventional techniques for esophageal and gastric variceal bleeding
- Understand the risks and outcomes, as well as alternatives for these techniques
The meaning of RED

Anatomy of the portal system

Definition of Portal Hypertension

- Pathological increase in the pressure of the portal venous system
- Clinical findings:
  - Splenomegaly
  - Ascites
  - Collateral veins
  - Stigmata of chronic liver disease, if cirrhotic
  - Thrombocytopenia, leucopenia and anemia
  - Esophageal varices
- Transjugular pressure measurement
  - Hepatic Gradient Pressure above 6 mm of Hg
**Etiology**

- **Cirrhotic**
  - Pre-hepatic
    - Portal Vein Thrombosis
  - Splenic Vein Thrombosis
  - Post-hepatic
    - IVC obstruction
    - Constrictive pericarditis

- **Non-cirrhotic**
  - Pre-hepatic
  - Portal Vein Thrombosis

- **Intra-hepatic**
  - Pre-sinusoidal
    - Schistosomiasis
  - Congenital hepatic fibrosis
  - Sinusoidal
    - Nodular regenerative hyperplasia
    - Vitamin A toxicity
  - Post-sinusoidal
    - Veno-occlusive disease
    - Budd-Chiari Syndrome

**Complications of portal hypertension**

- Ascites, not responsive to treatment
- Porto-caval encephalopathy
- Gastrointestinal bleeding
  - Rupture of varices
    - Progression of the variceal size is 5-30% per year
    - 30% of patients will bleed within 2 yrs
    - 70% re-bleed within 1 year
    - 30% of GI bleeding in cirrhotic patients occurs from other causes

**Clinical presentation of variceal bleeding**

- Hematemesis
- Abdominal pain
- Nausea
- Melena
- Signs and symptoms of blood loss
- Anemia
Esophageal Varices

- Dilated veins are arranged longitudinally in the esophagus
- Esophageal varices are classified as F1, F2 and F3, depending on their size
- Dilated venules are arranged longitudinally (red wale markings)
- Small patches of redness (cherry red spots)
- Localized blood collections
- Diffuse redness

Iwakiri, Y. Liver International, 2011

Esophageal Varices

Gastric Varices

- 27% of variceal bleeding in adults; < 5% in pediatrics
- More severe bleeding: varix fed from high-flow vessels
- Less likely to bleed because blood vessels in the stomach are located deeper in the submucosa
- Higher mortality
- Endoscopic Variceal Sclerotherapy is less successful
- TIPS is more effective in the prevention of re-bleeding

Sarin’s Classification of gastric varices

- Extension of esophageal varices
  - Gastroesophageal varix (GOV) 1: into the cardia or lesser curvature
  - GOV 2: to the fundus

- Isolated gastric varices
  - IGV1: isolated gastric fundal varices
  - IGV2: varices in the body, antrum or pylorus
  - Need further investigation for splenic vein thrombosis

Medical Management

- Admit to PICU
- Stabilize the patient
  - Do not over-transfuse (goal hemoglobin ~8g/dl)
  - Correct coagulopathy
  - Role of platelets?
- Octreotide or somatostatin
  - Bolus 2 mcg/kg or 100 mcg
  - Drip 1-2 mcg/kg/h or 50-100 mcg/h
- Antibiotics

References:
Management of the patient with bleeding varices

- Treatment of bleeding varices
  - Directly exclude the varices from the portosystemic system
    - Endoscopic
    - Endovascular
  - Indirectly decrease the pressure in the varices by decompressing the portal system
    - Endovascular
    - Surgical

Most patients do not require emergency overnight endoscopy
Most will tolerate transfer to an experienced center

Methods of endoscopic treatment

- Sclerotherapy
  - Remains the first choice in active bleeding
  - Ethanolamine for esophageal varices
  - Cyanoacrylate for gastric varices
- Intravariceal injection induces thrombosis and subsequent occlusion of the lumen of the varix
- Paravariceal injection occludes the varix by tamponade and induction of submucosal fibrosis

Methods of endoscopic treatment

- Endoscopic rubber band ligation (EVL)
  - Best approach for primary and secondary prophylaxis
  - Useful in active bleeding, if you can see the varix that is bleeding
  - Start distally, and move in a spiral upward motion
  - Avoid pushing the scope beyond the placed bands

- Cyanoacrylate therapy has been considered superior for gastric varices

Technique for cyanoacrylate injection

- Flush needle with D5, avoid ionizing solutions
- Remove needle fast from point of injection, to prevent embedment
- Protect the needle before withdrawal in the scope
- Mix with the lipid soluble contrast agent

References:
ASGE. Gastrointestinal Endoscopy 2004
Complications…

- Ulcerations at the site of injection or band placement
- Abdominal, pulmonary and intracerebral embolization
- Bacteremia
- Allergic or anaphylactic reactions
- Embedment of the needle in the varix
- Obstruction of the needle
- Damage to the equipment

ASGE. Gastrointestinal Endoscopy 2004

Alternatives to Endoscopy

- When to call the Interventional Radiologist
  - Patient continues to bleed despite endoscopic therapy
  - After significant bleeding and ongoing concern for re-bleeding
- Discuss
  - Patient’s global health
  - Short and long term goals
  - Absolute and relative contraindications

Transjugular Intrahepatic Portosystemic Shunts (TIPS)

- Limited by
  - Size of the patient
  - Expertise of the Interventional Radiology department
  - Degree of liver disease
- Contraindicated if
  - Tumor
  - Elevated bilirubin
  - Significant liver dysfunction (encephalopathy)

Transjugular Intrahepatic Portosystemic Shunts (TIPS)

EVS versus TIPS shunt for gastric variceal bleeding in patients with cirrhosis: A meta-analysis
Bai M., et al W. J. Gastrointest Pharmacol Ther 2014

Prevention of bleeding

Risk of encephalopathy
EVS versus TIPS shunt for gastric variceal bleeding in patients with cirrhosis: A meta-analysis
Bai M., et al. W. J. Gastrointest Pharmaco Ther 2014

Prevention of Mortality

Balloon-occluded Retrograde Transvenous Obliteration of gastric varices (BRTO)

- Indicated if
  - endoscopic management fails
  - transjugular intrahepatic portosystemic shunt is contraindicated

- Approach
  - Transjugular
  - Femoral
  - Requires the existence of a portosystemic shunt
  - Materials: Coils or Glue
Surgical Options

- Portosystemic shunts
  - Selective
  - Non selective
- Contraindicated in advanced liver disease
- Higher mortality if done during an episode of bleeding
- Esophago-gastric devascularization
- Liver transplantation

Management of Acute Variceal Bleeding

Variceal Hemorrhage Suspected

Initial Management
- Transfuse to hemoglobin ~8
- Early pharmacotherapy
- Antibiotic prophylaxis

Variceal obturation possible?
- NO
- YES

Bleeding controlled?
- NO
- YES

TIPS
- Surgical shunt
- RTO
- Variceal obliteration: +/- β-blockers
- Evaluation of liver disease


Take home message...

- Stabilize the patient
- Control bleeding
- Endoscopic procedures
- Interventional radiology
- Evaluate and treat according to type of liver disease
  - Surgical shunts
  - Liver transplantation
- Overall prognosis is determined by degree of end organ dysfunction at the time of the event
What is next?...

- Design high-quality clinical studies that would provide an evidence base for the management of varices in children
- Future studies in children should focus on
  - Development of noninvasive tests to diagnose the presence of varices and to predict the risk of bleeding
  - Evaluating the feasibility, efficacy, and safety of TIPS as a treatment modality for portal hypertension
  - Studying the efficacy of non-selective β-blocker as primary or secondary prophylaxis in the prevention of variceal bleeding
Emergency Techniques for Non-Variceal Upper GI Bleeding

Lee Bass, MD
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Ann & Robert H. Lurie Children’s Hospital of Chicago
NASPghan POST-Grad Course 2014

Financial Disclosures

I have the following financial relationships to disclose:
• Kadmon Pharmaceuticals
• McKesson Health Solutions

Products or services produced by these companies are not relevant to my presentation.

This talk will include discussion of some investigational/not yet approved techniques.
Objectives

- Know the appropriate differential diagnosis and causes of non-variceal upper GI bleeding
- Know the appropriate timing and preparation for emergency interventions in this group of patients.
- Learn the newest emergency interventional techniques for non-variceal bleeding (injection, clips, heat, hemospray, endoluminal suturing)

Upper GI Bleeding

Epidemiology

- Cohort study of pediatric ICU admissions demonstrated 10.2% of patients had UGI bleeding. 1.6% clinically significant.
- The proportion of endoscopy subjects with gastrointestinal (GI) bleeding has declined significantly to 5% during the last 20 years
  - Franciosi et al. JPGN 2010

Non Variceal UGI Bleeding

Common Etiologies
- Peptic Ulcer disease
- Mallory-Weiss Tears
- Gastritis
- Medication (NSAIDS)
- Dieulafoy lesion
- Vascular Anomalies

Less Common Etiologies
- Clotting Factor deficiency
- Tumors (Hemangiomas)
- Foreign body ingestion
- Henoch-Schonlein Purpura
- Anatomic Abnormalities
- Hemorrhagic disease of the newborn
- Crohn’s
### Risk Factors Associated with GI Bleeding in ICU (OR > 1)

- Trauma
- Shock
- PRISM score > 10
- Respiratory Failure
- Coagulopathy
- Mechanical Ventilation
- Enteral Feeding
- Pneumonia
- Surgery Time >3 hours
- Thrombocytopenia
- Organ Failure
- Corticosteroid administration

Reveiz et al. *Pediatr Crit Care Med* 2010

### Initial Evaluation

- A...B...C’s
- Significant GI Bleeding will first manifest as Tachycardia.
- Hypotension is indicative of imminent cardiovascular collapse
- Immediate Therapy:
  - Aggressive fluid and blood resuscitation
- Laboratory evaluation:
  - CBC, PT/PTT, Type and Cross, Renal Function Test, Esr/CRP, Reticulocyte count

### Transfusion Strategies

- Restrictive Strategy:
  - Transfuse if hgb < 7
- Liberal Strategy:
  - Transfuse if Hgb <9
- Restrictive Strategy
  - Significantly higher survival
  - Significantly lower transfusion rate and risk of re-bleeding

**ASGE Guideline**

- Adequate resuscitation of patient upon presentation
- NG Lavage
  - signals presence or absence of ongoing bleeding pre-pyloric
- Treatment with PPI reduces rates of high risk stigmata on endoscopy
  - No significant difference noted in mortality, rebleeding or progression to surgery
- Use of prokinetics
  - Increases likelihood of identification of a bleeding lesion

Hwang et al. GIE; 2012

---

**Preparation for Endoscopy**

- Airway secured
- Blood for transfusion present
- Water pump/irrigation method
- Suction tubing
- Epinephrine
- Clips/Cautery/APC with equipment in working order.
- Back up endoscope
- +/- Surgical or IR Consult/Back-up

![Image: Preparation for Endoscopy](image)

---
Therapy

Combination>Monotherapy

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Combination</th>
</tr>
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<tbody>
<tr>
<td>Normal Saline or dilute Epinephrine</td>
<td></td>
</tr>
<tr>
<td>Epinephrine may cause some Vasoconstriction</td>
<td></td>
</tr>
</tbody>
</table>

Injection

- The primary mechanism of action is tamponade resulting from a volume effect.

- Normal Saline or dilute Epinephrine
  - Epinephrine may cause some Vasoconstriction

Thermal Probes

- Bipolar Circuits- No grounding pad is required
- Uses coaptive coagulation to compress, fuse and seal the open wall of a bleeding vessel.
- Useful for contact thermal hemostasis
- Settings for ulcer, dieulafoy: 15-20W

Kay and Wyllie JPN 2007
Thermal Probe Video
15-20 Seconds in length

Hemoclips

Hemoclip Video
15-20 seconds in length
APC - With Video

- Non contact method of delivering monopolar electrosurgical energy to target tissue.
- Primarily used for superficial lesions.
- APC uses conductive properties of gas plasma to deliver the energy from the active electrode to the tissue.
- APC is applied until white coagulum appears.

Hemospray

- Highly absorptive Powder
- Forms cohesive stable mechanical plug when in contact with blood.
- Not absorbed, thus no systemic effects.
- Successful at achieving Hemostasis with Rate between 93-95%
  - Sulz MC et al. Endoscopy. 2014
- Not Currently approved for use in the United States.

Endoscopic Suturing

- Curved needle with detachable tip
- Driven through mucosa and “tied down” using a cinching device
Angiography

Future Directions

• Standardization/optimization strategies for pre-endoscopic management of GI bleeding

• Comparison between different endoscopic techniques in pediatrics

• Further research into newer techniques to control GI bleeding.

Summary

• Resuscitation of the patient is of utmost importance. Restrictive transfusion strategy may be beneficial, however patient should be resuscitated.

• Preparation prior to endoscopy will enhance chances of procedural success.

• Endoscopic therapy of bleeding lesions-
  – Combination therapy of injection + Mechanical/thermal/APC recommended

• New Techniques- Hemospray/Endoluminal suturing
Endoscopic Interventions for Biliary Tract Disease
Victor L. Fox, MD
NASPGHAN Post-Graduate Course
Atlanta 2014

Disclosure

• I have the following financial relationships to disclose:
  – Covidien Enteral Nutrition Advisory Board
  – Olympus* Consultant

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

Learning Objectives

• Learn the indications and techniques for endoscopic therapy of choledocholithiasis
• Recognize different types of biliary strictures and approaches to endoscopic treatment
• Understand the role of endoscopy in the management of accidental and surgical hepatobiliary injury
Background

• Therapeutic ERCP is the most technically challenging but also clinically rewarding procedure
• Requires advanced training to achieve high level of skill and experience
  – >200 cases needed to achieve selective cannulation required for interventions
  – Acquisition and maintenance of skills by pediatricians is controversial
• Often provides definitive treatment and eliminates need for major surgery
• No equipment is favorably designed for young or small children
  – “Off-label” use of accessories

Background

• Choledocholithiasis is the most common indication for interventional biliary endoscopy
• Childhood obesity is associated with a rising incidence of gallbladder disease, gallstones, and cholesterol stones
• Total ERCPs and percentage of therapeutic ERCPs in hospitalized children is rising in the US

ERCP in Adults

• Technical outcomes
  – selective duct cannulation (average >90%; experts >95%)
  – stone removal (85% std techniques, >90% adv techniques)
• Complications
  – low complication rate (5-10%)
    • Pancreatitis (average 1%-7%, range 1%-40%)
    • Hemorrhage (2%)
    • Perforation (<1%)

Mehta S et al. Pediatrics 2012;129:e82-8
Walker SK et al. Surgery 2013;154:927-31
ERCP. Baron TH, Kazanek R, and Carr-Locke D., eds. Saunders 2013
ERCP: Children vs Adults

- Varadarajulu et al 2004—retrospective case-controlled two center study
  - 116 pediatric and 116 adult cases matched for indications and procedural complexity

<table>
<thead>
<tr>
<th></th>
<th>Child</th>
<th>Adult</th>
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<tbody>
<tr>
<td>Age, median, y</td>
<td>8.1</td>
<td>49.7</td>
</tr>
<tr>
<td>Technical success, %</td>
<td>97.5</td>
<td>98</td>
</tr>
<tr>
<td>Complication rate, %</td>
<td>3.4</td>
<td>2.5</td>
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Pediatric ERCP Series

<table>
<thead>
<tr>
<th></th>
<th>No. Pts</th>
<th>Infants &lt; 2 yrs</th>
<th>Mean Age yrs</th>
<th>No. Proc</th>
<th>Therapy</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng 2005 (adult endo)</td>
<td>245</td>
<td>12</td>
<td>12.3</td>
<td>329</td>
<td>71.4% ES = 122 Dil = 26 Stent = 30 Stone = 32</td>
<td>11.2% Pancreatitis = 31 (9.4%) Bleeding = 5 (4.1% of ES)</td>
</tr>
<tr>
<td>Otto 2011 (adult endo)</td>
<td>167</td>
<td>18</td>
<td>11.4</td>
<td>231</td>
<td>69% ES = 96 Stent = 52 Stone = 55</td>
<td>4.8% Pancreatitis = 7 (3.0%) Bleeding = 2 (2.1% of ES)</td>
</tr>
<tr>
<td>Cretevidt 2013 (adult endo)</td>
<td>296</td>
<td>6</td>
<td>14.9</td>
<td>429</td>
<td>64.1% ES = 187 Stent = 118 Stone = 112</td>
<td>7.7% Pancreatitis = 27 (6.3%) Bleeding = 6 (1.4%)</td>
</tr>
<tr>
<td>Troendle 2013 (ped endo)</td>
<td>65 NA</td>
<td>15.2</td>
<td>67</td>
<td>100% ES = 65 Stone = 65</td>
<td>8% Pancreatitis = 3 (5%) Bleeding = 1 (1.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Equipment: Duodenoscopes

<table>
<thead>
<tr>
<th>Endoscope*</th>
<th>Infant Channel (mm)</th>
<th>JF 140F Channel (mm)</th>
<th>TIF Q180V Channel (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Channel (mm)</td>
<td>2.0</td>
<td>3.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Tip O.D. (mm)</td>
<td>7.5</td>
<td>12.0</td>
<td>13.7</td>
</tr>
</tbody>
</table>

*Olympus designations and specs. Similar dimensions for Pentax and Fujinon adult scopes.
Other Equipment

- Electrical generator
- CO2 insufflator
- Irrigation pump

Images courtesy of ERBE, Medivators, and Olympus

Stone removal accessories

Images courtesy of Cook Medical

Stricture dilation accessories

Images courtesy of Cook Medical, Boston Scientific
### Choledocholithiasis

**Risk Factors**
- Obesity
- Hemolytic disease
  - Hgb SS
  - Spherocytosis
- Idiopathic
  - Fetal or neonatal
- Hispanic ethnicity
- Female gender
- Medications

**Treatment**
- Observe for spontaneous passage
- 1-step: laparoscopic cholecystectomy (LC) with bile duct exploration
- 2-step: ERCP + LC

---

**Choledocholithiasis**

<table>
<thead>
<tr>
<th>Bilirubinate pigment stone</th>
<th>Cholesterol stone</th>
</tr>
</thead>
</table>

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**Hemolytic disease**

8 yr male with Hgb SS, acute abdominal pain, jaundice
Sphinctertomy/Balloon Extraction

Neonatal cholelithiasis
5 wk, 3.9 kg male with acholic stool and jaundice
### Biliary Strictures

**Causes**
- Congenital
- Post-operative
  - Anastomotic
  - Iatrogenic (post LC)
- Traumatic
- Inflammatory
  - Intrinsic (PSC)
  - Extrinsic (pancreatic)
- Ischemic
- Infectious
- Idiopathic
- Malignant or tumor-related

**Treatment**
- If crossed with a wire, most can be dilated and stented
- Stent replacement q 2-4 mo as needed
- Plastic preferred over metal stents for benign disease

---

**3.5 yr female with intermittent abdominal pain for 6 months**
- Elevated AST, ALT, Alk phos, nl bilirubin
- Abnl US and MRCP
  - Enlarged GB and dilated bile ducts
  - Suspected stricture at distal CBD

---

**Choledochoccele (type III CDC)**

![Image](image_url)
Anastomotic stricture

20 mo, 10.8 kg infant after whole graft liver transplantation

Extrinsic Pancreatic disease
“Double duct sign” in 10 yr male with 6 wks of abd pain, jaundice, mild lipase elevation
Immediate symptom relief after stent

Follow-up

- Symptoms resolved, labs normalized
- Stent removed after 2 mo
- Repeat MRCP after 6 mo
  - CBD stenosis resolved
  - Pancreatic duct improving

Idiopathic stricture
17 mo female with acute jaundice

Dilated hepatic ducts (MRI)
Non-excreting HIDA scan
Obstructed operative cholangiogram
Graduated catheter dilation of hilar stricture

Balloon catheter dilation

- Repeat dilation (balloon catheter) and stent at 2 mo F/U ERCP
- Stent removed and strictures resolved at 6 mo F/U ERCP
- Clinically well, non-dilated ducts, normal labs at 12 mo F/U evaluation

Bile leak

**Causes**
- Anastomotic leak due to post-operative ischemia
- Post-LC
  - Leak from cystic duct stump
  - Leak from gallbladder fossa (duct of Luschka)
- Liver laceration due to blunt trauma

**Treatment**
- Percutaneous drainage if large abdominal collection
- Short, large diameter transpapillary stent
- Or biliary sphincterotomy

Stenting for Bile Leak

Summary

- Endoscopic biliary interventions are increasingly employed in children with similar safety and technical success as adult patients
- 1-step vs 2-step approach to LC and CBD stone removal is determined by local expertise and availability
- Most strictures and leaks can be successfully managed endoscopically without need for surgical intervention
Extra-esophageal Manifestations of Gastroesophageal Reflux (GER)
Fact vs. Fiction

Benjamin D. Gold, MD, FAAP, FACG
Pediatric Gastroenterology, Hepatology and Nutrition
Children's Center for Digestive Healthcare, LLC

Or...

Is reflux really the scourge of the earth and the cause of every malady known to human-kind in the head, neck, and lungs...?

Disclosure

- I have a number of financial relationships with commercial entities from whom I receive compensation, for which my son who just graduated from Stanford and daughter who attends George Washington University are very grateful
  - Janssen/J&J, Nestle, Astra, Takeda, Pfizer, Prometheus, Mead Johnson Nutritional, Given and Horizon Pharma

- However, for this presentation, I have no disclosures regarding relationships with any commercial entity which presents conflict regarding the content and my preparation of this evidence-based presentation.
Learning Objectives

- Learn the extent of extra-esophageal manifestations of GERD (or GER) in the pediatric patient
- Describe evidence regarding extra-esophageal manifestations of GERD – respiratory, otolaryngologic
  - Biologically plausible?
  - Epidemiological association?
  - Cause and effect?
- Know the diagnostic testing modalities for the child with extra-esophageal manifestations of GERD
- Understand the evidence-based treatment approaches and options for the management of children with extra-esophageal manifestations of GERD

Differentiating GER From GERD in the Pediatric Patient

Are we really doing it right?

Airway Protective Mechanisms

- Esophageal distention
  - Small volume
  - UES contracts
- Large volume
  - Vagal reflexes
  - Vocal cords close
  - Central apnea occurs
  - UES relaxes

Refluxate enters pharynx

0.15 s

Swallowing clears pharynx

0.3 s

0.6 s

1.0 s

Respiration resumes

Aerodigestive reflexes are intact by 38 weeks gestation...

thus, it isn’t an “immature” LES that leads to GERD

Physiologic versus Pathologic Reflux and Age

Reason for physiologic differences between children and adults:
- angle of HIS (Gastric-Esophageal junction);
- position after feeds;
- more frequent feeds;
- stomach less compliance and capacity

GERD Pathophysiology in Children and Adults Is SIMILAR
- Transient relaxations of the lower esophageal sphincter
- Inhibition of esophageal body peristalsis plus exposure of mucosa to gastric refluxate (eg, acid, pepsin)

Physiologic versus Pathologic Reflux and Age

• Adults: swallowing occurs during the expiratory phase of respiration
• Neonates: swallowing can occur during inspiratory, expiratory and inter-phases.
• During normal swallowing a brief pause in breathing with cessation of air flow is evident;
  • Central deglutition apnea: a normal protective mechanism to prevent aspiration during swallowing

88
GERD in pediatric patients is present when reflux of gastric contents is the cause of troublesome symptoms and/or complications.

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GERD in pediatric patients is present when reflux of gastric contents is the cause of troublesome symptoms and/or complications

Extra-Esophageal GERD in Children

Extraesophageal Associations of GERD: Global Consensus Definitions

Definite associations
- Sandifer’s syndrome
- Dental erosion

Possible associations
- Bronchopulmonary
  - Asthma
  - Pulmonary fibrosis
  - Bronchopulmonary dysplasia
- Laryngotracheal and pharyngeal
  - Chronic cough
  - Chronic laryngitis
  - Hoarseness
  - Pharyngitis
- Rhinological and otological
  - Sinusitis
  - Serous otitis media
  - Infections
  - Parotitis

Extraesophageal Associations of GERD:
- Global Consensus Definitions

Sherman et al. Am J Gastroenterol. 2009;104:1278-95
Reflux and Pulmonary or ENT Disease
Biologically Plausible…
Does this equal causality?

- Bradford-Hill criteria;
  - Critical for the evaluation of disease and outcome or treatment response causality
  - Consistency
  - Strength of association
  - Specificity
  - Meaningful temporal relationship.

Reflux and Pulmonary or ENT Disease
Biologically Plausible…
Does this equal causality?

Should we refer to the “extra-esophageal manifestations” of GER as Sherlock Holmes advised Dr. Watson...,

“when you have eliminated the impossible, whatever remains, however improbable, must be the truth.”

Extra-esophageal Manifestations of GERD with “definitive” causality
GERD and Dental Erosions

- GERD may cause dental erosions in children
- Some studies link GERD with a higher prevalence of dental erosions while others do not
- A recent review found that children with GERD are at an increased risk of dental erosions
- Unclear how acid suppression changes the natural history of GERD or appropriate duration of treatment

Sandifer’s Syndrome

- Is a specific manifestation of pediatric GERD
- Abnormal posturing
  - Head tilt
  - Torticollis
  - Arching of the back
- Must be differentiated from
  - Seizures
  - Infantile spasms
  - Dystonia
- May be a vagally mediated reflex response to esophageal acid exposure
- Resolves with antireflux therapy

ENT Manifestations of GERD

Have they met the burden of proof for causality?
Normal Laryngeal Pharyngeal Reflux Disease

LERD OR LPR

Laryngeal: Normal vs. Erythema

Not all red in the airways = reflux!

Normal Laryngeal Pharyngeal Reflux

The Relationship Between Laryngeal Symptoms/Findings and GER

Chronic cough, chronic laryngitis, hoarseness, and asthma may be associated with GERD

- There are data showing a relation between reflux and upper airway disease are weak
- Airway symptoms attributed to reflux in adults include hoarseness, chronic cough, and globus sensation
- Affected adults rarely have typical reflux symptoms
- The sensitivity of laryngoscopic findings to identify reflux disease are poor

Respiratory Disease and Reflux

Causal?
Association?
True-True and Unrelated

Reflux and Respiratory Disease

- Recurrent pneumonia
- Cough
- Apnea/ALTE
- Asthma
- Nocturnal Acid Breakthrough

Association of GER with Apnea

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>Chest Wall Movement</th>
<th>Nasal Air Flow</th>
<th>Esophageal pH</th>
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<tbody>
<tr>
<td>0</td>
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<td>10</td>
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</tr>
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<tr>
<td>90</td>
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</table>

In infants with ALTE, prolonged SREs are associated with ineffective esophageal dysmotility characterized by frequent primary peristalsis and significant propagation failure. Thus this suggests dysfunctional regulation of swallow-respiratory junction interactions. Further, the authors recommend that treatment NOT target gastroesophageal reflux but proximal aerodigestive tract.
Although reflux causes physiologic apnea, it causes pathologic apneic episodes in only a very small number of newborns and infants.

Biological plausibility
- YES

Causality
- Not at present, more research needed

Neurophysiology of Cough
- Not every child who coughs or wheezes has asthma
- Think about aspiration syndromes

Other Causes of Persistent Cough
- Physical and chemical irritation
  - Tobacco smoke (active and passive)
  - Wood smoke (stoves, fireplaces)
  - Dry, dusty environment
  - Volatile chemicals
  - Irritation of external ear canal
- Involuntary vocalization/tic
- Psychogenic/habit cough
- Drugs: ACEI

Remember cough is primarily a normal defense mechanism!
Persistent Cough Cont'd

- Airway disease
  - Asthma
  - Allergic/vasomotor rhinitis w/ PND
  - Aspiration (liquid)
  - Direct, ie swallow dysfunction
  - Neuromuscular
    - Vocal cord paralysis
    - Anatomic abnormality (ie TEF, LTEC)
  - Bottle propping/bottle in bed
  - Maturational

- GER
  - Aspiration (solid)
  - Upper airway
    - Tracheobronchial
    - Esophageal

Always consider foreign body, especially if follows history of choking/gagging spell.

Consider if cough occurs during or after feeds.


- 94% of all coughs were detected by IEPR and on 48% of all coughs were reported by parents.
- Parental and patient symptom recording in children inadequate for making the diagnosis of reflux-related lung disease...
- IEPR should be the new standard

- Biological plausibility?
  - YES
- Causality
  - Probably, but likely multi-factorial

Asthma: When to Treat for GERD

- Persistent asthma with heartburn or regurgitation
  - Treat with a PPI
- Persistent asthma that is difficult to control or nocturnal-onset
  - Rule out other causes of wheezing;
  - Perform multichannel pH-impedance monitoring

GER is an unlikely contributor to asthma if reflux testing is negative

- Persistent asthma that is difficult to control or nocturnal-onset with abnormal pH-impedance monitoring
  - Trial with a PPI

There is insufficient evidence that GERD causes or exacerbates sinusitis, pulmonary fibrosis, pharyngitis and serous otitis media.

Chronic cough, chronic laryngitis, hoarseness and asthma are multifactorial disease processes and acid reflux can be an aggravating cofactor.

A Global Evidence-Based Consensus on the Definition of GERD in the Pediatric Population
There is insufficient evidence that GERD causes or exacerbates sinusitis, pulmonary fibrosis, pharyngitis and serous otitis media. Chronic cough, chronic laryngitis, hoarseness and asthma are multifactorial disease processes and acid reflux can be an aggravating cofactor.

Sherman PM et al. Am J Gastroenterol 2009;104:1278-1295

Biological plausibility

✓ YES

Causality

✓ Not at present, more research needed

Diagnosis of Extra-Esophageal GERD in Infants and Children

Testing for GERD

• Is there a single test for the extra-esophageal manifestations of GERD?
• What question does each test answer?
• How reproducible or reliable is the test?
• Does it guide our management?
• Do the results improve outcomes?
**Aspiration From Swallowing or GER?**

**Biomarkers in Bronchoscopy Fluid or Saliva**

- **Lipid Laden Macrophage Index (LLMI)**
  - Elevated in a variety of pulmonary diseases
  - Inconsistent relationship between the amount of gastroesophageal reflux and LLMI
  - No relationship between full column reflux by pH-MII and LLMI

- **Pepsin**
  - Found in neonates and children with pulmonary disease
  - Presence in the lungs correlated with proximal reflux by pH probe
  - Specificity? Sensitivity for detected reflux
  - Unclear if its presence predicts prognosis

- **Bile**
  - Found in children and adults with pulmonary disease
  - More sensitive than pepsin
  - Predicts worse prognosis in lung transplant patients; significance?
  - Correlates with weakly acidic (pH 4-7) reflux as measured by pH-MII

**Advantages and Disadvantages of Multi-Channel Intraluminal Impedance**

- **Advantages**
  - Detects non-acidic GER episodes which is ideal for post prandial reflux
  - Differentiates reflux from swallows
  - Able to accurately assess full column reflux
  - Sensitivity of pH-MII comparable to the pH probe in untreated patients and surpasses pH probe in treated patients.

- **Limitations**
  - Normal values in pediatric age groups not yet defined
  - Analysis of tracings time-consuming
  - How the results change management still

Pediatric studies are critically needed to determine if knowing the amount of nonacid reflux changes treatment or outcome
High Resolution Manometry

Combining HRM with pH-Impedance – even better?

Allows evaluation of esophageal dymotility and correlation of symptoms with distension and stretch; non-acid related symptoms

Pediatric studies are critically needed for validation of this testing method!

New Diagnostic Technologies
• To better correlate reflux with symptoms, new tools are being designed….
  - Oropharyngeal probes
  - Breath testing
  - Cough catheters
  - Cough microphone
  - New lung biomarkers


Management of GERD in Infants and Children
# Overview of GERD Treatments

<table>
<thead>
<tr>
<th>Nonpharmacologic</th>
<th>Pharmacologic</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>Oral antacids</td>
<td>Fundoplication (ie, Nissen)</td>
</tr>
<tr>
<td>• Formula thickening</td>
<td>• Surface agents (eg, sodium alginate, succralfate)</td>
<td></td>
</tr>
<tr>
<td>• Time-limited trial of hypoallergenic formula</td>
<td>• Gastrointestinal prokinetic agents (eg, domperidone, baclofen)</td>
<td></td>
</tr>
<tr>
<td>• Higher calorie formulas</td>
<td>• Acid-suppressive agents (H2RAs, PPIs, PCABs)</td>
<td></td>
</tr>
<tr>
<td>• Nasogastric/nasojejunal feeds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older children/adolescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Positioning/head-of-bed elevation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Weight loss (if overweight)</td>
<td></td>
<td></td>
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</tbody>
</table>

Note: The table above summarizes various treatment options for gastroesophageal reflux disease (GERD) categorized by type. The table includes nonpharmacologic, pharmacologic, and surgical treatments. Nonpharmacologic options include dietary modifications such as formula thickening and positioning, whereas pharmacologic options include medications like antacids, surface agents, and prokinetic agents. Surgical interventions involve procedures like fundoplication and esophagogastrectomy.

### Does Treatment for GERD Resolve Cough (Adults)


Response of Chronic Cough to Acid-Suppressive Therapy in Patients With Gastroesophageal Reflux Disease

Background: Epidemiologic and physiological studies suggest an association between gastroesophageal reflux disease (GERD) and chronic cough. However, the benefits of antireflux therapy for chronic cough remain unclear, with most relevant trials reporting negative findings. This systematic review aimed to evaluate the response of chronic cough to antireflux therapy in trials that allowed us to distinguish patients with or without objective evidence of GERD. Methods: PubMed and Embase systematic searches identified clinical trials reporting cough response to antireflux therapy. Data were derived from trials that used allometric to characterize patients with chronic cough.

Result: Nine randomized controlled trials of varied design that treated patients with acid suppression were identified. Eight used proton pump inhibitors (PPIs), one used ranitidine. Data from two crossover studies showed that PPIs significantly improved cough relative to placebo, albeit only in the acute receiving placebo first. Therapeutic gains in seven studies were greater in patients with pathologic esophageal acid exposure (range, 12.5%-35.9%) than in those without (range, 0%-5%).

Conclusion: A therapeutic benefit for acid-suppressive therapy in patients with chronic cough cannot be dismissed. However, evidence suggests that rigorous patient selection is necessary to identify patient populations likely to be responsive, using physiologically timed cough events during reflux testing, minimal patient selection because of prescriptive alternative diagnoses, and appropriate power to detect a modest therapeutic gain. Only then can we hope to resolve this ongoing clinical management problem.

Abbreviations: GERD = gastroesophageal reflux disease; LPR = laryngopharyngeal reflux; PPI = proton pump inhibitor.
• Two NIH-funded blinded, randomized placebo-controlled trials (RCT), one in adults (using esomeprazole), one in children (using lansoprazole)
  ▪ Showed NO difference in asthma outcomes comparing placebo and acid suppression therapy
• Another industry funded longer term (1 year) RCT comparing high dose lansoprazole to placebo
  ▪ Showed no difference in asthma outcomes and pulmonary function

Asthma and GERD: Treatment cont’d

Clinical trial data
1 year, double blind RCT (N=68)

• Asthma exacerbations no different between both groups; ACQ score decreased in both groups (p = .99)
• Both treatment groups demonstrated a decrease in self-reported GERD symptoms, $\chi^2 (1) = 30.54, p < .001$, as well as an increase in quality of life, $\chi^2 (1) = 53.58, p < .001$
• We demonstrated no difference between placebo and high dose acid suppression (per kg) in asthma outcomes over a 1 year duration
• Our study, the longest RCT to evaluate acid suppression in poorly controlled asthmatics, raises important questions regarding a GERD-asthma causal relationship
Other Effects of Acid Suppression
Outcome or Marker of Disease Pathobiology?

Methods
- 5-year prospective cohort study at a tertiary care center;
- Children ages 1 to 18 years were undergoing bronchoscopy and endoscopy for chronic cough
- Acid-suppression use was assessed through questionnaires

Objectives
- to determine if acid-suppression use results in gastric bacterial overgrowth,
- if there are changes in lung microflora associated with the use of acid suppression, and,
- if changes in lung microflora are related to full-column nonacid gastroesophageal reflux

Acid suppression resulted in gastric bacterial overgrowth, in particular organisms that cause pharyngeal and laryngeal disease

Full column non-acid reflux in acid suppression treated patients associated with greater bacterial concentrations in lungs

Could acid suppression for GERD result in, exacerbate or worsen the very same extra-esophageal disease it was used to treat?

Principles of Anti-reflux Surgery

- Restore intra-abdominal segment of esophagus
- Approximate diaphragmatic crura
- Wrap fundus around LES to reinforce antireflux barrier
- Reduce hiatal hernia when present
Antireflux Surgery and Extra-esophageal Symptoms

- Aspiration pneumonias may improve after fundoplication.
- Rates of other pneumonias after fundoplication may be unchanged or even higher than prior to fundoplication.
- Patients, who previously had not had a pneumonia, may develop them.
- Asthma improvement after fundoplication is variable depending on the case series.
- The majority of pediatric patients remain on reflux medications, even after surgery.

Extra-Esophageal GERD in Children: Controversies/Gaps in Knowledge

- Extra-esophageal GERD definitions in children
  - Need to establish and validate biological markers/surrogates for extra-esophageal disease.
  - Prime population for novel diagnostic modalities.
  - pH-impedance, intra-esophageal pressure recording.
  - High resolution manometry.
  - Pill cam.
- What does inflammation in the esophagus really mean?
  - Does esophageal disease have to exist in order to have extra-esophageal disease?
- How do we treat weakly acid and non-acid “reflux”
  - How is the dysmotility component of best EEM managed?

GERD and Extra-Esophageal GERD in Children: Controversies/Gaps in Knowledge cont’d

- Do we have the evidence to support extra-esophageal manifestations of GERD in October of 2014?
  - Otolaryngological (larynx, pharynx, middle ear)
    - Biologically plausible? YES.
    - Epidemiological Association YES.
    - Cause and effect? NO, more research needed.
  - Respiratory (cough, pneumonia, asthma)
    - Biologically plausible? YES.
    - Epidemiological Association YES.
    - Cause and effect? NO, more research needed.
- Opportunity for multi-disciplinary, multicenter collaborations using other successful models.
EoE: PPI, PPI-REE, TCS, OVB, SFED, 4FED......Alphabet Distress

Sandeep K Gupta, MD
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Director, Endoscopy Services
Clinical Director, Riley CEDAR Clinic,
Indiana University School of Medicine
Riley Hospital for Children, Indianapolis, Indiana

Disclosures

- Consultant/research: Abbott, Meritage, Nestle, QOL and Receptos

- The content of my presentation includes discussion of off-label/investigative use of medicine(s), medical devices, or procedures

Objectives

- Understand role of PPI in EoE

- Update on TCS (topical corticosteroid) therapies

- Review role of diet in EoE – SFED, 4FED, etc.
Introduction
• EoE is a chronic inflammatory condition
• Needs long-term therapy like other chronic conditions
• Rapid advancements in field

Current Treatment End-point: Eosinophils

EH: epithelial height
Normal: BCH (basal cell hyperplasia) ~ 15%, RP (rete peg) ~ 40%
Esophagitis: BCH ~ 30%, RP ~ 90%

Treatment Endpoints – Other Thoughts
• Histological remission – composite score vs eosinophil count; what count is cut-off?
• Symptomatic relief
• Endoscopic reversal
• Fibrosis status
• Combo-scoring system of above
• Important: QOL and patient/family preference due to chronicity
Objective 1: Role of PPI

- Current guidelines on PPI Therapy
- Data on PPI response in EoE
- PPI-responsive esophageal eosinophilia (PPI-REE) relation to EoE
- Long term management of PPI-REE

PPI Guidelines

- If ≥15 eos/hpf, do high-dose (HD) PPI (1 mg/kg/dose bid, to max adult dose, for 8-12 wks)
- Mechanism: not acid-suppression, ?molecular

Omeprazole Blocks STAT6 Binding to the Eotaxin-3 Promoter in Eosinophilic Esophagitis Cells

Xi Zhang1, Eudene Cheng2, Xiaofang Hua1, Chunhua Yu1, Qiyang Zhang1, Thi H. Pham2, David H. Wang1, Stuart J. Spechler1, Rhonda F. Souza3

PLos ONE 2012;7:e50037

Why do HD PPI Trial?

- 30% to 40% respond (<6 eos/hpf)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Design</th>
<th>Esophageal eosinophilia in treated with PPI</th>
<th>RR (95% CI) in %</th>
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<td>RCT</td>
<td>Yes</td>
<td>20 (95)</td>
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</table>

Dellon et al. AJG 2013
Who will respond to HD PPI?

Clinical and Endoscopic Characteristics do Not Reliably Differentiate PPI-Responsive Esophageal Eosinophilia and Eosinophilic Esophagitis in Patients Undergoing Upper Endoscopy: A Prospective Cohort Study

JASON E. DRANOVE, MD, DEBRA S. HORN, RN, MIRIAM A. DAVIS, BS, KEVIN M. KERNEK, MD, AND SANDEEP K. GUPTA, MD

PPI Responders vs Non-Responders

- Predictors of Response to Proton Pump Inhibitor Therapy among Children with Significant Esophageal Eosinophilia

JASON E. DRANOVE, MD, DEBRA S. HORN, RN, MIRIAM A. DAVIS, BS, KEVIN M. KERNEK, MD, AND SANDEEP K. GUPTA, MD

Long-term Management of PPI-REE

Distal relapsers (8/12) undergoing PPI increase (Omeprazole 40 mg bid)
Objective 2: Steroid-based therapies

- Options - prednisone, fluticasone (F), budesonide (B)
- Dosing
- Pros and Cons
- Maintenance therapy
Topical Corticosteroid Data

- Response: 50% - >70%
- Fluticasone: 110-220 mcg/puff (8 puffs/day) bid to qid
- Budesonide 1 or 2 mg (>10 yo)/day – 85% improved in 3-4 mo
- 36 adolescents/adults: 1 mg neb budesonide vs placebo bid x 15 days; swallow accumulating liquid for 10 minutes

Aceves 2007; Straumann Gastroenterology 2010

Efficacy and Safety of Oral Budesonide Suspension in Pediatric Patients with Eosinophilic Esophagitis

Comparison of Oral Prednisone and Topical Fluticasone in the Treatment of Eosinophilic Esophagitis: A Randomized Trial in Children
SCHAEFER, FITZGERALD, HOLLESTON, CROFFIE, PFEFFERKORN, CORKINS, LIM, STEINER, GUPTA Clin Gastroenterol Hepatol 2008
Pros and Cons of Topical Steroids

- Rapidity of response
- Ease of Rx administration
- Positive quality of life
- Thrush – oral, esophageal; <20% children (10% adults). Now seen less frequently
- Adrenal suppression and growth retardation
- Bone loss – less likely with TCS
- TCS lower risks due to limited absorption and high first-pass metabolism

Long Term: Can I Lower Dose?

Efficacy, Dose Reduction, and Resistance to High-dose Fluticasone in Patients with Eosinophilic Esophagitis.

- 1760 mcg/day F (n28) vs placebo (n14) 3-30 yr old
- 65% (n18) of F histologic remission at 3 months. Of these, 73% (n13) stayed remitted 3 months after 50% dose reduction

Objective 3: Review Dietary Therapy

- Types of Diet
- Efficacy Data
- Newer Diets
- Pros and Cons
Diet Terminology and Logistics

- **Elemental** – free amino acid-based formula mostly
- **Targeted Elimination** - allergy tests guided - skin prick/patch
- **Empiric Elimination** – milk, wheat, soy, egg, nuts, fish/combos
- Know how response is defined
- Need RD, allergist and GI; know quality of life

Histological Response to Diet

![Histological Response to Diet Chart]

Liacouras et al Clin Gastroenterol Hepatol 2005
“Effect of 4FED on Clinical and Histologic Outcomes in EoE”

- 24 children; 71% male; mean age 9.3 years

- 72% with histologic remission (<10/hpf)

- Ongoing multi-center study

- Faster food re-introduction >> fewer EGD

Amsden, Kagalwalla Falk Symposium 2013

Baked Milk Concept

Tolerance of baked milk in patients with cow’s milk-mediated eosinophilic esophagitis.

Leung J, Hundal NV, Katz AJ, Shreffler WG, Yuan Q, Butterworth CA, Hesterberg PE.
J Allergy Clin Immunol 2013

- 11/15 (73%) in histological remission (<10 eos/hpf) with baked milk ingestion

Pros and Cons: Reintroduction Protocols

Lucendo J Allergy Clin Immunol 2013
Quality of Life

Average American eats out 4.8 times per week

UPI 2011

Treatment Algorithm at Riley Hospital

FP Fluticasone propionate
OVB oral viscous budesonide
Do We Really Need to Worry About EoE??

Summary/Take-home Messages

• HD PPI for 8-12 weeks if >15 eos/hpf

• PPI-REE related to EoE

• TCS various options and doses available

• SFED, 4FED, Milk alone, baked-milk, etc. - look at response criteria and QOL

Future Directions

• Define who will respond to PPI

• Maintenance therapy with TCS

• Refining dietary interventions and patient evaluation
“Gotta keep on movin”: New tricks and treatments for motility disorders

Carlo Di Lorenzo, M.D.
@carlodilorenzo1

I have the following financial relationships to disclose:

QOL Medical
Sucampo Pharma
Ironwood Pharmaceuticals

Products or services produced by these companies are not relevant to my presentation

Outline

1) Confirm the dx
2) There is a differential diagnosis
3) Try everything
4) Even surgery
Confirm the diagnosis

Manometry: not new, but still important

Neuropathy
Myopathy

Normal colon
ASCENDING
TRANSVERSE
DESCENDING
SIGMOID

Manometry studies tell us:
• Whether a motility problem is indeed present
• Diagnosis of other conditions (rumination)
• What works and what does not (helps planning for transplant)
• Why it does not work
• How to make it work better (directs rx)
Importance of confirming a diagnosis of pseudo-obstruction

Can we use a less invasive test? The wireless motility capsule

System consists of:
- Capsule
- Data Receiver
- Docking Station
- MotiliGITM Software
- Computer Workstation
- Smartbar “standard” meal
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.
Myositis and eosinophilic ganglionitis

Treatment

Drugs Acting at Enteric Serotonergic (5-HT) Receptors

- Prucalopride: 5-HT₄ receptor agonist
- Serotonin (5-HT)
- Cisapride: 5-HT₄ receptor agonist K⁺ channel blocker
- Alosetron: 5-HT₃ receptor antagonist
- Prucalopride: 5-HT₄ receptor agonist

Ruuska TH, Gastroenterology 2002; Schäppi MG, Gut 2003
Prucalopride in children
Winter HS, et al. JPGN 2013;57:197-203
Open label rx with 0.01-0.03 mg/kg prucalopride administered once daily for 8 weeks to 38 children with a baseline BM frequency <2/week to investigate efficacy, safety and tolerability.

Diagnoses included isolated gastroschisis (n=3), gastroschisis, with intestinal atresia (n=4), necrotizing enterocolitis (n=2), and long-segment Hirschsprung’s disease (n=1).

Results: Median (IQR) change in percentage enteral energy intake was +19.9% (15.4–29.8%) during follow-up (p=0.01). 7 patients improved in enteral tolerance during treatment and 2 weaned completely from PN.

Cisapride Improves Enteral Tolerance in Pediatric Short Bowel Syndrome with Dysmotility
Bran P. Raphael, M.D.1,2, Samuel Hynko, M.D., M.P.H.1,3, Hoonjoo Jang, Ph.D.4, Kristen Hart, B.S.1,2, Daniel G. Kamin, M.D.5,6, Tom Jaksic, M.D., Ph.D.5,7, and Christopher Dugan, M.D., M.P.H.1,2

Diagnoses included isolated gastroschisis (n=3), gastroschisis, with intestinal atresia (n=4), necrotizing enterocolitis (n=2), and long-segment Hirschsprung’s disease (n=1).

Results: Median (IQR) change in percentage enteral energy intake was +19.9% (15.4–28.8%) during follow-up (p=0.01). 7 patients improved in enteral tolerance during treatment and 2 weaned completely from PN.

Secretagogues
Linaclotide (Linzess): Mechanism of Action

Linzess is approved with a Boxed Warning to alert patients and health care professionals that the drug should not be used in patients 17 years of age and younger.

Cyproheptadine is a first generation antihistamine with additional anticholinergic, antiserotonergic, and local anesthetic properties.
Fludrocortisone improves nausea in children with orthostatic intolerance (OI)

Fludrocortisone: 0.1-0.2 mg/day for 4 weeks

Iberogast

Iberogast is comprised of the following 9 ingredients:
Iberis amara, Angelica, Chamomile, Caraway Fruit, St. Mary’s Thistle, Balm Leaves, Peppermint Leaves, Celandine, and Liquorice Root.
**Iberogast in Functional Dyspepsia**


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

**Treat bacterial overgrowth**

The Rate of Bloodstream Infection Is High in Infants with Short Bowel Syndrome: Relationship with Small Bowel Bacterial Overgrowth, Enteral Feeding, and Inflammatory and Immune Responses

J Pediatr 2010;156:941-7

- SBBO increased 7-fold the odds for bloodstream infection
- Calprotectin levels were higher in children with SBS and SBBO vs those without SBBO and healthy control subjects
- Serum TNF-a and interleukin-1 b, -6, and -8 levels diminished with increased enteral nutrition

*Conclusion:* In children with SBS, SBBO increases the risk for BSI, and systemic pro-inflammatory response decreases with increasing enteral feeding and weaning parenteral nutrition.

**ORIGINAL ARTICLE: GASTROENTEROLOGY**

JPGN 2012;54: 780–784

Effect of Amoxicillin/Clavulanate on Gastrointestinal Motility in Children

Roberto Gomez, Sergio From

Intraduodenal infusion of A/C induced MMCs in 14/18 children
Amoxicillin or clavulanic acid?

Ciciora S, et al. unpublished data

- Long acting somatostatin analog
- Half life: 1-2 hours after s.c. injection
- Prolonged duration of action
- Antisecretory agent
- Enterokinetic in patients with scleroderma, CIPO
- Delays gastric emptying
- “Hypo-algesic” agent?

Octreotide

- Long acting somatostatin analog
- Half life: 1-2 hours after s.c. injection
- Prolonged duration of action
- Antisecretory agent
- Enterokinetic in patients with scleroderma, CIPO
- Delays gastric emptying
- “Hypo-algesic” agent?
Try everything!

Botulinum Toxin:
100-200 Units divided in 4 quadrants
"Every child with pseudo-obstruction on TPN needs a gastrostomy and an ileostomy"  

(me, now)
Effect of Gastric Electrical Stimulator (GES)

Improved total score (p<0.0001)

Next novel treatments?

Drug Evaluation

Elobixibat for the treatment of constipation

Introduction: Elobixibat (formerly AJ3969) is a first-in-class ileal bile acid transporter (IBAT) inhibitor for treatment of chronic idiopathic constipation (CIC).
Conclusions

• Treat the underlying cause if you find it
• You will not find it unless you look for it
• Off-label use of several medications may provide you (and your pt) with the best prokinetic effects
• Many new “motility medications” are on the horizon
• It is an exciting time to be a motilist!
What’s New in the Diagnosis and Management of Constipation

Manu Sood
Children’s Hospital of Wisconsin
Medical College of Wisconsin
Milwaukee

I have the following financial relationships to disclose:

Company: AbbVie

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

Objectives

• Understand when additional testing is indicated in the constipated child
• Review the data regarding biofeedback for treatment of dyssynergic defecation
• Learn about new treatments for constipation
Functional Constipation

Infant & toddler (<4 yrs. of age)

Must include 1 month of at least 2 of the following in infants up to 4 years of age:
1. Two or fewer defecations per week
2. At least 1 episode per week of incontinence after the acquisition of toileting skills
3. History of excessive stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large-diameter stools that may obstruct the toilet

Children (>4 yrs. of age)

Must include 2 months of at least 2 of the following with insufficient criteria for diagnosis of IBS:
1. Two or fewer defecations in the toilet per week
2. At least 1 episode of fecal incontinence per week
3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large-diameter stools that may obstruct the toilet

Test of the child/adolescent Rome III criteria: agreement with physician diagnosis and daily symptoms

Table 1. Rome categories by responder

<table>
<thead>
<tr>
<th>Rome category</th>
<th>Parent</th>
<th>Child</th>
<th>Physician</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional dyspepsia</td>
<td>16 (34.8%)</td>
<td>3 (6.1%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Abdominal bloating</td>
<td>43 (88.7%)</td>
<td>20 (41.6%)</td>
<td>22 (46.85%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>43 (88.7%)</td>
<td>20 (41.6%)</td>
<td>15 (31.9%)</td>
</tr>
<tr>
<td>Functional abdominal pain</td>
<td>1 (0.2%)</td>
<td>9 (1.8%)</td>
<td>36 (73.6%)</td>
</tr>
<tr>
<td>Functional constipation</td>
<td>31 (63.7%)</td>
<td>9 (18.9%)</td>
<td>63 (25.4%)</td>
</tr>
<tr>
<td>Anal incontinence</td>
<td>2 (4.0%)</td>
<td>7 (14.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Anorectal symptoms</td>
<td>2 (4.0%)</td>
<td>7 (14.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Cyclic constipation</td>
<td>3 (6.1%)</td>
<td>3 (5.1%)</td>
<td></td>
</tr>
<tr>
<td>Formation</td>
<td>3 (6.1%)</td>
<td>3 (5.1%)</td>
<td></td>
</tr>
</tbody>
</table>

- Parents were least aware of their child's bowel symptoms
- Physicians preferred to give a diagnosis of FC over IBS in a study
- In one adult study 90% of patients with IBS-c also qualified for functional constipation*

Symptoms

- Constipation starting extremely early in life (<1 month)
- Passage of meconium >48 h
- Family history of HD
- Ribbon stools
- Blood in the stools in the absence of anal fissures
- Failure to thrive
- Fever
- Bilious vomiting

Signs

- Abnormal thyroid gland
- Severe abdominal distension
- Perineum examination:
  - Perianal fistula
  - Abnormal position of anus
  - Extreme fear during anal inspection
  - Anal scar
- Absent anal or cremasteric reflex
- Decreased lower extremity strength/tone/reflex
- Tuft of hair on spine
- Sacral dimple
- Gluteal cleft deviation

- Digital rectal exam
- Abdominal Radiography
- Colon transit studies
- Milk allergy testing
Treatment of Functional Constipation

- Encourage normal fiber and fluid intake
- Disimpaction: PEG as effective as enemas but can cause more fecal incontinence
- PEG preparations superior to placebo, lactulose and milk of magnesia
- Patient and parental education
- Routine use of prebiotics and probiotics is not recommended

Outcomes of Childhood Constipation

- Almost 50% of patients experienced at least one relapse in first 5 yrs.
- Almost 20% of children were symptomatic at 10 yrs. follow up

Risk factors for poor outcome
- Older age at onset of symptoms
- Long delay between onset of symptoms and starting treatment
- Lower defecation frequency at study entry

Slow transit - 13% to 60% of children with constipation

Stool expulsion

Slow transit

Bennings MA, et al Arch Dis Child;2004
Chihara DR, et al Am J Gastroenterol;2004
Disorders of Stool Expulsion

Dyssynergic defecation
Anal achalasia

Rectal Suction Biopsy

Indications for Anorectal Manometry

- To diagnose a non-relaxing internal anal sphincter
- To assess anorectal motility in children with fecal incontinence
- Obstructive symptoms or fecal incontinence following surgery for Hirschsprung’s disease
- To evaluate the effect of botulinum toxin injection into the anal sphincter
- To evaluate patients with defecation problems following surgery for imperforate anus
- Biofeedback training in children with fecal incontinence
Anorectal Manometry

Rectal compliance and constipation

Baseline (n=101) rectal compliance
- Normal in 36%
- Moderately increased in 40%
- Severely increased in 24%
  • lower defecation frequency ($P = .03$),
  • more fecal incontinence ($P = .04$)

After 1 year, treatment success was similar between groups
- 42% normal,
- 41% moderately increased,
- 40% with severely increased compliance.


Randomized Controlled Trial of Biofeedback, Biofeedback, and
Biofeedback and Standard Therapy for Dysfunctional Defecation

After Biofeedback
- Number of complete spontaneous bowel movements increased
- Use of digital maneuvers decreased
- Global bowel satisfaction was higher
Biofeedback success defined as:
- defecation frequency >3/wk
- soiling
- encopresis <2/month
- no laxatives

At 1 year success accomplished in 59% of the CT and 50% of the CT+BF group

Assessment of the Effectiveness of Biofeedback in Children with Dysfunctional Defecation and Recurrent Constipation: Encopresis Does Home Biofeedback Improve Long-Term Outcomes

- Age 6-14 yrs. Mean 9.2 yrs.
- N=36, long term follow up in 30 patients
- After 5 sessions of bio-feedback all patients demonstrated relaxation of external anal sphincter during defecation

Transcutaneous needle-free injection of botulinum toxin: a novel treatment of childhood constipation and anal fissure

Botulinum toxin 200 unit injected at 3 and 9 o'clock position
- Injection site confirmed by USS
- Treatment group n=16, controls group n=31
- Symptom severity scores at 3 m and 12 m follow up significantly better in treatment group
Internal Anal Sphincter Achalasia

Rectal biopsy: ganglion cells present
Anorectal manometry: Lack of anal sphincter relaxation with rectal wall distension

Clinical Presentation
• Earlier onset constipation
• Infrequent fecal soiling
• Less withholding behavior

Several enzyme and immunohistochemical studies have shown altered intermuscular innervations in the IAS. Absence of nitrergic innervations within the IAS muscle is believed to be responsible for the motility dysfunction in these patients.

Comparison of posterior internal anal sphincter myectomy and intrasphincteric botulinum toxin injection for treatment of internal anal sphincter achalasia: a meta-analysis
Hultin Frødebaek - From Paris

• Meta-analysis of 16 studies published 1973-2009
• Anal achalasia 395
  – 58% IAS myectomy
  – 42% Botox injection
• Non response to treatment higher with Botox treatment (20%)
• Short and long term improvement was significantly more frequent with IAS myectomy.
• Transient fecal incontinence higher with Botox treatment

Slow transit - 13% to 60% of children with constipation

Beringsma MA, et al Arch Dis Child;2004
Chitkara DK, et al Am J Gastroenterol;2004
56% colon manometry and scintigraphy studies showed similar results
30% scintigraphy showed delayed transit but colon manometry was normal
11% scintigraphy was normal but colon manometry showed dysfunction of distal colon

- 5 patients had normal oro-anal transit and normal colon manometry
- 19 had slow oro-anal transit:
  - 52% normal colon manometry
  - 32% distal colon dysfunction on colon manometry
  - 16% colon inertia

Using closely spaced pressure sensors more detailed information of colon and rectal motor function is possible
Colon Manometry abnormalities are associated with histological abnormalities (neuropathy)
Allows real time evaluation of colon, rectum and anal pressure changes
Surgical management of chronic refractory constipation

- Success rates for ACE 65% to 89%
- Colon manometry can help predict ACE success
- Almost 40% of patients can stop ACE within 2 yrs.
- Those who fail to improve with ACE can benefit from segmental of total colectomy


How does SNT work?
- Alters rectal sensitivity
- Improves colon transit

Risk:
- Infection
- Pain (2 patients) improved with changing the settings

Summary
- In a majority of children a clinical diagnosis of functional constipation and treatment is possible
- Relapses are common in the first 5 years after diagnosis
- Between 20% to 50% of children have a chronic intractable disease course
- In these patients diagnostic work up should include anorectal manometry, transit studies, colon manometry
- Newer drugs and surgical interventions are not well studied and effect on disease course is not well understood
Take Home Messages

• Early treatment and close follow up is associated with improved outcome
• In the absence of alarm symptoms and signs clinical diagnosis is acceptable
• Rectal biopsy is the gold standard investigation if Hirschsprung’s disease is suspected
• GI transit studies, anorectal and colon manometry studies are helpful in evaluating children with intractable disease
• Newer medical and surgical therapeutic options hold promise but more evidence is needed
Diet and the Microbiome

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 Pharmaceuticals
• Takeda Pharmaceuticals
• AbbVie, Inc.

*Products or services produced by these companies are not relevant to my presentation*

Objectives

• Understand how diet influences the human microbiome
• Learn how the microbiome influences the response to diet and dietary components
• Become familiar with the potential ways to modify the microbiome to reduce risk and prevent or modify disease
The Gut Microbiota in Health and Disease

Therapeutic disruption of dysbiosis
- Antibiotics, Probiotics, Prebiotics
- Fecal Transplantation
- Dietary Intervention

Dysbiosis (altered microbiota composition associated with disease)

Health

Disease

Things that we ingest such as food (diet), antibiotics, and xenobiotics:
- Shape the composition of the gut microbiota
- Serve as substrates for the gut microbiota to produce metabolites

We are not the only organism consuming what we eat

Elements of Modern Lifestyle Lead to Changes in Gut Microbiota
Early Diet Affects Microbiome

Koenig J E et al. PNAS 2011;108:4578-4585

Development of the Human Microbiota modified by diet, genetics and the environment, throughout life


Enterotypes of the Human Gut Microbiome

- Enterotypes Abundance of one of three genera
  - Bacteroides
  - Prevotella
  - Ruminococcus
- The basis for enterotype clustering is unknown but appears to be independent of:
  - Nationality
  - Gender
  - Age
  - Body Mass Index (BMI)

COMBO - Cross-Sectional Study of Diet and Stool Microbiota

- Is there an association between overall composition of diet and composition of the gut microbiota?

Methods:
- Usual diet - Standardized food frequency questionnaires
- Recent diet – Three 24 hour diet recalls within 1 week prior to provision of the stool sample
- Demographics – Subject interviews and questionnaires

Bacterial Enterotypes and Long Term Diet

Associations seen with long term, but not with recent diet patterns


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

Other lessons learned from Burkina Faso and the agrarian diet

African children:
- Overall greater microbial richness
- Overall greater bacterial diversity
- Higher levels of short-chain fatty acids

De Filippo et al. PNAS 2010;107:14691–14696

The vegetarian or vegan diet

Table 2. Results of the comparison of the full and the reduced vegan and vegetarian samples with the respective control groups (control, CG) for 10 different bacterial taxa.

<table>
<thead>
<tr>
<th>Bacterial Taxa</th>
<th>Vegetarian/CG</th>
<th>Vegetarian/CG</th>
<th>Vegetarian/CG</th>
<th>Vegetarian/CG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 150/36</td>
<td>N = 146/36</td>
<td>N = 146/36</td>
<td>N = 146/36</td>
</tr>
<tr>
<td>Bacteroidetes</td>
<td>P = 0.885</td>
<td>P = 0.002 (NS)</td>
<td>P = 0.885</td>
<td>P = 0.002 (NS)</td>
</tr>
<tr>
<td>Firmicutes</td>
<td>P = 0.002</td>
<td>P = 0.012</td>
<td>P = 0.002</td>
<td>P = 0.002</td>
</tr>
<tr>
<td>Actinobacteria</td>
<td>P = 0.885</td>
<td>P = 0.885</td>
<td>P = 0.885</td>
<td>P = 0.885</td>
</tr>
<tr>
<td>Proteobacteria</td>
<td>P = 0.885</td>
<td>P = 0.885</td>
<td>P = 0.885</td>
<td>P = 0.885</td>
</tr>
</tbody>
</table>

Twelve taxa: C1, control group; NS, not significant. Stat values indicate significant differences (≥0.05) from the control group in each taxon. Statistical analysis was performed with the Kruskal-Wallis test. Abbreviations: CG, control group; NS, not significant. Stat values indicate significant differences (≥0.05) from the control group in each taxon. Statistical analysis was performed with the Kruskal-Wallis test.

Healthy volunteers
Randomized to high fat vs. low fat diet
10 day inpatient stay with same meals each day
Caloric intake adjusted to maintain current weight
Daily stool sample collection

CaFE Study - Controlled Feeding Experiment

- Will a standardized diet reduce microbiota intersubject variability?
- What is the time course over which a diet alters the composition of the human gut microbiota?
- Does short term dietary fat or fiber alter the composition of the human gut microbiota and switch the abundance of Bacteroides vs. Prevotella?
  - 10 Healthy volunteers
  - Randomized to high fat vs. low fat diet
  - 10 day inpatient stay with same meals each day
  - Caloric intake adjusted to maintain current weight
  - Daily stool sample collection

CaFE Study
Longitudinal analysis of microbiome under controlled feeding

Changes detectable within 24 hours!

Each color represents a different subject

Detectable changes during the 10 days but:
- No enterotype switching
- No reduction in intersubject variation

Importance of long term diet
Wu et al., Science. 2011

Dietary components regulate bacterial gene transcription

- Important function of the intestinal microbiome is metabolism of glycans (complex carbohydrates and polysaccharides)
- Bacteroides thetaiotaomicron
  - Highly abundant obligate anaerobe in the microbiota of most adults
  - Known for its ability to metabolize polysaccharides

Sonnenburg et al. Science. 2005
Diet, the Gut Microbiome, Metabolome, and Disease

Diet serves as a substrate for the microbiota to produce certain metabolites

Potential Mechanisms

Importance of Gut Microbial Metabolites

Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis
Humans who follow a vegan diet produce less trimethylamine oxide (TMAO) after eating a steak or taking carnitine than meat eaters.

Meat eaters given broad-spectrum antibiotics no longer produce TMAO after eating a steak.

The CutC Bacterial Gene Converts Choline into TMAO: Implications for Human Health

- Quantify the risk for heart disease by characterizing the abundance of bacteria in the gut that have a CutC gene.
- Reduce CutC expressing bacteria in the gut or develop drugs to inhibit CutC activity in bacteria.
- Develop "medical foods" to reduce the production of TMAO by bacteria from the diet.

Dietary-fat-induced taurocholic acid promotes colitis in Il102/2 mice

- Devkota et al. Nature 2012;487:104
- Devkota et al. Nature 2012;487:104
- Devkota et al. Nature 2012;487:104
- Devkota et al. Nature 2012;487:104
Diet and the pathogenesis of GI illness
The role of dietary elements on the pathogenesis of GI illness

<table>
<thead>
<tr>
<th>Disease</th>
<th>Dietary Item</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD</td>
<td>Iron</td>
<td>Oral, but not parental; iron exacerbates experimental colitis – results in human IBD is controversial, but IV iron may be better tolerated</td>
</tr>
<tr>
<td></td>
<td>SCFA</td>
<td>Lack of SCFA-producing bacteria is associated with IBD, and butyrate supplementation, replacement of selected bacteria offer potential treatments</td>
</tr>
<tr>
<td>SCFA</td>
<td>Milk fat</td>
<td>Milk fat promotes a bloom of the colitogenic bacteria through increased levels of taurocholic acid</td>
</tr>
<tr>
<td>SCFA</td>
<td>Omega-3 fatty acid</td>
<td>Reduced Th 17-mediated inflammation and disease severity in murine models of colitis</td>
</tr>
<tr>
<td>IBS</td>
<td>Fermentable sugars</td>
<td>A diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) reduced IBS symptoms</td>
</tr>
<tr>
<td>IBS</td>
<td>Gluten</td>
<td>Gluten alters barrier function in IBS-0 patients, particularly those with HLA-DQ2/8</td>
</tr>
<tr>
<td>NASH</td>
<td>Choline</td>
<td>Dietary choline def. predisposes patients to NASH with microbiomes with excessive metabolic breakdown of choline</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Gluten</td>
<td>Gluten intolerance to gluten in a genetically susceptible host</td>
</tr>
</tbody>
</table>


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


Dietary Factors and UC

- Study of 191 patients with UC in remission
- Followed over 1 year
- 52% of patients relapsed during this time period
- Consumption of meat, particularly red and processed meat increased the likelihood of relapse

Jowett et al. Gut. 2004
Conceptual Model for IBD

Susceptible Host (Genetics)

Environmental Trigger #1 Influences Steady State Gut Microbiome
(Mode of Delivery, Early Diet, Long Term Diet)

Environmental Trigger #2 Initiates Pathologic Inflammation
(Infection, Antibiotic or NSAID Exposure)

Diet Contributes to Perpetuation / Recurrence of Pathologic Inflammation
(Jack of Key Nutrients, Influencing Metabolite Production, Direct Action)

Summary/Take-Home Points

• Don’t tell your patients with non-stricturing IBD to eat a low fiber diet

• Consider telling your IBD patients
  – Decrease use of PO iron
  – Increase fiber in diet
  – Limit red meat intake
  – Follow a Mediterranean diet
  – Become a vegetarian (vegan)

Mediterranean Diet

Summary/Take-Home Points

• Studies associating diet with the intestinal microbiome have consistently associated agrarian-based diets with:
  – distinct bacterial taxa
  – an increase in bacterial richness at the taxonomic and gene level
  – better health, compared with Western diets.

• At a minimum, the intestinal microbiome might be a useful biomarker of long-term consumption of healthy or unhealthy diets.

• More intriguing is the possibility that diet-induced alterations in the intestinal microbiome contribute to disease development.
Future Direction

• The challenge moving forward will be to provide evidence for dietary influences on the intestinal microbiome that have meaningful effects on human physiology

  – Changing the intestinal microbiome through dietary modifications may ultimately provide a powerful approach to disease prevention and therapy

Thank You
Disclosure

- I have the following financial relationships to disclose:
  - QOL Medical LLC (research support)
  - Mead Johnson (consultant)

- No products or services produced by these companies are relevant to my presentation

Objectives

1) Describe the common characteristics of FODMAP carbohydrates and mechanism of action in triggering GI symptoms

2) Review the evidence to support their use in patients

3) Learn to identify and appropriately counsel patients in the use of the FODMAP diet
FODMAP
- Fermentable (bacterial metabolism)
- Oligosaccharides (fructans/galactans)
- Disaccharides (lactose)
- Monosaccharides (fructose)
- And
- Polyols (sugar alcohols - sorbitol)
- Poorly absorbed, osmotically active, rapidly fermented (produce gas)

Barrett et al. Pract Gastroenterol 2007;31:51-65

FODMAP Hypothesis
- Malabsorbed dietary carbohydrates
- Physiologic effects
- Luminal fluid
- Luminal distention
- Gas production
- Osmotic load
- Fermentable substrate
- Diarrhea
- Bloating
- Pain
- Gas

Barrett et al. Pract Gastroenterol 2007;31:51-65

FODMAP Characteristics
• Poorly Absorbed - Fructose
**FODMAP Characteristics**

- Poorly absorbed
  - Lactose
    - Lactase
  - Fructans/Galactans
    - Fructose/Galactose polymers
    - Lack human hydrolases
    - Essentially intact into colon
  - Sugar alcohols
    - Sorbitol, Xylitol, Mannitol
    - Passive absorption

---

**FODMAP Mechanism of Action**

- Osmotically active - Fructose

---

Sonnenburg et al. Cell 2010;141:1241


---

FODMAP Mechanism of Action

- Osmotically active
  - Mannitol increases small bowel water content 10x versus glucose in healthy volunteers\(^1\)
  - Dietary FODMAP content correlates with ileostomy output\(^2\)
    - Higher output with higher FODMAP content
  - Enteral formulas with lower FODMAP content cause less enteral nutrition-associated diarrhea\(^3\)

\(^1\) Marciani L et al. Gastroenterology 2010;138:469-77
\(^2\) Barret JS et al. Aliment Pharmacol Ther 2010;31:874-882

---

FODMAP Mechanism of Action

- Highly fermentable

![Graph showing glucose, fructose, and FODMAPs](image)


---

FODMAP Mechanism of Action

- Highly fermentable

![Images showing liver and transverse colon](image)

FODMAP Mechanism of Action

• Highly Fermentable

FODMAP Evidence Review

• Adult Irritable Bowel Syndrome (IBS)
  - 1 Double Blind Placebo Controlled Challenge Study
  - 3 Randomized Controlled Trials
  - Several uncontrolled studies (symptom improvement 56-94%)

• Pediatric IBS
  - One uncontrolled study (n=8, symptom improvement 50%)
  - 1 Randomized Cross-Over Trial (Abstract)

• Inflammatory Bowel Disease
  - Open-label studies
FODMAP Evidence Review

• Adult IBS – Double Blind Challenge Study

FODMAP Evidence Review

• Adult IBS Controlled Trials
  - Low FODMAP diet vs. IBS Diet¹
    • Parallel group, randomized n=41
    • 13/19 (68%) Low FODMAP vs. 5/22 (23%) habitual diet with adequate control of symptoms (P<0.005)
  - Low FODMAP diet vs. High FODMAP diet²
    • Cross-over, 48 hour intervention, n=15
    • High FODMAP symptoms median 6 (range: 2-9) vs. Low FODMAP symptoms median 2 (range: 0-7) (P=0.002)

¹Staudacher HM et al J Nutr 2012;142:1510-18
²Ong DK et al. J Gastroenterol Hepatol 2010;25:1366-1373

FODMAP Evidence Review

• Adult IBS – Randomized Crossover Trial (n=33)
FODMAP Evidence Review

• Healthy adults – Randomized Crossover Trial

[Graph showing comparison of pain scores between baseline, typical diet, and low FODMAP diet]

Halmos EP et al. Gastroenterology 2014;146:67-75

FODMAP Evidence Review

• Pediatric IBS – Randomized Crossover Trial (n=33)

[Bar graph showing number of daily pain episodes]

Chumpitazi BP et al. NASPGHAN 2014 abstract

FODMAP Counseling

• Overall goal: decrease intake of FODMAP carbohydrates
  - Not complete elimination

• Generally recommended: restrict all high FODMAP foods first
  - Subsequently re-introduce/challenge
  - Alternative strategies: 1) Breath testing to guide fructose and/or lactose avoidance 2) Selective restriction

• Registered dietitian recommended
FODMAP Counseling

• Fructose
  - Avoid Foods with Fructose/Glucose ratio >1
  - Limit amount of those with high fructose content
  - Avoid: Apples, mango, watermelon, honey, dried fruit, HFCS
  - Allowed alternatives: Banana, blueberry, cantaloupe, grapes, kiwi, oranges, pineapples, raspberry, strawberry

• Lactose
  - Avoid lactose containing dairy products
  - Alternatives: Lactose-free dairy

FODMAP Counseling

• Polysols
  - Avoid "stone fruits" such as apricots, nectarines, cherries
  - Avoid sugar alcohol sweeteners: sorbitol, xylitol, isomalt
    - Sugar-free gums and mints

• Fructans/Galactans
  - Avoid: Vegetables such as asparagus, legumes, onions
  - Avoid: Wheat as a major ingredient in pasta, crackers, biscuits
  - Avoid: Drinks/supplements with chicory, prebiotics such as inulin or fructo-oligosaccharides

FODMAP Counseling

• Allowed Foods
  - Vegetables: alfalfa sprouts, green beans, bok choy, carrots, corn, cucumber, lettuce, potato, tomato
  - Breads and cereals
    - Gluten free (fewer fructans)
    - Corn-based crackers
    - Oats (e.g. oat bran)
    - Rice (white and brown), rice cakes
  - Protein (meats, chicken, fish, tofu)
# FODMAP Counseling

<table>
<thead>
<tr>
<th>Category</th>
<th>Allowed</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetables</td>
<td>Alfalfa sprouts</td>
<td>Asparagus</td>
</tr>
<tr>
<td></td>
<td>Bok Choy</td>
<td>Artichokes</td>
</tr>
<tr>
<td></td>
<td>Carrots</td>
<td>Beans and legumes</td>
</tr>
<tr>
<td></td>
<td>Cucumber</td>
<td>Beets</td>
</tr>
<tr>
<td></td>
<td>Eggplant</td>
<td>Cauliflower</td>
</tr>
<tr>
<td></td>
<td>Green beans</td>
<td>Garlic</td>
</tr>
<tr>
<td></td>
<td>Green and red peppers</td>
<td>Green peas</td>
</tr>
<tr>
<td></td>
<td>Lettuce</td>
<td>Leeks</td>
</tr>
<tr>
<td></td>
<td>Parsnip</td>
<td>Mushrooms</td>
</tr>
<tr>
<td></td>
<td>Potato</td>
<td>Okra</td>
</tr>
<tr>
<td></td>
<td>Pumpkin</td>
<td>Onion</td>
</tr>
<tr>
<td></td>
<td>Spinach</td>
<td>Snow peas</td>
</tr>
<tr>
<td></td>
<td>Squash</td>
<td>Snap peas</td>
</tr>
<tr>
<td></td>
<td>Tomato</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Turnip</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zucchini</td>
<td></td>
</tr>
</tbody>
</table>

## Additional Resources
- Monash University (www.med.monash.edu/cecs/fodmap)
  - iPhone and Android application
- Shepherd Works
  - www.shepherdworks.com.au
  - The Low FODMAP Diet Cookbook
- Publications
  - Barrett JS et al. Practical Gastroenterology 2007;31:51-65

Limitation: Lack of information on US foods

## Future
- Further determination of the mechanism of action
- Identification of children with IBS who will be most likely to respond
- Formal study of North American foods for FODMAP content
- Determination of effective ways to teach and follow the diet
Take Home Points

- FODMAP carbohydrates are poorly absorbed, osmotically active, and rapidly fermented (produce gas)

- A low FODMAP diet ameliorates GI symptoms in adults with IBS. Data is emerging for children with IBS. Data for other conditions is currently uncontrolled.

- FODMAP restriction is comprehensive though many food options are still available while on the diet

Acknowledgements

- Robert Shulman  
  - Danita Czyzewski  
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- Ann McMeans
- Monash University

- Support
  - NASPGHAN Foundation
  - Texas Medical Center DDC (NIH DK56338)
  - NIDDK (K23 DK095943)
Nutrition in the Child with Neurological Disabilities

Kathleen J. Motil, M.D., Ph.D., F.A.A.P
USDA Children’s Nutrition Research Center
Baylor College of Medicine
Houston, TX 77030

Disclosure

- I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.
- I do not intend to discuss an unapproved or investigative use of a commercial product or device in my presentation.

Objectives

- Be able to identify and address issues of malnutrition
- Understand management of refeeding syndrome, who is at risk for complications
- Learn appropriate tube feeding schedules, transition to oral feedings
**Measures**

- Identify and interpret 1st determinant of nutritional status
- Identify two critical refeeding problems and two risk factors that predispose to these complications
- List two indications for tube feedings
- Calculate refeeding and maintenance dietary energy needs

**Prevalence**

- ↑ Prevalence of nutritional disorders in children with neurological disabilities*
  - 29-46% underweight (BMI < 5th %ile)
  - 23% linear stunting (height < 5th %ile)
  - 8-14% overweight (BMI > 85th %ile)


**Clinical Significance**

- Health consequences
  - Improve growth outcomes
  - Reduce frequency of infection
  - Increase physical activity
  - Quality of life
  - Alter behaviors associated with hunger/satiety
  - Improve alertness, cognitive function
Etiology

- Inappropriate dietary intake
  - Chew/swallow dysfunction
  - Gastrointestinal dysmotility
- Intrinsic metabolic abnormality
  - Hyperthyroidism
- Increased nutrient losses
  - Malabsorption
- Altered energy expenditure
  - ↓ Muscle mass
  - ↓ Physical activity

Nutritional Assessment

- Which component is most useful to assess nutritional status of child?
  - Medical, medication, social history
  - Growth, anthropometric measures
  - Physical examination
  - Feeding pattern, meal observation
  - Laboratory and diagnostic studies

Case

- 5-yr-old female with Rett syndrome
- Weight 28# (12 kg) for previous one year
- Has good appetite, consumes well-balanced diet of chopped table foods, beverages per parents
- Height 98 cm, weight 12 kg, BMI 13 kg/m²
- Small head, absent speech, hand stereotypies, scoliosis, ambulatory
Rett Syndrome

- Is patient malnourished?
  - Yes
  - Maybe
  - No
- How would you characterize child’s nutritional status?
  - Patient is 5 y of age
  - Brother is 3 y of age

Growth Chart – Height and Weight

- Based on height and weight, is child undernourished?
  - Yes
  - Maybe
  - No

Growth Chart - BMI

- Based on BMI, is child undernourished?
  - Yes
  - Maybe
  - No
- BMI essential determinant of nutritional status
Feeding Pattern/Meal Observation

- Feeding pattern
  - How long does it take to feed child?
  - Does child cough, choke, or gag with liquids or solids?
- Meal observation
  - Lip closure, rotary chewing motion, tongue coordination
  - Coughing, choking when swallowing liquids, solids

Anticipatory Guidance

- What approach would you choose to refeed child?
  - Oral?
  - Enteral?
    - Nasogastric tube?
    - Gastrostomy?
  - Parenteral?

Methods for Refeeding

- Oral
  - Almost always first choice
  - Allow 6-month trial
  - Calculate goal weight gain: ½ to 1-½ lb/month
  - Critical BMI ≤ 12 kg/m²
- Enteral
  - Introduce concept of nasogastric, gastrostomy tube feeding
Oral Refeeding

- No need for calorie count
- Chopped, pureed table foods
- High calorie additives (margarine, honey, peanut butter)
- Commercial formula supplement (school setting)
- Multivitamin, mineral supplement
- Thickening agent for liquids
- Periodic weight to confirm goal

Indications for Tube Feedings

- Poor weight gain, weight loss > 6 months
  - BMI < 5th %ile
  - Flat weight curve
- Chewing/swallowing dysfunction
- Aspiration (Swallow Function Study)
- Parental request
  - Feeding refusal (meal time >30-45 min)
  - Medication administration

Formula Sources

- Commercial
  - Whole milk protein, hydrolysate, amino acid
  - Lactose absent
  - Supplemental vitamins, minerals usually not necessary
  - Fiber helps constipation; may increase gas
- Homemade blender preparations
  - Cost approximates commercial formulas
**Nutrient Needs for Refeeding**

- Fluid first limiting nutrient
- Minimum 80% body weight
- Daily energy estimate
  - 1-3 y: 100 kcal/kg IBW/HT
  - 4-6 y: 90 kcal/kg IBW/HT
  - 7-10 y: 70 kcal/kg IBW/HT
- Continuous nighttime drip and multiple daytime bolus feeds
- Ad lib oral feedings

**Complications of Refeeding**

- Refeeding syndrome
  - Shift from fat to CHO metabolism (↑ insulin triggers cellular uptake of fluid, nutrients)
  - Manifested as ↓ serum PO₄, K, Mg, glucose, thiamine
  - Risk factors include weight loss > 10% over 2-3 months or actual weight <70% IBW
  - CHF, arrhythmia, pulmonary edema, hemolysis, rhabdomyolysis, myopathy, seizures, coma, death

- Aspiration pneumonia
- Hypermetabolism
  - Hyperthermia, sweating
  - Increased sleeping
  - Hair loss
  - Hepatomegaly
  - Obesity
**Maintenance Feeding**

- Energy needs approximate RMR (1000-1500 kcal/d)
  - Assess physical activity
  - Monitor weight gain
  - Set goal BMI 25-50th %ile
- May need to supplement
  - Protein (1.2 g/kg/d)
  - Calcium (1000-1300 mg/d)
  - Vitamin D (600 units/day)

**Take Home Message**

- BMI essential component of nutritional assessment
- Dietary energy needs based on RMR and energy cost of growth
- Alternative feeding modalities indicated for persistent poor weight gain, chewing and/or swallowing dysfunction
- Refeeding syndrome requires monitoring serum PO₄, K
- Favorable nutritional status constitutes basis for success of other medical therapies

**Future Research**

- Identify more precisely energy and nutrient requirements for individual neurological disorders
- Identify molecular mechanisms that contribute to altered linear growth and deficits in muscle mass, poor bone mineralization in children with neurological disabilities
Disclosures

I have the following financial relationships to disclose:

Pfizer – Therapeutic Scientific Advisory Board; Grant Support
Eisai – IBD Advisory Board
Ironwoods – IBD Advisory Board
Cubist – IBD Advisory Board
Abbvie – IBD Advisory Board
Hoffman La-Roche – IBD Advisory Board, Consultant
Jannsen – IBD Advisory Board, Consultant

* No products or services produced by these companies are relevant to my presentation.

Objectives

• Review immunodeficiencies that may present with intestinal inflammation

• Understand the phenotype, genetics and prognosis for Very Early Onset IBD (5yrs and younger)

• Learn an appropriate immunological evaluation of a child with Very Early Onset IBD
Crosstalk Between Host Cells and Microbes in Health and Disease

Incidence of IBD is Increasing Dramatically Worldwide

Pathogenesis of IBD

Genetics and IBD in the Adult and Pediatric Population

- Increased risk of IBD in 1st degree relatives (26 fold increase for CD; 9 fold increase for UC)
- 30% of children have one or more family members with IBD
- Concordance rate much greater in monozygotic vs dizygotic twins
  - 10-15% in UC; 25-30% in Crohn’s
Unique Aspects of Pediatric IBD

• ~20% of IBD presents in children
• Children with UC – more extensive disease
• Children with CD – upper intestinal tract involvement common
• Young children often present with Crohn’s colitis with perianal involvement

Mermel P, Ann J Gastro 2002
Heyman MB, J Pediatr 2003

Unique Clinical Features of VEO-IBD*

<table>
<thead>
<tr>
<th>VEO - IBD</th>
<th>Adolescent and Adult-Onset IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic involvement - 80% at &lt; 10 years of age</td>
<td>Colonic involvement - &lt;20%</td>
</tr>
<tr>
<td>Ileal involvement – less common at age &lt; 10 yrs</td>
<td>Ileal involvement – up to 80%</td>
</tr>
<tr>
<td>Family history – 40-50%</td>
<td>Family history – 14-20%</td>
</tr>
<tr>
<td>Extension of disease – up to 40%</td>
<td>Extension of disease – up to 16%</td>
</tr>
</tbody>
</table>

* Defined as Age < 10 by the Paris Classification


Unique Aspects of Infantile IBD (< 2yo)

• Often isolated Colonic Disease
• Severe Course – refractory to multiple immunosuppressant medications, often requiring surgery, occasionally fatal
• > 40% with one or more family members with IBD
• 25% first manifestation of underlying immunodeficiency

Ruemmele 2006 JPGN
Cannito 2009 EJP
Heyman 2005 J Ped
Greatest Increase in IBD Incidence
Very Early Onset IBD

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>IBD</th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>6mo-4yr</td>
<td>+56.8% (P=0.11)</td>
<td>+51.0% (P=N/A)</td>
<td>+38.1% (P=0.95)</td>
</tr>
<tr>
<td>5-9 yr</td>
<td>+65.7% (P&lt;0.001)</td>
<td>+58.9% (P&lt;0.001)</td>
<td>+57.9% (P&lt;0.001)</td>
</tr>
<tr>
<td>10-14 yr</td>
<td>+34.1% (P&lt;0.001)</td>
<td>+36.3% (P&lt;0.001)</td>
<td>+38.9% (P&lt;0.001)</td>
</tr>
<tr>
<td>15-17 yr</td>
<td>+25.1% (P&lt;0.001)</td>
<td>+12.1% (P=0.016)</td>
<td>+27.4% (P=0.03)</td>
</tr>
</tbody>
</table>

* By Poisson regression analysis, controlling for sex

GWAS Studies Have Identified over 180 Inflammatory Bowel Disease Susceptibility Loci

Key Pathways Arising From Gene Discovery In Crohn’s Disease And Ulcerative Colitis

www.neopics.org
Have Large Scale Genetic Efforts Missed Key Dominant Pathways Causing Infantile and VEO-IBD?

Adapted from Kaser A, Zeissig S & Blumberg RS, Dig Dis 2010

Primary Immunodeficiencies Often Present with Intestinal Inflammation

- IPEX syndrome
- Wiskott-Aldrich syndrome
- Chronic granulomatous disease
- Enterocolitis
- Superficial cryptitis
- XIAP (X-linked inhibitor of apoptosis)
- NEMO (NF-κB Essential Modulator) Deficiency
- Estrogen/progesterone

Since these are Rare Diseases an International Effort is Required to Advance our Understanding

NEOPICS/Care-for-Rare IBD Alliance

Principal Investigators:
- Aleixo Muise – Sick Kids, UT
- Christoph Klein – University Children’s Hospital Munich
- Scott Snapper – Boston Children’s, HMS

NEOPICS – expanded to 80 Centers (250 scientists) on 5 continents with access to over 1000 VEO-IBD patients
Case

- Presented in 1st year of life with severe colitis
- Persian ancestry
- Multiple enterocutaneous fistulae, recurrent folliculitis, recurrent infections, impaired wound healing

Genetic Evaluation Identified Mutation in IL-10 Receptor

IL10R Pathway

- IL10 restricts excessive immune responses
- Inhibits secretion of pro-inflammatory cytokines - TNFα, IL12, and IFNγ
- Receptor: IL10R has two subunits:
  - Alpha (A/1) – IL10
  - Beta (B/2) – IL10, -22, -26
- Acts through JAK1, TYK2, and STAT3
- IL10, TYK2, and STAT3 have been identified in IBD GWAS

www.neopics.org
IL10R Deficiency Results in Infantile-Onset IBD

- IL10RB and IL10RA mutations have now been found in numerous locations within each gene – to date each having similar presentations and similar signaling defects

- Hematopoietic stem cell therapy can be curative


Case 2

- Patient ET
  - Presented at 2 months of age:
  - Blood in stool
  - Diagnosed with cow’s milk protein allergy
- Diagnosed < 1 yo with Crohn’s colitis.
- Developed perianal and small bowel disease < 2 years of age.
- No evidence of chronic infections or immunodeficiency.
- No family history of IBD, parents not consanguineous.
- Has abnormal low normal reactive oxygen species (ROS) production (3x).


Hypothesis:

Defects in the NADPH oxidase genes that do not cause overt Chronic Granulomatous Disease (CGD) are associated with susceptibility to IBD.

NADPH Oxidase Genes and CGD

- CYBB: gp91phox (X-Linked, Recessive) frequency ~65%
- CYBA: p22phox (Autosomal, Recessive) frequency <5%
- NCF1: p47phox (Autosomal, Recessive) frequency ~25%
- NCF2: p67phox (Autosomal, Recessive) frequency ~5%
- NCF4: p40phox (Autosomal, Recessive) frequency <1%

Lam et al., 2010

Sequencing of NADPH Oxidase Genes in Infantile and VEO-IBD Patients Identifies Deleterious Mutations

- Identified a novel NCF2 variant - (c.113 G/A) resulting in a mutation in p67phox R38Q.
- Variant results in aberrant Rac2 binding
- Examined this mutation – 2 independent VEO-IBD cohorts
  - 4% of VEO-IBD patients (11/268)
  - 0.3% of older IBD patients (1/330)
  - 0.2% of healthy controls (1/480)


NADPH oxidase Genes and VEO-IBD

Sequenced NADPH oxidase genes – 314 VEO-IBD patients compared to 4300 controls - Found novel and rare mutations in VEO-IBD patients (replicated and validated)

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Protein Domain</th>
<th>Population Frequency</th>
<th># of Patients (N=122)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYBB</td>
<td>rs14756032</td>
<td>Ferric Reductase</td>
<td>0.005%* (Males)</td>
<td>1 Predicted Damaging</td>
<td></td>
</tr>
<tr>
<td>NCF1</td>
<td>rs13447</td>
<td>PX Domain</td>
<td>8.5%** (Hetero.)</td>
<td>12 Reduces ROS Production</td>
<td></td>
</tr>
<tr>
<td>NCF2</td>
<td>G561R</td>
<td>SH3 Domain</td>
<td>0*</td>
<td>1 Predicted Damaging</td>
<td></td>
</tr>
<tr>
<td>NCF2</td>
<td>P5454</td>
<td>PX Domain</td>
<td>0.005%* (Hetero.)</td>
<td>1 Strong ESE Lost</td>
<td></td>
</tr>
<tr>
<td>NCF4</td>
<td>R308Q</td>
<td>PB1</td>
<td>8x10^-5*</td>
<td>1 Predicted Damaging</td>
<td></td>
</tr>
<tr>
<td>RAC2</td>
<td>Non-coding</td>
<td>Intron 5</td>
<td>0*</td>
<td>1 Isoform A site gained</td>
<td></td>
</tr>
</tbody>
</table>

Dhillon et al, Gastro in Press
How do we assess the heritability of the remaining fraction?

1. Deep sequencing of GWAS loci for identification of rare variants
2. Immunochip analysis of selected genes in similar cohort
3. Whole Exome Sequencing (WES)/Whole Genome Sequencing (WGS)

WES in VEO-IBD patient leads to identification of mutation in XIAP (associated with X-linked lymphoproliferative syndrome – XLP2)

Case 3 – WES
Multiple Intestinal Atresia (MIA), SCID and Apoptotic Enterocolitis

- A female patient born at term
  - Unrelated parents
  - Presented with high output secretory hematochezia at birth
  - Lymphopenia and hypogammaglobulinemia
- Colonoscopy demonstrated
  - Chronic inflammation with severe friability exfoliative mucosal changes
  - Sloughed mucosa within the colonic lumen
  - Crypt apoptosis and exploding crypts
- WES

Mutations in Tetrameric Repeat Domain 7A Result in a Severe Form of Very Early Onset Inflammatory Bowel Disease

Whole-exome sequencing identifies tetramer repeats in patients with intestinal atresia

TTC7A mutations disrupt intestinal epithelial agglomerosis polarit

JMG 2013

Gastroenterology 2014

JACI 2013

JCI 2014
TTC7A Mutations Cause Apoptotic Enterocolitis

- Little is known about the function of the Tetratricopeptide Repeat Domain 7 (TTC7A) gene
- Studies suggest it plays a critical role in PI4KIIIα regulation? ROCK regulation
- Defects in murine Ttc7 gene
  - result in the flaky skin (fsn) mutant mice
  - develop pleiotropic abnormalities, including runting syndrome, anemia, psoriasis, diarrhea, and intestinal apoptosis

Conclusions: TTC7A-Deficiency and VEOIBD

- Severe intestinal inflammatory process likely at least partially driven by a primary epithelial defect
- Associated with multiple intestinal atresia (and recurs post-resection)
- Associated with SCID (severe combined immunodeficiency)
- Intestinal disease seems to not respond to hematopoietic stem cell transplant

Evolving Approach to VEO-IBD

First – Screen for Genes known to Cause VEOIBD
Next Examine Genes in Common Pathways
Examine Novel Variants
Functional Examination of Variants

Uhlig, Elkadi, Ouahed, Snapper, Muise et al, Gastro 2014

www.neopics.org
VEO-IBD: Take Home Points

- GWAS have shown that genetics in adult and adolescent pediatric IBD overlap considerably.
- Immunodeficiencies account for a significant percentage of patients presenting with infantile IBD
- Unique genetic abnormalities may be more dominant in VEO-IBD (e.g., IL-10R; NCF2); however, data is limited
- Whole exome sequencing (and ultimately whole genome sequencing) will greatly expand our ability to detect rare variants in individual patients

www.neopics.org
“Luminitis – When inflammation is NOT IBD”

Robbyn Sockolow, MD
Associate Professor of Clinical Pediatrics
Weill Cornell Medical School
New York-Presbyterian Hospital

I have the following financial relationships to disclose:

Janssen
AbbVie
Abbott
Lupin

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

Objectives

• Understand the diagnostic criteria and differential diagnosis for microscopic colitis
• Review the treatment of lymphocytic and collagenous colitis
• Discuss the diagnostic criteria and treatment of eosinophilic colitis, including the approach in transplant patients
Microscopic Colitis

- Inflammatory condition marked by chronic or intermittent watery nonbloody diarrhea with a normal endoscopic appearance
- Prevalence of 4 to 13% in Adult pt with chronic diarrhea; pediatric prevalence unknown (Narla et al JPNN 2013;57:557-561)

Definition of Microscopic Colitis

Normal endoscopic appearance and abnormal histology

- **Lymphocytic Colitis**
  - Lymphocytes increased in the colonic tissue (>20 intraepithelial lymphocytes/100 colonocytes, mixed inflammation in the LP and normal crypt architecture)
- **Collagenous Colitis**
  - Lymphocytes increased in the colonic tissue (subepithelial collagenous band > 10 micrometers, inflammation in the LP with normal crypt architecture)
  - Thick layer (up to 30 micrometers) of collagen in the tissue

Comparative Colonic Biopsies:
Normal, Collagenous, Lymphocytic
Signs and Symptoms of Microscopic Colitis

- Persistent watery non-blood diarrhea
- Abdominal pain
- Distention
- Weight loss
- Nausea
- Dehydration
- Fecal incontinence

Adult vs. Pediatric

**Adults**
- >>>Female
- Autoimmune association
- Exposure to medications
- CC mostly in women
- LC more equal M:F
- Often Diarrhea alternating Constipation

**Pediatrics**
- Girls > boys (3:2)
- Autoimmune association
- Exposure to medications
- Tends to resolve over time but longer duration of symptoms
- LC > CC

Work up for Chronic Nonbloody Diarrhea

- Stool for infectious causes; Guaiac
- Stool for malabsorption often abnormal
- Blood work (include Celiac markers, TFTs)
- EGD/Colonoscopy with multiple biopsies to include the right and transverse colon, EM
- Radiologic testing
Causes/Risk Factors

- Unknown etiology
- Possible etiologies
  - Medications
  - Infections: Bacteria that produce toxins/Viruses
  - Immune disorders (Celiac, RA, Type I DM, thyroid disease: Hashimoto’s or Graves disease)
  - Collagen synthesis abnormalities
Lymphocytic Colitis

Treatment of Lymphocytic and Collagenous Colitis

- Diet: low fat & low fiber diet; ?gluten/dairy free diet
- Discontinue any possible medication related cause
- Medication:
  - Steroids: budesonide
  - Antidiarrheal medications
  - Cholestyramine resin
  - Mesalamines
  - Immunosuppressives

Eosinophilic Colitis

- Well recognized syndrome in infants usually related to food allergen
- Histological hallmark of colonic infiltration with eosinophils
- Assoc w/ atopy, helminthic infections, IBD, autoimmune diseases, Celiac disease and drug reactions (e.g. tacrolimus tx Post OLT)
Signs and Symptoms of Eosinophilic Colitis

- +/- Bloody diarrhea
- Abdominal pain
- +/- Weight loss
- +/- Peripheral Eosinophilia
- Elevated serum IgE
  - Higher the IgE the more eosin infiltration on bx
- Transplant patients on tacrolimus with new onset food allergies (increased RAST)

Transverse Colon’s Endoscopic Appearance

www.medscape.com

Eosinophilic infiltration of lamina propria

Saeed et al Pediatr Transplantation 2008: 10: 730–735
Eosinophilic colitis


Tacrolimus Associated EoC

• Post liver transplantation (LR or OLT)
• Symptoms develop several mos after
  – High serum IgE
  – Eosinophilia
  – Histological infiltration of eos on colonic bx
  – IgE-positive RAST for foods esp. milk protein
  – Bloody diarrhea

Possible Mechanisms For Tacrolimus induced EoC

• Known to induce increased intestinal/colonic permeability1,2,3
• Altered cytokine production (e.g. inhibition of IL-2 resulting in augmentation of IgE production) leading to eosinophilia4,5

Management of Eosinophilic Colitis

- Elimination or elemental diet
- Avoidance of RAST or SPT positive allergens
- Discontinue any possible medication related cause
- Decrease or discontinue tacrolimus therapy
- Medication:
  - Steroids: budesonide
  - Immunosuppressives: thiopurines

Conclusions

- **Microcytic colitis** is a nonbloody diarrheal presentation that appears normal on colonoscopy but should be biopsied throughout the colon to look for microscopic evidence of disease
- **Eosinophilic colitis** is a bloody diarrheal presentation where food allergy should be suspected; new onset bloody diarrhea in transplant patients on tacrolimus may be at risk
Crohn’s and UC - What to do when anti-TNF isn’t working?

Athos Bousvaros MD MPH
Boston Children’s Hospital
NASPGHAN 2014

Disclosures

• Consulting: Millennium, Dyax, Cubist, Nutricia
• Research support: Prometheus
• Every medication I discuss in this talk is not approved in adult or pediatric IBD
• Most of the data I give in this talk will be from adult studies
• This data should NOT be extrapolated to very young children with IBD, especially those with suspected immune deficiencies.

Overview

• How well do anti-TNF’s work?
• Rescue treatments
  – Calcineurin inhibitors for UC
  – Thalidomide for Crohn disease
  – Natalizumab for Crohn disease
  – Vedolizumab for Crohn disease and UC
  – Ustekinumab for Crohn disease
  – Tofacitinib for UC
• All are off-label in children, and only vedolizumab is currently FDA approved for adult inflammatory bowel disease
Infliximab and adalimumab in pediatric Crohn’s Disease

- REACH trial (infliximab)
  - 88% response rate after 3 months
  - 55% remission rate after 12 months
  - Mostly combination therapy

- IMAGINE trial (Adalimumab)
  - Standard induction, then hi vs. low dose maintenance
  - Approximately 60% on 'immunosuppressants'

- Results (clinical remission, high dose)
  - Week 52
    - 45% infliximab naïve, 19% if prior infliximab

How effective is infliximab as “step up therapy” in pediatric UC?

- Open-label trial of 60 children with UC
  - 5mg/kg infliximab
  - Only 50% previously treated with 6MP/AZA
  - 70% “response” after two months
  - Overall remission rate at 1 year – 29%
  - Increasing dosage and decreasing interval may increase remission to 40-50%

Optimizing use of anti-TNF

- Make sure you have the right diagnosis
- Don’t overuse anti-TNF therapies
  - ASA
  - Immunomodulator (6MP, AZA, MTX)
- Take steps to minimize risk of loss of response
  - Scheduled infusions
  - Combination therapy (risk vs. benefit)
  - Therapeutic drug monitoring
- Increase dose before “giving up”
When anti-TNF really doesn’t work, options are very limited

- Weigh benefit to risk ratio
- Is surgery preferable?
  - Ulcerative colitis – colectomy with/without pouch
  - Crohn’s – limited resection, diversion, colectomy
- Is long term nutritional therapy an option?
- Pediatric rescue medication data is limited
  - Tacrolimus, cyclosporine for ulcerative colitis
  - Thalidomide for Crohn’s disease
  - Natalizumab for Crohn’s disease

Calcineurin inhibitors (Tacrolimus and Cyclosporine)

- Fallen out of favor because of increasing and improving experience with anti-TNF agents and newer treatments.
- CYSIF Trial (France, adults) - Cyclosporine vs. IFX
  - “Treatment failure” about 60% in both groups
    - Lack of response by 7 days
    - Flare within first 98 days
    - Colectomy
- Conclusion: “Cyclosporine was not more effective than infliximab in patients with acute severe ulcerative colitis ... in clinical practice, treatment choice should be guided by physician and centre experience”


Severe colitis (CH Boston experience)
Outcomes of tacrolimus therapy
(Watson et al, IBD Journal 2011)

<table>
<thead>
<tr>
<th>HOSPITAL</th>
<th>46 patients tacrolimus induction</th>
<th>3 colectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mos</td>
<td>43 patients discharged PUCAI 85 pre, 22 post</td>
<td>6 colectomy within 3 months, 1 infliximab, 1 returned to other hospital</td>
</tr>
<tr>
<td></td>
<td>35 transitioned to maintenance therapy</td>
<td>12 colectomy between 3 months and end of followup</td>
</tr>
<tr>
<td>LONG TERM</td>
<td>23 stable on maintenance therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 6-mercaptopurine, 8 infliximab, 1 neither (longest remission 14 years)</td>
<td></td>
</tr>
</tbody>
</table>
**Tacrolimus or cyclosporine**

- Consider if:
  - New onset severe UC (alternative to anti-TNF, but needs to be a short term "bridge" to another agent)
  - Acute UC unresponsive to anti-TNF
    - Salvage therapy is highly controversial
    - Discuss risks and benefit with patient.
- Using calcineurin inhibitors
  - Cyclosporine - 2-4 mg/kg/day IV bid
  - Tacrolimus – 0.1 mg/kg/dose PO bid
- Monitor renal function, glucose, blood pressure, and drug levels.

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**Thalidomide**

- Used in pediatric Crohn’s disease for over a decade.
  - Role in UC less clear
- Both TNF inhibitor and anti-angiogenesis
- Placebo controlled trial*
  - 28 children thalidomide (1.5-2.5 mg/kg/day)
  - vs. 26 placebo, with rescue option
- Primary endpoint - >75% reduction in PCDAI by week 8.
- 46% improvement vs. 11% in placebo.
- Overall, 31 of 49 children achieved remission.

*Fang et al., JAMA. 2012;310(20):2164-2173

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**Thalidomide data**

Lazzarin, JAMA. 2013;310(20):2164-2173
Felipez et al. 2012;JPGN 54:28-33
Why don’t more people use this drug?

- Fear of side effects
  - Birth defects
  - Neuropathy
  - Sedation
  - Clots
- Regulatory issues
  - STEPS program
- Dose
  - 2.5 mg/kg induction (150 mg)
  - Maintenance (50 mg)

Thomas Quadtolf

Natalizumab for pediatric CD

- 31 patients received 3mg/kg for 3 infusions
  - PCDAI >30
  - Ages 11-17
- Well tolerated
- Response 45%
- Remission 15%
- PML risk
  - 1/1000
  - JC virus Ab + patients at higher risk

(Hyams et al, JPGN 2007;44:185)

Natalizumab

- Use of natalizumab to treat Crohn’s will be very limited in the future, because vedolizumab has been approved by the FDA, and does not cross the blood brain barrier.
New meds to the rescue

- Vedolizumab
  - UC and Crohn’s
- Ustekinumab
  - Crohn’s
- Tofacitinib
  - Ulcerative colitis

Vedolizumab

- Humanized IgG 1 monoclonal antibody to α4β7 integrin
- Modulates gut, but NOT brain lymphocyte trafficking
- Less risk of PML compared to natalizumab

Vedolizumab as induction and maintenance therapy for UC

- Combination placebo controlled and open-label trial
  - 374 patients – vedolizumab or placebo
  - 521 patients – open label vedolizumab
- Inclusion – active UC
  - Mayo score 6-12, endoscopy subscore of 2.
- Induction – two doses – week 0 and 2
- Maintenance
  - Responders continued on active drug, or randomized to placebo

Vedolizumab - results

- Week 6
  - Response – 47% vedolizumab vs. 25% placebo
  - Remission – 17% vedolizumab vs. 8% placebo
- Week 52
  - Remission (in the responders)
    - 45% of patients getting vedolizumab monthly
    - 42% of patients getting it every other month
    - 16% of patients randomized to placebo

Vedolizumab also works in Crohn’s disease, but it takes time!

- Overall trial – superior to placebo at week 6, but the main effect was seen in anti-TNF naïve patients
- Sands et al – in anti-TNF failures (about 50%):
  - 6 week remission rate (15%) similar to placebo
  - 12 week remission rate (27%) much higher vs. placebo (12%)

IL-12/23 in IBD
Ustekinumab in Crohn’s

- Antibody to IL12 and IL23 (p40 subunit)
  - Approved for use in psoriasis
- 526 patients from 153 centers
- Four arm study – 3 different doses and placebo
- Inclusion criteria:
  - Crohn’s for at least 3 months
  - Active CDAI (220-450)
  - Failure of anti-TNF therapy
  - Loss of response or serious adverse event
  - Stable doses of ASA, 6MP, MTX, or prednisone allowed


Ustekinumab results (Crohn’s)

- Week 6 response
  - 35% ustekinumab (3mg/kg)
  - 23% placebo
- Week 22 remission
  - 42% ustekinumab
  - 27% placebo
- Mucosal healing evaluation was limited
- Dose –
  - 90 mg SQ monthly
  - 3mg/kg

Ustekinumab Adverse events

- Serious infections
  - 7 patients (6 ustekinumab) during induction
  - 11 patients (4 ustekinumab) during maintenance
- Antibodies rare
- 1 basal cell CA in an ustekinumab pt
- Infusion reactions 5% across the board (including in the placebo group)
- Psoriasis trials suggest overall good safety profile, with no significant increase in infections or cardiovascular events.
Intermission – what is a “Mayo score”?

- Mayo Endoscopic Scoring of Ulcerative Colitis

Tofacitinib

- Small molecule
- JAK kinase inhibitor
  - Affinity for JAK 1 and 3
  - Inhibits cytokine signaling
- Approved for RA that has not responded to MTX
- Metabolized by liver – (CYP3A4)
- Phase 2 clinical trial suggests efficacy in ulcerative colitis

Tofacitinib in active ulcerative colitis

- Phase 2 placebo RCT
  - 194 adults active UC assigned to 4 different doses of tofacitinib or placebo
- Mayo score of 6-12, and active score on endoscopy (Mayo score of 2-3)
- Prior meds
  - 40% immunomodulator failure
  - 30% prior anti-TNF exposure
- Short term trial – only 2 months

Tofacitinib results

- Clinical remission at 2 months
  - 48% at tofacitinib, 10 mg bid vs. 10% on placebo
- Endoscopic remission
  - 30% on tofacitinib 10 mg bid vs. 2% on placebo

Tofacitinib adverse events

- Myelosuppression
- Lipid abnormalities
  - Increase in both LDL and HDL
  - Some patients need statins to control
- Serious infections
  - Pneumonia, cellulitis, zoster, UTI
- Liver function abnormalities
- Malignancies (including lymphoma)

“Off label” does not necessarily mean “experimental” – FDA statement

- The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such “unapproved” or, more precisely, “unlabeled” uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

Scott, Drugs 2013; 73; 857
Conclusions

• Options for our patients with IBD who respond poorly to biologics are limited.

• Three new drugs with potential in IBD, but limited data, especially in children, are:
  – Vedolizumab
  – Ustekinumab
  – Tofacitinib

• Vedolizumab has been FDA approved for treatment of CD and UC over age 18 years.