



OCTOBER 23, 2014









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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)*<sup>TM</sup> Physicians should only claim credit commensurate with the extent of their participation in the activity.

#### NASPGHAN POSTGRADUATE COURSE

THURSDAY OCTOBER 23, 2014 Grand Ballroom, Atlanta Hilton

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

#### **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

12:25 PM - 1:50 PM

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-THE 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**

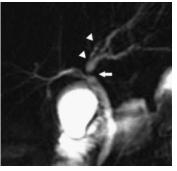
- Learn the etiology and progression of PSC.
- Understand how to appropriately screen.
- Review the treatment controversies, including ursodiol and vancomycin.

## **Autoimmune Liver Disease**

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

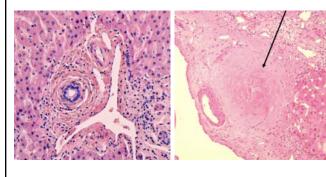
# **Primary Sclerosing Cholangitis**

 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 endstage liver disease



Alexopoulou et al, JPGN 55:308, 2012

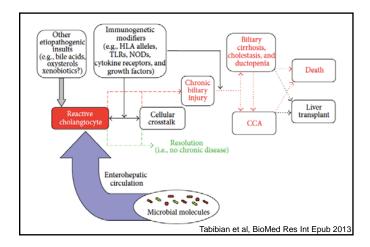
# **Primary Sclerosing Cholangitis**



# PSC/AIH Overlap

# **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



## **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

# IBD and PSC Genetic Overlap IBD 103 loci Crohn's disease 30 loci 7 loci Multiple MHC associations Karlsen and Boberg, J Hepatol 59:571, 2013

#### **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? Children Active autoimmunemediated bile duct injury Active autoimmunemediated bile duct injury Active autoimmunemediated 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**

- PedilBD 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

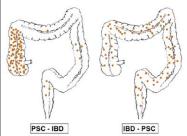
Jose et al, Inflamm Bowel Dis 15:63, 2009

#### **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

Joo et al, Am J Surg Path 33:854, 2009

#### **Colitis and PSC**



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

Schaeffer et al, Dig Dis Sci 58:2608, 2013

#### **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

Goyal and PIBDCRG, JPGN 59:321, 2014

# 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

-	

## **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

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# **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 Immunmodulatory 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 Lindor et al, Hepatology 50:808, 2009 Imam et al, Aliment Pharmacol Ther 34:1185, 2011 Wunsch et al, Hepatology epub, 2014 **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?

and PSC/AIH overlap (WUP PSC, ClinicalTrials.gov NCT01088607)

 Multicenter prospective trial underway sponsored by FDA OOPD to study effects of UDCA withdrawal and reinstitution in children with PSC

#### **Vancomycin in Adults**

- Recent randomized, double-blind trial of vancomycin or metronidazole
  - 35 adult patients 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

Tabibian et al, Aliment Pharmacol Ther 37:604, 2013

### 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

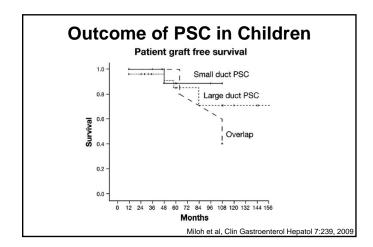
Davies et al, JPGN 47:61, 2008 Abarbanel et al, J Clin Immunol 33:397, 2013 Davies et al, Case Rep Transplant epub 2013

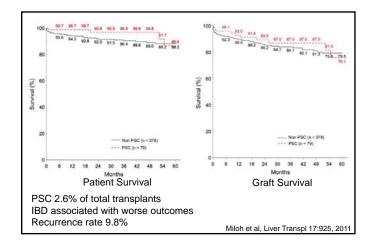
#### Course of PSC in Children

- 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

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# **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	
<ul><li>New drugs</li><li>C-23 UDCA analogue nor-UDCA</li></ul>	
<ul> <li>Nuclear receptor agonists</li> </ul>	,
<ul> <li>Better biomarkers</li> </ul>	
■ miRNAs	
■ Fibrosis	
<ul><li>Inflammation</li></ul>	
"Useful" genetic data	
<ul><li>Insight into disease mechanisms</li><li>Individualize therapy</li></ul>	
<ul><li>Impact of NAFLD on PSC?</li></ul>	
Thank you!	





## The Jaundiced Infant

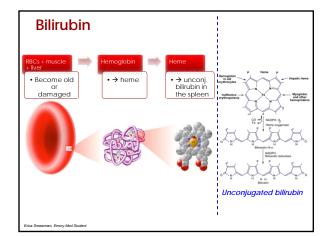
#### Saul J. Karpen, M.D., Ph.D.

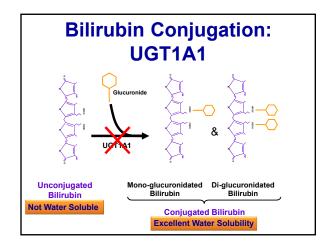
Raymond F. Schinazi Distinguished Biomedical Chair Professor of Pediatrics Emory University School of Medicine Children's Healthcare of Atlanta NASPGHAN PG Course, Atlanta October 23, 2014 No disclosures

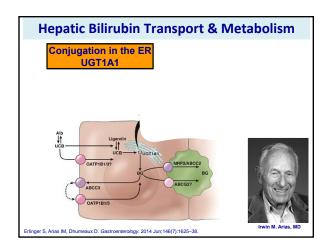


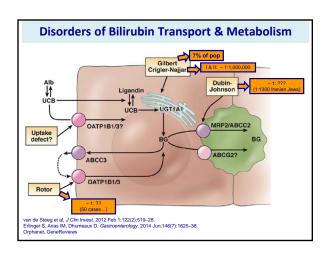
# **Topics**

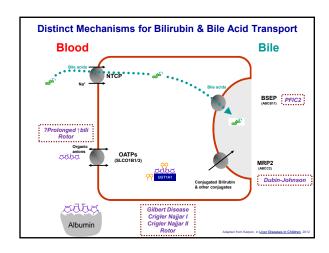
- Bilirubin Primer
- DDx of Jaundice with & Common Etiologies
- Impact of Genetic Testing & Other Diagnostic Modalities
- Available & Future Treatments

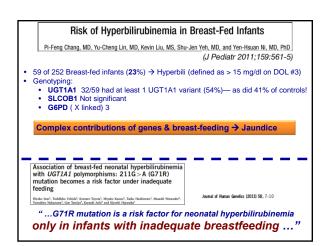


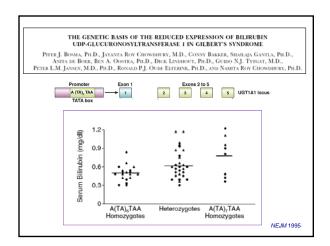






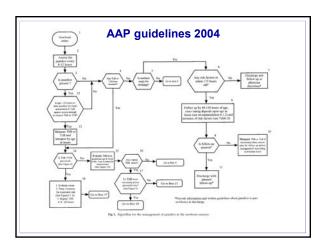




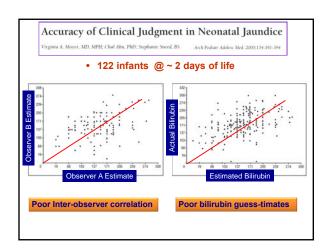


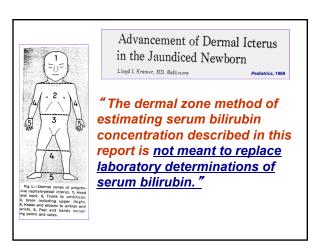
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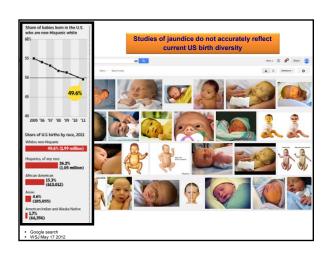
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# Maternal factors Race or ethnic group Asian Native American Greek Islander Complications during pregnancy Dubetes mellitus Rh incompatibility ABO incompatibility Use of oxyocin in hypotonic solutions during labor Brease feeding\* Perinatal factors Birth trauma Cerbalhematoma Ecohymoses Infection Bix terrial Viral Protozoal Proto







• Q: What is in breast milk that leads to jaundice?

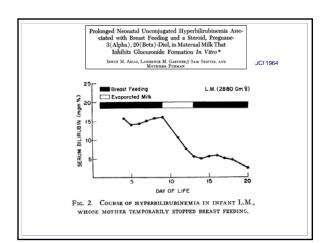
## Brest milk jaundice: How long is too long?

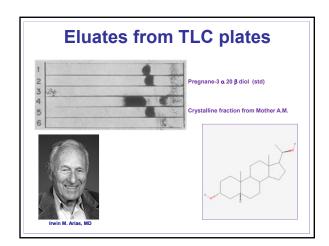
Archives of Disease in Childhood, 1978, 53, 506-516 Winfield & Macfaul

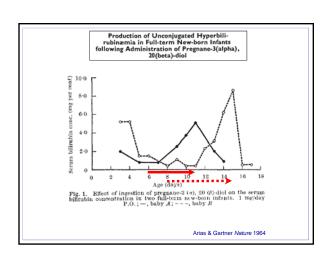
#### Short reports

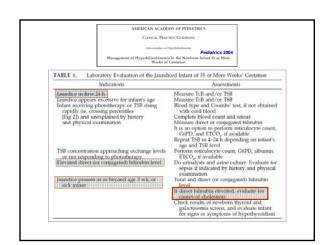
Clinical study of prolonged jaundice in breast- and bottle-fed babies

- 893 infants (Aldershot, England)
- 55% BF
- 12 were jaundiced > 3 weeks ( ~ 2 %)





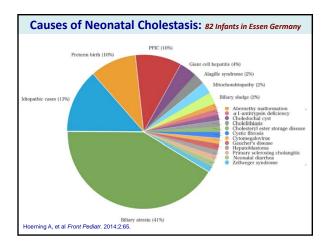




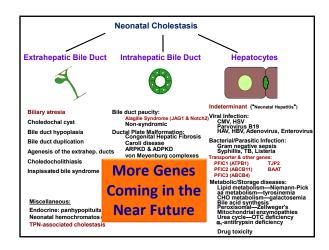
#### **Burden of pediatric liver disease**

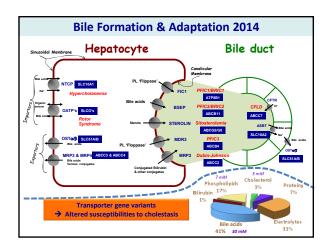
- Incidence of liver disease in newborns → 1:2,500
  - Mainly cholestatic & metabolic liver diseases
- No effective medical treatments for cholestasis
- ~ 10% of adults have liver disease → starts during childhood
  - Genetic predisposition & contribution from obesity
- Biliary atresia 1:10,000 newborns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

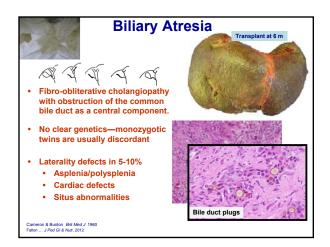
Arya & Balistreri, J GI & Hepatology, 2003



# Think anatomic Intrahepatic bile ducts Extrahepatic bile ducts & Gall Bladder Hepatocytes

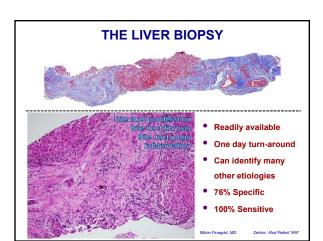






# Best means to diagnose BA

Modality	Sens.	Spec.	PPV	NPV	Diagnostic Accuracy
Liver Biopsy	34/34 <b>100%</b>	33/35 <b>94%</b>	34/36 <b>94%</b>	33/33 <b>100%</b>	97%
Hepatobiliary Scintigraphy	30/34 88%	16/35 45%	30/49 61%	16/20 80%	66%
Ultrasound	17/34 50%	29/35 82%	17/23 74%	29/46 63%	65%
MRCP	29/34 85%	20/35 57%	29/44 66%	20/25 80%	71%



#### Design and validation of a diagnostic score for biliary atresia

Mohamed Abdel-Salam El-Guindi<sup>1</sup>, Mostafa Mohamed Sira<sup>1</sup>, Ahmad Mohamed Sira<sup>1</sup>, Tahany Abdel-Hameed Salem<sup>1</sup>, Osama Loffy El-Abd<sup>2</sup>, Hatem Abdel-Sattar Konsowa<sup>1</sup>, Dina Shehata El-Azab<sup>2</sup>, Alif Abdel-Hakim Allam<sup>3</sup>

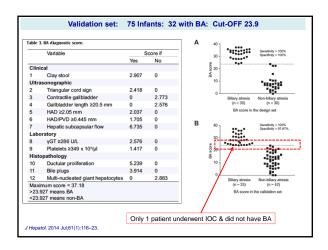
Entry criteria: Direct hyperbilirubinemia: ALL subjects underwent Liver bx Design set: 60 Infants: (~ 65 dol)

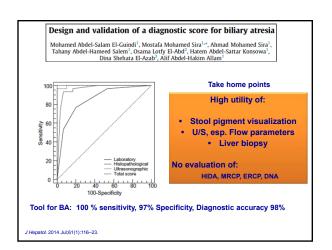
Category	Parameter	BA (30)	Non-BA (30)	P value
	S	ignificant		
Clinical	Acholic stools	28 (93%)	13 (43%)	<0.0001
Lab	GGT	411 +/- 204	204 +/- 270	<0.0001
U/S Flow	Triangular Cord GB Length (mm) GB Contractility Subcapsular Flow HA Diameter	19 (63) 21 +/- 19 2 (5) 29 (96) 2.5 +/5	4 (13) 33 +/- 11 16 (53) 1 (3) 1.9 +/6	<0.0001 <0.0001 <0.0001 <0.0001 <0.001
Liver bx	Duct Proliferation Duct Plugs Multi-nucleated cells	29 (96) 29 (96) 8 (26)	4 (13) 11 (36) 26 (86)	<0.0001 <0.0001 <0.0001

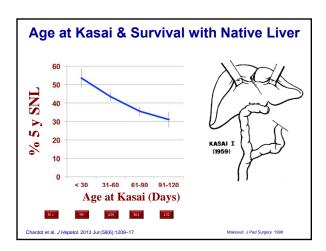
Not significant

Exam: Liver or Spleen Enlargement Labs: ALT & AST, AP, WBC, Hgb Total & Direct Bili (10/6) USS: \*Ahormal GB" Biopsy: Grade of Fibrosis

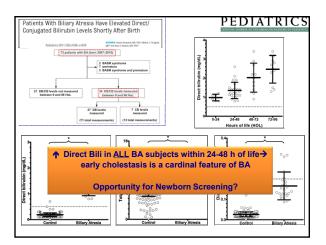
J Hepatol. 2014 Jul;61(1):116-23.

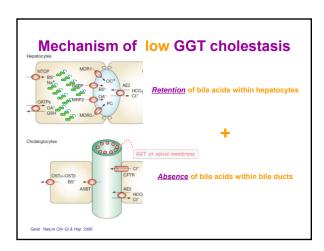


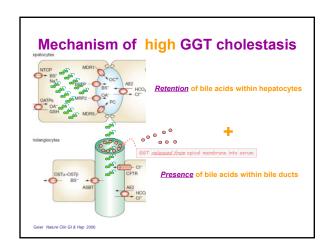


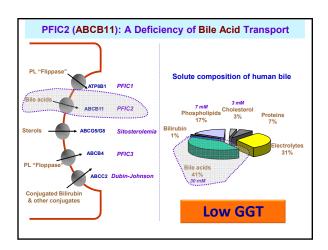


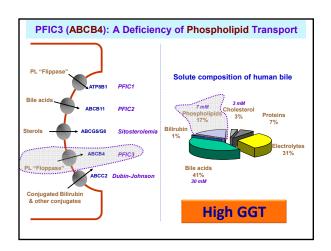
# Q: When does BA start?





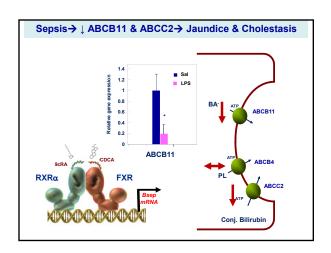






	PFIC1	PFIC2	PFIC3
Feature	ATP8B1	ABCB11	ABCB4
Direct HyperBili	Birth-6m	Birth-6m	Birth - 20+ years
GGT	LOW	LOW	HIGH
Earliest time to cirrhosis	2+ y	6 m	5 m
Extrahepatic Sx	Diarrhea, Hearing Loss, Pancreatitis, Pneumonia	NO	NO
Pruritus	YES	YES	YES/NO
Cholelithiasis	NO	YES	YES (Intrahepatic)
Cancer	?	HCC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

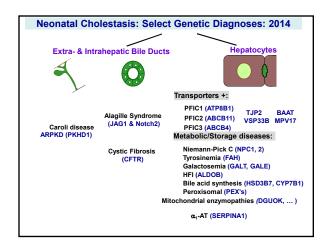
PFIC1 PFIC2 PFIC3 Infants		al Confounders	
Infants	Lov	v GGT	High GGT
	PFIC1	PFIC2	PFIC3
DEIC2 • DEIC1 • BA		Infants	
	ile Acid Synthesis & onjugation Defects	Conjugation Defects	



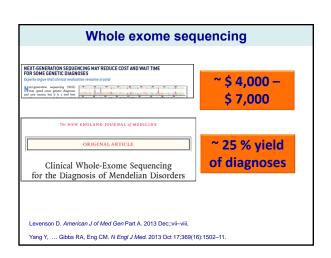
# **Topics**

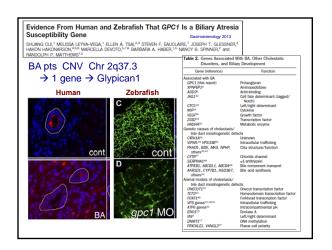
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# 2014 & Beyond: Genotype or Phenotype First? Lu JT, Campeau PM, Lee BH. Genotype-Phenotype Correlation — Promiscuity in the Era of Next-Generation Sequencing: N. Engl J Med. 2014 Aug 14;371 (7):593-6.



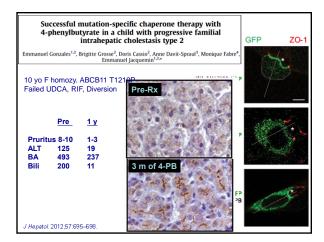
#### The Emory Cholestasis 56 gene Panel Many more to come, including whole exome sequencing CC2D2A HNF1B CFTR HSD3B7 ABCB4 NPHP1 PEX10 POLG VPS33B ABCD1 CYP27A1 JAG1 NPHP4 PEX12 SLC25A13 ABCG5 CYP7A1 LIPA PEX1 PEX13 SLC27A5 CYP7B1 MKS1 PEX2 PEX14 SMPD1 AKR1D1 DGUOK MPV17 PEX3 TJP2 PEX16 BAAT FAH NPC1 PEX6 \*All genes on the next generation sequencing panel may be or are subject to change. Please visit www.geneticslab.emc PEX26 TRMU | Neonatal and Adult Cholestasis: Gene Sequencing Panel | 81223 (x1), 81330 (x1), 81332 (x1), 81404 (x1), 81405 (x1), 81406 (x1) MM340

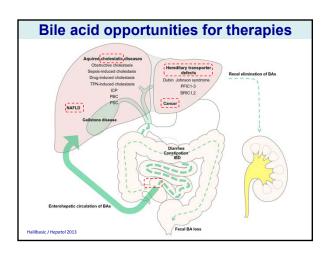




# **Topics**

- Bilirubin Primer
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Bile acid based therapeutic trials (~ 200 in clinicaltrials.gov)

Glycocholic Acid: BA Synthesis Defect

FXR agonists: Obeticholic Acid NASH

BA diarrhea Alcohol Fibrosis PSC NorUDCA: PSC

TGR5 agonists: Satiety Constipation

Pruritus in cholestasis (ALGS, PFIC's) IBS-C **ASBT** inhibitors:

**BA Sequestrant: Colesevelam** Diabetes

NASH Obesity

#### Take home points: Jaundiced infants

- New molecular understandings of conjugated & unconjugated hyperbilirubinemia.
- Transporter genes drive bile formation, & their *dysfunction* → *cholestasis*

PL Flippase BA Exporter PL Floppase • ATP8B1 PFIC1 BRIC1 • ABCB11 PFIC2 BRIC2 • ABCB4 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



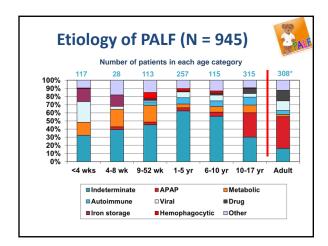
#### **Disclosures**

**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

43			



## **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 workup
  - 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

J Pediatr 2009;155:801-6

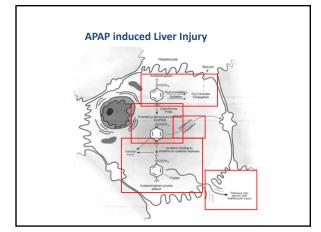
# **Role of Liver Biopsy**

- 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)</li>
  - Values > 5000 IU/mL
  - All 30 patients with normal levels survived
- Immunedysregulation
  - Should we treat with steroids

Bucuvalas, J JPGN 2013;56: 311-315



## **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)</li>
    - 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)</li>
  - ALT higher (2384 vs 855, p<0.001), but lower than SE (5140, p<0.0001)</li>
  - Spontaneous survival higher for CE vs NE
    - 68% vs 49%, p=0.008

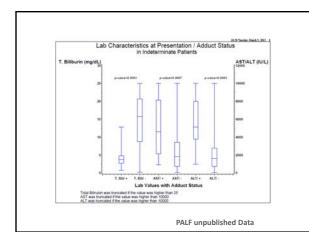
Leonis et al, Pediatrics 2013;131:e740)

#### **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)

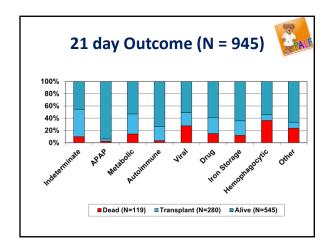
Pediatrics 2006;118(3):e676-81 Unpublished PALF Data



#### **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

Squires et al. *J Pediatr* 2006;148:652-8 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
  - Cardio-vascular 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

Agarwal, et al Journal of Hepatology 2012;57:780-6 Stravitz, et al Hepatology 2013;58:304-13

#### **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/m<sup>2</sup>

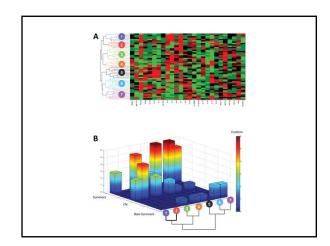
Harry R, et al *Hepatology* 2002;36:395-402 Stravitz et al *Nat Rev Gastroneterol Hepatol* 2009;6:542-53

# 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

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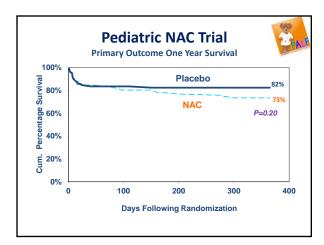


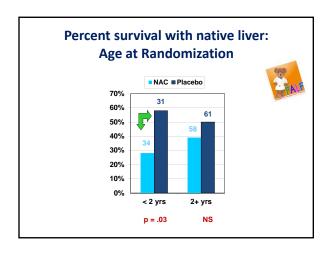
#### **Pediatric NAC Trial**

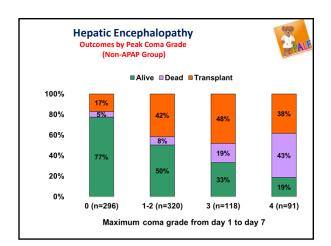


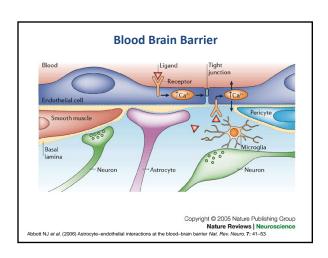
- RCT with minimization scheme to maintain balance
  - Age: less than 2 years vs. at least 2 years
  - Coma score: 0-I vs. II-IV
- Non-APAP PALF patients received a continuous IV infusion of NAC (150 mg/kg/d) or D5W for up to 7 days
- Estimate that a sample size of 184 patients (92 in each arm)to provide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

Squires, et al Hepatology 2013;57:1542-9









#### **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 NH<sub>4</sub> delivery
- Abnormalities in brain glucose metabolism
  - Decreased glucose and O<sub>2</sub> consumption and increased lactate concentrations
- Inflammation
  - Pro-inflammatory cytokine levels parallel ICP

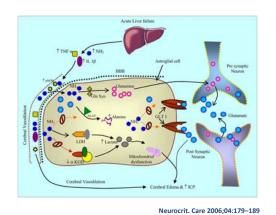
Blei AT, Journal of Hepatology 2007;46:553-582

#### Ammonia and Prevention of Cerebral Edema

#### • Ammonia

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

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



# 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**

EEG Findings	Spontaneous Survival	LT or Death	p Value
All Patients (n=18)			p<0.05
Normal to mildly abnormal	9	2	
Moderately or severely abnormal	1	6	
Patients with Admission HE Score ≤ 2 (n=16)			P<0.05
Normal or mildly abnormal EEG	9	2	
Moderately or severely abnormal	1	4	

# **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

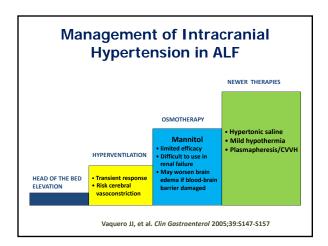
Raghavan M, et al. Neurocritical Care 2006;4:179-189

# **Hypothermia**

- Whole body cooling to 32°-35°C
- Supporting evidence in animal models
  - Reduces CBF
  - Reduces concentration of NH<sub>4</sub> in CSF
  - May improve brain oxidative metabolism of glucose
  - Decreases arterial IL-1 $\beta$ , TNF- $\alpha$  and IL-6
- Successful uncontrolled trials
- May increase infection risk and decrease regeneration

Stravitz and Larsen Crit Care Med 2009;37:S258-64

#### **Putative Mechanisms of Hypothermia** Adapted from Crit Care Med 2009;37:S258-64 ↓ Arterial and brain concentrations **↓** Production of intestinal bacteria Prevents brain lactate and alanine **Brain Osmolarity** accumulation Brain extracellular space **↓** Accumulation of glutamate and **↓**glutamate induced astrocyte swelling Improved cerebral blood flow, $\ensuremath{\downarrow}$ cerebral toxin uptake Cerebral Hemodynamics **Brain Glucose** $\d\downarrow$ Cerebral metabolic rate of glucose and oxygen ↓ De novo synthesis of lactate and alanine Metabolism Inflammation **↓** Production of cytokines Shifts from pro to anti-inflammatory milieu



### **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

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# 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

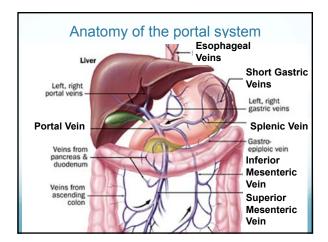
#### Conflict of interest

 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





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

    Splenic Vein
    Thrombosis
  - Post-hepatic
  - IVC obstruction
  - Constrictive pericarditis

- 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

Romano G., et al. G Chir 2014

#### Clinical presentation of variceal bleeding

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

Khawaja A., et al. E J of GI & Hepatology 2014

## **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</li>
- 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

Procaccini N.J., et al. Gastrointest Endosc 2009 Bai M., et al. W. J. Gastrointest Pharmacol Ther 2014 Chikamori F., et al. Dig Surg 2001

#### 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

Sarin S.K., et al. Am J Gastroenterol 1989 Chikamori F., et al. Dig Surg 2001 Bai M., et al. W. J. Gastrointest Pharmacol Ther 2014

# Sarin's Classification of gastric varices Gov 2 Gov 2 IGV 2

#### **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

Corley D.A., et al. Gastroenterology. 2001

# 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

Patel A., et al. Amer J. I. of Roentgenology. 2012

- 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

Khawaja A., et al. E J of Gl & Hepatology 2014 Lo G.H., et al. Hepatology 2001 Hou M.C., et al. Hepatology 1995

# Methods of endoscopic treatment



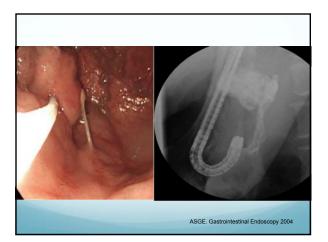
- Endoscopic rubber band ligation (EVL)
  - Best approach for primary and secondary prophylaxis
  - Useful in active bleeding, if you can see the varix that is bleeding
- Start distally, and move in a spiral upward motion
- Avoid pushing the scope beyond the placed bands

#### Methods of endoscopic treatment

- 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

Khawaja A., et al. E J of Gl & Hepatology 2014 Lo G.H., et al. Hepatology 2001

ASGE. Gastrointestinal Endoscopy 2004 Hou M.C., et al. Hepatology 1995



#### 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

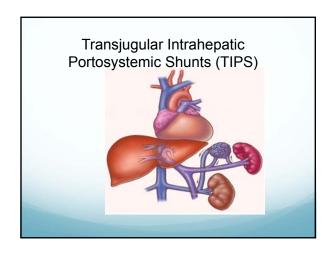
- When to call the Interventional Radiologist
  - Patient continues to bleed despite endoscopic therapy
  - After significant bleeding and ongoing concern for rebleeding
- Discuss
  - Patient's global health
  - Short and long term goals
  - Absolute and relative contraindications

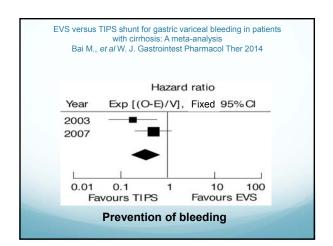
# Transjugular Intrahepatic Portosystemic Shunts (TIPS)

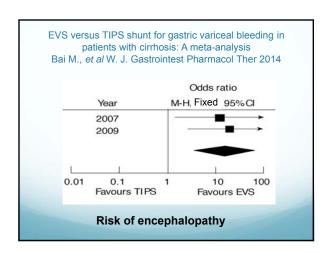
- Limited by
  - Size of the patient
  - Expertise of the Interventional Radiology department
  - Degree of liver disease
- Contraindicated if
  - Tumor
  - Elevated bilirubin
  - Significant liver dysfunction (encephalopathy)

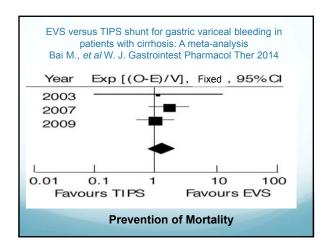
Khawaja A., et al. E J of GI & Hepatology 2014

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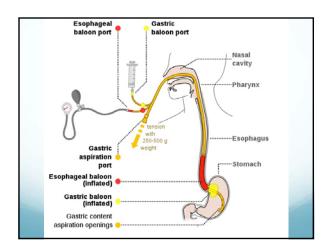




#### Balloon-occluded Retrograde Transvenous Obliteration of gastric varices (BRTO)

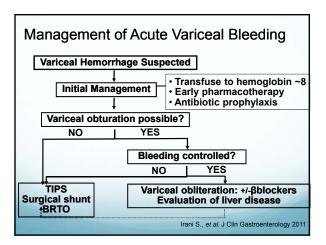
- Indicated if
  - endoscopic management fails
  - transjugular intrahepatic portosystemic shunt is contraindicated
- Approach
  - Transjugular
  - Femoral
  - Requires the existence of a portosystemic shunt
  - Materials: Coils or Glue

Patel A., et al. A. J. of Roentgenology. 2012



## **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



#### 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 βblocker as primary or secondary prophylaxis in the prevention of variceal bleeding

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NASPGHAN POSTGRADUATE COURSE- Non 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 company 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.
  - Chaïbou M et al. Pediatrics 1998
- 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

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# Risk Factors Associated with GI Bleeding in ICU (OR > 1) • Enteral Feeding

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

Reveiz et al. Pediatr Crit Care Med 2010

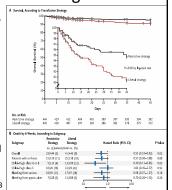
#### **Initial Evaluation**

- 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</li>
- Liberal Strategy-Transfuse if Hgb <9
- Restrictive Strategy
  - Significantly higher survival
  - Significantly lower transfusion rate and risk of re-bleeding



Villanueva et al. N Engl J Med, 2013

#### **ASGE Guideline**

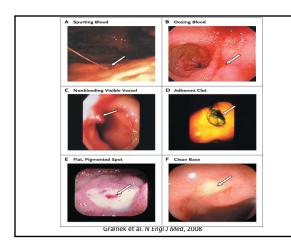
- Adequate resuscitation of patient upon presentation
- NG Lavage
  - signals presence or absence of ongoing bleeding prepyloric
- Treatment with PPI reduces rates of high risk stigmata on endoscopy
  - No significant difference noted in mortality, rebleeding or progression to surgery
- Use of prokinetics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

Hwang et al. GIE; 2012

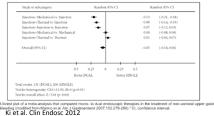
## **Preparation for Endoscopy**

- 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





# Therapy Combination>Monotherapy



## Injection

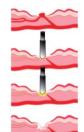
- The primary mechanism of action is tamponade resulting from a volume effect.
- Normal Saline or dilute Epinephrine
  - Epinephrine may cause some Vasoconstriction



Kay and Wyllie JPGN 2007

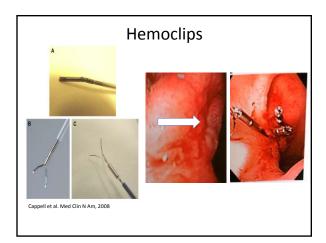
#### **Thermal Probes**

- 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 JPGN 2007

# Thermal Probe Video 15-20 Seconds in length



Hemoclip Video 15-20 seconds in length

# APC- With Video

- Non contact method of delivering monopolar electrosurgical energy to target tissue.
- Video Placeholder- 10-15 seconds in length
- 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 adsorptive 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.



Ki et al. Clin Endosc 2012

# **Endoscopic Suturing**

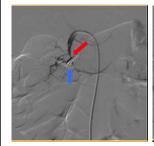
- Curved needle with detachable tip
- Driven through mucosa and "tied down" using a cinching device





Leunk Ki et al. Clin Endosc 2012

# Angiography





# **Future Directions**

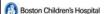
- Standardization/optimization strategies for pre-endoscopic management of GI bleeding
- Comparison between different endoscopic techniques in pediatrics
- Further research into newer techniques to control GI bleeding.

# 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

# **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

<sup>\*</sup>Products or services produced this company are relevant to my presentation

# 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

Mehta S et al. Pediatrics 2012;129:e82-8 Walker SK et al. Surgery 2013;154:927-31 Pant C et al. J Pediatr Gastroenterol Nutr 2014

# **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%)

ERCP. Baron TH, Kozarek R, and Carr-Locke DL eds. Saunders 2013

# **ERCP: Children vs Adults**

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

	Child	Adult
Age, median, y	8.1	49.7
Technical success, %	97.5	98
Complication rate, %	3.4	2.5

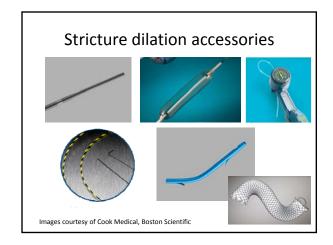
Varadarajulu S, et al. Gastrointest Endosc 2004;60:367-71

### **Pediatric ERCP Series** Cheng 2005 (adult endo) 11.2% Pancreatitis = 31 (9.4%) Bleeding = 5 (4.1% of ES) 245 12 12.3 329 71.4% ES = 122 Dil = 26 Stent = 30 Stone = 32 Otto 2011 167 18 11.4 231 69% 4.8% ES = 96 Stent = 52 Pancreatitis = 7 (3.0%) Bleeding = 2 (2.1% of ES) (adult endo) Stone = 55 Enestvedt 2013 296 (adult endo) 7.7% Pancreatitis = 27 (6.3%) 6 14.9 429 64.1% ES = 187 Stent = 118 Bleeding = 6 (1.4%) Stone = 112 Troendle 2013 (ped endo) 100% ES = 65 8% Pancreatitis = 3 (5%) 65 NA 15.2 67 Stone = 65 Bleeding = 1 (1.5%)

## **Equipment: Duodenoscopes** Infant 2 -10 y 10 y-adult Endoscope\* PJF 160 JF 140F TJF Q180V Channel (mm) 2.0 4.2 3.2 Tip O.D. (mm) 13.7 7.5 12.0 \*Olympus designations and specs. Similar dimensions for Pentax and Fujinon adult scopes.







# Choledocholithiasis

## **Risk Factors**

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

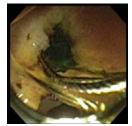
## **Treatment**

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

Buxbaum J. Gastrointest Clin N Am 2013;23:251-75

# Choledocholithiasis

Bilirubinate pigment stone



Cholesterol stone



# Hemolytic disease 8 yr male with Hgb SS, acute abdominal pain, jaundice









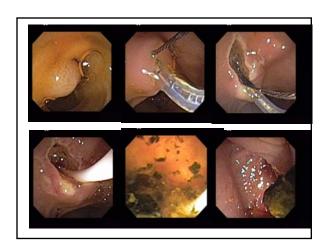




# Sphinctertomy/Balloon Extraction

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





# **Biliary Strictures**

### Causes

- Congenital
- <u>Post-operative</u>
- Anastomotic
  - latrogenic (post LC)
- Traumatic
- Inflammatory
- Intrinsic (PSC)
- Extrinsic (pancreatic)
- Ischemic
- Infectious
- <u>Idiopathic</u>
- 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

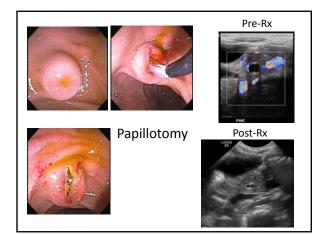
Karakayali F et al. Transplant Proc 2013;45:3524-7

# 3.5 yr female with intermittent abdominal pain for 6 months

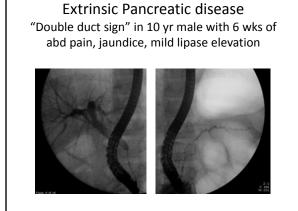
- Elevated AST, ALT, Alk phos, nl bilirubin
- Abnl US and MRCP
  - Enlarged GB and dilated bile ducts
  - Suspected stricture at distal CBD



# Choledochocele (type III CDC) IV-A IV-B V Higure from: Iodani I et al. J Hepatobiliary Pancreat Surg. 2003;10:340-4

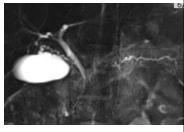


# Anastomotic stricture 20 mo, 10.8 kg infant after whole graft liver transplantation



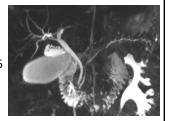
# Immediate symptom relief after stent





# Follow-up

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



# Idiopathic stricture 17 mo female with acute jaundice

Dilated hepatic ducts (MRI) Non-excreting HIDA scan









# 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
- Clinically well, non-dilated ducts, normal labs at 12 mo F/U evaluation

# Bile leak

# **Causes**

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

# **Treatment**

- if large abdominal collection
- Short, large diameter transpapillary stent
- Or biliary sphincterotomy

Soukup ES et al. J Pediatr Surg 2014;49:345-8

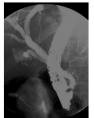
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# Stenting for Bile Leak

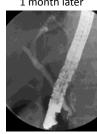
Stump leak

10 Fr x 2 cm stent

1 month later







# 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 ESCARE Children's Center for Digestive HealthCare, LLC Children's Center for Digestive HealthCare, LLC Children's Center for Digestive HealthCare, LLC Children's Center for Digestive HealthCare, LLC



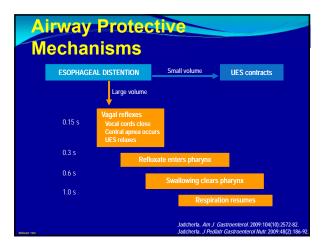
# I have a number of financial relationships with commercial entities from whom I receive compensation, for which my son who just graduated from Stanford and daughter who attends George Washington Universtiy are very grateful Janssen/J&J, Nestlé, Astra, Takeda, Pfizer, Prometheus, Mead Johnson Nutritionals, 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 plausibile?
   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 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

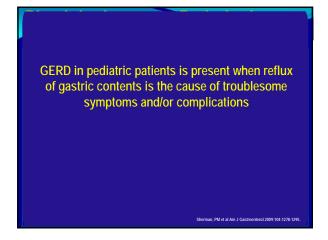
- ✓ Transient relaxations of the lower esophageal sphincter
- ✓ Inhibition of esophageal body peristalsis plus exposure of mucosa to gastric refluxate (eg, acid, pepsin)

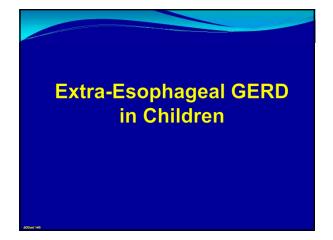
Bolx-Ochoa J. et al. J Pediatr Surg. 1980;15:74-78.
Davidson G, et al. J Pediatr Gastroenterol Not. 2003;37:S17-S22. g
Cuigley EM. Am J Gastroenterol. 1992;37:1707-1075.
Sondheimer JM. J Pediatr. 1980;96:804-807.

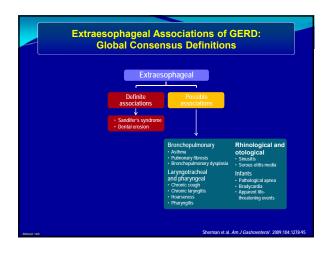
# Physiologic versus Pathologic Reflux and Age

- 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

Hasenstab KA, Jadcherla, S. J Pediatr 2014; 165:250-255







# 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.

Hill, AB. Proc Royal Soc Med. 1965; 58, 295-30

# 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





Pace et al. Aliment Pharmacol Ther. 2008;27(12):1179-86.
Sherman et al. Am. | Gestroenterol. 2009:104:1278-95

# 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

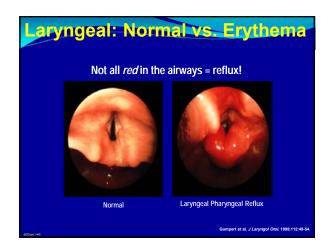


Sherman et al. Am J Gastroenterol. 2009;104:1278-95. Vandennias, et al. J Pediatr Gastroenter Nutr. 2009;49-498-547.

# **ENT Manifestations of GERD**

Have they met the burden of proof for causality?

# Laryngo-esophageal Pharyngeal Reflux Disease LERD OR LPR



# 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

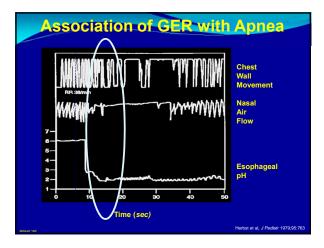
BDGold 1540

# Reflux and Respiratory Disease

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

BDGold 1140

Pearson JP S et al. Aliment Pharmacol Ther. 2011;33 Suppl 1:1-7 May JG et al. Ann Otol Rhinol Laryngol. 2011;120(2):116-122. Gherzi M et al. Respir Med. 2011;105(7):972-978



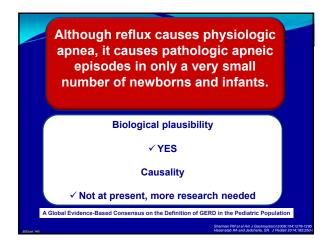
# Apparent Life Threatening Episodes (ALTE) and Apnea cont'd ORIGINAL Www.jpeds.com • The Journal of Pediatrics ARTICLES Respiratory Events in Infants Presenting with Apparent Life Threatening Events: Is There an Explanation from Esophageal Motility? Kathryn A. Hasenstab, BS, BME¹, and Sudarshan R. Jadcherts, MD, FRCPI, DCH, AGAF¹³ Objective: To test the hypothesis that proximal aerodigestive clearance mechanisms mediated by pharyngoesophageal motility during spontaneous respiratory events (SREIs and edisticnt in infants with apparent life threatening events (ALTEs). Study design Twenty infants (10 with proven ALTE, 10 healthy controls) had pharyngoesophageal manometry to investigate motility changes concurrent with respiratory events delected by respiratory inductance plethyamography and ranall thermstor methods. We measured changes in selfing upper esophageal and power esophageal in cluded mixed models; data presented as mean ± SD, median frangel, or percentage. Results infants with ALTE (so ventorie) had (1) delays in resolution generoid section promasory as included by more frequent (P = .03) and prolonged SRES p(P < .01); (2) a lower magnitude of protective upper esophageal sphincter contractine reflexee (P = .01); (3) swallowing as the most frequent ecophageal event requart mixed plance mechanism (44) vs. 35%, (P < .01); (4) a high primary pointstails as the most prominent aerodigestive clearance mechanism (44) vs. 35%, (P < .01); (6) a high primary pointstails as the most prominent aerodigestive clearance mechanism (44) vs. 35%, (P < .01); (6) a shift primary pointstails as the most prominent aerodigestive clearance mechanism (44) vs. 35%, (P < .01); (6) a shift primary pointstails as the most prominent aerodigestive clearance mechanism (44) vs. 35%, (P < .01); (6) a shift primary pointstails as the most prominent aerodigestive clearance mechanism (44) vs. 35%, (P < .01); (6) a shift primary pointstails and singminent propagation failure, thus suggestive of dysturctional regulation of swallow-

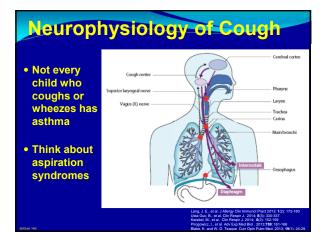
# Paparent Life Threatening Episodes (ALTE) and Apnea cont'd ORIGINAL WWW.jpeds.com • THE JOURNAL OF PEDIATRICS ARTICLES Respiratory Events in Infants Presenting with Apparent Life Threatening Events: Is There an Explanation from Esophageal Motility? Kathryn A. Hasenstab, BS, BME\*, and Sudarshan R. Jadcherla, MD, FRCPI, DCH, AGAF\*2 • 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.

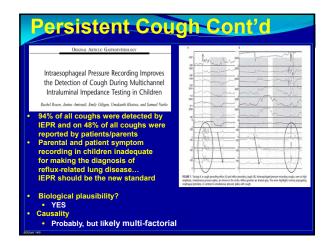
When reflux causes pathological apnea, the infant is more likely to be awake and the apnea is more likely to be obstructive in nature.

A Global Evidence-Based Consensus on the Definition of GERD in the Pediatric Population





# 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 Cough, snort, throat clearing: Tourette's Loud, honking cough absent with sleep. Look for history of family/school conflicts. Diagnosis of exclusion. Diagnosis of exclusion. Diagnosis of exclusion. Diagnosis of exclusion.



## **Asthma: When to Treat for GERD** Persistent asthma with heartburn or Treat with a PPI regurgitation Persistent asthma that is difficult to control or GER is an unlikely nocturnal-onset contributor to Rule out other causes of wheezing; asthma if reflux Perform multichannel pH-impedance testing is negative monitoring Persistent asthma that is difficult to control or nocturnal-onset with abnormal pH-impedance 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

# 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 extraesophageal 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?



# Biomarkers in Bronchoscopy Fluid or Saliva

- Lipid Laden Macrophage Index (LLMI)

   Elevated in a variety of pulmonary diseases

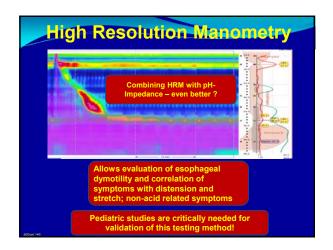
   Inconsistent relationship between the amount of gastroesophageal reflux and LLMI
  - No relationship between full column reflux by pH-MII and LLMI

### 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

- 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. Drop in pH to less than 4 Normal values in pediatric age groups not yet defined Analysis of tracings time-consuming How the results channe mananement still Pediatric studies are critically needed to determine if knowing the amount of nonacid reflux changes treatment or outcome the amount of nonacid reflux changes treatment or outcome | Pedia Comment | Pedia Pedia Comment | Pedia Pedi



# 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

Nonpharmacologic	Pharmacologic	Surgical
Infants  Formula thickening  Time-limited trial of hypoallergenic formula  Higher calorie formulas  Nasogastric/nasojejunal feeds  Older children/adolescents  Positioning/head-of-bed elevation  Weight loss (if overweight)	Oral antacids     Surface agents (eg, sodium alginate, sucralfate)     Gastrointestinal prokinetic agents (eg, domperidone, baciofen)     Acid-suppressive agents (H <sub>2</sub> RAs, PPIs, PCABs)	Fundoplication (le, Nissen)     Enteral feeding device     Esophagogastri dissociation

# **Does Treatment for GERD Resolve** Cough (Adults) **CHEST** Original Research SIGNS AND SYMPTOMS OF CHEST DISEASES Response of Chronic Cough to Acid-Suppressive Therapy in Patients With Gastroesophageal Reflux Disease Peter J. Kahrilas, MD; Colin W. Howden, MD; Nesta Hughes, PhD; and Michael Molloy-Bland, DPhil

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

Background: Epidemiologic and physiologic studies suggest an association between gastroesophageal reflux disease (CERD) and chronic cough. However, the benefit of antireflux therapy for chronic cough remains unclear, with most relevant trials reporting negative findings. This systematic review aimed to reevaluate the response of chronic cough to antireflux therapy in trials that allowed us to distinguish patients with or without objective evidence of CERD. Methods: PubMed and Embase systematic searches identified clinical trials reporting cough response to antireflux therapy. Datasets were derived from trials that used pH-metry to characterize patients with chronic cough.

Results Nine randomized controlled trials of varied design that treated patients with acid suppression were identified (eight used proton pump inhibitors [PPIs], one used ranitidine). Datasets from two crossover studies showed that PPIs significantly improved cough relative to placebo, ableit only in the arm receiving placebo first. Therapeutic gain in seven datasets was greater in patients with pathologic esophageal acid exposure (range, 12-5%-53.5%) with no overlap between groups.

Conclusions: 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 exclusion because of presumptive alternative diagnoss, and appropriate power to detect a modest therapeutic gain. Only then can we hope to resolve this vexing clinical management problem.

CHEST 2013; 143(3):605-612

Abbreviations: CERD = gastroesophageal reflux disease; LPR = laryngopharyngeal reflux; PPI = proton pump tnlubtior

# Asthma and GER: Treatment cont'd

- Two NIH-funded blinded, randomized placebocontrolled trials (RCT), one in adults (using esomeprazole), one in children (using lansoprazole
  - Showed NO difference in asthma outcomes comparing placebo and acid suppression
- 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 GER: Treatment cont'd

## The NEW ENGLAND JOURNAL of MEDICINE

Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma

Despite a high prevalence of asymptomatic gastroesophageal reflux among patients Delpite a sign (Free cutor to a preparation granteen with prooms) controlled as abona, reteamen with prooms/pumpi inchibins 5 dets not controlled as abona, reteamen with prooms/pumpi inchibins 5 dets not controlled as abona, reteamen with prooms/pumpi inchibins 5 dets not controlled as abona, reteamen with proof pumpion as abona controll. Asymptomic granteen pumpion in the total of clothers with poorly controlled as abona, without symptoms controlled as abona, with the controlled as abona, the deletion of the support of the properties of the support of th

# Lansoprazole for Children With Poorly Controlled Asthma A Randomized Controlled Trial

Results The mean age was 11 years (SD, 3 years). The mean difference in change (sunopazule minus placebol in the ACO core was Q2 units (95% C, 0.04 Q3 units). The There were no distriction (synigentized differences in the mean difference in other between the result of the sex and other positions of forced explantity values in the first second (0.01; 95% C, 0.24 Dx 11), attended enalty with (1-95% C, 0.23 Dx 11). The control of the sex o

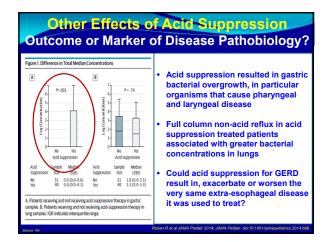
Trial Registration clinicaltrials.gov Identifier: NCT00442013

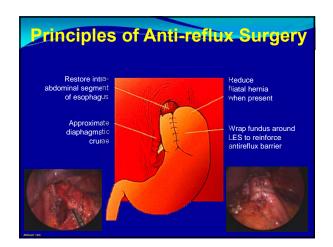
# **Asthma and GERD** Clinical trial data

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 selfreported 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? Network Original Investigation Changes in Gastric and Lung Microflora With Acid Suppression Acid Suppression and Bacterial Growth Reade Rosen, Mr. Marke, James, Americal, District, Pathology, Linguistic Microflora, With Acid Suppression Acid Suppression and Bacterial Growth Reade Rosen, Mr. Marke, James, Americal, District, Pathology, Linguistic Microflora, With Acid Suppression \*\*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





# Antireflux Surgery and Extraesophageal 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

Srivastava . BMJ. 2010;340(7737):85. Srivastava et al. BMJ. 2009;18;339;b4411. Srivastava . Pediatrics. 2009;123(1):338-4

Sinustana et al. BMJ. 2007. Sinustana . Pelialirica 2009 Leve et al. J Pediatri Surg. 20

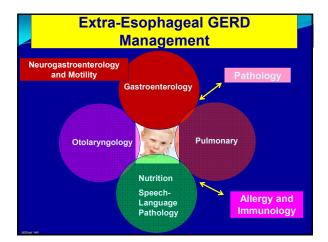
# Extra-Esophageal GERD in Children: Controversies/Gaps in Knowledge

- 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 extraesophageal manifestations of GERD in October of 2014
  - Otolaryngological (larynx, pharynx, middle ear)
  - Biologically plausibile? YESEpidemiological Association YES
  - Cause and effect?
     NO, more research needed
  - Respiratory (cough, pneumonia, asthma)
    - Biologically plausible? YESEpidemiological Association YES
    - Cause and effect?
       NO, more research needed
- Opportunity for multi-disciplinary, multicenter collaborations using other successful models

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# EoE: PPI, PPI-REE, TCS, OVB, SFED, 4FED......Alphabet *Distress*

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





# Disclosures

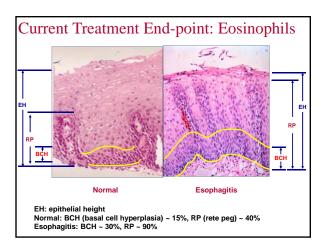
- Consultant/research: Abbott, Meritage, Nestle, QOL and Receptos
- The content of my presentation includes discussion of off-label/investigative use of medicine(s), medical devices, or procedures

# 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



# 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

9/8/2014

# 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 Zhang<sup>1</sup>, Edaire Cheng<sup>3</sup>, Xiaofang Huo<sup>1</sup>, Chunhua Yu<sup>1</sup>, Qiuyang Zhang<sup>1</sup>, Thai H. Pham<sup>2</sup>, David H. Wang<sup>1,6</sup>, Stuart J. Spechler<sup>1</sup>, Rhonda F. Souza<sup>1,4</sup>s

PLos ONE 2012;7:e50037

# Why do HD PPI Trial?

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



# 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

Evan S. Delton, MD, MPH<sup>2</sup>, Olga Speck, MD, PhD<sup>3</sup>, Kimberly Woodward, MD<sup>3</sup>, Jessica H. Gebhart, MSHS<sup>3</sup>, Ryan D. Medanick, MD<sup>12</sup>, Sidney Levinson, MD<sup>12</sup>, Karen J. Fritchie, MD<sup>3</sup>, John T. Woosley, MD, PhD<sup>3</sup> and Nicholas J. Shaheen, MD, MPH<sup>12</sup>

Am J Gastroenterol 2013;108:1854-60

# • 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 J Pediatr 2009;154:96-100 ■PPI Responders (n=17) 110 100 90 80 70 60 50 40 30 20 10 100 ■PPI Non-Res (n=26) 73 59

Furrows (%)

29 31

Eos/hpf

Symptom Improvement on PPI (%)

Abnormal pH test (%)

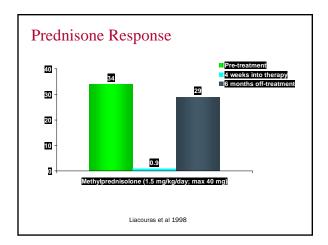
PPI Responders vs Non-Responders

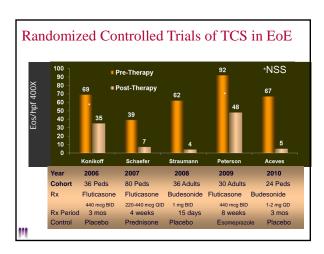
Male (%)

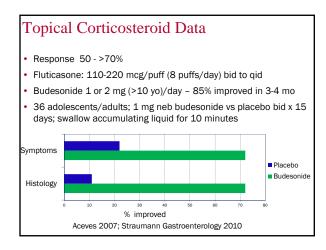
# Long-term Mangement of PPI-REE 140 120 Distal relapsers (8/12) undergoing PPI increase (Omeprazole 40 mg bid) 100 80 60 40 20 0 Slide courtesy of Dr Molina-Infante - DDW 2014

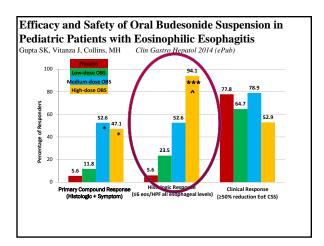
# Objective 2: Steroid-based therapies

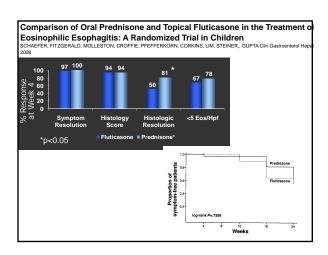
- Options prednisone, fluticasone (F), budesonide (B)
- Dosing
- Pros and Cons
- Maintenance therapy











## Pros and Cons of Topical Steroids

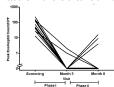
- · Rapidity of response
- Ease of Rx administration
- · Positive quality of life
- Thrush oral, esophageal; <20% children (10% adults).</li>
   Now seen less frequently
- ?Adrenal suppression and growth retardation
- Bone loss less likely with TCS
- TCS lower risks due to limited absorption and high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

## Long Term: Can I Lower Dose?

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

 $\begin{array}{l} \text{Butz BK}^1, \text{Wen T}^1, \text{ Gleich GJ}^2, \text{ Furuta GT}^3, \text{ Spergel J}^4, \text{ King E}^8, \text{ Kramer RE}^3, \text{ Collins MH}^6, \text{ Stucke E}^1, \\ \text{Mangeot C}^5, \text{ Jackson WD}^7, \text{ O'Gorman M}^7, \text{ Abonia JP}^1, \text{ Pentiuk S}^8, \text{ Putnam PE}^8, \text{ Rothenberg ME}^9, \\ \end{array}$ 

- 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



9/8/2014

Gastroenterology 2014

# Objective 3: Review Dietary Therapy

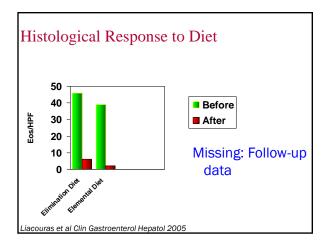
- Types of Diet
- Efficacy Data
- Newer Diets
- Pros and Cons

9/8/2014

## 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

9/8/20



Efficacy of Dietary Interve n Patients With Eosinophi					
n Patients With Eosinophi					
n Patients With Eosinophi	lic Esophagitis	: AS	ystematic I	Revie	hne we
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ingel Arias, 1 Jesús González-Cerve	era," Jose M. Tenia:	s, and	Alfredo J. Luc	endo	
Table 2.Summary of Histologic Rem		for the 0	Different Dietary Tre	eatment	Options Publishe
Table 2.Summary of Histologic Rem Children and Adults With Ed		for the l	Different Dietary Tre	satment	Options Publishe
		for the 0	Different Dietary Tre Children, %	satment n	Adult, %
Children and Adults With Ed	sinophilic Esophagitis <sup>a</sup>	_			
Children and Adults With Ed Dietary treatment	Overall effect, %	n	Children, %	n	Adult, %
Children and Adults With Ec Dietary treatment	Overall effect, % 66.3 (56.9-75)	n 47	Children, % 67.2 (55.9-77.5)	n 36	Adult, % 63.6 (47.8–77.5
Children and Adults With Ec Dietary treatment All Bemental diets	Overall effect, % 66.3 (56.9-75) 90.8 (84.7-95.5)	n 47 13	Children, % 67.2 (55.9-77.5) 90.4 (83.5-96.5)	n 36 12	Adult, % 63.6 (47.8-77.5 94.4 (17/18)
Children and Adults With Ec Dietary treatment All Bemental diets Allergy testing-direct elimination diets	Overall effect, % 66.3 (56.9-75) 90.8 (84.7-95.5) 45.5 (35.4-55.7)	n 47 13 14	Children, % 67.2 (55.9-77.5) 90.4 (83.5-96.5) 47.9 (36.8-59.1)	n 36 12 12	Adult, % 63.6 (47.8–77.5 94.4 (17/18) 32.2 (17.8–48.7
Children and Adults With Ec  Dietary treatment  All  Bemontal diets  Allory testing-direct elimination diets  SFED	Overall effect, % 66.3 (56.9-75) 90.8 (84.7-95.5) 45.5 (35.8-78.1) 53.4 (35.7-70.6)	n 47 13 14 7	Children, % 67.2 (55.9-77.5) 90.4 (83.5-96.5) 47.9 (58.8-59.1) 72.8 (62.5-82) 60 (9/15)	n 36 12 12	Adult, % 63.6 (47.8-77.5 94.4 (17/18) 32.2 (17.8-48.7 71.3 (61.7-80) 46.2 (6/13)
Children and Adults With Ec Dietary treatment All Bemontal diets Allongy testing-direct elimination diets SFED FFED	overall effect, % 66.3 (56.9-75) 90.8 (84.7-95.5) 45.5 (35.4-55.7) 72.1 (65.8-78.1)	n 47 13 14 7 2	Children, % 67.2 (55.9-77.5) 90.4 (83.5-96.5) 47.9 (36.8-59.1) 72.8 (82.5-82)	n 36 12 12	Adult, % 63.6 (47.8-77.5 94.4 (17/18) 32.2 (17.8-48.7 71.3 (61.7-80)

# "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

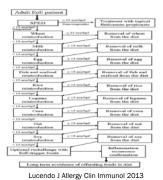
Tolerance of baked milk in patients with cow's milk-mediated eosinophilic esophagitis.

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

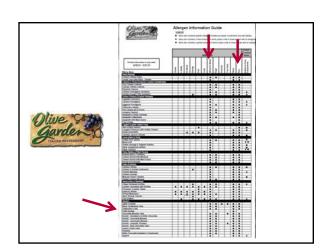
11/15 (73%) in histological remission (<10 eos/hpf) with baked milk ingestion</li>

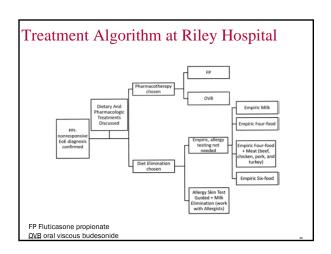
9/8/20

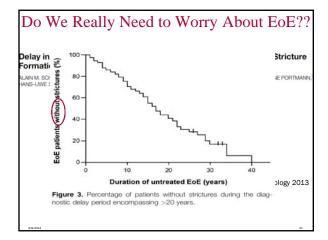
#### **Pros and Cons: Reintroduction Protocols**









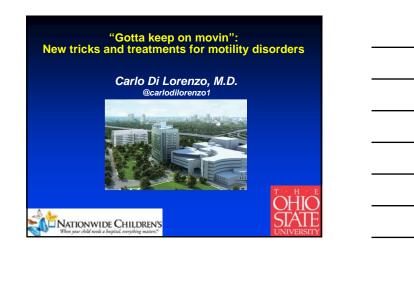


## Summary/Take-home Messages

- 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



I have the following financial relationships to disclose:

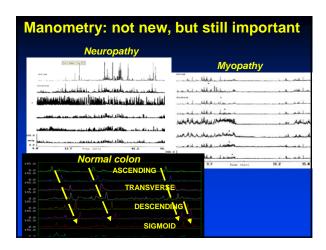
QOL Medical Sucampo Pharma Ironwood Pharmaceuticals

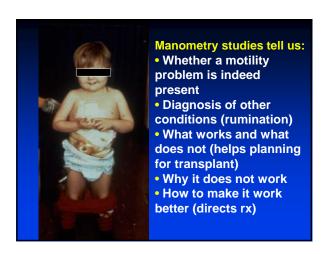
Products or services produced by these companies are <u>not</u> relevant to my presentation

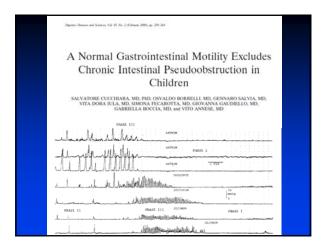
# **Outline**

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





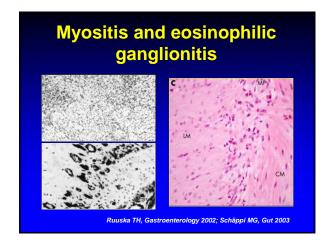




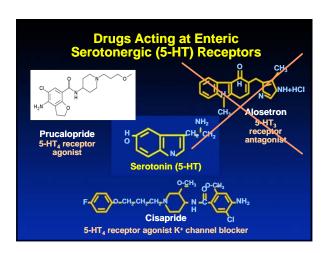
# Importance of confirming a diagnosis of pseudo-obstruction Tracceier Proc. 1886 0ct.26(5) 2796-1. "Muchausen by provy" syndrome in a small bowel transplant recipient. Kooman's B. Taddel S. Feyes J. Todo S. Pettury Transplant buffe, Criste not Hought of Pitthoury, PA 15213-2580, USA. Murchausen by Provy is potentially one of the most harmful forms of child abuse with a reported mortally rate of nearly 10% and may be a secondary cause of chronic intertinal resource substitution. If MPP is suspected, prompt action should be taken to separate the mother and child to determine if the symptoms are legitimate or fabricated. Successful the athrent depends on the collaboration between disciplines and cooperation of all staff members. It is important that MPP be ruled out in cases of CIP when these children are evaluated for bransplant to prevent needless morbidly.

# Can we use a less invasive test? The wireless motility capsule System consists of: Capsule Data Receiver Docking Station MotiliGI<sup>TM</sup> Software Computer Workstation Smartbar "standard" meal

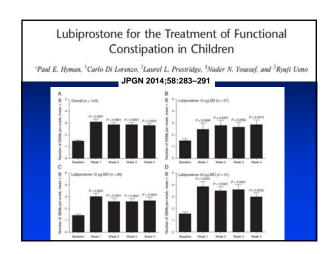
THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGIN	V.
J Pediatr. 2013;162:1181-7 ARTIC	
Wireless Motility Capsule Test in Children with Upper Gastrointestinal Symptoms	
Alex D. Green, DO <sup>1,a</sup> , Jaime Belkind-Gerson, MD <sup>2,a</sup> , Brian C. Surjanhata, BS <sup>3</sup> , Hayat Mousa, MD <sup>1</sup> , Braden Kuo, MC and Carlo Di Lorenzo, MD <sup>1</sup>	9.
22 patients (>8 y/o): They had WMC, scintigraphic gastric emptying studyand antro-duodenal manometry	
Conclusion: In symptomatic pediatric patients, the wireless motility capsule test is <i>highly sensitive</i> compared with scintigraphic gastric emptying studies in detecting gastroparesis, and seems to be more sensitive than ADM in detecting motor abnormalities	
	-
Treat the underlying disease	
Treat the underlying disease	
	-
0.411	
Getting tissue	
hownd of Polistic Gattonetrology and Natriline 33:54-37 G bby 2001 Leptworn Williams & Williams, Inc., Polishelphia	
Laparoscopic Full-Thickness Intestinal Biopsies in Children	
Mark V. Mazziotti and Jacob C. Langer	
Department of Surgery, Decision of Pediatric Surgery Washington University School of Medicine, St. Louis, Missouri, U.S.A.	
ORIGINAL ARTICLE: Clinical Endoscopy Gastrointest Endosc 2011;73:949-54	
Percutaneous endoscopically assisted transenteric full-thickness gastric	
biopsy: initial experience in humans ** Christopher N. Andrews, MD, MSc, FRCPC, Paul Minichev, Emil Neshev, MD, Hughie F. Fraser, MD, FRCPC, Martin Storr, MD, Oliver F. Bathe, MD, FRCSC, Stefan J. Urbanski, MD	-



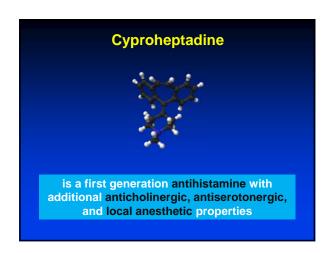
# **Treatment**

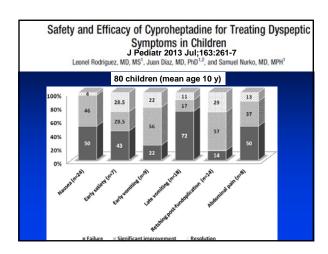


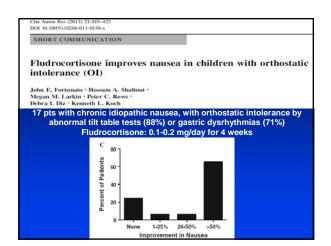
# Prucalopride in children Winter HS, et al. JPGN 2013;57:197-203 Open label rx with 0.01-0.03 mg/kg prucalopride administered once daily for 8 weeks to 38 children with a baseline BM frequency <2/week to investigate efficacy, safety and tolerability. n=37 n=37 n=35 n=35 n=34 n=33 n=31 n=29 Cisapride Improves Enteral Tolerance in remainic Snort Bower Syndrome with Dysmotility Bram P. Raphael, M.D.<sup>1,2</sup>, Samuel Nurko, M.D., M.P.H.<sup>1,3</sup>, Hongyu Jiang, Ph.D.<sup>4</sup>, Kristen Hart, B.S.<sup>1,3</sup>, Daniel S. Kamin, M.D.<sup>1,2</sup>, Tom Jaksic, M.D., Ph.D.<sup>2,5</sup>, and Christopher Duggan, M.D., M.P.H.<sup>1,2</sup> J Pediatr Gastroenterol Nutr 2011; 52: 590-594 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. **Secretagogues**

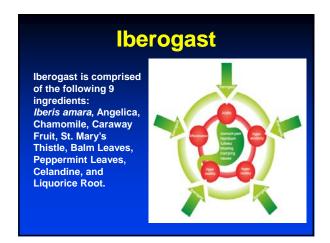


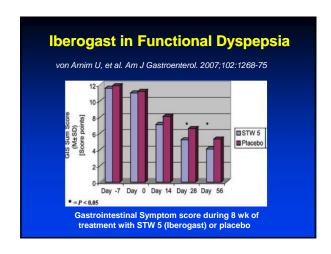










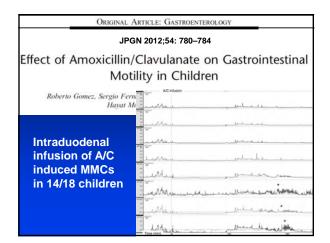


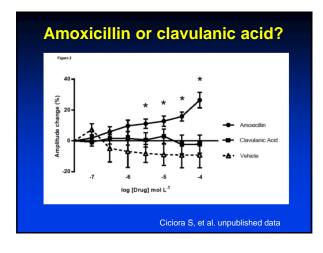
# **Treat bacterial overgrowth**

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

Conrad R. Cole, MD, MPH, MSc, Juliana C. Frem, MD, Brian Schmotzer, MS, Andrew T. Gewirtz, PhD,
Jonathan B. Meddings, MD, Benjamin D. Gold, MD, and Thomas R. Ziegler, MD

- SBBO increased 7-fold the odds for blood stream 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.





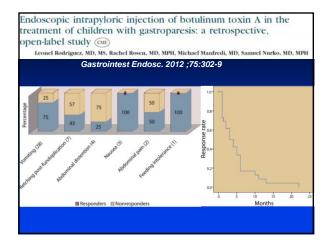
# **Octreotide**

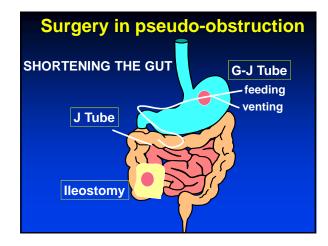
- Long acting somatostatin analog
- Half life: 1-2 hours after s.c. injection
- Prolonged duration of action
- Antisecretory agent
- Enterokinetic in patients with scleroderma, CIPO
- Delays gastric emptying
- "Hypo-algesic" agent?

WARRIED TO THE TOTAL PROPERTY OF THE TOTAL P		
e efficacy of treatment of patien urrent pseudo-obstruction with		7.0
O'Dea, S. J. H. Brookes and D. A. Wattchow	Colorectal Dis	sease 2010 12, 54
nents of Surgery and of Human Physiology, Rinders Medical Centre and R	inders University, bedion	Park, South Australia
10 mg BID starting dose	Slow transit constipation	Intestinal pseudo-obstruction
Number of patients (% of total)	6 (42.85)	7 (57.15)
		The state of the s
Age (years)	24-59	22-80
	24-59	22-80
Age (years)	24-59	3
Age (years) Gender	100000	27,271
Age (years) Gender Men	100000	27,271





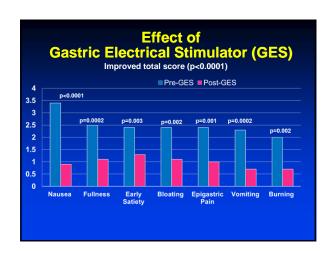


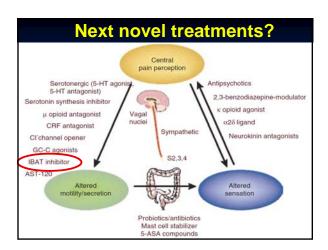


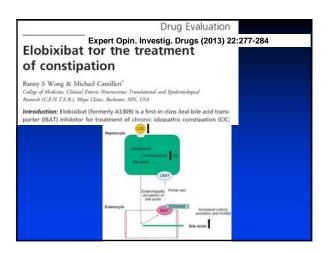
"Every child with pseudoobstruction on TPN needs a gastrostomy and an ileostomy"

(me, now)









# **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



Evaluation and Treatment of Functional Constipation in Infants and Children: Evidence-Based Recommendations From ESPGHAN and NASPGHAN

M.M. Tabbers, C. DiLorenzo, M.Y. Berger, C. Faure, M.W. Langendum, S. Nurko, A. Staiano, Y. Vandenplas, and M.A. Benninga





## **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

- 1. Two or fewer defecations per week
- At least 1 episode per week of incontinence after the acquisition of toileting skills
   History of excessive stool retention
- History of painful or hard bowel movements
- 5. Presence of a large fecal mass in the rectum
- History of large-diameter stools that may obstruct the toilet

#### Children (>4 yrs. of age)

Must include 2 months of 2 or more of the following with insufficient criteria for diagnosis of IBS:

- 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
- 5. Presence of a large fecal mass in the rectum
- History of large diameter stools that may obstruct the toilet



Gastroenterology 2006

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

Table 1 Rome categories by respondent

Rome category	Parent	Child	Physician
Functional dyspepsia	16 (13.6)%	3 (5.3%)	6 (5.1%)
Irritable bowel syndrome	51 (43.2%)	26 (45.6%)	22 (18.6%)
Abdominal migraine	43 (36.4%)	15 (26.3%)	1 (0.8%)
Functional abdominal	5 (4.2%)	3 (5.3%)	34 (28.8%)
Functional abdominal pain syndrome	1 (0.8%)	0	0
Functional constipation	31 (26.3%)	9 (15.8%)	63 (53.4%)
incontinence	1 (0.929)	U	U
Aerophagia	17 (14.4%)	11 (19.3%)	0
Cyclic vomiting	1 (0.8%)	3 (5.3%)	0
Rumination	1 (0.8%)	2 (3.5%)	0

- 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  $constipation^*\\$



<sup>\*</sup> Wong R, et al. Am J Gastroenterol 2010



Evaluation and Treatment of Functional Constipation in Infants and Children: Evidence-Based Recommendations From ESPGHAN and NASPGHAN

M.M. Tabbers, C. Dilaresten, M.Y. Berger, C. Faure, M.W. Langendum, S. Nurko, A. Statone, Y. Fandesplas, and M.A. Bennings

#### **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



Evaluation and Treatment of Functional Constipation in Infants and Children: Evidence-Based Recommendations From ESPGHAN and NASPGHAN

M.M. Tabbers, C. DiLorenzo, M.Y. Berger, C. Faure, M.W. Langendum, S. Nurko, A. Statano, Y. Fandenplas, and M.A. Bennings

#### Signs

- Abnormal thyroid gland
- Severe abdominal distension
- Perineum examination:
  - Perianal fistula
     Abnormal position of anus
  - Extreme fear during anal inspection

  - Anal scars
     Absent anal or cremasteric reflex
- Decreased lower extremity strength/tone/reflex
- Tuft of hair on spine
- Sacral dimple
- Gluteal cleft deviation





Milk allergy testing







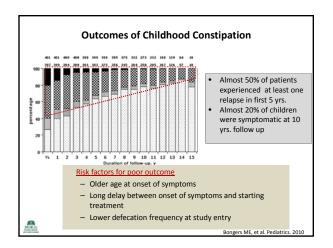


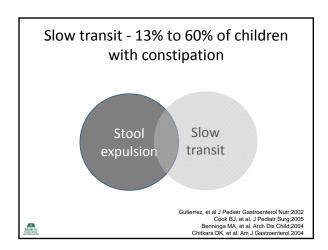


#### Treatment of Functional Constipation

- 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





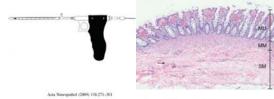


# **Disorders of Stool Expulsion**

# Dyssynergic defecation Anal achalasia



## **Rectal Suction Biopsy**



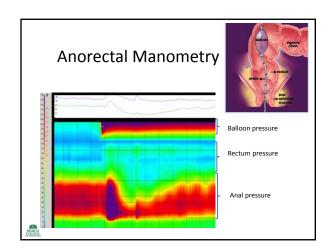
Gastrointestinal neuromuscular pathology: guidelines for histological techniques and reporting on behalf of the Gastro 2009 International Working Group



## **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

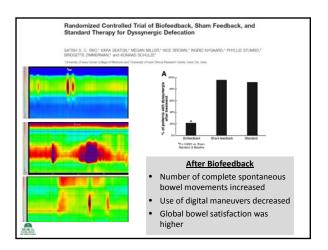


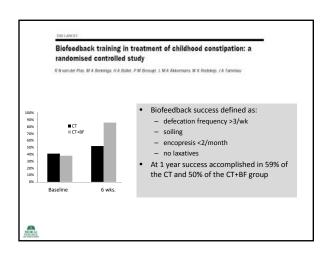


# Rectal compliance and constipation

- 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.

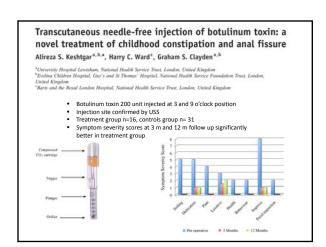
Van den Berg MM, et al. Gastroenterology 2009





Assessment of the Effectiveness of
Biofeedback in Children with Dyssynergic
Defectation and Recalcitrant
Constipation/Encopersis: Does Home
Biofeedback Improve Long-Term Outcomes

When the Mills of th



#### Internal Anal Sphincter Achalasia

Ciammara P et al, J Pediatr Gastroenterol 2003;37:315

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 intramuscular innervations in the IAS Absence of nitrergic innervations within the IAS muscle is believed to be

Absence of nitrergic innervations within the IAS muscle is believed to be responsible for the motility dysfunction in these patients.

Fujimoto T, et al. Pediatr Surg Int 1992, Hirakawa H, et al. JPGN 199

Pediatr Surg Int 2012

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

Florian Friedmacher · Prem Puri

- 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

	Table 5 Data on classification of enterior after treatment for LAS actualists of included studies						
1	Clavification of outcome <sup>4</sup>	Posterior IAS negociones	Intrasphineteric Boton injuction				
	Escrient	58/218 (26.6)	34/166 (14.5)				
	Good	129/229 (56.3)	73/166 (44/0)				
	Fair/resdering	14(218 (6.4)	32/166 (19.3)				
	Burr	14/218 (6.4)	35/166 (71.1)				

Date are presented to A/V (%)

# Slow transit - 13% to 60% of children with constipation Stool Slow transit Gutierrez, et al J Pediatr Gastroenterol Nutr. 2002 Cook BJ, et al. J Pediatr Surg 2005 Benninga MA, et al. Arch Dis Child: 2004 Childran DK, et al. Arch Dis Child: 2004

# Colonic Manometry and Colonic Scintigraphy as a Diagnostic Tool for Children With Severe Constipation

Suzanne M. Mugie, <sup>1</sup>Maria E. Perez, <sup>\*</sup>Rosu Burgers, <sup>1</sup>Elizabeth A. Hingsbergen, 
\*Anya Panati, <sup>\*</sup>Hayat Mousa, <sup>1</sup>Mare A. Benninga, and <sup>\*</sup>Carlo Di Lorenzo

JPGN 2013

- 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













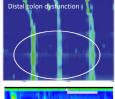
Do Oro-anal Transit Markers Predict Which Children Would Benefit From Colonic Manometry Studies?

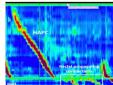
Neelesh A. Tipnis, Khalil I. El-Chammax, Colin D. Rudolph, Steven L. Werlin, and Manu R. Sood JPGN 2012



- 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

# High Resolution Colon Manometry





- 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

Giorgio V, et al. Neurogastroenterol Motil 2013 El Chammas K, et al. JPGN 2014

#### 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



Youssef N, et al. J Pediatr Gastroenterol Nutr. 2002 van den Berg MM, et al. J Pediatr Surg. 2006 Bonilla S, et al. J Pediatr Surg 2012

Sacral Neuromodulation Therapy: A Promising Treatment for Adolescents With Refractory Functional Constipation

#### 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

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

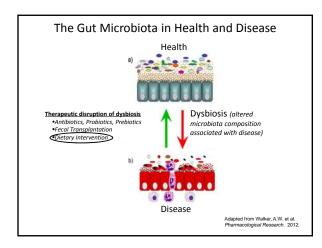
- Janssen Pharmaceuticals
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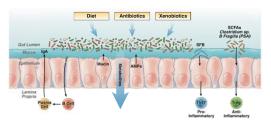
#### Objectives

- 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

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#### The Gut Microbiota in Health and 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







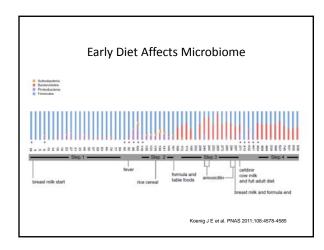


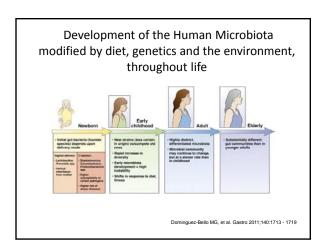


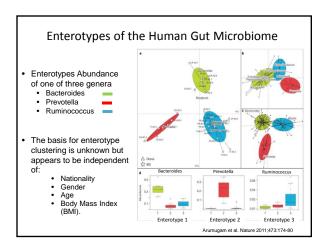












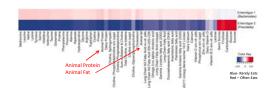
# COMBO - Cross-Sectional Study of Diet and Stool Microbiota

• 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

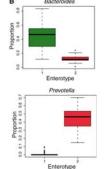
#### Bacterial Enterotypes and Long Term Diet



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

Wu G, et al. Science. 2011 Oct 7;334(6052):105-8

# 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 carbohydratebased diet more typical of agrarian societies

Wu G, et al. Science. 2011 Oct 7;334(6052):105-8

### 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

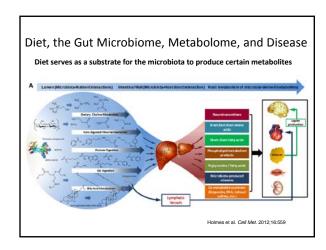
### The vegetarian or vegan diet Vegan/CG1 N = 105/105 Vegetarian/CG1 N = 144/144 Zimmer et al. Eur J Clin Nutr. 2012.

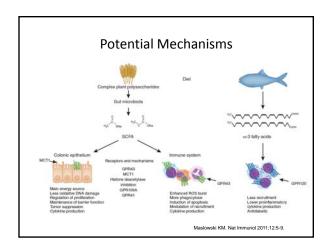
#### CaFE Study - Controlled Feeding Experiment

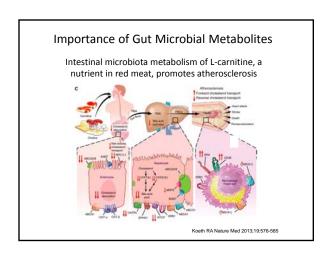
- Will a standardized diet reduce microbiota intersubject variability?
- What is the time course over which a diet alters the composition of the human gut microbiota?
- Does short term dietary fat or fiber alter the composition of the human gut microbiota and switch the abundance of Bacteroides vs. Prevotella?
  - 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

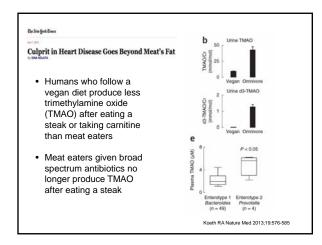
# CaFE Study Longitudinal analysis of microbiome under controlled feeding Changes detectable within 24 hours! Each color represents a different subject 10 day study Arrow is day 0 (pre-diet) Detectable changes during the 10 days but: • No enterotype switching • No reduction in intersubject variation Importance of long term diet We 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 Highly abundant obligate anaerobe in the microbiota of most adults Known for its ability to metabolize polysaccharides

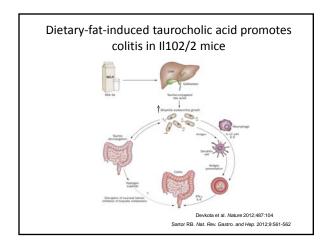








## The CutC Bacterial Gene Converts Choline into TMAO: Implications for Human Health Choline TMA-lyase (CutC Gene) Trimethyl Amine (TMAO) Developing Innovative Strategies to Prevent and Treat Human Disease Quantify the risk for heart disease by characterizing the abundance of bacteria in the gut that 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.



#### Diet and the pathogenesis of GI illness The role of dietary elements on the pathogenesis of GI illness Oral, but not parental, iron exacerbates experimental colitis — results in human IBD is controversial, but IV iron may be better tolerated IBD Iron Lack of SCFA-producing bacteria is associated with IBD, and butyrate supplementation, replacement of selected bacteria offer potential treatments Milk fat promotes a bloom of the colitogenic bacteria through increased levels of taurocholic acid Milk fat Omega-3 fatty Reduced Th 17-mediated inflammation and disease severity in murine models of colitis Fermentable A diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) reduced IBS symptoms sugars Gluten alters barrier function in IBS-D patients, particularly Gluten those with HLA-DQ2/8 NAFLD/ NASH Dietary choline def. predisposes patients to NAFLD/NASH with microbiomes with excessive metabolic breakdown of choline Choline Celiac Immune intolerance to gluten in a genetically susceptible host

#### 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 IIC.
- High fiber and fruit intakes were associated with decreased CD risk
- High vegetable intake was associated with decreased UC risk.

Hou JK et al. American Journal of Gastro 2011;106:563-73

Goldsmith and Sartor. J Gastroenterol. 2014.

#### **Dietary Factors and UC**

- Study of 191 patients with UC in remission
- Followed over 1 year

disease

- 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 (Lack 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)

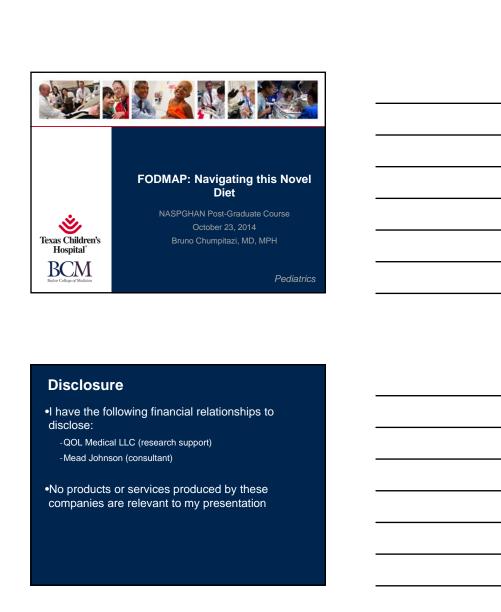


Mediterranean Diet

#### 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	



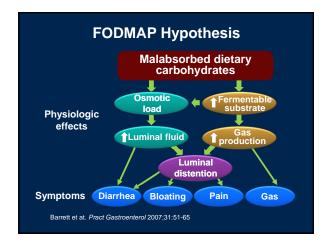
#### **Objectives**

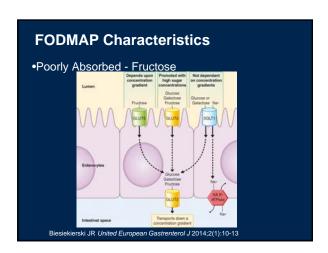
- 1) Describe the common characteristics of FODMAP carbohydrates and mechanism of action in triggering GI symptoms
- 2) Review the evidence to support their use in patients
- 3) Learn to identify and appropriately counsel patients in the use of the FODMAP diet

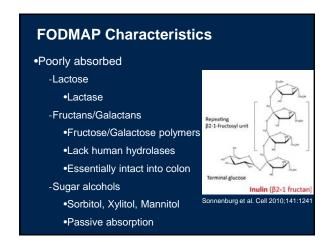
#### **FODMAP**

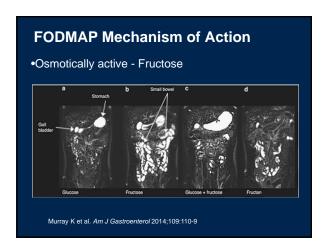
- Fermentable (bacterial metabolism)
- Oligosaccharides (fructans/galactans)
- <u>D</u>isaccharides (lactose)
- Monosaccharides (fructose)
- <u>A</u>nd
- Polyols (sugar alcohols sorbitol)
- Poorly absorbed, osmotically active, rapidly fermented (produce gas)

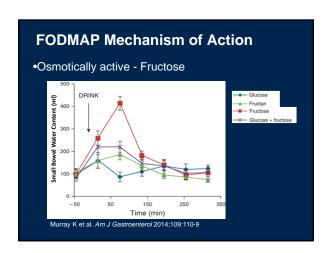
Barrett et at. Pract Gastroenterol 2007;31:51-65











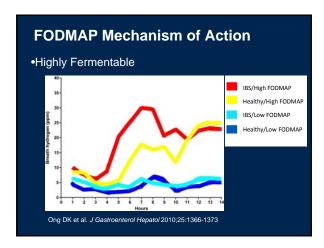
#### **FODMAP Mechanism of Action**

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

<sup>1</sup>Marciani L et al. *Gastroenterology* 2010;138:469-77 <sup>2</sup>Barret JS et al. *Aliment Pharmacol Ther* 2010;31:874-882 <sup>3</sup>Halmos EP *J Gastroenterol Hepatol* 2013;28(Suppl4):25-28

## FODMAP Mechanism of Action •Highly Fermentable Online Onlin

# FODMAP Mechanism of Action •Highly Fermentable Liver Transverse colon Sigmoid colon colon Murray K et al. Am J Gastroenterol 2014; 109:110-9



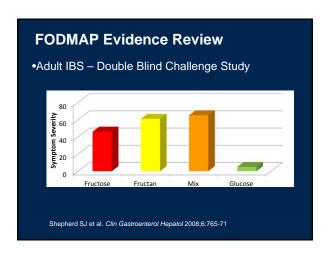
#### **FODMAP Mechanism of Action**

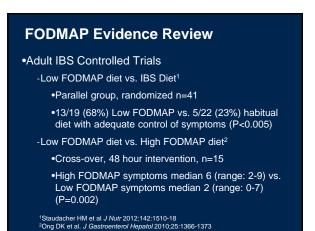
- •Microbiome Composition Changes
  - -Low FODMAP diet reduces luminal Bifidobacteria1
  - -Low FODMAP diet vs. habitual diet2
    - •Lower abundance but greater diversity
    - •Decreased relative abundance Clostridium cluster XIVa, Akkermansia muciniphila, Ruminococus
  - -Low FODMAP diet vs. habitual diet in children<sup>3</sup>
    - •Increased Clostridiales and decreased Bacteriodetes
    - •Responders with different baseline composition

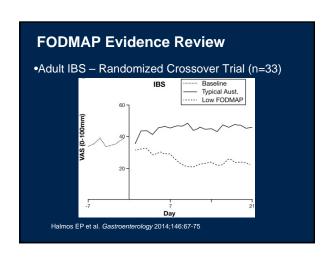
<sup>1</sup>Staudacher HM et al. *J Nutr* 2012;142:1510-1518 <sup>2</sup>Halmos EP et al. *Gut* 2014;Jul 12 [Epub] <sup>3</sup>Chumpitazi BP et al. *Gut Microbes* 2014;5:1-11

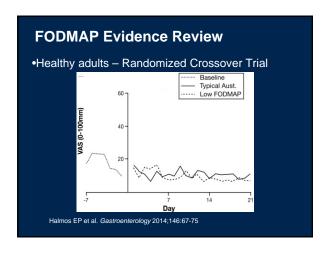
#### **FODMAP Evidence Review**

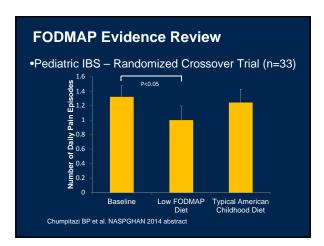
- •Adult Irritable Bowel Syndrome (IBS)
  - -1 Double Blind Placebo Controlled Challenge Study
  - -3 Randomized Controlled Trials
  - -Several uncontrolled studies (symptom improvement 56-94%)
- •Pediatric IBS
  - -One uncontrolled study (n=8, symptom improvement 50%)
  - -1 Randomized Cross-Over Trial (Abstract)
- •Inflammatory Bowel Disease
  - -Open-label studies











## FODMAP 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, -Allowed alternatives: Banana, blueberry, cantaloupe, grapes, kiwi, oranges, pineapples, raspberry, strawberry •Lactose -Avoid lactose containing dairy products -Alternatives: Lactose-free dairy **FODMAP Counseling** Polyols -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)

Category	Allowed	Avoid
egetables	Alfalfa sprouts	Asparagus
	Bok Choy	Artichokes
	Carrots	Beans and legumes
	Cucumber	Beets
	Eggplant	Cauliflower
	Green beans	Garlic
	Green and red peppers	Green peas
	Lettuce	Leeks
	Parsnip	Mushrooms
	Potato	Okra
	Pumpkin	Onion
	Spinach	Snow peas
	Squash	Snap peas
	Tomato	
	Turnip	
	Zucchini	

#### **FODMAP Counseling**

- •Additional Resources
  - 1) Monash University (www.med.monash.edu/cecs/fodmap)
    - •iPhone and Android application
  - 2) Shepherd Works
    - www.shepherdworks.com.au
    - •The Low FODMAP Diet Cookbook
  - 3) Publications
    - •Barrett JS et al. Practical Gastroenterology 2007;31:51-65
    - •Biesiekierski JR et al. J Hum Nutr Diet 2011; 24:154-176

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

#### Acknowledgements

- Robert Shulman
  - Danita Czyzewski
  - Mariella Self
- Cynthia Tsai
- Ann McMeans
- Monash University

Pediatrics

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-Texas Medical Center DDC (NIH DK56338)

-NIDDK (K23 DK095943)

Texas Children's Hospital Book Circles of Malicon

### 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 1° 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 <5<sup>th</sup> %ile)
- > 23% linear stunting (height <5<sup>th</sup> %ile)
- > 8-14% overweight (BMI > 85th %ile)

\*Marchand V, Motil KJ. J Pediatr Gastroenterol Nutr 2006

#### Clinical Significance



Health consequences

- > Improve growth outcomes
- > Reduce frequency of infection
- Increase physical activityQuality 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

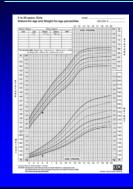
- > 5-yr-old female with Rett syndrome
- ➤ Weight 28# (12 kg) for previous one year
- ➤ Has good appetite, consumes well-balanced diet of chopped table foods, beverages per parents
- ➤ Height 98 cm, weight 12 kg, BMI 13 kg/m²
- ➤ Small head, absent speech, hand stereotypies, scoliosis, ambulatory

#### Rett Syndrome



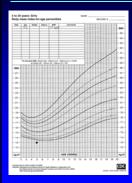
- ➤ Is patient malnourished?
  - > Yes
  - > Maybe
  - > No
- How would you characterize child's nutritional status?
- > patient is 5 y of age
- > brother is 3 y of age

#### 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  $\leq$  12 kg/m<sup>2</sup>

#### ➤ 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
  - $\rightarrow$  BMI < 5<sup>th</sup> %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 PO<sub>4</sub>, K, Mg, glucose, thiamine
  - Risk factors include weight loss > 10% over 2-3 months or actual weight <70% IBW</p>
- CHF, arrhythmia, pulmonary edema, hemolysis, rhabdomyolysis, myopathy, seizures, coma, death

#### Complications of Refeeding



Aspiration pneumoniaHypermetabolism

- > 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 PO<sub>4</sub>, 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







Very Early Onset Inflammatory Bowel Disease
- Immunology, Presentation, and Practical
Considerations -

Scott B. Snapper, M.D., Ph.D.

October 23, 2014 NASPGHAN Post-Graduate Course Atlanta, Georgia







#### **Disclosures**

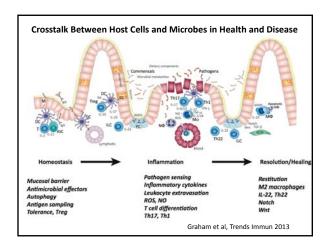
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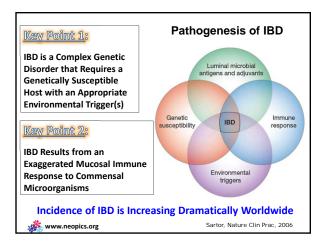
Pfizer – Therapeutic Scientific Advisory Board; Grant Support Eisai - IBD Advisory Board Ironwoods – IBD Advisory Board Cubist – IBD Advisory Board Abbvie – IBD Advisory Board Hoffman La-Roche – IBD Advisory Board, Consultant Jannsen – IBD Advisory Board, Consultant

\* 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





### Genetics and IBD in the Adult and Pediatric Population

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

Loftus et al., Gastroenterol. 2004 Bengtson et al. J. Crohn's Colitis 2009 Brant., IBD J. 2011 Ruemmele Curr Opin Gastroenterol 2010

#### **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

Mamula P. Am J Gastro 2002 Heyman MB J Pediatr 2005

#### **Unique Clinical Features of VEO-IBD\***

#### VEO - IBD Adoles

- Colonic involvement 80% at < 10 years of age</li>
- Ileal involvement less common at age < 10 yrs</li>
- Family history 40-50%
- Extension of disease up to
- Adolescent and Adult-Onset IBD
- Colonic involvement <20%</li>
- Ileal involvement up to
- 80% Family history – 14-20%
- Extension of disease up to 16%

Griffiths (2004) Best Pract Res Clin; Heyman et al (2005) J Ped; Ruemmele et al (2005) JPGN; Kappelman et al (2008) IBD; Louis et al (2008) Gastro, van Limbergen et al (2008) Gastro, Vernier-Massoulle (2008) Gastro: Le

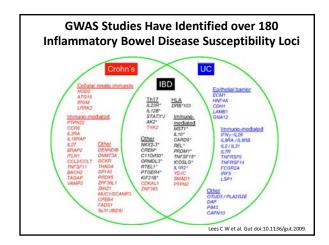
#### Unique Aspects of Infantile IBD (< 2yo)

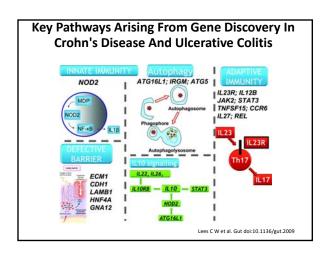
- Often isolated Colonic Disease
- Severe Course refractory to multiple immunosuppressant medications, often requiring surgery, occasionally fatal
- > 40 % with one or more family members with IRD
- 25% first manifestation of underlying immunodeficiency

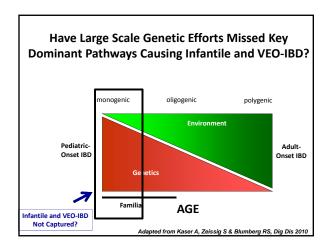
Ruemmele 2006 JPGN Cannioto 2009 EJP Heyman 2005 J Ped

<sup>\*</sup> Defined as Age < 10 by the Paris Classification

#### **Greatest Increase in IBD Incidence Very Early Onset IBD** Age at diagnosis IBD UC +51.0% (P=N/A)\* +56.8% (P=0.11) 6mo-4yr +38.1% (P=0.95) +65.7% (P<0.0001) +58.9% +57.9% 5-9 yr (P=0.0003) (P<0.0001) 10-14 yr +34.1% (P<0.0001) (P=0.002) (P=0.09) +12.1% +27.4% 15-17 yr (P=0.009) (P=0.006) (P=0.03) \* By Poisson regression analysis, controlling for sex Benchimol et al (2009) Gut 48:1490-97; Benchimol et al (2014) Gastro (in press) www.neopics.org







# Primary Immunodeficiencies Often Present with Intestinal Inflammation PEX syndrome - Frequent enteropathy Wiskott-Aldrich syndrome - 10% with collts Chronic granulomatous disease - Gastric granulomatous disease - Grown's-like colltis NEMO (NF-kB Essential Modulator) Deficiency - enterocolltis - superficial cryptitis XIAP (X-linked inhibitor of apoptosis) - severe fistulizing perianal disease in about 20% of patients - Common variable immunodeficiency - Frequent enteropathy Since these are Rare Diseases an International Effort is Required to Advance our Understanding Holm Unlig Gut 2013

# NEOPICS/Care-for-Rare IBD Alliance interNational Early Onset Pediatric IBD Cohort Study 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 HELMSLEY LEGIS R. AND HAMEY B HELMSLEY Care-for-Rare FOUNDATION

#### Case

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



Severe Colitis





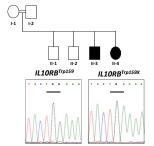


Perianal disease with multiple fistulas

Joint effusions

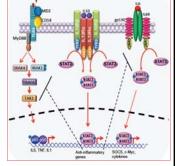
Glocker, Snapper, Grimbacher, Klein NEJM 2009

### **Genetic Evaluation Identified Mutation in IL-10 Receptor**



#### **IL10R Pathway**

- IL10 restricts excessive immune responses
- Inhibits secretion of proinflammatory cytokines -TNFα, IL12, and IFNγ
- Receptor IL10R has two subunits:
  - 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





Shouval, Muise, Snapper, Adv. Immunol. 2013

#### **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

Glocker, EO. Klein, C. NEJM. 2009; EO Glocker Lancet 2010; B Begue Am J Gastro 2011; Moran CJ, et al, IBD Journal 2012 Engelhardt et al, J Allergy Clin Immunol. 2013.

#### 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





Muise, et al Gut, 2011

#### **Hypothesis:**

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

Muise, et al Gut, 2011

#### **NADPH Oxidase Genes and CGD** CYBB: X-Linked ~65% gp91phox Recessive CYBA: p22phox Autosomal <5% Recessive Autosomal ~25% NCF1: p47phox Recessive NCF2: p67phox Autosomal ~5% Recessive NCF4: p40phox Autosomal < 1%

Lam et al., 2010 www.neopics.org

#### 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)

w.neopics.org





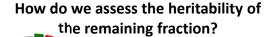


Muise, et al Gut, 2011

#### **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)

Gene	SNP	Protein Domain	Population Frequency	# of Patients (N=122)	Function
CYBB	G364R rs141756032	Ferric Reductase	0.005%* (Males)	1	Predicted Damaging
NCF1	R90H rs13447	PX Domain	5.5%** (Hetero.)	12	Reduces ROS Production
NCF2	G501R	SH3 Domain	0*	1	Predicted Damaging
NCF2	P454S rs55761650		0.005%*	1	Strong ESE Lost
NCF4	R308Q	PB1	8x10 <sup>-5</sup> *	1	Predicted Damaging
RAC2	Non-coding	Intron 5	0*	1	hnRNP A1 site gained
🌉 www.	neopics.org		Dhil	lon et al. Ga	stro in Press



■ IL10RA (n = 5) ■ IL10RB (n = 7) ■ unknown (n = 71)

- 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 – XLPS2)



EA Worthey Genetics in Medicine 2011

#### 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 af 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

Mutations in Tetratricopeptide Repeat Domain 7A Result in a Severe

WES



www.neopics.org





FUIIII OF VERY Early One	set illiallilliatory bower bisease				
Zhen Zhao, Abdul Elkadri, Abdul Elka	uo, <sup>5.</sup> Lucas A. Mastropaolo, <sup>5</sup> Ehsan Bahrami, <sup>4</sup> I. Sandeep Dhillon, <sup>7</sup> Raya Murchie, <sup>6</sup> Ramo Fatto <sup>7</sup> , <sup>7</sup> Paul W. Wales, <sup>5</sup> Emest Cut; <sup>7</sup> Yochi Kakuti meier, <sup>6</sup> Ficora Powine, <sup>5</sup> Nell Shah, <sup>7</sup> Christoph Tohrar, <sup>5</sup> Joseph Roman, <sup>5</sup> John H. Bumel, <sup>5,5,5</sup> Anne M. Geffisse, <sup>5,6</sup> Marya Maji, <sup>6</sup> Maryam Monajemzadeh, <sup>6,6</sup> Maji, <sup>6,6</sup> Maji	uh."  Walz."  Gastroenterology 2014			
	domain 7A (TTC7	uencing identifies tetratricopeptide repeat A) mutations for combined y with intestinal atresias			
JACI 2013	John Manis, MD," Hogume Im, PhD Philippe Lacroute, PhD," Keith Bet Elecoror Galle, MD," Giovanna M Waterd Al-Herz, MD," Wasmi Alfah Sung-Yun Pal, MD," Graziella Caste	Not Chem. PRO."* Sinks Glissel, PRO."* Genten Lavot, Pro.". Genryst Max. PRO." Sinks Loneodi, Sil." Karry Dolbha, Sil. Jahn Maxs. MC: Teppor in N. Rol." annier E. Genfyser. PRO.". Stronger in Presented, PRO." Olis Stackshine, PRO.". Stronger in Presented, PRO. "Olis Stackshine, PRO." Stronger in Presented Glissel, Pro. "Stronger in Presented Glissel, Pro." Stronger in Presented Glissel, Prof. Stronger in Presented			
TTC7A mutations disrupt intestinal epithelial apicobasal polarity  Amdie I. Bigorger, <sup>1,4</sup> Henre F. Farn, Flasme Lemone, <sup>1,4</sup> Naze Mariaca, <sup>1,4</sup> Naze Mariaca, <sup>1,4</sup> Nazie Mar					
Christine Bloir-Fayord, Filterion, Reacher, Flocide Brouses, <sup>(n)</sup> Alain Fischer, <sup>(3,5)</sup> Hans Clavers, <sup>2</sup> and Generalize de Barri Baste <sup>(3,5)</sup> JMG 2013		Exome sequencing identifies mutations in the gene TTC7A in French-Canadian cases with hereditary multiple intestinal atresia			
		Mark E Samuels, <sup>1</sup> Jacek Majevski, <sup>2</sup> Najmeh Alirezale, <sup>2</sup> Isabel Fernandez, <sup>1,3</sup> Fertan Casals, <sup>1</sup> Natalie Pates, <sup>1,4</sup> Hélène Decaluse, <sup>1,5</sup> Isabelle Gosseln, <sup>6</sup> Elle Haddad, <sup>1,3,5</sup> Allan Hodgkinson, <sup>1</sup> Youself Idaghdour, <sup>2</sup> Vallerie Marchand, <sup>1,5</sup>			

#### TTC7A Mutations Cause Apoptotic Enterocolitis

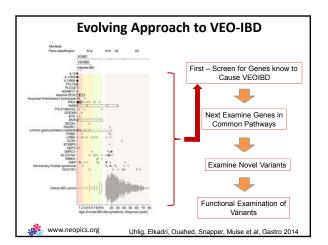
- Little is known about the function of the Tetratricopeptide Repeat Domain 7 (TTC7A) gene
- Studies suggest it plays a critical role in PI4KIII
   regulation/? ROCK regulation
- Defects in murine Ttc7 gene
  - result in the flaky skin (fsn) mutant mice
  - develop pleiotropic abnormalities, including runting syndrome, anemia, psoriasis, diarrhea, and intestinal apoptosis

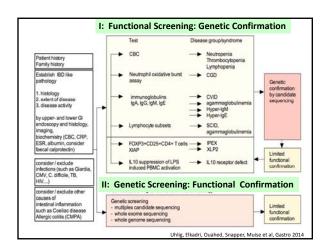


#### **Conclusions: TTC7A-Deficiency and VEOIBD**

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







#### **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





Thanks to the patients and 250 scientists at > 80 Centers around the world

Leslie Grushkin-Lerner, Ph.D. (NEOPICS Program Manager)

Karoline Fiedler (NEOPICS Project Coordinator)
Alexandra Griffith (NEOPICS Project Coordinator)

# "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 JPGN 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 Flylib.com; justintimemedicine.com; commons.wikimedia.org Weill Cornell Medical College NewYork-Presbyterian The Work Cornell Medical College NewYork-Presbyterian Center for Children's Health

# Signs and Symptoms of Microscopic Colitis

- Persistent watery non bloody 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 <u>with</u> multiple biopsies to include the right and transverse colon, EM
- Radiologic testing



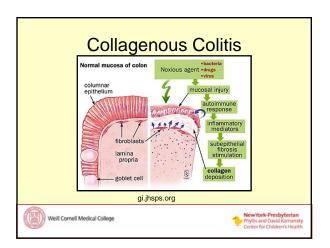


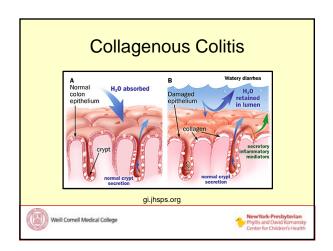
# Causes/Risk Factors

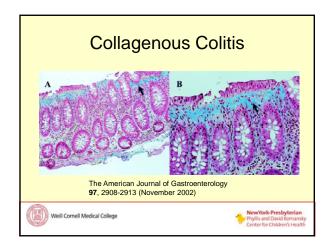
- Unknown etiology
- · Possible etiologies
  - Medications
  - Infections: Bacteria that produce toxins/Viruses
  - Immune disorders (Celiac, RA, Type I DM, thyroid disease: Hashimoto's or Graves disease)
  - Collagen synthesis abnormalities

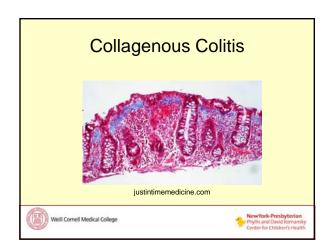


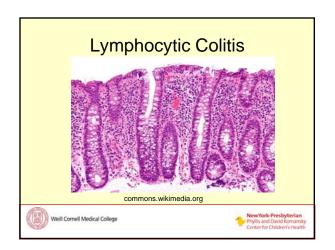


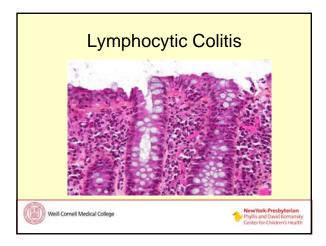












# Treatment of Lymphocytic and Collagenous Colitis

- 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



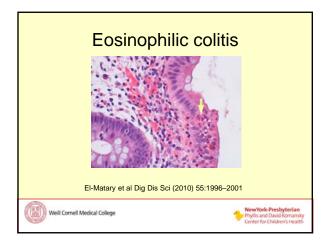


# Eosinophilic infiltration of lamina propria



Saeed et al Pediatr Transplantation 2006: 10: 730-735





# 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 permeability<sup>1,2,3</sup>
- Altered cytokine production (e.g. inhibition of IL-2 resulting in augmentation of IgE production) leading to eosinophilia<sup>4,5</sup>

<sup>1</sup>Madsen, et al *Gastro* 1995, <sup>2</sup>Gabe eta I *Gastro* 1998, <sup>3</sup>Yankar *Transpl* 1996, <sup>4</sup>Renz et al *Exp. Dermat* 1995, <sup>5</sup>Arikan et al *Transpl Proc* 2003



NewYork-Presbyterian
Phyllis and David Komansky
Center for Children's Health

# 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

Hyams et al Gastro 2007;132:863 Hyams et al. Gastro 2012: 143:365-74

# 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%





Hyams 2012;CGH 4:391

# 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"

Laharie et al, Lancet. 2012 1:1909-15.

# Severe colitis (CH Boston experience) Outcomes of tacrolimus therapy (Watson et al, IBD Journal 2011) HOSPITAL 46 patients tacrolimus induction 46 colectomy within 3 months 1 infliximab 1 returned to other hospital LONG TERM 23 stable on maintenance therapy 14 6-mercaptopurine, 8 infliximab, 1 neither (longest remission 14 years)

# 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.

### **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.

\*Lazzerini et al, JAMA. 2013;310(20):2164-217

# Thalidomide data Thalidomide prop (n-28) Tha

# 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 Ouasthof

# Natalizumab for pediatric CD

- 31 patients received 3mg/kg for 3 infusions
  - PCDAI >30
  - Ages 11-17
- Well tolerated
- Response 45%
- 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

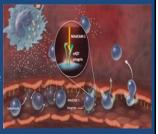
- Vedolizumab
  - UC and Crohn's
- Ustekinumab
- Crohn'sTofacitnib
  - Ulcerative colitis





# Vedolizumab

- Humanized IgG 1 monoclonal antibody to alpha4 beta7 integrin
- Modulates gut, but NOT brain lymphocyte trafficking
- Less risk of PML compared to natalizumab



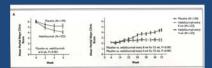
Takeda website

# 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

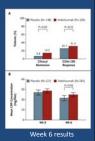
Feagan et al NEJM 2013; 369:699

# 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%)



Sandborn et al, NEJM 2013:369:711-21 Sands et al: Gastroenterology 2014 147:618-627

# Bacterial Antigens Adantive immune Pathways\* Thelper 1/ Thelper

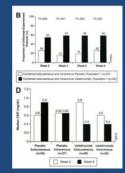
### Ustekinumab in Crohn's

- 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

Sandborn et al, Gastro 2008 135:113

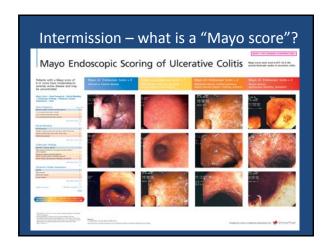
# Ustekinumab results (Crohn's)

- 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.



# **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





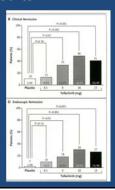
### Tofacitinib in active ulcerative colitis

- Phase 2 placebo RCT
  - 194 adults active UC assigned to 4 different doses of tofacitnib 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

Sandborn et al 2012: 367:616

### Tofacitinib results

- Clinical remission at 2 months
  - 48% at tofacitnib, 10 mgbid 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)

Scott, Drugs 2013; 73; 857

# "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.

# **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.

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