NASPGHAN POSTGRADUATE COURSE
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Continuing Medical Education

NASPGHAN CME Mission Statement

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

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

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

Physicians

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

AMA PRA Statement

NASPGHAN designates this educational activity for a maximum of 7.25 *AMA PRA Category 1 Credit(s)*^{TM} Physicians should only claim credit commensurate with the extent of their participation in the activity.

THURSDAY OCTOBER 18, 2012 NASPGHAN POSTGRADUATE COURSE
Challenges in Practice: Beyond Usual Therapies

8:00 am - 8:10 am **WELCOME AND INTRODUCTION**
Sandeep Gupta MD

8:10 am - 9:20 am **MODULE A: WHAT GOES IN, MUST COME OUT: CLINICAL GASTROINTESTINAL ISSUES**
Moderators: Melanie Greifer MD and Cary Qualia MD

FROM PROPRANOLOL TO INDUCING COMA: CARING FOR A CHILD WITH INTRACTABLE CYCLIC VOMITING SYNDROME (CVS)
B Li MD, Medical College of Wisconsin

Learning objectives:

1. Describe pathogenesis of and evaluation of CVS
2. Learn prophylactic acute management of CVS
3. Know newer interventions for CVS

INCONTINENCE WITHOUT FECAL IMPACTION
Joseph Croffie MD, Riley Hospital for Children

Learning objectives:

1. Describe how to evaluate for causes of incontinence without fecal impaction
2. Learn initial management of these patients
3. Know the newer therapies and role of motility in these patients

ELIMINATION DIETS: RISKS AND BENEFITS
Maria Mascarenhas MD, Children's Hospital of Philadelphia

Learning objectives:

1. Describe various elimination diets
2. Learn the nutritional issues associated with elimination diets including alternative milks
3. Recognize how to counsel and navigate quality of life issues with dietary modifications

9:20 am – 10:30 am **MODULE B: LIVER BEYOND VIRUS, METABOLIC, STORAGE, TUMORS**
Moderators: Sandeep Gupta MD and James Daniel MD

METABOLIC LIVER DISEASE: WORKING THROUGH THE MAZE
Saul Karpen MD, PhD, Emory University

Learning objectives:

1. Know when to suspect metabolic liver disease
2. Learn a staged approach to diagnosis of metabolic liver diseases
3. Understand urgent versus emergent evaluation and treatment of metabolic liver diseases

UPDATE ON ALPHA-1-ANTITRYPSIN DEFICIENCY
Jeffrey Teckman MD, St. Louis University

Learning objectives:

1. Review the genetics and pathophysiology of α1AT
2. Know the complications, including cirrhosis, of α1AT
3. Learn the newer therapies for α1AT

THERE IS A LIVER MASS ON THE ULTRASOUND: WHERE DO YOU GO FROM HERE?
Kathleen Schwarz MD, Johns Hopkins University

Learning objectives:

1. Learn the differential diagnosis of hepatic tumors
2. Know the evaluation including laboratory tests, imaging, and histopathology of hepatic tumors
3. Understand the treatment options of hepatic tumors

10:30 am – 10:50am **BREAK**

10:50 am – 12:20 pm **MODULE C: THE INFLAMED INTESTINE**
Moderators: Sandeep Gupta MD and Edward Hoffenberg MD

GI Inflammation, Immune Function and IBD
Harland Winter MD, Massachusetts General Hospital for Children

Learning objectives:

1. Understand basic gastrointestinal mucosal immunology
2. Learn ways to manipulate gastrointestinal immunology
3. Know clinical application of these interventions

MY STOMACH IS BUGGING ME!: THE MICROBIOME IN IRRITABLE BOWEL SYNDROME
Robert Shulman MD, Baylor College of Medicine

Learning objectives:

1. Understand the microbiome of the gut
2. Describe role of gut microbiome in irritable bowel syndrome u
3. Learn the use of targeted therapy for irritable bowel syndrome based on the microbiome

THE SORE BOTTOM: PERIANAL INFLAMMATORY BOWEL DISEASE
Anne Griffiths MD, The Hospital for Sick Children

Learning objectives:

1. Learn evaluation of perianal disease
2. Know medical management of perianal disease
3. Describe surgical therapy of perianal disease

RESCUE ME FROM MY IBD: UPDATES ON INFLAMMATORY BOWEL DISEASE THERAPY
Athos Bousvaros MD, MPH, Children's Hospital Boston

Learning objectives:

1. Know appropriate usage and complication of immune-modulators
2. Review use of biologic agents
3. Learn use of rescue therapies in non-responders to biologics

12:20 pm – 1:50 pm **LEARNING LUNCHES (separate registration required)**

1. THE TROUBLESOME TUMMY: INTRACTABLE NAUSEA AND CONSTIPATION
B Li MD and Joseph Croffie MD — Moderator: Emily Contreras MD

2. ELIMINATION DIETS: FADS, FACTS, AND FICTIONS
Maria Mascarenhas MD and Charles Vanderpool MD — Moderator: Anupama Chawla MD
3. MANAGING THE METABOLIC LIVER DISEASE PATIENT
Saul Karpen MD, PhD and Sanjiv Harpavat MD, PhD — Moderator: Cary Qualia MD

4. SORTING THROUGH THE STORAGE DISEASES
Jeffrey Teckman MD — Moderator: Ozlem Bulut MD

5. LIVER TUMORS: BEYOND THE BENIGN
Kathleen Schwarz MD and Ghassan Wahbeh MD — Moderator: James Daniel MD

6. INFLAMED AND IMMUNODEFICIENT: HOW TO MAKE THE GUT WORK FOR THE PATIENT
Harland Winter MD and Christopher Moran MD — Moderator: Stanley Fisher MD

7. BUGS AND GUTS
Robert Shulman MD and Bruno Chumpitazi MD — Moderator: Christine Waasdorp Hurtado MD

8. GETTING TO THE BOTTOM OF THINGS: PERIANAL INFLAMMATORY BOWEL DISEASE
Anne Griffiths MD and Eric Benchimol MD — Moderator: Edward Hoffenberg MD

9. RESCUE THERAPY FOR CHILDREN WITH COMPLICATED INFLAMMATORY BOWEL DISEASE
Athos Bousvaros MD, MPH and Michael Docktor MD — Moderator: Sunny Hussain MD

10. POST-OPERATIVE INFLAMMATORY BOWEL DISEASE MANAGEMENT
Marla Dubinsky MD and Ashish Patel MD — Moderator: Henry Lin MD

11. THE SMALL INTESTINE: INVESTIGATING AND INTRUDING
Victor Fox MD and Robert Kramer MD — Moderator: Marsha Kay MD

12. PANCREATOBILIARY IMAGING
Douglas Fishman MD and Quin Liu MD — Moderator: Raza Ali Patel MD, MPH

13. HOW TO KEEP A NEW LIVER HAPPY: POST LIVER TRANSPLANT CARE
Simon Ling MB, ChB and Marialena Mouzaki MD — Moderator: Vicky Ng MD

14. POST-INTESTINAL TRANSPLANT CARE
Valeria Cohran MD and Evelyn Hsu MD — Moderator: John Pohl MD

1:50 pm – 3:15 pm **MODULE D: IMAGING AND ACCESSING THE TUBES**
Moderators: Sandeep Gupta MD and Marsha Kay MD

LOOKING DEEPLY INTO THE NOT SO SMALL INTESTINE
Victor Fox MD, Children's Hospital Boston

Learning objectives:

1. Understand the various modalities for intestinal visualization: push enteroscopy, SBE, DBE, spiral enteroscopy, and capsule endoscopy
2. Recognize the complimentary roles of capsule endoscopy and deep enteroscopy
3. Know new and emerging techniques including narrow-band imaging and confocal laser endomicroscopy

PUTTING TUBES WITHIN TUBES: ENTERAL THERAPEUTIC ACCESS
Robert Kramer MD, The Children's Hospital Colorado

Learning objectives:

1. Learn the various types of enteral access including G, GJ, J, and cecal tubes/buttons
2. Recognize the indications and appropriate usage for various access options
3. Know proper placement and care techniques to minimize complications

IMAGING THE PANCREATO-BILIARY TREE
Douglas Fishman MD, Texas Children's Hospital

Learning objectives:

1. Know who, when, and if to image beyond ultrasound
2. Pros/cons of various imaging techniques (MRCP, ERCP, EUS)
3. Describe potential therapeutic interventions with these techniques

UPDATE ON CRITICAL FOREIGN BODY INGESTIONS
Petar Mamula MD, Children's Hospital of Philadelphia

Learning objectives:

1. Be familiar with critical issues with foreign body ingestions
2. Understand evaluation and management of these ingestions
3. Learn about NASPGHAN's efforts highlighting this public health issue

3:15 pm – 3:35 pm **BREAK**

3:35 pm – 5:05pm **MODULE E: WHEN ALL ELSE FAILS: LIVER, INTESTINE AND POUCH**
Moderators: Melanie Greifer MD and Stanley Fisher MD

THE KID IS ON THE LIST: KEEPING COMPLICATIONS AT BAY FOR THE NON-TRANSPLANT HEPATOLOGIST
Simon Ling MB, ChB, The Hospital for Sick Children

Learning objectives:

1. Initial management of hepatorenal syndrome
2. Medical versus surgical management of ascites
3. Evaluation and management of encephalopathy

TRICKS OF THE TRADE FOR INTESTINAL FAILURE
Valeria Cohran MD, Children's Memorial Hospital, Chicago

Learning objectives:

1. How to optimize enteral nutrition
2. Tricks with parenteral nutrition
3. List newer surgical techniques and procedures

GASTROINTESTINAL AND LIVER COMPLICATIONS OF BONE MARROW TRANSPLANT
Ghassan Wahbeh MD, Seattle Children's Hospital

Learning objectives:

1. Know evaluation of liver complications in bone marrow transplant
2. Learn evaluation of gut complications in bone marrow transplant
3. Describe management of these complications in bone marrow transplant patients

POUCH DYSFUNCTION AND SURVEILLANCE: WHAT ARE MY OPTIONS?

Marla Dubinsky MD, Cedars-Sinai Medical Center

Learning objectives:

1. Learn how to recognize pouch dysfunction
2. Describe medical versus surgical options for pouch dysfunction
3. Know routine surveillance for cancer in patients with pouch

MODULE A: WHAT GOES IN, MUST COME OUT: CLINICAL GASTROINTESTINAL ISSUES
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3. Recognize how to counsel and navigate quality of life issues with dietary modifications

From propranolol to inducing coma for a child with intractable Cyclic Vomiting Syndrome

B U.K. Li, MD
Professor of Pediatrics
Medical College of Wisconsin (Milwaukee)

Children's Hospital of Wisconsin
A member of Children's Hospital and Health System

MEDICAL COLLEGE OF WISCONSIN

Disclosure

- **No disclosures**
- **Off-label use of medications will be discussed**

Objectives

- **Describe the pathogenesis and evaluation of CVS**
- **Learn prophylactic and acute management of CVS**
- **Know newer interventions for CVS**

NASPGHAN Consensus Statement: *5 questions to a diagnosis!*

- ≥ 3 attacks/6 months or 5 total?
- Nausea/vomiting episodes 1h-10days?
- Well (to baseline) in between? ***88%!***
- Each attack similar to others? ***98%!***
- Vomiting ≥ q. 15 min at worst? ***77-92%***

Li et al. NASPGHAN Consensus Statement on CVS JPGN 2008;47:379

CVS gets its own diagnostic code

- **Current ICD 9 code**
  - **536.2 = persistent vomiting – *can't do epidemiology***
- ***New* ICD 10 code in 2013**
  - **G43.A0 Cyclical vomiting, not intractable**
  - **G43.A1 Cyclical vomiting, intractable**

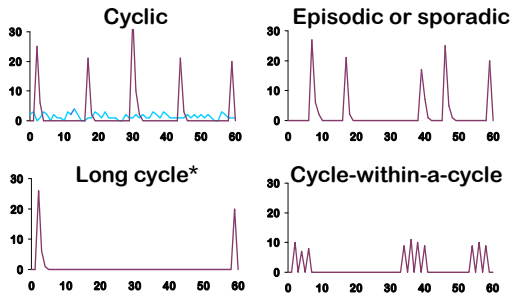
CVS, Celiac and Crohn: *Comparisons*

	Prevalence	Incidence
CVS	**1.9-2.3%†**	**3.2 per 100,000 (IR)‡**
Celiac	**0.75%**	**2-7 per 100,000**
Crohn	**0.043%**	**4.56 per 100,000 (WI)**

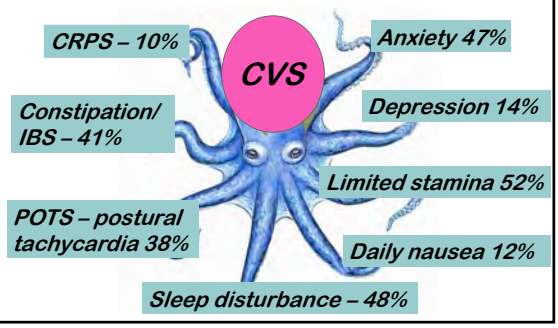
† Cullen & MacDonald Med J Aust 1963;2:167-173.

† Abu Arafeh & Russell JPGN 1995;21:454-458.
‡ Fitzpatrick & Drumm Am J Gastroenterol 2008;103:991-5

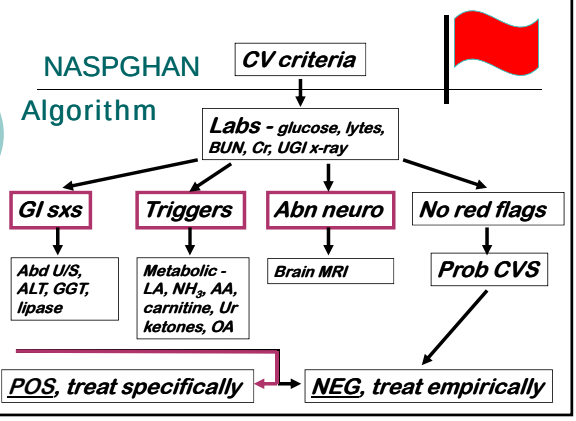
Four 'cyclic' patterns (51% non-cyclic)



Co-morbid octopus – *tenacious! (n=100)*



NASPGHAN Algorithm



- *No longer requires exclusionary testing, screening: glucose, electrolytes, BUN, Cr + UGI x-ray*
- *Can treat empirically for two months or two cycles before further testing*

Mechanisms involved

- **Migraine-related**
- **HPA axis activation *(Sato variant)***
  - **↑CRF, ACTH, ADH, cortisol, catecholamines**
- **Autonomic nervous system**
  - **↑ sympathetic, normal parasympathetic**
- ***Mitochondrial dysfunction**

Evidence of mitochondrial dysfunction

- **Maternal inheritance pattern** [J Pediatr 1999;134:567; Am J Med Gen 2005;133A:71]
- **Abnormal mito metabolism in *migraine***
  - **^{31}P-NMR ↓ muscle ATP** [Neurology 1994;44:666]
  - **CVS: ↑ ketones, lactic acid, Kreb's**
- **Two mt SNPs 16519C→T, 3010G→A**
  - **OR for CVS & MH 17X, 15X** [Cephalgia 2009;29:719]
- **Response to L-carnitine & Coenzyme Q10** [Clin Pediatr 2002:41:171, BMC Neurol 2010;10:10]

NASPGHAN Consensus Statement

- **lifestyle modifications**
- **prophylactic**
- **abortive**
- **rescue – *ED and hospital protocol***
- **psychological – *stress reduction***
- **treat co-morbidities *– anxiety, sleep, POTS, constipation***

Lifestyle changes - ≤ 70% may respond!

- ***Having a diagnosis + education!***
- **Sleep hygiene:** ∅ **sleepovers, melatonin**
- **Hydration: maintenance +**
- **Avoid triggers: loss of sleep, food allergens, MSG, aged cheese, chocolate**
- **Energy: low glycemic index carbohydrates, nut and protein bars**
- **Exercise**

Prophylaxis – NASPGHAN Consensus

- **< 5 years of age:**
  - **cyproheptadine 1st *(39-66%*)***
  - ***propranolol 2nd***
- **≥ 5 years of age:**
  - **amitriptyline 1st *(52-73%*)***
  - ***propranolol 2nd***

* Andersen JM Pediatrics 1997;100:977.

Amitriptyline: *Titrate, titrate, titrate*

- **Mechanism:** $5HT_2$; anti-migraine
- **Dose:** titrate from 0.3 mg/kg by 5-10 mg every 1-2 weeks to 1.0-1.5 mg/kg q.hs
- **Efficacy:** 52-73%
- **Side effects:** dry mouth, sedation
- **Monitoring:** EKG before/after, blood level
- **Contraindications:** prolonged QTc
- **Alternatives:** nortriptyline, desipramine

Prophylactic – daily regimen

- cyproheptadine
- *amitriptyline
- propranolol

primary

- phenobarbital
- topiramate
- levitiracetam
- zonisamide

anticonvulsants

- *mitochondrial supplements

Mitochondrial supplement: Coenzyme Q10 *Boles BDC Neurology 2010;10:10*

- **Parent survey – recall-based**
  - CoQ10 (~ 10 mg/kg divided b.i.d.), *n = 32*
  - Amitriptyline, *n = 249*
- **Outcome measures: vomiting (frequency, duration, # emeses) & nausea**
  - Similar efficacy (68 vs. 72%)
  - Low side effect profile (0 vs. 50% and 21% stopped amitriptyline)

Abortive – NASPGHAN Consensus

- **Triptans – *all/none response, especially if episodes < 24 hrs***
  - **sumatriptan 20 mg nasally, 6 mg SQ**
  - **zolmitriptan 5 mg nasally**

Other occasionally effective

- **ondansetron (antiemetic)**
- **rectal valium (sedative)**
- **hydromorphone (analgesic)**

Rescue – Pre-written ED protocols
NASPGHAN *Consensus – example*

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

Home rescue – topical ondansetron

- **Pharmaceutical grade ondansetron in pluronic lecithin organogel (PLO)**
- ***Onset of action:* 15-30 min**
- ***Application:* inside of wrist q. 4-6 h**
- ***Cost:* $30 for 20 (X 8 mg/mL) doses vs. $42 for one Zofran ODT 8 mg tab**

What to do with intractable CVS?
Beyond guidelines, off label

- **Reconsider specific diagnoses:** redo history, physical, testing (e.g. POTS screening, U/S during episode)
- **Reconsider ongoing triggers:** psychological stressors, cannabis overuse
- **Combine therapies ('kitchen sink'):**
  - amitriptyline + coQ10 + L-carnitine
  - amitriptyline + propranolol or topiramate or phenobarbital

Inducing coma: *Big Sleep!*

- **Deep sleep** precedes recovery in 72%
  - alleviates nausea and vomiting
  - may 'reboot the brainstem'
- **Medications**
  - lorazepam, *rectal* prochlorperazine or diazepam, *IV* phenobarbital *or* chlorpromazine + diphenhydramine
- **General anesthesia** (proof of concept)
  - dexmedetomidine X 18 hrs stops episode
  - 0.5 μg/kg/bolus, 0.25 μg/kg/hr infusion

Khasawinah Am J Ther 2003;10:303

Dihydroergotamine (DHE)

- **Peripheral arterial constriction ($5HT_{1D}$):** DHE < E, but more effect on veins
- **Mechanism:** ↓ "neurogenic inflammation" + prolonged receptor binding
- **Relapses:** DHE < sumatriptan
- **Chelimsky:** 115 adults, 67% pain-free, lasts 28 days!
- **Kabbouche:** 32 children, 74% pain-free

Kabbouche & Hershey Headache. 2009;49:106-9.

DHE protocol and side effects

- **PICU Protocol: 0.25, 0.5, 0.75, 1.0 mg q. 8 hrs to 9 mg total ± ondansetron, prochlo-perazine, diphenhydramine, metoclopramide *avoid narcotics and benzodiazepines***
- **Side effects (especially 1st hour):**

Nausea	57%	91% in kids
Leg cramping	26%	
Re-siting of IV cannula	26%	
Diarrhea	11%	
Abdominal cramps	10%	

Future directions

- ***New* antimigraine (vasoconstricting):**
  - **Almotriptan nmolar affinity for $5HT_{1B/1D/1F}$**
- ***New* antimigraine (non-constricting):**
  - **Lasmiditan $5HT_{1F}$ blocks trigeminal pain**
  - **Telcagepant CGRP antagonist blocks trigeminal pain**
- ***Newer* antiemetics:**
  - **Palonosetron ↑ affinity, ↑ T½ ≤ 7d**
  - **IV fosaprepitant (phosphoryl prodrug)**

Take home messages

- **Positive criteria + no red flags + normal screening = CVS ⇒ empiric treatment**
- **Mitochondrial dysfunction may be contribute and supplements may help**
- **NCS: cyproheptadine < 5, amitriptyline ≥ 5, anticonvulsants next step up**
- **Induced sleep or IV DHE may be last resort**

NCS = NASPGHAN Consensus Statement

Cyclic Vomiting Syndrome Syndrome

B Li MD, Medical College of Wisconsin

Board Style questions

1. Which NASPGHAN Consensus diagnostic criteria for CVS is the most specific?
    a. positive family history of migraine
    b. vomiting at least 4 times/hour at peak
    c. well between episodes of vomiting
    d. each attack resembles the others
    e. associated pallor and listlessness

2. All of the potential mechanisms below have been implicated in CVS *except*:
    a. HPA axis activation
    b. migraine vascular changes
    c. autonomic nervous dysfunction
    d. mitochondrial dysfunction
    e. serotonin receptor polymorphisms

3. NASPGHAN recommended evaluation of a child with episodic vomiting:
    a. electrolytes, BUN, Cr
    b. electrolytes, BUN, Cr & UGI
    c. electrolytes, BUN, Cr, UGI & ultrasound
    d. electrolytes, BUN, Cr, UGI, ultrasound & endoscopy
    e. electrolytes, BUN, Cr, UGI, ultrasound, endoscopy & MRI

4. Which is the best initial approach to the 11 year old child with CVS who has failed multiple medications and missed 4 weeks of school?
    a. consult psychology for anxiety and stressors
    b. redo all laboratory and radiographic testing
    c. consider induced sleep in the PICU
    d. hospitalize and observe teenager in episode
    e. add a second prophylactic medication

5. Which statement best applies to the preventative approach to CVS?
    a. step-wise increases in medicines are rarely required
    b. life style modifications are not recommended
    c. after anti-migraine agents, anticonvulsants are used
    d. toddlers should receive propranolol first line
    e. topirimate does not cause cognitive dysfunction

1. d; 2. e; 3. b; 4. a ; 5. c

Incontinence Without Fecal Impaction

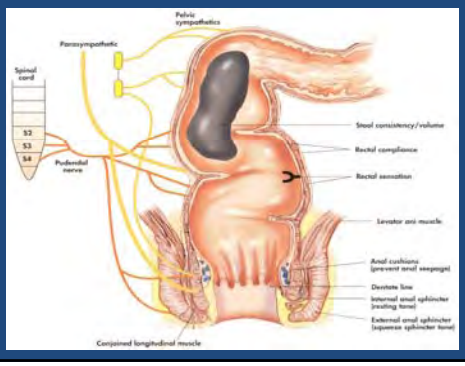
Joseph M. Croffie, MD, MPH
Professor of Clinical Pediatrics
Indiana University School of Medicine
James Whitcomb Riley Hospital for Children

I have no financial relationships with any commercial entity to disclose

Objectives

- Discuss causes of incontinence in the absence of fecal impaction.
- Describe the evaluation for causes of incontinence in the absence of fecal impaction.
- Discuss the management of these patients.
- Discuss the role of motility testing in these patients.
- Discuss new therapies for fecal incontinence.

Normal Anorectal Anatomy



Mechanisms of Fecal Continence

Distention of rectum by stool

↓

Internal anal sphincter relaxes and stool enters anal canal.
Internal anal sphincter returns to baseline.

↓

Sensation of stool in anal canal + sensation of rectal distention

↙ ↘

↑ Intraabdominal pressure
Relaxation of external sphincter and puborectalis

↓

Defecation

Contraction of external sphincter and puborectalis + rectal accommodation

↓

Continence

Pathophysiology of Fecal Incontinence

Requirements for fecal continence:

- Conscious perception of rectal distention
- Adequate internal sphincter resting pressure
- Ability to appropriately contract EAS and puborectalis to prevent defecation
- Adequate rectal compliance

Requirements for fecal incontinence:

- Any disruption in the requirements for continence
  (disregard of sensory cues, altered sensation, weak IAS/EAS, poor rectal compliance)

Definition of Fecal Incontinence

Organic Fecal incontinence :

- Presence of anatomic or physiologic abnormality associated with fecal incontinence

Functional Fecal incontinence (Rome III classification):

1. Functional retentive fecal incontinence :
   - Child is a normal child and has a history of constipation with fecal retention
2. Functional nonretentive fecal incontinence:
   - Child is a normal child and has no history of constipation or fecal retention

Causes of Non-retentive Fecal Incontinence

Anatomic Causes	Non-anatomic Causes
Congenital: o Anorectal malformations o Neurological abnormalities o Spinal abnormalities o Sacrococcygeal mass (e.g. Teratoma as in Currarino triad) o	Functional: o Behavioral/psychological disturbances Chronic diarrhea: o IBD o IBS o Post- cholecystectomy
Acquired: o Traumatic injury: o Spinal cord o Anal sphincter o Postsurgery: o Hirschsprung's disease o IBD	

Epidemiology of Non- retentive Fecal Incontinence

Patient group	Prevalence
>4 7yrs 10-11 Male: Female= 4:1*	1-4% 1-2% 1.6%
Post repair of anorectal malformation**	25%
Post repair of Hirschsprung's disease***	10.5%
Neural tube defects****	>95%

* Bongers, et al. JPGN 2007;44.
** Levitt, et al. Orphanet J Rare Dis 2007;2.
*** Chumpitazi, et al. JPGN 2011;53.
**** Zickler, et al. J Pediatr Health Care 2004;18.

Evaluation

Clinical history:

- Age of onset of problems
- Frequency of incontinence
- Time of day of incontinence
- Consistency and size of stools
- Signs and symptoms suggestive of fecal withholding
- Presence of blood in stools

Evaluation

Clinical history:

- Presence of urinary tract/bladder problems
- History of psychological or behavioral problems
- History of anorectal, neurological or spinal abnormalities
- History of GI surgery
- List of medications
- History of underlying medical conditions
- History of sexual abuse

Evaluation

Examination:

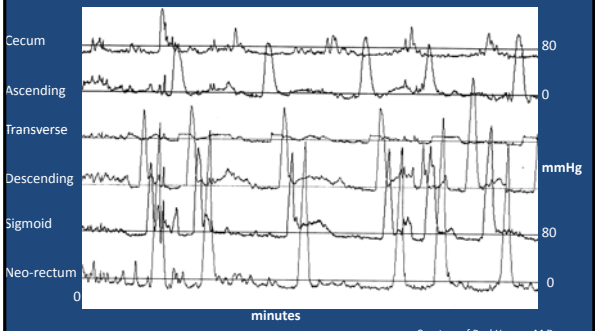
- Detailed abdominal examination
- Detailed neurological examination
- Detailed back and spinal examination
- Detailed perianal inspection and rectal examination:
  - Position of anus and presence of perianal disease
  - Resting and squeeze tone
  - Attempted defecation
  - Size of rectum
  - Amount and consistency of stool in rectum
  - Presence of anal wink

Helpful Tests

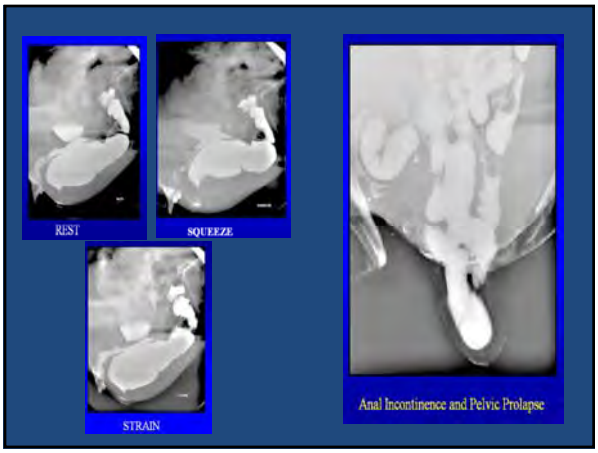
Diagnostic test	Indication
Abdominal X-ray	To exclude fecal impaction
Barium enema	To exclude megarectosigmoid
MRI of spine	To exclude tethered cord/other lesions
Defecography	To examine pelvic floor anatomy/ function
Endoanal ultrasound	To examine anal sphincters
Anorectal manometry	To examine anorectal function
Colonic transit study	To assess colonic transit
Colonic manometry	To exclude abnormal motility

Breath Hydrogen testing	Exclude CHO malabsorption
Endoscopy	Exclude mucosal abnormalities

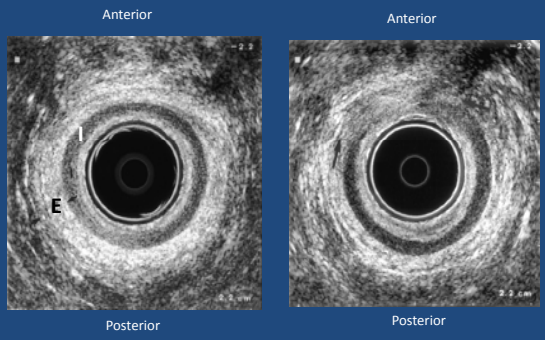
Hirschsprung's Disease - Incontinence



Courtesy of Paul Hyman, M.D.



Anal Ultrasound



Management
Goals for non-retentive Fecal Incontinence

- Restore continence
- Improve quality of life

Treatment of non –retentive fecal incontinence

- No large randomized control trials in children
- Supportive measures/lifestyle modifications
- Anti-motility medications
- Bulking agents
- Behavioral modification/consultation with mental health professional
- Biofeedback
- Surgery

Supportive Measures for Non-retentive Fecal Incontinence

- Patient/family education and awareness
- Dietary modification:
  - Avoid offending foods
- Toilet training:
  - Child sits on the toilet for 5-10 minutes after meals
- Hygiene:
  - Moist wipes, barrier cream, topical antifungal

Medications for non-retentive fecal incontinence

Anti-motility and other medications

- Loperamide
- Diphenoxylate/Atropine
- Cholestyramine
- Amitriptyline
- Clonidine

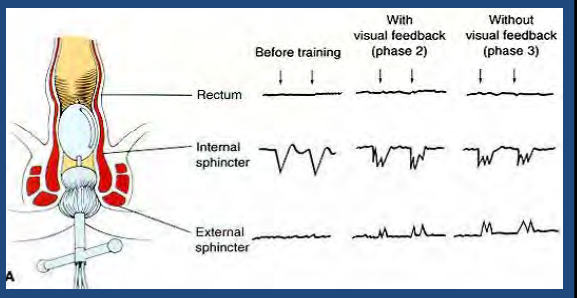
Bulking agents: Soluble fiber supplements

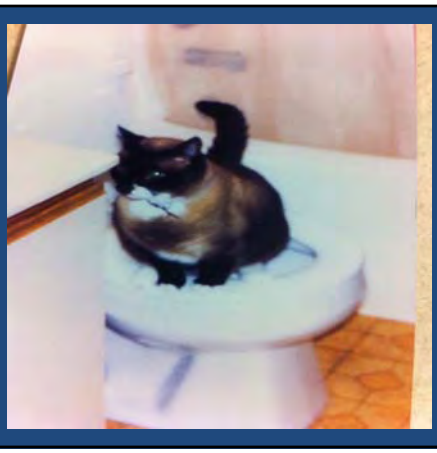
- Psyllium
- Pectin

Biofeedback for non-retentive fecal incontinence

- Operant conditioning: Visual and verbal reinforcement
- Goals:
  - Strengthen the anal sphincter muscle
  - Increase puborectalis tone
  - Improve rectal sensation
  - Improve recto-anal coordination
- Maneuvers:
  - Voluntary squeezes
  - Sensory conditioning
- Home practice

Biofeedback Therapy



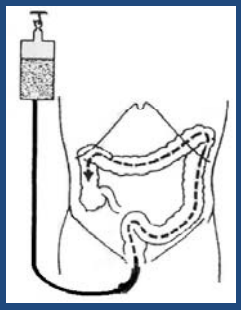


Predictors of Poor Outcome with Biofeedback

- Significant psychological problems
- Unable to follow instructions
- Underlying neuromuscular problems
- Poor prognosis anorectal malformation

Retrograde Colonic Irrigation

- Some data on effectiveness in children with spina bifida, anorectal malformations and Hirschsprung's disease*

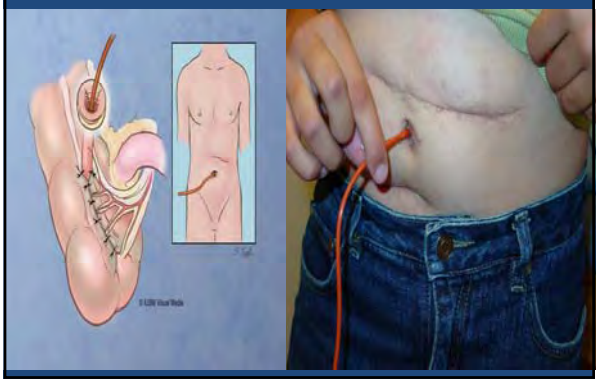


* Cazemier, et al. World J Gastroenterol 2007;14.

Surgery

- Reoperation for imperforate anus
- Appendicostomy/ Cecostomy
- Colostomy

MACE



Emerging Therapies

- Anal plugs: Some data on efficacy and tolerability in children available* ** although not available in U.S.
- Muscle transposition (graciloplasty, gluteoplasty): Limited data in children*** **** *****
- Artificial anal sphincter: No data in children
- Injectable gels (hyaluronic acid): No data in children
- Sacral nerve stimulation: No data in children

* Van Winckel, et al. J Urol 2006;176.
** Bond, et al. J Clin Gastroenterol 2007.
*** Pickrell KI, et al. Ann Surg 1952; 135
**** Koch SM, et al. Dis Colon rect 2004; 47
*****Farid M, et al. Coloproctology, 2003; 7

Summary/ Take home points

- Non-retentive fecal incontinence occurs less frequently than retentive fecal incontinence.
- Treatment is multimodal.
- Surgical options should be considered for patients who fail conservative therapy.
- Newer therapies being used in adults with fecal incontinence have not been tested in children.

Future directions

- Large randomized controlled trials to compare different treatment modalities.
- Large randomized controlled trials to determine the role of emerging therapies.

INCONTINENCE WITHOUT FECAL IMPACTION

Joseph Croffie MD, Riley Children's Hospital

Board Style questions

1. A 17-year old obese girl presents with a 1 year history of fecal incontinence. She had no bowel problems until she underwent a laparoscopic cholecystectomy. She denies constipation and says she passes loose stools daily but she always seems to have some stool in her underwear and this is quite embarrassing for her. Her physical examination, including a thorough rectal examination is unremarkable. A stool work-up for infectious agents and a colonoscopy with biopsies were normal. What would you do next?

A. Order an endoanal ultrasound
B. Institute empiric therapy with cholestyramine
C. Order a defecography
D. Order a barium enema
E. Refer her to a psychologist

2. A 16 year old young lady presents with a 9 month history of fecal incontinence. Physical examination revealed a slightly decreased anal tone and a small amount of soft stool in the rectum. Anorectal manometry revealed normal resting anal pressure but weak squeeze pressure. MRI of the lumbo-sacral spine did not reveal any significant abnormalities. Defecography revealed diminished anal sphincter and puborectalis muscular tone with rectal incontinence at rest. There is no history of trauma. Which of the following will be appropriate in the management of this young lady?

A. A plain X-Ray of the abdomen

B. A barium enema

C. Colonoscopy

D. Endoanal ultrasound

E. None of the above

3. A 5 year-old boy with a history of Hirschsprung's disease who underwent a Soave pull-through procedure in infancy is referred to you by a pediatric surgeon for evaluation of fecal incontinence. His mother tells you that he passes stool in the toilet every day and yet he has to wear a pull-up diaper because he soils his underwear several times a day. He is getting ready to start school and mother is very worried about his incontinence. Abdominal examination is normal and rectal examination reveals

perianal soiling with feces, a normal anal tone and no fecal impaction. Which of the following is most likely to reveal the etiology for this patient's fecal incontinence?

A. Anorectal manometry
B. Colonoscopy
C. Colonic motility testing
D. Fecal Calprotectin test
E. None of the above

Answers:

1. B
2. D
3. C

Elimination Diets: Risks and Benefits

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Disclosure

- I have no financial relationships to disclose

Learning Objectives

- Describe the various elimination diets & their uses
- Discuss the nutritional issues associated with these diets including alternative milks
- Review quality of life issues with dietary modification & counseling families

Background

- Elimination of 1 or more foods from diet
- Increasing used & not only in cases of food allergies
  - Autism: casein, gluten, preservative & dye free
  - Constipation: milk
  - IBS: FODMAP, gluten, soluble fiber, other offending foods
- Common restricted foods in patients with food allergies
  - Eggs, milk, soy, wheat, peanuts/tree nuts, fish/shellfish
- Better understanding of the relationship between diet & disease

Significance of Elimination Diets

- Elimination of foods can have a major impact on quality of diet & lead to nutritional deficiencies
- At risk: protein, fat, calories & specific micronutrients
  - Autism: protein, vitamin D, Fe, Ca
  - Vegans: Ca, vitamins D & B12, Zinc
- Periodically reassess whether elimination needed or not
- ? Effect on microbiome
- Concern: unbalanced diet for a long time that starts in childhood may affect
  - Growth & final height
  - General health as an adult: bone, DM, obesity, CV health

Barker, 1995

Uses of Elimination Diets

- Diagnosis of allergy/intolerance
- Treat allergy or hypersensitivity
- Improve symptoms: lactose intolerance, IBS, dietary fructose intolerance
- Mucosal healing: celiac disease, IBD
- Cancer prevention: celiac disease, colon cancer
- Prevent obstruction: small bowel strictures in IBD
- Seizure control: ketogenic diet
- Avoid buildup of toxic metabolic products: PKU

Types of Elimination Diets

- Physician prescribed or parent "prescribed"
  - Physician: celiac disease, food allergies
  - Parent: autism, "natural diets"
- Strict or partial
  - Strict: celiac disease
  - Partial: gluten in patients with IBS
- Permanent or temporary
  - Permanent: celiac disease, metabolic disorders
  - Temporary: IBS

Examples of Diets used in "GI"

- Celiac disease: gluten
- EoE: specific allergenic foods
- Carbohydrate intolerance
  - lactose, sorbitol, fructose
- Toddler's diarrhea: fluid & fat
- IBS: FODMAP
- IBD: fiber
- Constipation: milk
- Autism: casein & gluten free

IBS and FODMAP Diet

- **F**ermentable **O**ligo, **D**i & **M**onosaccharides **A**nd **P**olyols
- Short-chain carbohydrates: poorly absorbed in small intestine, highly osmotic , rapidly fermented by bacteria in the gut, leading to increased gas, distention, bloating, cramping, diarrhea
- Global reduction rather than individual reduction; 2/3 improve; gradual reintroduction; RD supervision
- Breath test: identify lactose & fructose malabsorption; modify diet

Oligosaccharides	Fructo-oligosaccharides (frutans) Galacto-oligosaccharides (galactans)	artichokes, asparagus, beets, cabbage, brussel sprouts, broccoli, fennel, garlic, leeks, okra, onions, peas, inulin, shallots, wheat, rye, barley, legumes, lentils, chickpeas, apples, peaches, persimmon, pistachios, watermelon
Polyols	Sugar alcohols	apples, apricots, cherries, pears, nectarines, peaches, plums, prunes, watermelon, avocado, cauliflower mushrooms, snow peas, artificial sweeteners (sorbitol, mannitol, maltitol, xylitol)
Fructose	Fructose	watermelon, asparagus, artichokes, sugar snap peas, honey, high fructose corn syrup
Lactose	Lactose	milk, yogurt, ice cream, custard, soft cheeses

McKenzie 2012; Gibson 2009

Elimination Diets: Eosinophilic Esophagitis

- Elemental diet (95% success); hypoallergenic vitamin & fiber supplements
- Elimination diet based on individual testing (75% success)
- Empiric 6 food elimination diet
  - 6 week trial of 6 foods (milk, egg, soy, wheat, peanut/tree nuts, fish/shellfish)
  - Elimination diet vs. elemental formula (74 vs. 88% success)
  - Diet: Better acceptance & compliance, cheaper
  - Short term nutrition data; no data on diet composition
  - Failure to thrive
    - 5/35 had FTT in diet group vs. 16/25 in formula group
    - All patients had improved weight gain except for 1 patient in the formula group

Spergel 2005 & 2008; Kelly 1995, Kagalwalla 2006

EoE: Re-introduction of Foods

A	B	C	D
Vegetables (Non legume)	**Tropical fruits**	**Allergenic fruits & vegetables**	**Most common allergenic foods**
Carrots, squash, sweet potato, string beans, broccoli, lettuce	Bananas, kiwi, pineapples, mangoes, papayas, guavas, avocados	Apples, potatoes, peas	Corn, chicken, wheat, beef, soy, eggs, milk
Fruit(non-citrus, non-tropical)	**Melons**	**Grains**	
Pears, peaches, plums, apricots	Honeydew, cantaloupes, watermelon	Rice, oats, barley, rye	
Citrus fruits	**Berries**	**Meat**	
Oranges, grapefruit, lemons, limes	Strawberries, blue berries, raspberries, cherries	Lamb, chicken, turkey, pork, fish/shellfish	
	Legumes	**Peanuts/tree-nuts**	
	Lima beans, chickpeas, white/black/red beans	Peanuts, almonds, walnuts, hazelnuts, brazil nuts, pecans	

Spergel 2008

Autism: Casein & Gluten Free Diet

- Cochrane review 2008
  - Difficult to follow, costly, increased amino acid deficiency & bone loss
  - Not to be used in patients who eat 5 or < foods
- Whiteley 2010
  - *ScanBrit* diet; improvement at 8,12 & 24 months in core autistic & related behaviors of pre-pubertal children; most improvement seen within first 8 months
- Buie 2010
  - Consensus: not enough evidence
- Pennesi 2012
  - Parental report of improvement

Impact on Nutritional Status

- Children with 2 or > food hypersensitivities compared to children with 1 food hypersensitivity
  - were shorter in length & height
  - intake of Ca, vitamins D & E was inadequate
- Greatest risk: children with 2 or more food hypersensitivities & those reacting to milk

Christie et al, 2002

Impact on Nutritional Status

- N = 25; range: 2 to 7 years; normal growth percentiles
- Allergies: egg, milk, fish, legumes, meat, cereals, fruits, vegetables
- Diet assessment (3 day) & fatty acid profiles
- Results:
  - Dietary intake
    - Protein: supplements needed in 33%
    - Fat: 76% met RDA, not balanced
    - Ca: 72% met RDA
    - Fe: 29% met RDA
  - Fatty acid profile: 85%; abnormal omega 6:3 ratio; pro-inflammatory profile

Aldamix-Echevarria et al, 2008

Examples of Types of "Milks"

Type of Milk (per 8 oz)	Calorie (kcal)	Protein (g)	Fat (g)	Calcium (mg)	Vitamin D (IU)
Cow milk: whole	150	8	8	300	120
Cow milk: 1%	100	8	2.5	300	120
Silk soy vanilla natural	100	6	3.5	300	120
Rice dream enriched original	120	1	2.5	250	100
Almond dream original	50	1	2.5	300	100
Hemp dream original	100	4	6	300	100
Pacific foods hazelnut original	110	2	3.5	300	100
Pacific foods organic oat dream	130	4	2.5	350	100
Dari Free potato vanilla milk	70	0	0	300	100
Elemental formula (infant)	160	4.5-5	7.2-8.6	154-199	82-98
Elemental formula (child)	240	6-8.1	3.6-8	144-288	74-146

Courtesy M Girten RD, CHOP; Keller 2012

Alternative "Milks"

Milk (8oz)	Calories (kcal)	Protein (gm)	Comment
Soy	100-150	5-8	Acceptable. Lactose free, contains fiber and omega-3 FA. Fortified with Ca, riboflavin, vitamins A, D, B12
Rice	110-130	1	Unacceptable. Enriched with Ca, vit. A, D, B12. High carbohydrate content. Hard to cook with because it is watery.
Almond	60	1	Unacceptable. No vitamins, Zn, Cu, EFA. Good source of vitamin E. Good for baking.
Hemp	100-150	1-4	Unacceptable unless oral intake is excellent & eating adequate amounts of protein foods. Contains omega-3 FA.
Oat	130	4	Unacceptable. Can use if oral intake excellent and eating adequate amounts of protein foods. High in fiber, Fe, & has vitamin E & folate

Courtesy M Girten, RD, CHOP

Summary: Alternative "Milks"

- Soy milk: only appropriate substitution for cow's milk other than appropriate formula
- Rice, almond, hemp, potato, coconut & oat milk are not an equal substitute for cow's milk or soy milk
- Alternative milks: inadequate in protein & micronutrients
- Evaluate diet before picking a milk alternative
- Use if oral intake is excellent & eating adequate amounts of protein foods
- Micronutrient supplementation
- RD consultation

Elimination Diet: Practical Aspects

- Identify foods to be eliminated & their nutritional value
- Appropriate protein, micronutrient & multivitamin supplements
  - Carlson, Freeda, Kirkman, Schiff, Citracal
- Education:
  - Spend time educating family; provide written materials
  - Monitor diet at office visit; ask about problems
  - Ongoing education, including good websites
  - Product information can change
  - All family members, households, residential facilities, daycare, school
- 3 day diet record: week day/weekend day, both households
- Good RD support invaluable if available
- Support groups

Elimination Diet: Practical Aspects

Food	Provides	Replace with	Check label for
Milk	Protein, phosphorus, Ca, riboflavin, pantothenic acid, vitamins A, D & B12	Fortified rice, hemp, potato & oat milk	Milk
Eggs	Protein, choline, vitamins A & B12, riboflavin, Se, biotin, pantothenic acid	Egg replacer	Egg
Wheat	Fe, niacin, riboflavin, thiamin, folate, fiber	Quinoa, barley, oat, amaranth, millet, tapioca, rice, potato, arrowroot	Wheat
Soy	Protein, thiamin, riboflavin, pyridoxine, folate, Ca, Mg, phosphorus, Fe, Zn	Fortified rice, hemp, potato & oat milks	Soy (soy lecithin and soybean oil are OK)
Corn	Magnesium, vitamin B6	Quinoa, barley oats, amaranth, millet, tapioca, rice, potato, arrowroot	Corn syrup, corn oil, maize, popcorn, grits, corn meal, chips & tortillas, baking soda, caramel coloring, corn starch
Peanut/ Tree nut	Protein, vitamin E, fiber, Mn, Mg, Zn, niacin	Sunflower seeds	Peanuts/tree nuts
Fish/ Shellfish	Protein, omega 3 fatty acids, vitamins A, D & B12		Fish/shell fish

McCarthy TC, 2008

Elimination Diet: Monitoring

- Growth
  - Weight: important, not just at visits
  - Growth charts
  - Bone age
- Diet record analysis, medication, herbal supplement use review & food diary
- Laboratory
  - Protein status
  - Micronutrients: vitamins, minerals, trace elements, fatty acid profile
- Other: DXA

Elimination Diets: Problems

- Developmental/behavioral feeding problems
  - continue to feed jarred baby food
  - do not prepare allergen-free food at home
  - do not feed family meal to the older infant
  - food aversions
- Reliance on safe fast foods to avoid food preparation
  - may lead to potentially nutritionally deficient foods
- Creative or ethnic recipes lead to allergens found in unexpected places
  - Reactions: desserts 43%, entrees 35%, appetizers 13%

Furlong et al 2001

Elimination Diets: Formulas

- Used in children with severe food allergies or metabolic disorders via tube/orally
- Advantages: avoid allergens/metabolites; provide balanced nutrition
- Disadvantages: taste, restrictive, expensive, social problems, invasive, feeding aversion, age appropriate, required volume to meet micronutrient needs
- Solutions: flavor packets, letters of medical necessity, counseling, social worker

Counseling: Role of the RD

- Instruction to avoid all necessary foods
  - food labeling, terminology, cross contamination
- Suggest alternative foods, provide recipes & meal plans
- Ensure adequacy & enjoyment of diet
- Make sure family can recognize food reactions
- Educate families
  - how to eat away from home & at social events
  - how to deal with other family members & schools where food is served
- Monitoring: compliance, food diary, growth
- IF NO RD AVAILABLE, THEN WHAT?

Counseling: At Home

- Everyone at home follows same diet
  - Minimizes amount of time spent on cooking
  - Reduces chance of cross-contact with allergen containing foods
- Start with fresh, unprocessed foods or single ingredients
- If allergen brought into the house
  - Wash hands & cooking utensils
  - Always prepare the allergen free meal first & then the other allergen containing foods
  - All sit at the same table, wash hands after eating to avoid spread of allergens into other rooms in the house
  - Designate safe areas in pantry & refrigerator

Furlong et al 2001

Counseling: Going Out

- Eating out
  - high risk, not telling staff about allergy, cross-contact between foods, restaurant errors
  - avoid buffet service, sauces, combination foods, fried foods & desserts
- Social events
  - stressful
  - feed child or take food to the event
- Educate
  - grandparents, close friends & schools/day care

Quality of Life Issues

- Can be ameliorated by thorough education, close monitoring & support of patient & family
- Positives
  - Better disease control
  - Improvement in symptoms
  - Better growth
- Negatives
  - Significant stress & need to support families

Sicherer et al 2001

Quality of Life: Negatives

- Families are anxious, feel out of control, vulnerable, & helpless. These fears are picked up by child leading to food fears.
- Changes to normal living & eating patterns
  - Children no longer participate in food preparation
  - Celebrations & family gatherings
  - Daily routines & structured meal times
- Family decisions change
- Feeding tube is invasive & time consuming
- Cannot use convenience foods; little variety in diet
- Learn a lot, make new foods they have never heard about
- Increased grocery bills

Quality of Life: Celiac Disease

- Roma 2009: Children
  - Compliance 58%: poor palatability, eating outside home, availability of foods, lack of symptoms
  - Coping: label reading difficult (65%), angry parents (23%); diet not helpful (47%); avoided restaurants (46% & travelling (17%); participated in all school activities (80%); felt no different from peers (65%)
  - Felt they would have improved QOL: food labeling (76%) & food availability in supermarkets (58%) & restaurants (42%)
- Hauser 2006: Adults
  - Lower HRQOL: physical & mental co-morbidities, younger age at diagnosis, non-adherence
  - Physician knowledge gap (diet) was a problem

Conclusion

- Elimination diets are used in a variety of conditions & not always evidenced based
- Practitioners need to be aware of the nutritional consequences of these diets
- Alternative milks are available & have varied nutrient composition

Future Directions

- Long term consequences of diets including prospective studies
  - Growth
  - Nutritional complications
  - Quality of life
  - Bone health
- Clinical efficacy of elimination diets in specific diseases & mechanisms of action
- Effect of elimination diets on the microbiome

ELIMINATION DIETS: RISKS AND BENEFITS

Maria Mascarenhas MD, Children's Hospital of Philadelphia

Board Style questions

Question 1: Which "alternative milk" is closest to whole milk in terms of protein content?

1. Hemp milk

2. Soy milk

3. Rice milk

4. Oat milk

Correct answer 2.

Question 2: What is the most important parameter to be monitored in children on elimination diets?

1. Bone density or DXA

2. Fat soluble vitamin status

3. Zinc status

4. Growth: weight, height and head circumference (if applicable)

Correct answer 4.

Question 3: When counseling a patient who is to start on an elimination diet, which of the following are applicable?

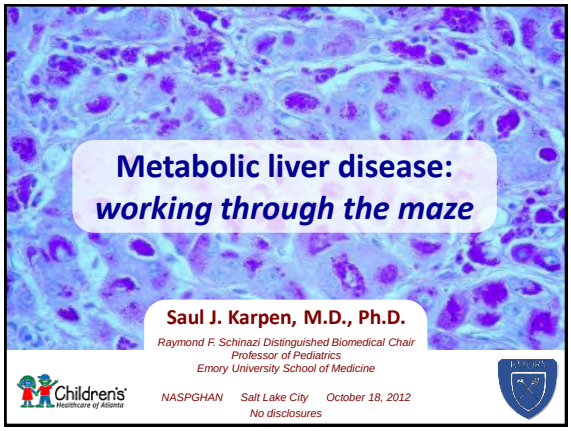
1. Instructing the patient and family on how to read food labels so that they recognize the food or foods that need to be eliminated

2. Determining patient macro and micronutrient requirements and providing sample menus

3. Supplementing those nutrients which will be missing in the patient's diet

4. All of the above

Correct answer 4.



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NASPGHAN

Objectives

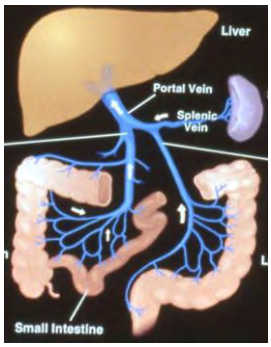
- *Know when to suspect metabolic liver disease.*
- *Learn a staged approach to diagnosis of metabolic liver diseases.*
- *Understand urgent vs. emergent evaluation and treatment of metabolic liver diseases.*

Topics

- The myriad metabolic functions of the liver
- An approach to evaluation
- An illustrative case
- Preparing for the future:
  - →Incorporation of powerful new genetic tools

Metabolic Functioning of the Hepatocyte

- Diet
  - Lipids
  - Sterols
  - Carbohydrates
  - Amino acids
- Processing
  - Detoxification
  - Transport
- Export
  - Serum Proteins



Impaired gene responsible for a key metabolic function

+

No "work-around" pathway

→ Metabolic Disease

Red Flags for Metabolic Disease

- History:
  - FTT
  - Poor feeding, lethargy
  - Prolonged neonatal jaundice
- Exam:
  - Poor tone
  - Hepato(spleno)megaly
- Labs:
  - Elevated ALT +/- CPK
  - Direct Hyperbilirubinemia
  - Hypoglycemia (esp. with absent urinary ketones)
  - Hyperammonemia

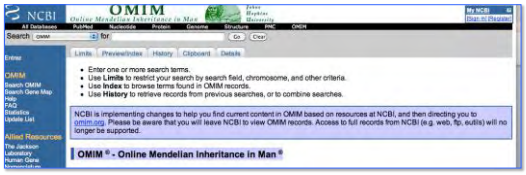
Planning Your Workup

- One size does not necessarily fit all
  - Babies: new to the world, so cast a broad DDX
- Is it liver-specific or not?
- Overlapping presentation with sepsis
- Imaging (Liver, Brain, Heart…)
- Urgency

Tools

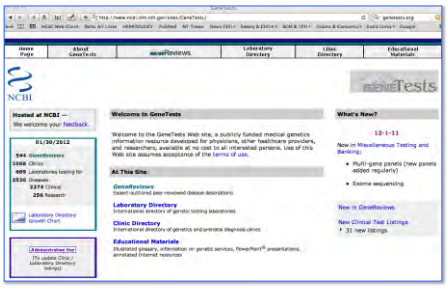
- Blood
  - Metabolites
    - e.g., Amino acids, Lipids, Bile acids
  - Biochemical hallmarks
  - Ammonia
  - Gene Tests
- Urine
  - Metabolites (e.g. succinylacetone)
- Textbooks & Internet Resources
- Liver Biopsy

OMIM

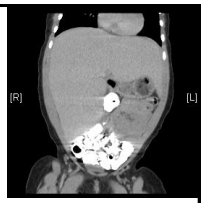


- **Cross Links with Genetests.org, Pubmed, Etc…**
- **Good for when you don't know which diseases to pursue**
- **Good for when you don't know which gene(s) to pursue**

genetests.org



Case



- **Previously well 1 yo AA female, 2nd child.**
- **seen by PCP for OM→ noted prominent abdomen.**

- **CT & U/S: Isolated hepatomegaly**
- **Referred at 13 months**

- **Labs:**
  - **ALT 872 AST 918 AP 542 T Bili 0.9 GGT 207 Albumin 4.4 INR 1.1**
  - **CBC & Chem 7 unremarkable**
  - **CPK 719 Glucose 85 Amylase 42 Lipase 60**

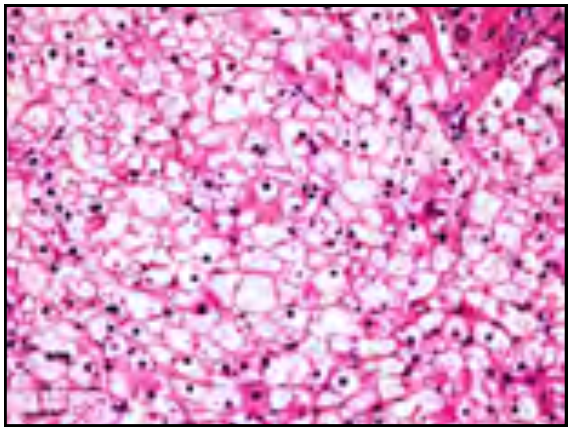
→ Next steps?

Case (2)—Next Step Choices

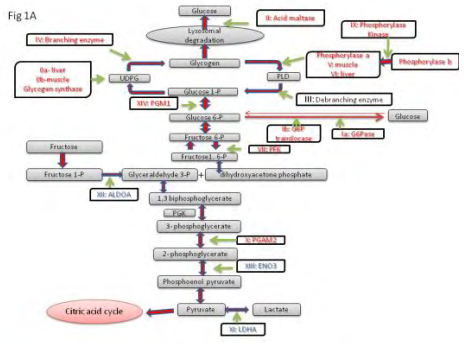
- Wait & see
- TORCH & other titers
- Autoimmune markers
- Viral PCRs (HSV, CMV, Adeno, Entero…)
- Ceruloplasmin, Copper, Iron Panel
- Serum amino acids, carnitine profile
- Urine Organic acids, Polyols
- Genetics & Surgical consultations
- Wedge liver biopsy +/- muscle biopsy
- Percutaneous Liver Biopsy

The Role of a Liver Biopsy

- Reduces
  - Blood sample volume
  - Costs of non-directed screening
  - Time of non-directed screening
- Advantages
  - Directs a focused workup
  - May provide a diagnosis
  - Allows for use of specific histological stains
  - Electron microscopy
  - Overnight turnaround



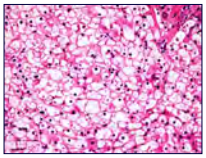
Glucose & Glycogen Pathways



Courtesy L-J Wong, BCM

Dx: Glycogen Storage Disease

→ *Roman Numerology*



1960's-2000's

- Frozen Core for Biochemical analysis
- Wedge Liver biopsy +/- Muscle Biopsy

2000's: Same + individual Gene tests

→2010's:

- One Genetic Panel

Sent a GSD Panel (10 Genes at once)

- **Advantages:**
  - Unknown which GSD
  - Small Blood volume (2 cc)
  - Time saving
  - Cost saving
    - Panel $~ 3600 by NGS for all 10
    - Individual Gene by Sanger method ~ $ 10,920
  - No Wedge biopsy, serial tests, etc.

6 weeks later:
GSD Gene Panel Results

Deleterious mutation found:

AGL gene (Debrancher Enzym	
Nucleotide change	c.256C>T
Amino acid change	p.Q86X
Location	Exon 4
Zygosity	Homozygous

Dx: GSD III

No known deleterious mutations were detected in the G6PC, GAA, GBE1, GYS2, PHKA2, PHKB, PHKG2, PYGL, and SLC37A4 genes of this individual.

Topics

- The myriad metabolic functions of the liver
- An approach to evaluation
- An illustrative case
- **Preparing for the future:** powerful new genetic tools

What is EXOME Sequencing?

- **The "Exon Genome"**
  - **Only ~ 25 million bp (0.4% of the genome)**
  - **Every exon of all 23,000 genes**
  - **Sequences only the coding regions that determine each proteins' function.**
  - **No need to know to look for individual mutations (e.g. ΔF508 in CFTR).**

October 3, 2012

ORIGINAL ARTICLE

Diagnostic Exome Sequencing in Persons with Severe Intellectual Disability

EDITORIAL

Diagnostic Exome Sequencing — Are We There Yet?

"In this era of genomic medicine, we should proceed with both optimism and careful thought …"

- **100 patients, IQ < 50**
- **Exome Sequencing**
- **Diagnosis in 16**
- **4 new genes**

"… the movement of exome sequencing into clinical diagnostic laboratories has been remarkably quick, so there is bound to be a ***steep learning curve*** *related to*

- ***implementation of the technology,***
- ***interpretation of the data,*** *and*
- ***reporting of the output***

in a manner that is understandable to both physicians and families of patients."

Realizing Genomic Medicine

Elizabeth G. Phimister, Ph.D., W. Gregory Feero, M.D., Ph.D., and Alan E. Guttmacher, M.D.

February 23 2012;366:757–759.

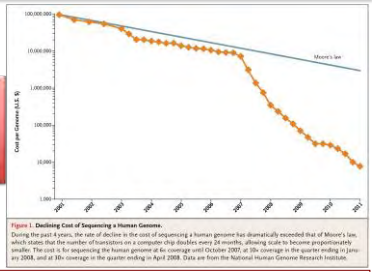


Figure 1. **Declining Cost of Sequencing a Human Genome.**
During the past 4 years, the rate of decline in the cost of sequencing a human genome has dramatically exceeded that of Moore's law, which states that the number of transistors on a computer chip doubles every 24 months, allowing scale to become proportionately smaller. The cost is for sequencing the human genome at 6× coverage until October 2007, at 30× coverage in the quarter ending in January 2008, and at 30× coverage in the quarter ending in April 2008. Data are from the National Human Genome Research Institute.

- NIH funding: ~70,000 Exomes/ whole genomes by Dec. 2012.
- HIPAA, GINA, ADA, CLIA, EMR
- The "*incidentalome*"

"Current paradigms for providing genetic services, which were developed to handle rare chromosomal and monogenic conditions, break down in the setting of genomic approaches to more common and etiologically complex conditions."

www.ScienceTranslationalMedicine.org 3 October 2012 Vol 4 Issue 154

Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units

Editor's Summary: **Speed Heals**

"These findings strengthen the notion that WGS can ***shorten the differential diagnosis process*** *and quicken to move toward targeted treatment and genetic and prognostic counseling.*

The authors note that the speed and cost of WGS continues to rise and fall, respectively."

A Diagnosis in **50** hours.

The New York Times

October 2, 2012

Infant DNA Tests Speed Diagnosis of Rare Diseases

By GINA KOLATA

From the day she was born, the girl had seizure after seizure. Doctors at Children's Mercy Hospital in Kansas City, Mo., frantically tried to keep her alive. Weeks passed and every medication failed. Finally, her family decided to let their baby go, and the medical devices were withdrawn. She was 5 weeks old.

Her doctors suspected a genetic disorder, and as it happened the hospital had just begun a study of a new technique for quickly analyzing the DNA of newborns, zeroing in on mutations that can cause disease.

Evolution and Functional Impact of Rare Coding Variation from Deep Sequencing of Human Exomes

Jacob A. Tennessen,[1*] Abigail W. Bigham,[2*†] Timothy D. O'Connor,[1*] Wenqing Fu,[1] Eimear E. Kenny,[3] Simon Gravel,[1] Sean McGee,[1] Ron Do,[4,5] Xiaoming Liu,[6] Goo Jun,[1] Hyun Min Kang,[7] Daniel Jordan,[8] Suzanne M. Leal,[8] Stacey Gabriel,[9] Mark J. Rieder,[1] Goncalo Abecasis,[7] David Altshuler,[4] Deborah A. Nickerson,[1] Eric Boerwinkle,[6,10] Shamil Sunyaev,[4,5] Carlos D. Bustamante,[3] Michael J. Bamshad,[1,2] Joshua M. Akey,[1] Broad GO, Seattle GO, on behalf of the NHLBI Exome Sequencing Project

Science
May 17, 2012

- Exome sequencing of:
  - 2440 Europeans
  - 1088 Africans
- 15,585 Exomes
- ~ 22.4 Mb DNA/subject
- 63.4 TERAbases of DNA seq.
  - 503,481 SNV's (98% confirmed)

"On average, individuals possess between 318 and 580 predicted functional protein-coding SNVs …"

The Human Genome Project: Past, Present, and Future

JAMES D. WATSON

Science, 1990

It would be naïve to expect that any extensive human sequence data will be released by a sequencing group until it has a reasonable time to explore its implications.

1953 → 2008

55 years

Office Conversation 2015 …

"Here's my kid's exome.

Explain it to me"

Office Conversation 2020 …

"Here's your child's exome.

Let me explain it to you"

Take home points: Metabolic Diseases

- ***Suspect metabolic liver disease, esp. early in life.***
- ***Use a staged approach : → role for liver biopsy***
- ***The rapidly evolving diagnostic landscape involves new genetic tools: → cannot avoid knowing about genes & genomics any longer.***

Exome sequencing from **4** individuals → Disease Etiology

Exome sequencing makes medical genomics a reality

Leslie G Biesecker

Massively parallel sequencing of the exomes of four individuals with Miller syndrome, combined with filtering to exclude benign and unrelated variants, has identified causative mutations in *DHODH*. This approach will accelerate discovery of the genetic bases of hundreds of other rare mendelian disorders.

Nature Genetics 2010;42:13–14.

Costs

Watson *Science* 1990

> Today, DNA sequencing usually costs between $3 and $5 per base pair

Wheeler *Nature* 2008

> . In this study we sequenced the genome of Dr Watson for less than US$1 million,

MODULE B: LIVER BEYOND VIRUS, METABOLIC, STORAGE, TUMORS
Moderators: Sandeep Gupta MD and James Daniel MD

METABOLIC LIVER DISEASE: WORKING THROUGH THE MAZE
Saul Karpen MD, PhD, Emory University

Learning objectives:

1. Know when to suspect metabolic liver disease
2. Learn a staged approach to diagnosis of metabolic liver diseases
3. Understand urgent versus emergent evaluation and treatment of metabolic liver diseases

UPDATE ON ALPHA-1-ANTITRYPSIN DEFICIENCY
Jeffrey Teckman MD, St. Louis University

Learning objectives:

1. Review the genetics and pathophysiology of α1AT
2. Know the complications, including cirrhosis, of α1AT
3. Learn the newer therapies for α1AT

THERE IS A LIVER MASS ON THE ULTRASOUND: WHERE DO YOU GO FROM HERE?
Kathleen Schwarz MD, Johns Hopkins University

Learning objectives:

1. Learn the differential diagnosis of hepatic tumors
2. Know the evaluation including laboratory tests, imaging, and histopathology of hepatic tumors
3. Understand the treatment options of hepatic tumors

METABOLIC LIVER DISEASE – WORKING THROUGH THE MAZE

Saul J Karpen MD, Emory University

Board Style questions

1. A percutaneous liver biopsy is being considered to evaluate a 4 month old with elevated liver enzymes, hepatomegaly, and a previous history of conjugated hyperbilirubinemia. Which of the following analyses should be considered while planning for appropriate utilization of the biopsy specimen:

a.) viral culture
b.) EBV immunostaining
c.) FISH analysis
d.) electron microscopy
e.) brancher enzyme activity

2. Recent studies indicate that mutations in hepatobiliary canalicular transporter genes are associated with cholestasis that can present at any age. Which of the following clinical scenarios are **not** associated with canalicular transporter gene defects:

a.) cholestasis of pregnancy
b.) drug-induced cholestasis
c.) Gilbert Syndrome
d.) Dubin-Johnson Syndrome
e.) Byler Syndrome

3. A 5 year old male with elevated liver enzymes is sent to you for evaluation. Other than mild developmental delay, the patient's history is unremarkable. His examination is notable for a normal abdominal exam, but he has a short step walk and staccato run in your Clinic hallway. Which **blood** test may be helpful in this evaluation to determine the next steps and may preclude the need for a liver biopsy:

a.) glucose
b.) RBC phosphorylase kinase activity
c.) creatine phosphokinase
d.) lipid profile
e.) carnitine profile

4. A 4 year old male arrives in your PICU in liver failure, Grade 3 coma. His recent medical history suggests an intercurrent illness that preceded his deterioration. The parents report some mild developmental delay. He recovers somewhat from his Grade 3 coma but has continued lethargy for the next two weeks, with an INR that is maintained in the 2-3 range, Direct bilirubin at 4-5 mg/dl. As you begin your evaluation for liver transplantation, you consider sending a genetic test to determine if transplantation is an appropriate choice. Which of the following genetic test should you send that would likely preclude transplantation as a choice:

a.) ATP7B (Wilson Disease)
b.) DGUOK (mitochondrial DNA depletion syndrome)
c.) MCAD (medium chain acyl-CoA Dehydrogenase)
d.) CFTR (Cystic fibrosis transmembrane regulator)
e.) CPS (Carbamoyl Phosphate Synthetase)

5. Which of the following is associated with hepatocellular carcinoma as early as 1-2 years of age?
a) Gilbert Syndrome
b) Wilson disease
c) PFIC1 (ATP8B1/FIC1 deficiency)
d) PFIC2 (ABCB11/BSEP deficiency)
e) Mitochondrial hepatopathy

Answer Key:
1. d
2. c
3. c
4. b
5. d

Update on Alpha-1-antitrypsin Deficiency

Jeffrey Teckman, M.D.

Professor of Pediatrics and Biochemistry
Associate Chair of Pediatrics for Research
Director, Pediatric Gastroenterology and Hepatology
St. Louis University School of Medicine
Cardinal Glennon Children's Medical Center
St. Louis, Missouri USA

Disclosure

- **Grant support:** NIH, Alpha-1 Foundation, March of Dimes, American Liver Foundation, Saint Louis University Liver Center, Alnylam Pharmaceuticals.
- **Consultative relationships:** Alpha-1 Foundation, Alpha-1 Association, Alynlam Pharmaceuticals, Isis Corp., Agios Pharmaceuticals.

Learning Objectives

- Review the genetics and pathophysiology of a1AT deficiency.
- Know the complications, including cirrhosis, of a1AT deficiency.
- Learn the newer therapies for a1AT deficiency.

Alpha-1-antitrypsin

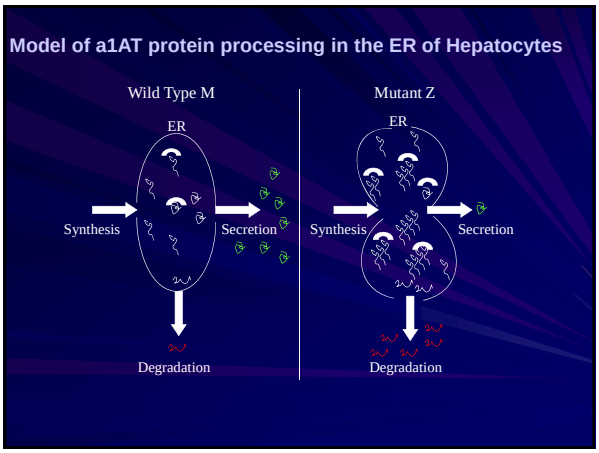
- An abundant serum protein primary synthesized in the liver.
- Physiologic function is inhibition of neutrophil proteases to protect host tissues during inflammation. This is especially important in the lung.
- Z mutant is the common disease variant

Alpha-1-antitrypsin Mutant Z

- Mutant Z: A point mutation that encodes a single aa substitution.
- Z mutant accumulates and polymerizes in the liver – not secreted.
- Low secretion results in “deficient” serum level.

ZZ Alpha-1-antitrypsin Deficiency

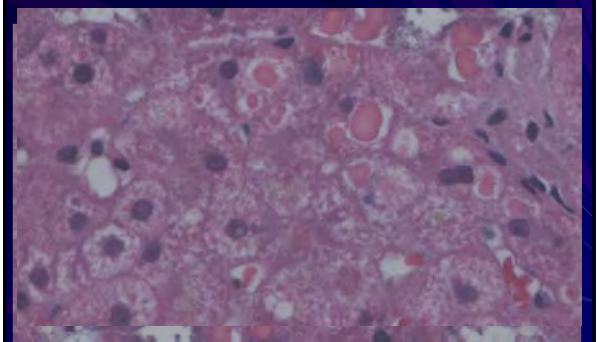
- Autosomal recessive (co-dominant).
- Homozygous ZZ is the classic form, 1 in 2,000-3,500 births.
- Associated with liver disease in children and adults and lung disease in adults.
- Highly variable disease progression.



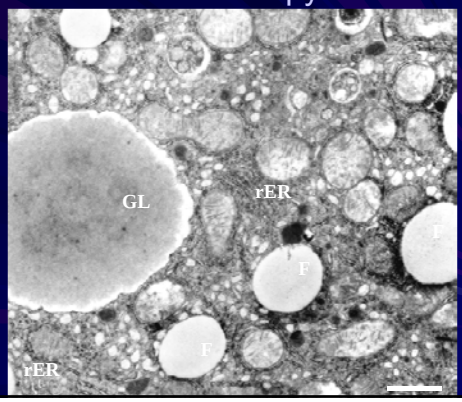
Disease Pathophysiology

- Liver: Accumulation of mutant Z protein in hepatocytes causes liver injury.
- Lung: “Deficient” serum level leaves host tissues susceptible to damage by neutrophil proteases. Exquisitely susceptible to smoking injury.

H&E of Human ZZ Liver



Electron microscopy ZZ liver



Pathophysiology-Liver

- Mutant Z protein accumulates in hepatocytes.
- Compensatory proteolytic pathways degrade most of the mutant Z protein.
- Some mutant Z molecules escape degradation
- Hepatocytes with the largest burdens of mutant Z protein suffer a cascade of intracellular damage ending in apoptosis.
- The chronic cycle of hepatocellular apoptosis and regeneration leads to fibrosis and organ injury.

Genotypes

- ZZ homozygous, classical disease.
- SZ similar disease to ZZ, ? Less risk.
- MZ heterozygous carrier state (2% of population), regarded as healthy and asymptomatic, possible effect as modifier condition in adults. *Many other rare genotypes.*

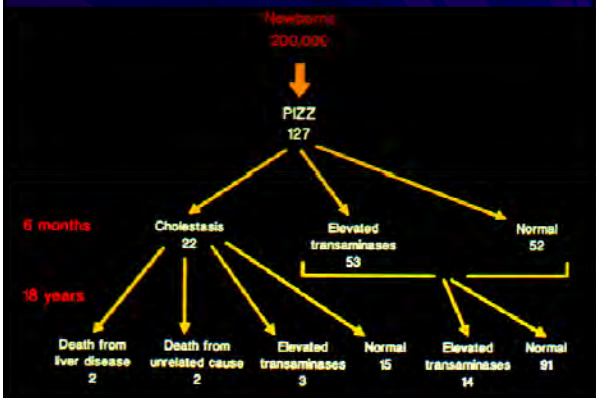
Diagnosis

- Gold standard is “phenotype” analysis of protein in serum or “genotype” of DNA. *Not performed in US newborn screen.*
- Some clinicians use serum level as a screening test. Gold standard test must be applied if ANY deviation from normal.
- Liver biopsy not required for diagnosis

Disease Risk – Variable

- 5% risk of life-threatening liver disease in childhood?
- 15-50% risk of various liver dysfunction in childhood.
- >50% life-long risk of cirrhosis (possibly everyone who lives long).
- Risk of liver cancer is increased, but magnitude is unclear (usually found in older adults).
- No emphysema in children, ?30% of adults.

Newborn Screening Study, Sweden



Co-morbid Associations

- Increased risk of low birth weight.
- Risk of feeding difficulties, FTT.
- Coagulopathy (subclinical cholestasis?)
- Risk of asthma and recurrent, non-destructive respiratory symptoms.
- Panniculitis in adults.
- Many of these not seen in Swedish cohort.

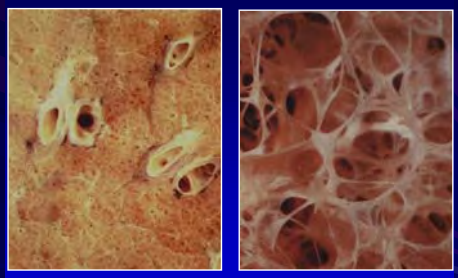
Management - Conventional

- Liver: No specific therapy, except supportive care and liver transplantation.
  - Fat soluble vitamins if cholestatic.
  - Provision of adequate nutrition.
  - Management of cirrhosis and portal hypertension.
  - Avoid obesity and limit alcohol, as per AASLD guide.
  - Liver transplant (no longer deficient).
- Lung: Protein replacement.
  - Has no benefit to the liver.

Management - Conventional

- Patients of all ages should be urgently cautioned to avoid second hand smoke, personal smoking and environmental inhalation exposures.

Human Lung



Normal

Antitrypsin deficiency

Management - Conventional

- Asthma is common in ZZ children and given usual management.
- Asymptomatic children should have an adult pulmonary evaluation at 18 years as baseline.

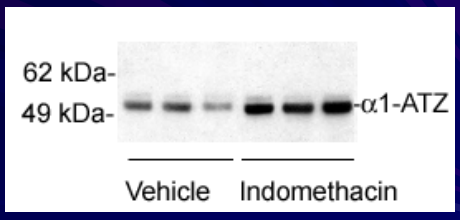
Management - Conventional

- Genetic counseling should be offered to all patients and families.
- Alpha-1 Foundation genetic counseling line: 1-800-785-3177
- Excellent layman literature available
- Prenatal diagnosis is available.

Management - Conventional

- Lab studies show that NSAIDS increase Alpha-1-AT mutant Z synthesis in the liver and increase accumulation.
- NSAIDS are associated with *increased* liver injury in animal models.
- Unusual sensitivity to acetaminophen not found

Indomethacin-Treated PiZ Mice Exhibit Increased α1-ATZ Protein Expression



Standardized quantitative immunoblot of a1AT from six individual model mouse livers.

Therapy: Under Investigation

- Several approaches to liver disease treatment are being investigated.
  - *Increased* accumulation in the liver is likely to be detrimental.
  - *Decreased* accumulation in the liver is likely to be therapeutic. ? Other mechanisms, too?
- To date, no specific drug therapy can be recommended outside of clinical trials.

Therapy: Ursodeoxycholic Acid

- In vitro studies suggest possible theoretical benefit.
- Uncontrolled human use reports inconclusive.
- Commonly used during cholestasis but not supported by data.

Therapy: 4-Phenylbutyrate

- In vitro and animal studies suggest benefit.
- Not effective in human studies due to intolerable side effects before therapeutic level reached.
- Not recommended at this time outside of trials.

Therapy: Sirolimus

- In vitro and animal studies suggest benefit via increased intrahepatic degradation.
- No human studies.
- Not recommended at this time outside of trials.

Therapy: RNA Interference Drugs

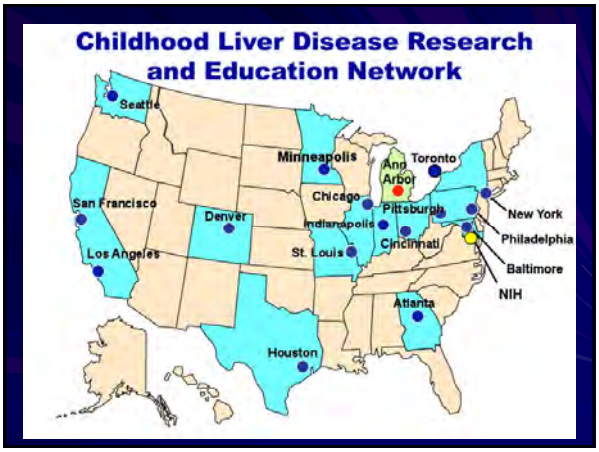
- In vitro and animal studies suggest benefit by blocking synthesis and reducing intrahepatic accumulation.
- Human studies underway in adults.
- Not recommended at this time outside of trials.

Therapy: Carbamazepine

- In vitro and animal studies suggest benefit of megadose (10 x usual) to increase degradation.
- Human studies at conventional dose underway in patients with end stage cirrhosis. U of Pittsburgh.
- Not recommended at this time outside of trials.

Observational Studies

- The Childhood Liver Disease Research and Education Network (ChiLDREN) is an NIH-sponsored consortium focused on the study of pediatric liver diseases
- 16 North American tertiary care centers
- The study enrolls patients with CF, EHBA, Neonatal cholestasis, Alagille, PFIC, Bile Acid Synthetic Defects, and *A1AT*



Observational Studies

- Adult Alpha-1 Liver Disease Study.
- Saint Louis University, U of Florida, UCSD.
- 5 year, prospective analysis of adult liver disease.
- Contact: Teckmanj@slu.edu

Observational Studies and Advocacy

- Alpha-1 Registry. A self-report patient data-base and contact registry.
  - www.alphaoneregistry.org,
  - email alphaone@musc.edu
  - 1-877-886-2383.
- Alpha-1 Foundation
- Alpha-1 Association
- AlphaNet (lung Rx)
- AIR Registry (Europe)

Future Directions and Needs

- Increased awareness and improved collaboration (lung-liver doctors and pediatric-adult doctors).
- Improved understanding of genetic and environmental modifiers for insights into prognosis and therapies
- Liver disease therapies.

Summary/Take Home Points

- The majority of ZZ children will do well with minimal intervention.
- Animal studies support avoidance of NSAIDS as they may increase liver injury.
- Genetic and environmental disease modifiers are likely important, but are poorly understood.

Summary/Take Home Points

- Avoidance of cigarette smoke is critical.
- Typical liver disease supportive care or transplant is the only recommended therapy at this time.
- Many studies and registries are underway.

UPDATE ON ALPHA-1-ANTITRYPSIN DEFICIENCY

Jeffrey Teckman MD, St. Louis University

Board Style questions

Question: The gold standard for the diagnosis of Alpha-1-antitrypsin deficiency is

a. Serum phenotype testing
b. Assays of patient DNA samples
c. Liver biopsy
d. Serum testing confirmed by liver biopsy
e. a or b are both considered gold standards.

Answer: e

Discussion: Serum testing has been the gold standard for many years, but recently DNA based assays are regarded as equally useful. Liver biopsy is not required to make the diagnosis.

Question: Which of the following is true:

a. Most ZZ patients with neonatal cholestasis go on to liver transplant.
b. Very few ZZ children have chronically elevated ALT.
c. Most ZZ children are generally healthy in childhood with minimal intervention.
d. All 50 states have begun newborn screening for alpha-1-antitrypsin deficiency.

Answer: c

Discussion: Most ZZ children are not cholestatic, most do not need liver transplantation, and no states currently offer newborn screening for this disease.

Question: Which of the following is not part of typical recommendations when a patient is newly diagnosed with alpha-1:

a. The patient should avoid personal smoking and second hand smoke.
b. The patient and the family should be offered genetic counseling
c. The patient should be counseled about alcohol consumption as per AASLD guidelines.
d. Routine liver disease follow up is not needed.

Answer: d

Discussion: Follow up at least yearly, or more if liver disease is present is common practice, as are the other items.

Question: Which of the following drug treatments should be initiated when a patient is diagnosed with alpha-1:

a. Sirolimus

b. Carbamazepine
c. 4-phenylbutyrate
d. Ibuprofen
e. None of the above.

Answer: e

Discussion: There is no drug treatment known to be specifically effective for this disease. Some of these medications have been, or are now, in various phases of testing but as of yet cannot be recommended for routine administration.

There's a liver mass on ultrasound – where do you go from here???

Kathleen B. Schwarz, M.D.
Johns Hopkins University SOM
President, NASPGHAN

Disclosures

- Roche/Genentech – research grant
- Genentech – research grant
- BMS – research grant
- Vertex – research grant
- NIDDK – research grants
- Novartis - consulting

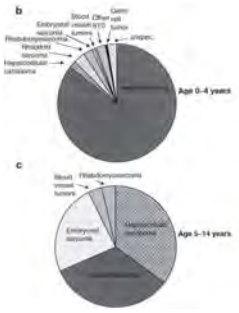
Learning objectives

- A. Learn the differential diagnosis of hepatic tumors
- B. Know the evaluation including laboratory tests, imaging and histopathology of hepatic tumors
- C. Understand the treatment options of hepatic tumors

What might prompt the liver ultrasound?

- Abdominal swelling
- Hepatomegaly
- Weight loss
- Acute abdomen
- Early puberty in boys
- Jaundice - rare
- Risk factors

Relative frequencies of specific liver tumors by age group



Zimmerman et al Pediatric Liver Tumors Springer-Verlag 2011

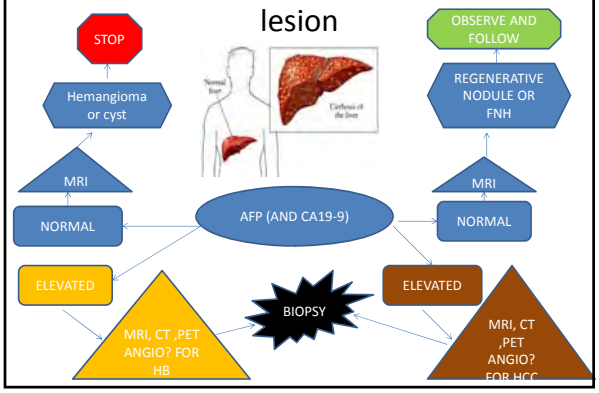
Congenital or genetic syndromes with hepatoblastoma

Genetic syndrome	**Presumed gene function**
• Beckwith-Weideman	• Fetal growth factor
• FAP/Gardner	• Antagonist of Wnt signaling
• Li-Fraumeni	• Inducer of cell cycle arrest
• Simpson-Golabi-Behmel	• Regulator of cell division
• Soto syndrome	• Histone methyltransferase
• Neurofibromatosis I	• Negative regulator of ras

Genetic & other syndromes with HCC

Disease	Associated gene
Hereditary tyrosinemia	Fumarylacetoacetate hydrolase
Glycogen storage diseases	
Familial adenomatous polyposis	*APC*
Alagille syndrome	*Jagged 1*
Other familial cholestatic syndromes	*FIC1, BSEP (also cholangiocarcinoma)*
Neurofibromatosis	*NF-1*
Ataxia telangiectasia	*ATM*
Fanconi anemia	*FAA, FAC, others (20%)*
Other reported associations	
TPN	
Osteogenesis imperfecta	*COLIA1, COLIA2, (CRTAP,LEPRE1)*
Congenital hepatic fibrosis	
Abnormal abdominal venous drainage	

Diagnostic algorithm for solitary liver lesion



Alpha fetoprotein values in normal infants

Age (days)	AFP mean ng/ml	AFP 95.5% ng/ml
0	41,687	91,20 – 190,546
7	16,107	3,524 – 73,621
29 - 45	417	30 – 5,754
91 - 120	36	3 - 417
181 - 720	8	0.8 - 87

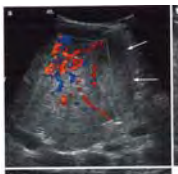
Blohm ME, et al 1998 Alpha-1-fetoprotein reference values in infants up to 2 years of age Pediatr Hematol Oncol 15 (2):135-142

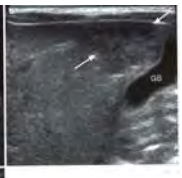
Liver tumors according to age and AFP

Age	AFP normal	AFP 10 – 10^4 ng/ml	AFP > 10^4 ng/ml
0 – 3 years	Hemangioma	Hemangioma	
	Mesenchymal hamartoma	Mesenchymal hamartoma	
	Rhabdoid	Hepatoblastoma	Hepatoblastoma
	Biliary rhabdo		
3 – 10 years	Biliary rhabdo		Hepatoblastoma
	Undiff sarcoma		Transitional
	Mes hamartoma	Mes hamartoma	Hepatocellular C
	Rhabdoid		
10 – 15 years	Fibrolamellar car	Transitional	Transitional
	Undiff sarcoma	HCC	HCC
	FNH		

Use of ultrasound to evaluate pediatric liver tumors

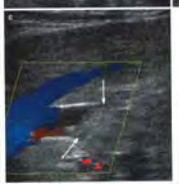
a. 2 yr old with HCC – low frequency sector transducer with color Doppler





b. Infant with HB high frequency linear array transducer

c. Vascular invasion with high frequency linear array transducer and color Doppler



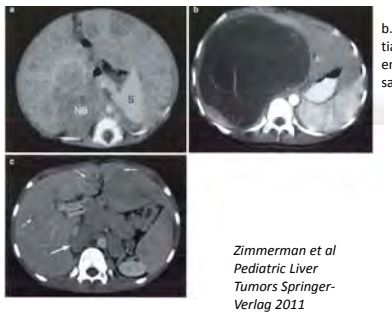
Zimmerman et al Pediatric Liver Tumors Springer-Verlag 2011

Pediatric Liver Neoplasms from www.RadDaily.com

Lesion	Age	Solid/cystic	Calcification	Serum markers
Infantile hemangio-blastoma	<1 years	Solid	Ca++	AFP negative
Mesenchymal hamartoma	<2 years	Cystic	No calcifications	AFP negative
Hepatoblastoma	<3 years	Solid	Ca++, vascular	AFP positive
Hepatocellular carcinoma	>4 years	Solid	vascular	AFP positive
Embryonal rhabdomyo sarcoma	<5 years	Solid>cystic	Mild vascularity	AFP negative
Undifferentiated embryonal sarcoma	>6 years	Cystic>solid	No calcifications	AFP negative
Metastases	any	Solid or cystic	Possible	AFP negative

CT

a. Stage IV neuroblastoma with diffuse liver metastases



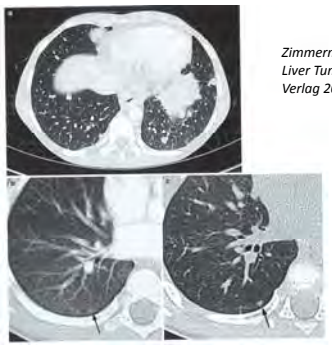
b. Undifferentiated embryonal sarcoma

c. Multi-focal fibrolamellar carcinoma in an 11 year old

Zimmerman et al Pediatric Liver Tumors Springer-Verlag 2011

CT essential for lungs

a. 11 year old with fibrolamellar carcinoma



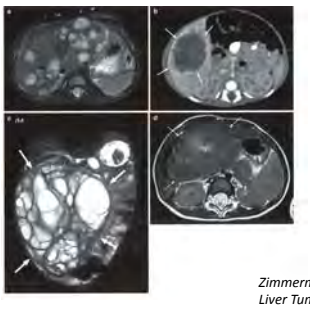
Zimmerman et al Pediatric Liver Tumors Springer-Verlag 2011

b. Multidetector CT 5mm slices in a 5 year old male

c. 1 mm slices in the same patient

Common benign liver tumors MR

a. Infantile hemangioma



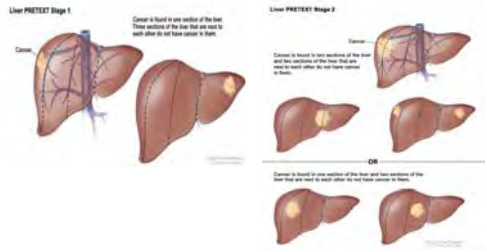
b. Rapidly involuting congenital hemangioma

c. Mesenchymal hamartoma

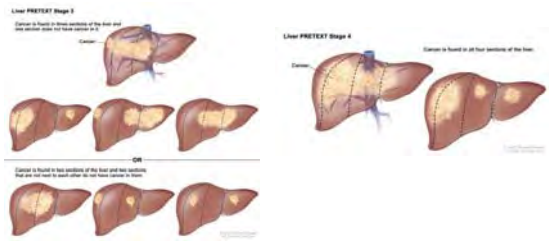
d. Focal nodular hyperplasia in a 3 year old

Zimmerman et al Pediatric Liver Tumors Springer-Verlag 2011

Liver cancer Pretext Stages 1 and 2



Liver cancer Pretext Stages 3 and 4

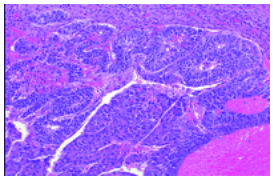


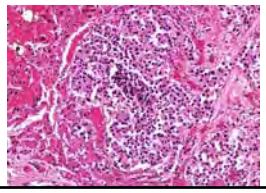
When and how to biopsy?

- Hemangioma? LEAVE ALONE
- Suspect hepatoblastoma? Open or percutaneous biopsy under US guidance to tumor to avoid seeding
- Suspect hepatocellular carcinoma? AVOID OPEN BIOPSY BECAUSE OF DISSEMINATION – use percutaneous biopsy/US

Histopathology

- Hepatoblastoma – fetal or embryonal, high nucleus:cytoplasm ratio, pure fetal may have better prognosis
- HCC – intratumor hemorrhaging, necrosis, microinvasion, pleomorphic hepatocytes

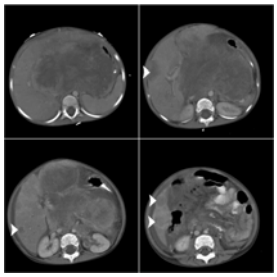




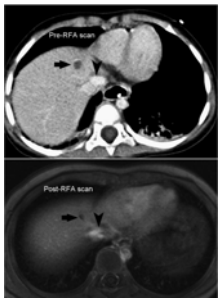
Treatment

- Hepatoblastoma – partial or complete hepatectomy/transplant depending on the stage, with or without preresection chemo; primary liver transplantation much better than rescue transplant
- Hepatocellular carcinoma – complete excision necessary but possible only in 1/3; in well-selected cases liver transplant the best option – 1,5, and 10 year survival 86, 63, and 58%
- Neoadjuvant therapies being explored – chemoembolization, intra-arterial chemotherapy, radiofrequency ablation
- Supportive

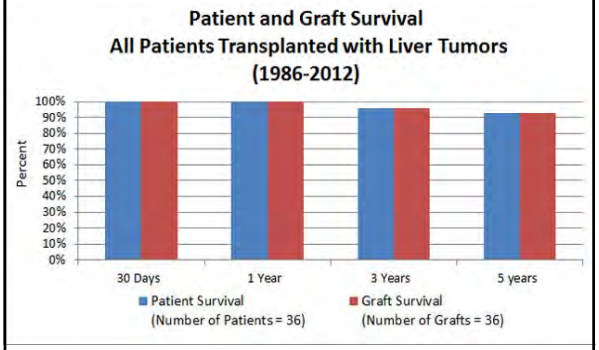
Pretext 4 Hepatoblastoma



At presentation



Post chemo, pre and post RFA



Includes hepatoblastoma, hepatoma, hepatocellular carcinoma and other specific liver tumors; does not include hemangioendothelioma
**Source: Organ Procurement and Transplantation Network (OPTN) data as of April 20, 2012 – Cincinnati Children's Hospital

Take home points

- Symptoms usually subtle
- Hemangiomas most common – reassure
- Hepatoblastoma 80% of malignant, majority resection candidates, chemorx important adjuvant
- Hepatocellular second most common primary malignant liver tumor, chemo unproven
- Transplantation in selected patients promising

Future Directions

- Develop better tumor markers than AFP to improve early detection
- Improve understanding of oncogenetic mechanisms in each of the described tumors so as to develop more rational therapies
- Refine indications and contraindications for liver transplantation
- Elaborate most cost effective approaches

References

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- Blohm ME, et al 1998 Alpha-1-fetoprotein reference values in infants up to 2 years of age Pediatr Hematol Oncol 15 (2):135-142
- McDiarmid SV – Liver Transplantation for Malignancies in Children *Liver Transplantation 16 #10 Suppl 2 2010:ppS13-S21*
- Web site of the NCI http://www.cancer.gov/cancertopics/pdq/treatment/
- childliver
- Zimmerman A et al Pediatric Liver Tumors Springer-Verlag, 2011

THERE IS A LIVER MASS ON THE ULTRASOUND

Kathleen B. Schwarz MD, Johns Hopkins University School of Medicine

Board Style questions

1. A five year old previously healthy male presents to his pediatrician for a well-child check-up and hepatomegaly is noted. Liver ultrasound shows a solid 3cm mass. Alpha feto protein is 3510 ng/ml. Which of the following statements are true?
    a. Hepatoblastoma is most likely
    b. Hepatocellular carcinoma is most likely
    c. Hepatoblastoma and hepatocellular carcinoma are equally likely
    d. Embryonal sarcoma is most likely
    e. Rhabdomyosarcoma is most likely

2. A 16 year old female taking oral contraceptives has vague right upper quadrant pain. Liver ultrasound shows a 4 cm nodule. Alpha fetoprotein is 5 ng/ml and CA-19 9 is 25 ng/ml. (normal 0 - 35.) A liver MRI is consistent with focal nodular hyperplasia. Appropriate next step is
    a. CT angio of the liver
    b. Needle biopsy of the lesion
    c. Wedge biopsy of the lesion
    d. Surgical resection
    e. Observation

3. Routine liver ultrasound is performed in a a one year old Asian female with materno-fetal acquisition of hepatitis B. A 1 cm vascular mass consistent with a hemangioma is found. Alpha fetoprotein is 8 ng/ml. The most appropriate management is
    a. Follow up ultrasound
    b. CT angio of the liver
    c. Needle biopsy of the lesion
    d. Wedge biopsy of the lesion
    e. Surgical resection

4. The most accurate statement about the role of liver transplantation in the management of liver tumors is
    a. The best results in children with hepatoblastoma are with rescue transplant
    b. 10 year post transplant survival rates for children with HCC are 20%
    c. Liver transplantation is never successful in children with hemangioendothelioma
    d. Five year patient and graft survival rates for all tumors are ~90%
    e. Graft survival rates are 20% lower than patient survival at 1 year

Answer Key:

1. c
2. e
3. a.
4. d

MODULE C: THE INFLAMED INTESTINE

Moderators: Sandeep Gupta MD and Edward Hoffenberg MD

GI INFLAMMATION, IMMUNE FUNCTION AND IBD

Harland Winter MD, Massachusetts General Hospital for Children

Learning objectives:

1. Understand basic gastrointestinal mucosal immunology
2. Learn ways to manipulate gastrointestinal immunology
3. Know clinical application of these interventions

MY STOMACH IS BUGGING ME!: THE MICROBIOME IN IRRITABLE BOWEL SYNDROME

Robert Shulman MD, Baylor College of Medicine

Learning objectives:

1. Understand the microbiome of the gut
2. Describe role of gut microbiome in irritable bowel syndrome u
3. Learn the use of targeted therapy for irritable bowel syndrome based on the microbiome

THE SORE BOTTOM: PERIANAL INFLAMMATORY BOWEL DISEASE

Anne Griffiths MD, The Hospital for Sick Children

Learning objectives:

1. Learn evaluation of perianal disease
2. Know medical management of perianal disease
3. Describe surgical therapy of perianal disease

RESCUE ME FROM MY IBD: UPDATES ON INFLAMMATORY BOWEL DISEASE THERAPY

Athos Bousvaros MD, MPH, Children's Hospital Boston

Learning objectives:

1. Know appropriate usage and complication of immune-modulators u
2. Review use of biologic agents
3. Learn use of rescue therapies in non-responders to biologics

GI Inflammation, Immune Function and IBD

Harland S. Winter, MD
Director, Pediatric Inflammatory Bowel Disease Program
MassGeneral Hospital *for* Children
Associate Professor of Pediatrics
Harvard Medical School
Boston, MA
hwinter@partners.org

Disclosures

- Research:
  - Shire Pharmaceuticals, Prometheus Laboratories, UCB Pharma, Janssen Pharmaceuticals, Nutricia, Warner Chilcott, Autism Research Institute
- Consultant:
  - Janssen Pharmaceuticals, Salix Pharmaceuticals, Pediatric IBD Foundation
- Royalties:
  - UpToDate
- Speaker's Bureau:
  - none

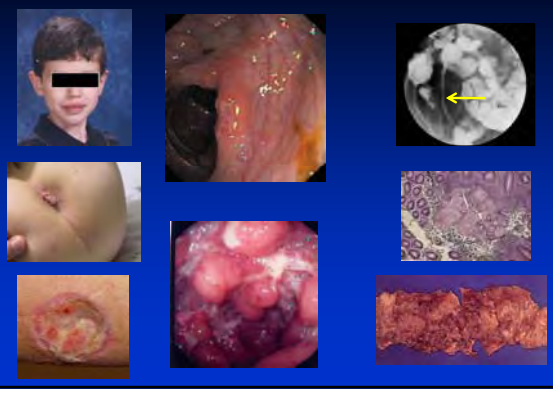
Learning Objectives: Relate GI immunology to IBD therapeutics

A. Understand basic GI mucosal immunology
B. Learn ways to manipulate GI immunology
C. Know clinical applications of these interventions

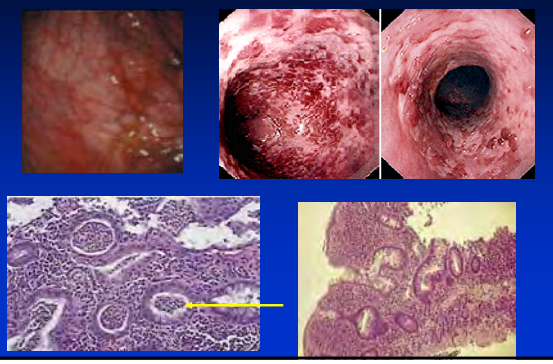
Where are we going?

- Pathogenesis of IBD
- Understanding immunity
- The impact of genetics
- The role of the microbiome
- From bugs to drugs

Crohn's Disease



Ulcerative Colitis

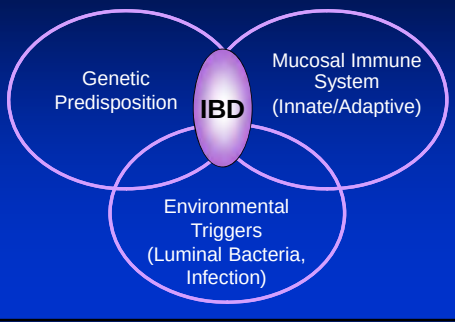


The Etiology of IBD

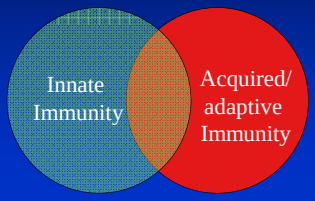
- The etiology of IBD is thought to be related to a failure to control the host immune response to commensal microbes in the genetically susceptible host.
  - Microbial biodiversity is decreased in IBD
  - *Bacteroidetes and Firmicutes* are reduced
  - *Enterobacteriaceae* are increased
  - *Genetic mutations result in altered immune response (NOD2)*

Manichanh C, et al. Gut 2006;55:205

Etiologic Theories in Inflammatory Bowel Disease



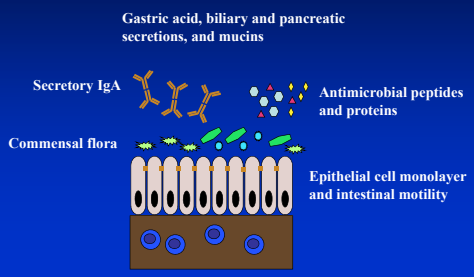
Human Immune System



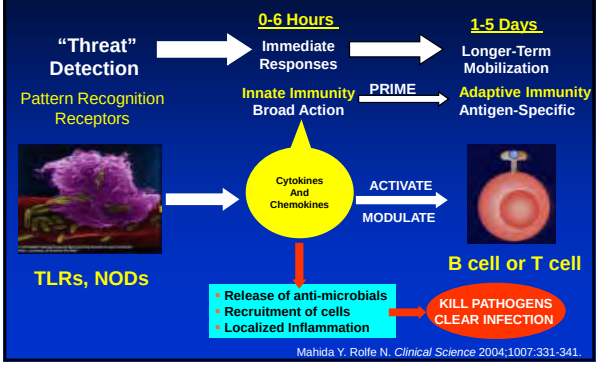
Innate *vs* Adaptive Immunity

	Innate	Adaptive
Response	Immediate	Delayed (days to weeks)
Triggers	Limited (bacterial LPS, HSP, etc)	Variable
Receptors	Toll-like receptors (TLR)	MHC-T Cell Receptor
Cells	DC, MΦ, NK, IEL	T and B lymphocytes
Mechanisms	Multiple	Cellular and humoral immune responses
Specificity	Non-specific	Immunologic memory

Components of Intestine Innate Immune System

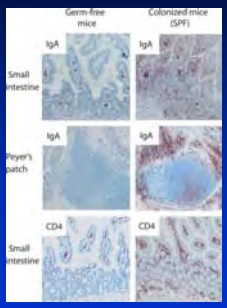


Innate and Adaptive Immunity are Linked



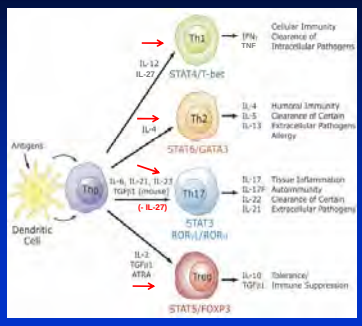
Mahida Y. Rolfe N. *Clinical Science* 2004;1007:331-341.

IgA Production Depends on Luminal Bacteria



Macpherson AJ, et al. Immunologic Reviews . 2012;245:132.

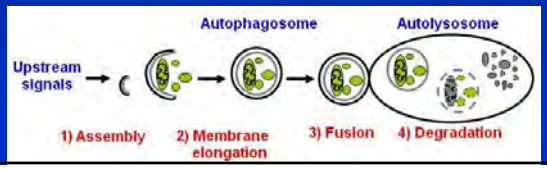
T Cell Activation and Diversity



Adapted from Brand S. Gut 2009;58,1153

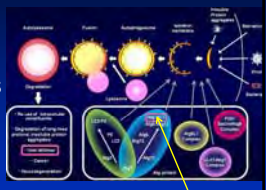
Autophagy

- From the Greek: self-eating
  - *"auto"* (oneself) and *"phagy"* (to eat)
- A mechanism whereby damaged cells, organelles or intracellular pathogens are sequestered into an *autophagosome* for degradation in *autolysosomes*



Autophagy genes: *ATG16L1, IRGM*

- Lysosome-dependent intracellular degradation of cytosolic proteins/ organelles and clearing bacteria
- Specific for CD
- *ATG16L1* knockout impairs killing of intracellular *S. typhi*
- *IRGM* defects may be related to persistent subpathogenic *E. coli*



Rioux JD et al. Nature Genetics 2007; 39:596-604
Darfeuille-Michaud A et al. Gastroenterology 2004; 127:412-421
Xie Z et al. Nature Cell Biology 2007; 9(10):1102-1109
Yano T. Nature Immunology 2009; 10(9): 134-136

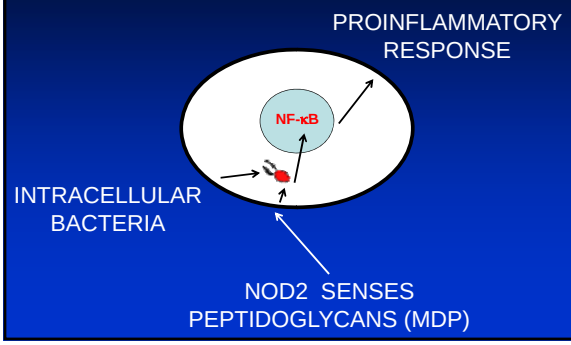
The Impact of Genetics

A frameshift mutation in *NOD2* associated with susceptibility to Crohn's disease

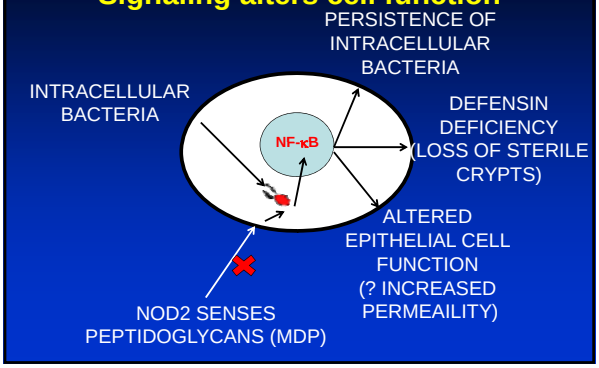
Yasunori Ogura*†, Denise K. Bonen‡†, Naohiro Inohara*, Dan L. Nicolae§, Felicia F. Chen*, Richard Ramos‡, Heidi Britton‡, Thomas Moran‡, Reda Karaliuskas‡, Richard H. Duerr‖, Jean-Paul Achkar¶, Steven R. Brant#, Theodore M. Bayless#, Barbara S. Kirschner**, Stephen B. Hanauer‡, Gabriel Nuñez*†† & Judy H. Cho‡††

Nature 2001;411:604

Innate Immunity: NOD2 Signaling Activates Proinflammatory Cytokines



Innate Immunity: Failure of NOD2 Signaling alters cell function



Crohn's Disease, Paneth Cells,and Defensins

- Deficiency of Paneth cell α-defensin HD5 may predispose to Crohn's disease
- Loss of function of NOD2 or a disturbance in the Wnt pathway transcription factor TCF7L2/TCF4 results in reduced production of defensins in Paneth cells
- Cows that develop Johne's disease (granulomatous ileitis caused by paratuberculosis) lack intestinal α-defensins

Wehkamp J, StangeEF. J Crohns Colitis 2010;4:523.
Schurr E, et al. N Engl J Med 2010:361;27
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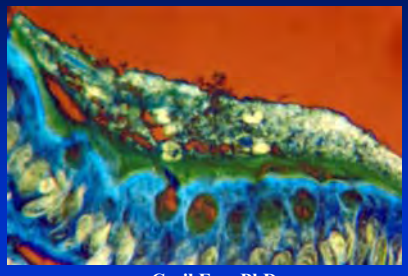
The Role of the Microbiome



Cecil Fox, PhD

Environment
You Are Only 10% Human

$= 10^{12}$ to 10^{13} Cells

$= 10^{13}$ to 10^{14}
Intestinal Bacteria

http://www.google.com/imgres?q=intestines+cartoon&hl

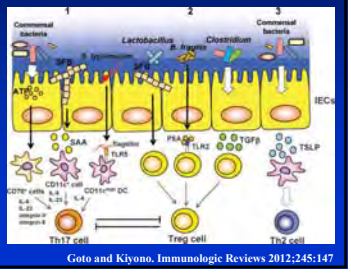
Effect of Microbial Exposure in Early Life on Severity of Colitis

- Immune effects of exposure to microbes in infancy persist throughout life
- Germ-free mice have increased morbidity in models of IBD than mice who are colonized with bacteria.
- Neonatal germ-free mice, but not adult mice, that are colonized are protected
- Early contact with commensal bacteria protects against developing colitis

Olszak T, et al. Science 2012;336:489

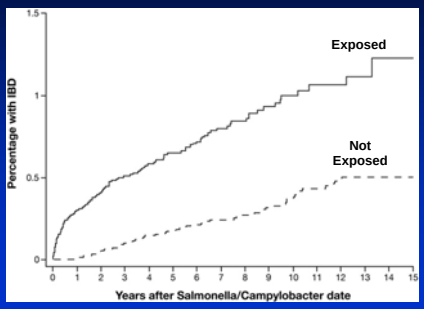
Gut-Microbiota-Epithelium Interaction

- Regulation of immunologic homeostasis
- Pathogenic bacteria are detected by Toll-like receptors on dendritic cells inducing differentiation of Th 17 cells
- TGF-beta and Polysaccharide A induce Tregs
- Thymic stromal lymphopoietin enhances Th2 differentiation



Goto and Kiyono. Immunologic Reviews 2012;245:147

Increase in IBD Incidence for Patients Exposed to Salmonella/Campylobacter



Gradel K et al. Gastroenterology 2009;137:495

From Bugs to Drugs

- How the microbiota communicates with the host to maintain homeostasis will lead to an understanding of how gut bacteria:
  - Promote Tregs that may treat IBD
  - Reduce activation of the adaptive immune system
  - Alter immune responses
- The development of novel bacterial therapies that modulate inflammation is not far off

Treatment for IBD I

- Alteration of the microbiome
  - Antibiotics:
    - Active CD
      - 10 RCTs: AB superior to placebo, 95% CI = 0.73-0.99, P=0.03
    - Quiescent CD
      - 3 RCTs: AB superior to placebo, 95% CI = 0.46-0.84
    - Active UC
      - 9 RCTs: AB beneficial in inducing remission, 95% CI = 0.43-0.96
  - Probiotics
    - Specific probiotics or fecal transplantation
  - Prebiotics (AKA Food)

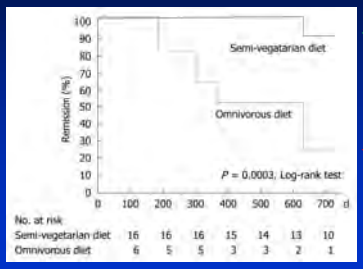
(Khan KJ, et al. Am J Gastro 2011:106:661

Can a semi-vegetarian diet prevent relapse of Crohn's disease?

- Daily
  - rice, miso soup
  - egg, yogurt, milk
  - vegetables, fruit, legumes, algae
- Fish once a week
- Meat once every 2 weeks

Chiba M, et al. World Journal of Gastroenterology 2010;16 (20):2484-95

Can a semi-vegetarian diet prevent relapse of Crohn's disease?



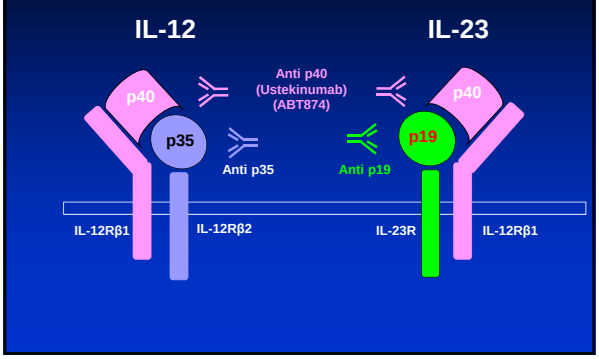
Chiba M, et al. World Journal of Gastroenterology 2010;16 (20):2484-95

Treatment for IBD II

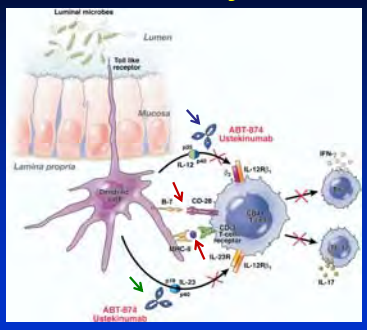
- Immunomodulation (inducing remission)
  - Anti-TNF
    - Superior to placebo (95% CI 0.80-0.94)
  - Natalizumab (anti-α_4-integrin antibody)
    - Superior to placebo (95% CI 0.83-0.94)

Ford AC, et al. Am J Gastro 2011;106:644

Monoclonal Antibodies IL-12 and IL-23

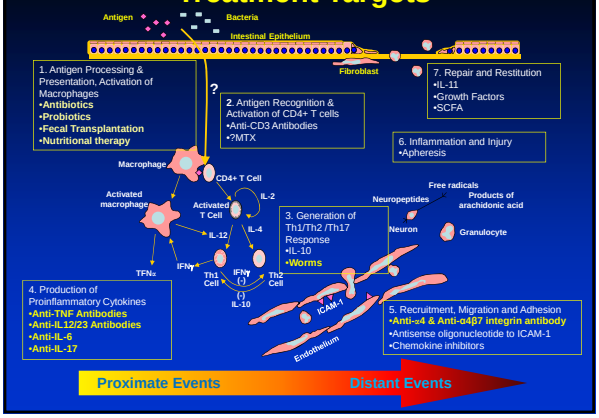


Inhibition of the Interleukin-12/23 Pathway



Adapted from Rutgeerts et al. Gastro 2009;136:1182

Treatment Targets



Where have we been?

- Understanding pathogenesis has led to novel therapies
- The immune system, genetics, and the microbiome are interrelated.
- Immunosuppression may not be the treatment of choice in the future

Points to Remember

- The innate immune system is relevant to understanding the pathogenesis of IBD
- Perturbations of the microbiome may alter immune function
- Genetic mutations such as NOD2 alter Paneth cell function and impair innate immunity
- Cows get what looks like Crohn's disease

Future Research and Speculations

- Systems biology and bioinformatics will unravel the relationships between the microbiome, transcriptome, metabolome, epigenome, and genome.
- Genetic mutations may be more relevant in children with onset of IBD in infancy. Exome sequencing is available without charge at MGH.
- Contact: hwinter@partners.org

GI INFLAMMATION, IMMUNE FUNCTION AND IBD

Harland Winter MD, MassGeneral Hospital for Children

Board Style questions

1. Which of the following statements is true:
   A. The innate immune response is delayed and may take weeks
   B. The T cell receptor plays an integral part in innate immunity
   C. Intra-epithelial lymphocytes are part of adaptive immunity
   D. Adaptive immunity has immunologic memory
   E. Toll-like receptors are essential for development of antibody

2. Gastrointestinal luminal bacteria are necessary for:
   A. Production of IgA in the small intestine
   B. Secretion of pancreatic enzymes following a fatty meal
   C. Development of T cells
   D. Expression of HLA-DR on epithelial cells and macrophages
   E. Defensin production by Paneth cells

3. NOD2 mutations are related to:
   A. Excessive production of α-defensin by Paneth cells
   B. Granulomatous ileitis in ruminants
   C. Esophageal Crohn's disease
   D. Mild cases of Crohn's disease with onset in older adults
   E. Lack of intestinal IgA

Correct answers:

1. D Innate immunity is immediate and intra-epithelial lymphocytes are part of innate immune function. Toll-like receptors are involved in innate immune function, T cell receptors are part of adaptive immunity. Antibodies are produced by plasma cells as part of adaptive immunity.

2. A Animals that are reared with a sterile GI tract have minimal IgA in the lamina propria. Paneth cells, T cells, macrophages, and the pancreas are not significantly impacted by the presence of luminal bacteria

3. B Cows (ruminants) with a mutation in NOD2 lack intestinal α-defensins and acquire Johne's disease, a condition similar to Crohn's but caused by paratuberculosis. Patients with NOD2 mutations tend to have fibrostenosing ileal disease

My Stomach is Bugging Me: The Microbiome in Irritable Bowel Syndrome (IBS)

Robert J. Shulman, M.D.
Professor of Pediatrics

Disclosures

I have the following financial relationships to disclose:

Gerson Lehrman Group
QOL Medical

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

NASPGHAN

Outline

- Definitions
- Development of, and factors influencing the gut microbiome
- Gut microbiome in IBS vs health
- Therapy for IBS based on microbiome

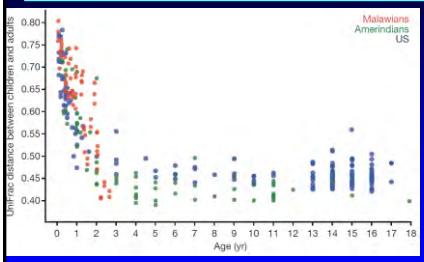
Definitions

- Microbiota: microbial community
- Microbiome: collective genomes/gene products of resident microbes
- Metagenome: collection of all genomes within a given location (e.g., microbial and human in the gut)

(Johnson CL. Pediatrics 2012;129:950)

Development of, and Factors Influencing the Gut Microbiome

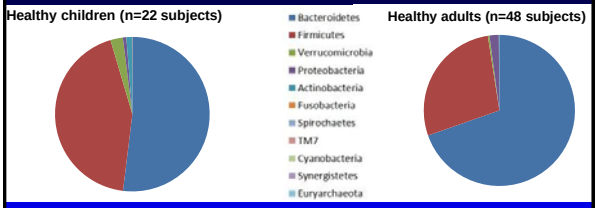
Changes in Gut Microbiota with Age and Geography



- Composition becomes adult-like within 3 yr.
- Greater variation in composition in infants vs children
- Geographic impact on composition

(Yatsunenko T. Nature 2012;486:222)

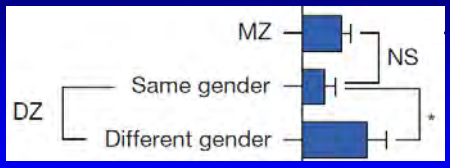
Phylum Distributions in Children and Adults



(Versalovic J . In process)

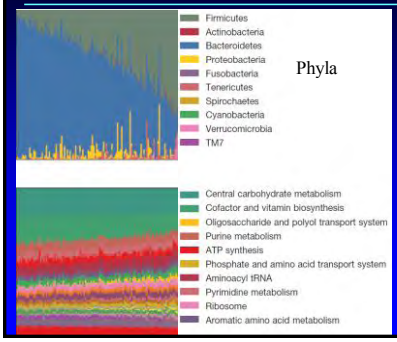
Small Genetic Contribution to Microbiome Composition

13 – 17-year-old American Children



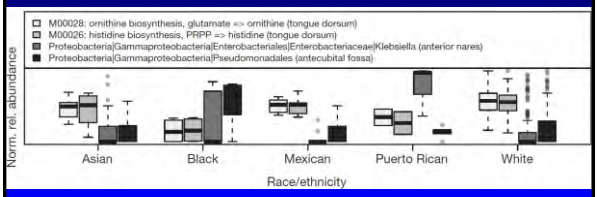
(Yatsunenko T. Nature 2012;486:222)

Microbes Vary Among Subjects but Metabolic Pathways are Stable



(HMP. Nature 2012;486:207)

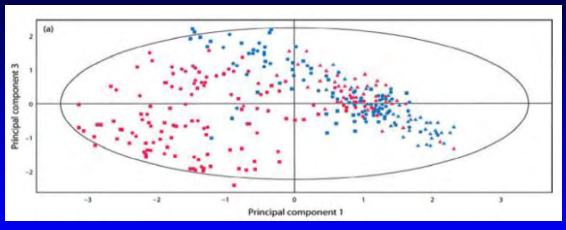
Microbiota, Metabolic Pathways and Race/Ethnicity



(HMP. Nature 2012;486:207)

Diet and the Gut Microbiome

Feeding and Development of GI Microbiota

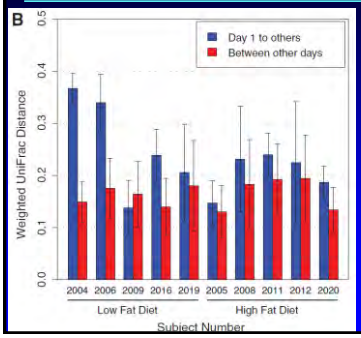


Breast

Formula

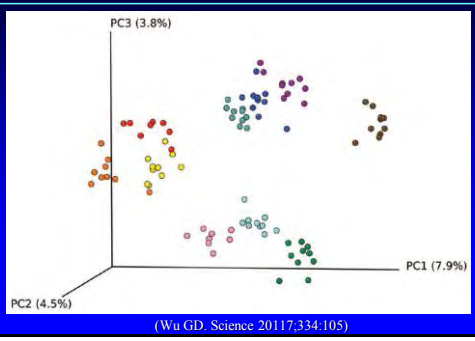
(Roger LC. Microbiology 2010;156:3317)

Short Term Effect of Diet on Microbiota



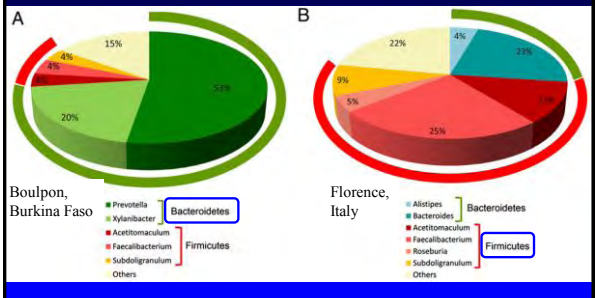
(Wu GD. Science 2011;334:105)

Short Term Effect of Diet on Microbiota



(Wu GD. Science 20117;334:105)

Long Term Effect of Diet on Microbiota



Boulpon, Burkina Faso

Florence, Italy

(De Fillippo C. PNAS 2010;107:14691)

Gradient of Microbes in the Gut

Factors Affecting Bacterial Population of Gut

- Stomach - 10^2-10^3 cells/mL
  - Low pH
  - Rapid luminal flow
- Small intestine - 10^4 cells/mL
  - Rapid luminal flow
  - Bactericidal effect of bile acids
  - IgA
  - Epithelial, goblet, and Paneth cell production of antimicrobials

(Walter J. Ann Rev Microbiol 2011;65:411) (Hooper L. Nat Rev Immunol 2010;10:159)

Factors Affecting Bacterial Population of Gut

- Colon – 10^{11}-10^{12} cells/mL
  - Longer retention time due to slow peristalsis
  - Large volume
  - Low concentrations of bile salts
  - Lack of Peyer's patches

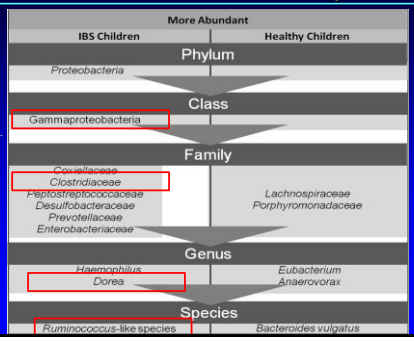
(Walter J. Ann Rev Microbiol 2011;65:411)
(Hooper L. Nat Rev Immunol 2010;10:159)

Child Gut Microbial Composition IBS vs Healthy

Differences in Relative Abundance at Different Taxonomic Levels between IBS vs Healthy Children

(Rajilić-Stojanović M. Gastroenterology 2011;141:1792)

(Saulnier DM. Gastroenterology 2011;141:1782)

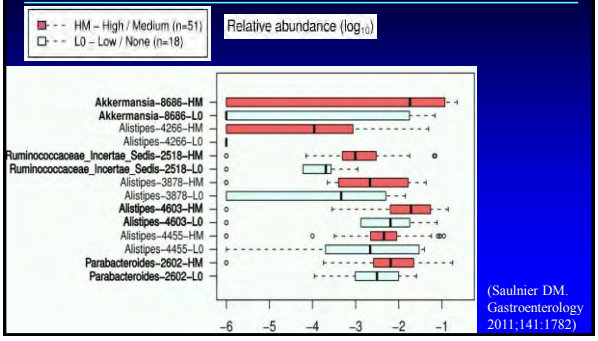


Bacterial Associations Relative to Pain

Healthy children
Average path length = 5.06

IBS - Medium to High Pain
Average path length = 2.81

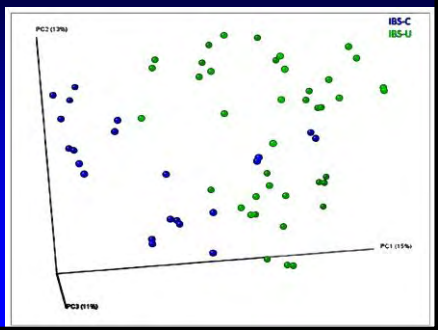
Gut Microbiota and Abdominal Pain in IBS



(Saulnier DM. Gastroenterology 2011;141:1782)

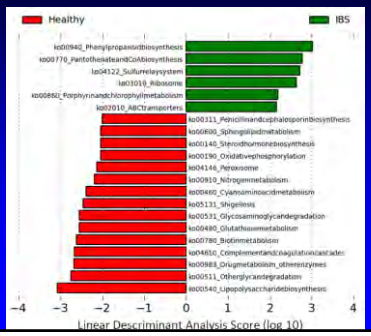
Relative Abundance of OTUs Define Stooling Pattern

IBS-U
IBS-C



(Saulnier DM. Gastroenterology 2011;141:1782)

Taxonomy and Function via Whole Genome Shotgun Sequencing (Metagenomics)



Gut Microbiota-Directed Therapy for IBS

Probiotics in Children

- Lactobacillus rhamnosus GG
  - Meta-analysis (3 RCT) in IBS/FAP/FD
  - Higher rate of treatment responders (no or decreased pain) and decreased pain intensity in overall group (NNT 7)
  - Not significant in FAP (2 RCT) or FD (1 RCT)
- VSL#3
  - RCT (crossover) in IBS
  - Global relief, decreased pain, bloating
  - Analysis potentially prejudiced against placebo

(Horvath A. Aliment Pharmacol Ther 2011;33:1302)
(Guandalini S. J Pediatr Gastroenterol Nutr 2010:51:24)

Antibiotics (rifaximin)

- Pediatric RCT
  - IBS/FAP/FD (n=75) treated for 10 d
  - Lactulose breath test (BT)
    - N=68 abnormal (Yu D. Gut 2010; 60:334)
  - No response in pain, stooling, bloating
- Adult meta-analysis
  - Modest benefit in global improvement and bloating (OR ~1.5, NNT~10)
  - Comparable to other proven treatments

(Collins BS. J Pediatr Gastroenterol Nutr 2011;52:382)
(Menees SB. Am J Gastroenterol 2012;107:28)

Diet – Adverse Effects of FODMAPs

- **F**ermentable, **O**ligosaccharides, **F**ructans/Galactans, **D**i- **M**onosaccharides, **A**nd **P**olyols
- Increase GI symptoms via increased water delivery to distal bowel and fermentation
- Evidence for benefit in adults with IBS
- Current trial in children

(Shepherd SJ. Clin Gastroenterol Hepatol 2008;6:765)
(Barrett JS. Aliment Pharmacol Ther 2010;31:874)
(Gibson PR. Am J Gastroenterol 2012;107:657)

Sources of FODMAPs

- Fructo-oligosaccharides (fructans)
  - Wheat, rye, onions, garlic, artichokes
- Galacto-oligosaccharides
  - Legumes
- Lactose
- Fructose
  - Honey, apples, pears, watermelon, mango
- Sorbitol
  - Apples, pears, stone fruits, sugar-free mints/gums
- Mannitol
  - Mushrooms, cauliflower, sugar-free mints/gums

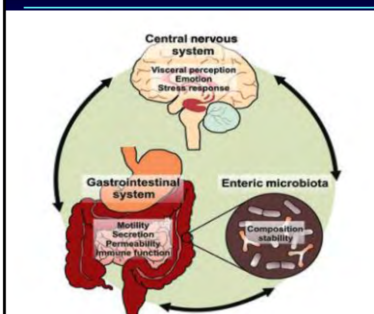
(Barrett J. Ther Adv Gastroenterol 2012;5:261) (Biesiekierski JR. J Hum Nutr Diet 2011;24:154)

Diet – Added Fiber

- Controversial in treatment of adults
  - Possible benefit of psyllium
- Too few data in pediatrics
- Studies do not address subtypes
- Randomized, double blind pediatric trial in progress

(Ford AC. BMJ 2008;337:a2313)
(Ruepert L. Cochrane Database Syst Rev 2011;(8):CD003460)
(Huertas-Ceballos A. Cochrane Database Syst Rev 2008;(1):CD003019)

Gut-Brain-Microbiota Axis



(Cryan JF. Neurogastroenterol Motil 2011;23:187)

Questions
- How and where do microbes exert their effects?
- How do microbes interact?
- Do developmental changes in microbiome account for child vs adult symptom differences?

- Gut microbiome differ in IBS and altered composition related to symptoms
- Clinical improvement from probiotics, antibiotics, dietary changes support importance of microbiota

Acknowledgments

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Baylor Bioinformatics Research Lab
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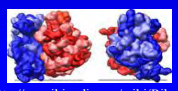
R34 AT006986
P30 DK56338
USDA

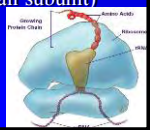
Thanks to the Children, their Families, and Physicians/Staff

Ribosomes

- Subcellular complexes of protein and RNA
  - Responsible for translating RNA code into proteins
  - Present in all cellular organisms
  - Structure highly conserved but contains enough variation to allow organisms of different lineages to be discerned from one another
  - Consist of two parts, referred to as the large (red) subunit and small (blue) subunit (16S found in small subunit)



(http://en.wikipedia.org/wiki/Ribosome)
(http://publications.nigms.nih.gov/insidethecell/chapter2.html)



Taxonomy

Defining groups of biological organisms on the basis of shared characteristics

Group organisms based on DNA sequence similarity using sequencing of 16S ribosomal RNA gene = Operational Taxonomic Units (OTUs)

(http://en.wikipedia.org/wiki/Phylum)

Identification of Organisms

- Comparison of sequences with databases
  - Genboree Microbiome Toolset
  - National Center for Biotechnology Information (NCBI)/Genbank
  - EMBL Nucleotide Sequence Database
  - GreenGenes -Lawrence Berkeley National Lab
  - Ribosomal Database Project (RDP)
- Uncultured/uncharacterized
  - OTU approach – based on sequence similarity (97% threshold)
  - Bayesian – uses curated database and probability models

The Microbiome in Irritable Bowel Syndrome

Robert J. Shulman MD, Texas Children's Hospital

Board Style questions

1. The factor that appears to have the largest effect on the composition of the gut microbiome over the long term in healthy individuals is:
    a. Maternal genetics
    b. Geography
    c. Vaginal vs cesarian birth
    d. Diet
    e. Antibiotic usage

2. The probiotic that to date has the most evidence of efficacy in treating irritable bowel syndrome in children is:
    a. Lactobacillus rhamnosus GG
    b. Bifidobacterium infantis 35624
    c. VSL#3
    d. Lactobacillus acidophilus
    e. Saccharomyces boulardii

3. All of the following are FODMAPs EXCEPT:
    a. Sorbitol
    b. Fructose
    c. Mannitol
    d. Lactose
    e. Sucrose

Answer Key

1. D
2. A
3. E

The sore bottom: perianal IBD

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NASPGHAN Postgraduate Course 2012

SickKids NASPGHAN UNIVERSITY of TORONTO

I have the following financial relationships to disclose:

*Janssen Canada: consultant; speaker; IBD program support
*Merck: speaker; consultant
*Abbott Canada and Abbott International: speaker; consultant; research support; IBD program support
*Johnson and Johnson: consultant

** Products or services produced by this these companies are relevant to my presentation.*

+Nestle: consultant
+Shire: consultant
+Pfizer: consultant

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

NASPGHAN

Lecture outline based on assigned objectives

- Definitions and epidemiologic data
- Methods of assessment
- Evidence of efficacy of medical treatments
- Need for combined medical/surgical management

Perianal lesions observed in children with Crohn disease

- Skin tags
- Fissures
- Ulcers
- Anal strictures
- **Abscesses**
- **Anoperineal fistula(e)**
- Anovaginal and rectovaginal fistula(e)

Prevalence in children with Crohn disease

- Skin tags: 22%
- Fissures: 31%
- **Abscesses: 8 %**
- **Perineal fistula(e): 9%**

Retrospective review of single-center experience with 325 children with CD

Palder SB, Shandling B et al. J Pediatr Surg, 1991

Some clinical pearls

- Perianal skin tags:
  - are not hemorrhoids!
  - should not be removed
- Perianal abscesses:
  - are painful!
  - draining perianal fistulae are not
- Beware anal strictures

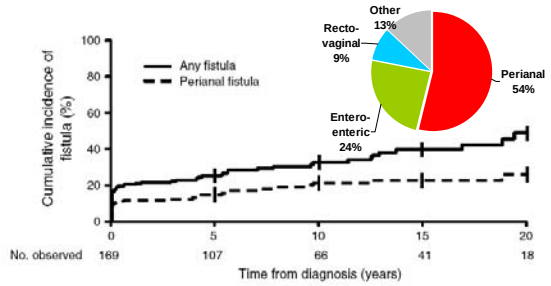
Paris Classification of Pediatric IBD

Crohn Disease

Location	Behavior	Modifiers
L1 - Terminal Ileum	B1 – Inflammatory	L4a, L4b and L4ab – upper gastrointestinal
L2 – Colon	B2 – Stricturing	**P – Perianal (fistulae)**
L3 – Ileocolon	B3 – Penetrating	**Growth**
	B2B3	G0, G1

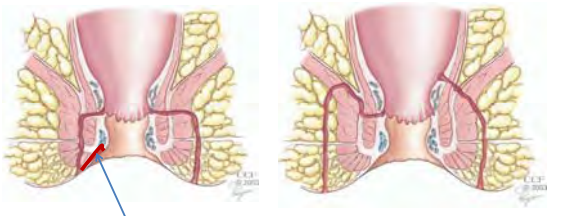
Levine A et al, Inflamm Bowel Dis 2011; 17(6):1314-21

Prevalence of fistulizing CD over time



Schwartz et al Gastroenterology 2000.

Park's Classification of anoperineal fistulae based on relation to anal sphincters

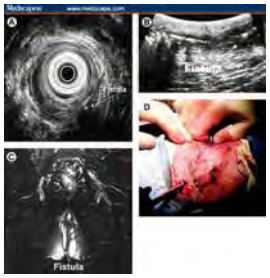


Intersphincteric | Transsphincteric | Suprasphincteric | Extrasphincteric

Superficial: below internal and external sphincters

Diagnosis: comparison of rectal EUS, pelvic MRI, and EUA

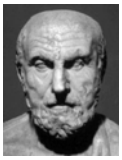
- Prospective, triple blind study
- N=34 adults with CD
- Gold standard: consensus agreement after all tests
- EUS 91%, MRI 87%, EUA 91%.
- 100% with any combination



Schwartz DA, et al. Gastroenterology 2001

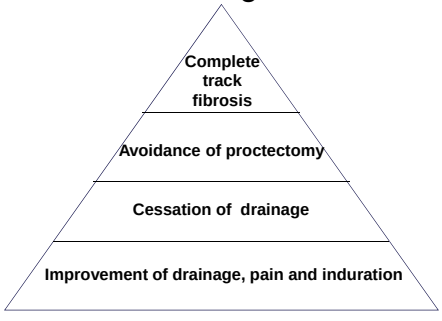
Wherever there is pus, drain it

Use MRI perineum to exclude abscess

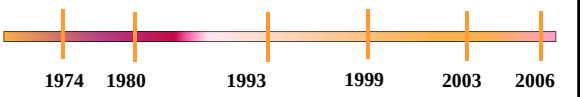


(Hippocrates of Kos, Aphorisms 400 BC)

Treatment goals in perianal fistulizing CD



Medical treatments for fistulizing CD Levels of evidence: response (not fistula closure) as primary endpoint



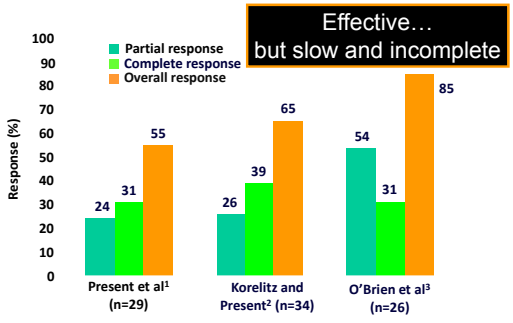
1974	1980	1993	1999	2003	2006
Antibiotics	AZA/6-MP	cyclosporine	infliximab	tacrolimus	adalimumab
IIb, Gr C non-controlled	Ib, Gr B secondary outcomes in RCT's	IIb, Gr C Non-controlled	Ib, Gr A RCT Induction and maintenance	Ib, Gr A RCT	Ib, Gr B secondary outcomes

LEVELS OF EVIDENCE

Medical Treatments: Summary

- Antibiotics: observational data (small series) concerning metronidazole and ciprofloxacin
- Immunemodulators:
  - Thiopurines: randomized controlled trials (and observational studies) in fistulizing disease have included some perianal fistulae
  - Methotrexate: very limited observational data specifically in fistulizing disease

Fistulizing CD: efficacy of AZA or 6-MP



Mean time to response =3.1 Months
Maximal response =8 Months

1.Present DH et al. *N Engl J Med*. 1980;302:981–987.
2.Korelitz BI, Present DH. *Dig Dis Sci*. 1985;30:58–64.
3.O'Brien JJ, et al. *Gastroenterology*. 1991;101:39–46.

Medical Treatments: Summary

- Calcineurin inhibitors:
  - Cyclosporin: observational studies of fistulizing disease have included some perianal fistulae
  - Tacrolimus: one randomized controlled trial specifically in perianal fistulizing disease
- Anti-TNF therapy: **level I evidence specifically in perianal fistulizing Crohn disease**

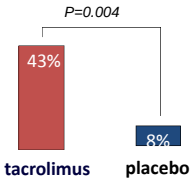
Evidence of efficacy in clinical trials

Randomized controlled trials examine fistula "response"

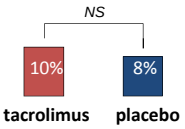
No RCT was ever performed with fistula closure as its primary outcome

Tacrolimus in fistulizing Crohn Disease

Fistula response



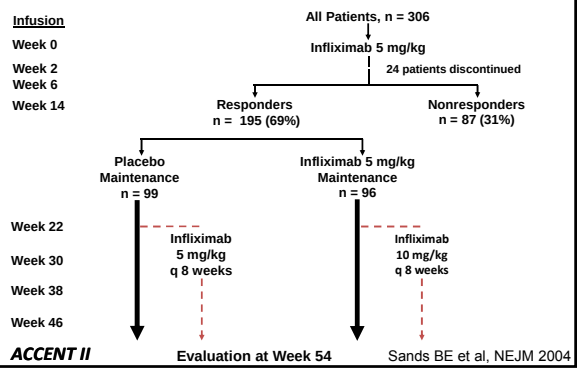
Fistula remission



More side effects in the tacrolimus group: renal function

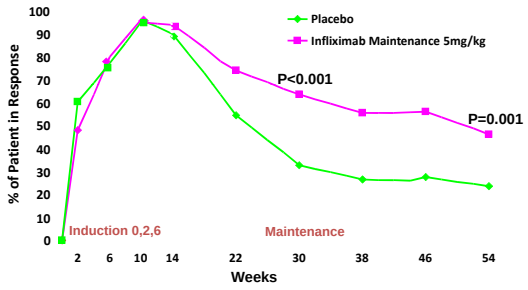
Sandborn et al. 2003

Infliximab in Fistulizing Crohn Disease



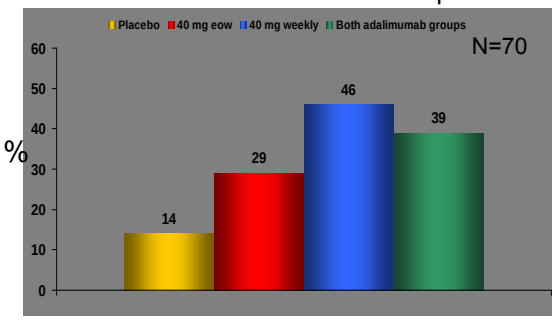
Sands BE et al, NEJM 2004

Patients in Fistula "Response"



Sands et al, NEJM 2004

Secondary data analysis: Adalimumab Complete Healing of Draining Fistulas at Both Wks 26 and 56: Randomized Responders



Schwartz, ACG 2006 (Secondary analysis of CHARM data)

Adjunctive benefit of antibiotics

Infliximab +placebo

vs

Infliximab+ ciprofloxacin

1º outcome: drainage stopped in >50% of fistulas

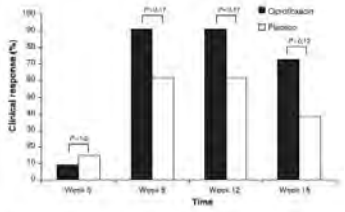
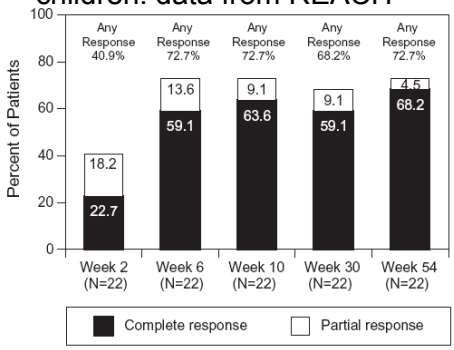


Figure 1. Clinical response at week 6, 8, 12 and 18 in the ciprofloxacin and placebo group.

West et al, Aliment Pharmacol Ther 2004

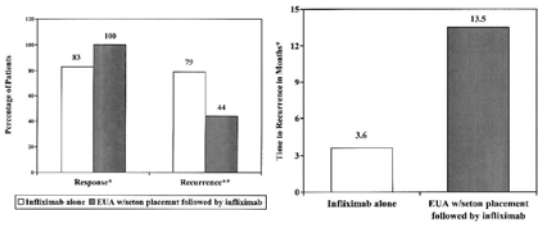
Infliximab for perianal Crohn's disease in children: data from REACH



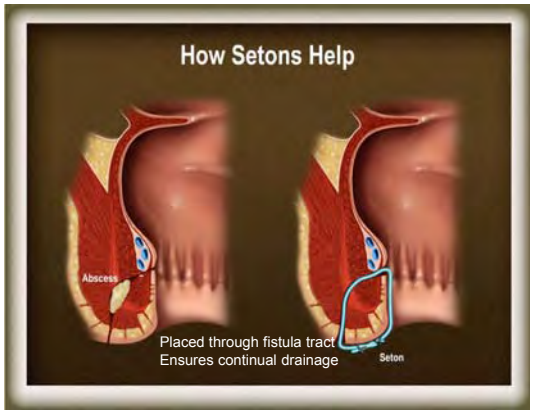
Crandall W et al. J Ped Gastroenterol Nutr 2009

The best outcomes have been achieved when surgical and medical therapies are used in conjunction

EUA + seton placement improves outcomes with infliximab therapy



Regueiro, Inflamm Bowel Dis 2003



Perianal fistulizing Crohn's disease an orchestrated effort…

•ASSESS

- Examination under anesthaesia (EUA)
- MRI
- Assess colonic disease

•TREAT

- Combined surgical and medical approach
- Long term medical strategy

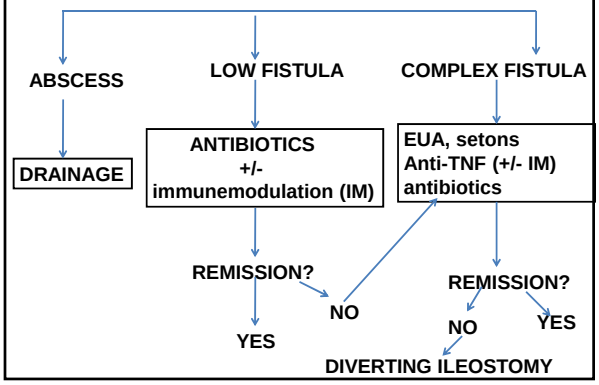
•RE-ASSESS

In conclusion

Take-home messages

- Examine the perianal area as part of IBD follow-up care
- Recognize pathologic perianal skin tags, but never refer for excision
- Severe perianal pain probably means abscess
- Perianal fistulae require careful assessment
- Successful management is challenging: requires medical treatment and surgical consultation

Management of Perianal Fistulae in CD



Future Research

- Pathogenesis: what causes perianal disease to develop?
- Better understanding of evolution of fistulae now identified “pre-clinically” on MRI
- More effective treatments

THE SORE BOTTOM: PERIANAL INFLAMMATORY BOWEL DISEASE

Anne Griffiths MD, The Hospital for Sick Children

Board Style questions

1. Severe perianal pain in a child with Crohn's disease is an indication of:

A. A draining transphincteric perianal fistula
B. Development of an anal stricture
C. A perianal abscess
D. Any of the above

2. Which of the following statements concerning perianal skin tags is true?

A. They are commonly mistaken for external hemorrhoids.
B. They are rarely painful even when large and swollen.
C. Excision should be undertaken only by an experienced colorectal surgeon.
D. All of the above

3. Which of the following statements concerning the medical treatment of perianal fistulizing disease is true?

A. Metronidazole and ciprofloxacin are the only antibiotics studied in a randomized placebo-controlled trial of efficacy specifically in perianal fistulizing Crohn's disease.
B. Ciprofloxacin has been shown in a randomized placebo-controlled trial to be of adjunctive benefit when combined with infliximab in the treatment of perianal fistulizing Crohn's disease.
C. In the ACCENT II trial, 3 dose induction with infliximab (5 mg/kg/dose) achieved closure of perianal fistulae in over 80% patients at week 10.
D. Although sometimes used empirically, the efficacy of calcineurin inhibitors has not been studied in a randomized controlled trial.

4. Which of the following statements concerning the management of new onset painful perianal fistulizing disease is true?

A. MRI of perineum is helpful in assessing anatomy and planning surgical strategy.
B. Optimal first-line management includes antibiotics, EUA with surgical drainage of abscess, seton placement followed by infliximab induction and maintenance therapy.
C. The goal of a seton is to plug the fistula tract so that drainage does not occur.
D. A and B
E. All of the above.

Answers with explanations

Question One

Correct answer is C (perianal abscess). The other lesions tend not to be painful. Pain implies collection of pus in a closed space

Question Two

Correct answer is A. Perianal skin tags are often mistaken for hemorrhoids. B is incorrect: when tags are inflamed and swollen, they can be painful. C is incorrect: they should never be excised, as the result is a non-healing wound.

Question Three

Correct answer is B. The other answers have erroneous information in them. Metronidazole is used in management, but evidence comes from open trials, not RCT's. The ACCENT II study reported fistula "response" as >80% at week 10 (not fistula closure). There has been a small RCT of tacrolimus versus placebo.

Question Four

Correct answer is A and B. Essentially the most important message of the talk: perianal fistulizing disease, when painful, is very difficult to treat and requires collaboration of surgeons with optimization of medical treatment.

Rescue me from my IBD: optimizing Crohn's therapy, and rescuing nonresponders

Athos Bousvaros MD, MPH

October 2012

I have the following financial relationships to disclose

- UCB – subinvestigator, clinical trial*
- Merck – honorarium, research support*
- Millennium – consultant
- Dyax – advisory board
- Prometheus – investigator, clinical study

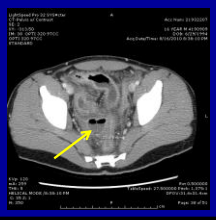
*Products or services by these companies may be relevant to my presentation

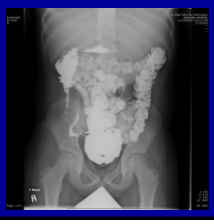
Overview of talk

- Goals and principles of therapy
- Crohn's disease
  - Seminal pediatric IBD studies
  - Loss of response to anti-TNF
  - (UC to be discussed in learning lunch)
- Rescue therapies
  - Natalizumab, thalidomide
- My current practice

Treatment of children with IBD 1

- Aim for clinical remission, not just response
- Don't overuse corticosteroids when immunosuppressants and biologics are needed.
- Don't overuse immunosuppression when surgery is needed
  - Abdominal abscess, ileal stricture





Treatment of children with IBD 2

- Monitor your patient carefully
  - Every 3 month visits
  - Use labs and mucosal healing, not just clinical appearance
  - Monitoring for drug toxicities
  - Monitoring growth parameters and micronutrients
  - Monitoring for postoperative recurrence
- Treat "the whole patient'
  - Monitoring for anxiety or depression
  - Monitor for compliance

Principles of Crohn's treatment

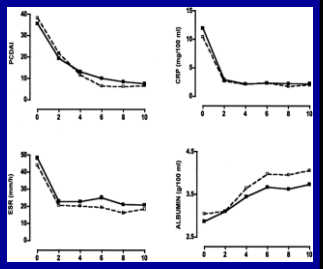
- Accelerated "step up" therapy
  - "top down" in selected high risk patients
- Mucosal healing as a goal
- If biologics started, avoid loss of response
  - Scheduled infusions
  - Premedication with hydrocortisone
  - Combination therapy with immunomodulators

Treatment options for UC and Crohn disease

	Ulcerative colitis	Crohn's disease
Induction	Aminosalicylates Corticosteroids Infliximab Calcineurin inhibitors	Enteral nutrition Corticosteroids Anti-TNF agents
Main-tenance	Aminosalicylates 6MP/azathioprine Infliximab	Aminosalicylates? Antibiotics? 6MP/azathioprine Methotrexate Anti-TNF agents

Enteral nutrition (EN) and corticosteroids are similarly efficacious as induction therapies.

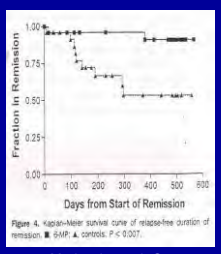
- 10 week randomized open label trial
- 19 received polymeric formula
- 18 corticosteroids
- PCDAI and lab parameters improved in both groups
- Mucosal healing ONLY in EN group



Borrelli et al, Clin Gastro Hep 2006; 4:744

Thiopurine maintenance in Crohn's disease: how good is it ?

- Markowitz 2000
  - Much better than placebo at maintaining remission
- Dubner et al 2009
  - Not as good as we think
  - Minimal benefits on:
    - Growth
    - Lean muscle mass
    - Bone density

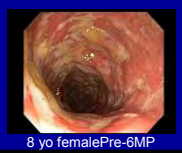


Markowitz et al, Gastro 2000; 119:895-902

Mucosal healing assessment with immunomodulators

Baert Gastro 2010; 138:463

- Followup study from a randomized controlled trial performed in adults
  - Steroids/azathioprine vs. Infliximab/azathioprine
- Endoscopy after 2 years, followed for another 2 years
- Mucosal healing predicted steroid free remission
  - 27% of patients with inflammation in remission
  - 71% of patients with normal mucosa in remission



8 yo femalePre-6MP

2 years after 6MP started

Anti-TNF agents are more effective than immunomodulators in therapy of CD

- Clinical trials of anti-TNFs largely performed in patients who have failed immunomodulators
- SONIC study
  - Clinical remission
  - Mucosal healing
- REACH trial in children

Results of SONIC trial

(508 adults in 92 centers)

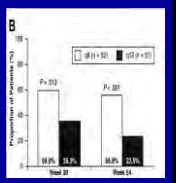
- 26 week results - remission
  - Combination therapy 57%
  - Infliximab alone 44%
  - AZA alone – 30%
- 50 week results – steroid free remission
  - Combination therapy 46%
  - Infliximab alone 35%
  - AZA alone 24%

Questions about SONIC

- Was azathioprine “disadvantaged” ?
  - Is remission really 30% on 6MP?
  - Levels not used to optimize therapy
  - TPMT intermediate patients not included
- Antibodies to infliximab – week 30
  - 0.9% (1/116) combination therapy
  - 14.6% (15/103) infliximab alone

Infliximab in pediatric Crohn’s (REACH trial)

- Children with active CD
  - Infliximab 5mg/kg
    - 0,2, 6 weeks then q 2 months
    - 88% response rate after 3 infusions
    - 56% remission rate after 12 months
- However:
  - Concomitant immunomodulators used for duration of study
- REACH describes efficacy of combination therapy



Hyams et al Gastro 2007;132:863

Combination therapy (AZA/infliximab) in selected new-onset CD patients

- Extensive disease (especially mid-small bowel disease)
- Severe rectal or perianal disease
- Steroid-unresponsive disease
- Growth failure in mid to late puberty

Why not just use anti-TNF on every child with moderate to severe CD?

- Some patients enter clinical remission with immunomodulators
  - "How good is "clinical remission"?
- Cost
- Infection
- Lymphoma
- Loss of response

Loss of response – natural history

(Oussalah et al; AJGastro 2010,)

- Probability of infliximab failure
  - Increasing dose, shortening interval, surgery, or hypersensitivity
  - 15% at 12 months
  - 41% between 24 and 32 months
  - Withdrawal of AZA strongly associated with infliximab failure
- Increasing dose only works if you don't have antibodies (Afif, Am. J. Gastro 2010)
- Keeping immunomodulator on board is associated with reduced antibody formation
  - Good evidence for AZA/IFX
  - Weaker evidence for MTX/IFX

The therapeutic "pendulum"

2004 – everyone on combination therapy

2008 – everyone on biologic monotherapy

2011 – selected patients on combination therapy

Lymphoma risk in children: 1/2221 patient-years if on a thiopurine (Ashworth IBD Journal 2011)

Treatment of patients who lose response to infliximab

- Increase dose / add in immunomodulator
- Change to another anti TNF antibody
  - Adalimumab
- Utilize a non-antibody TNF inhibitor
  - Thalidomide
- Change medication classes altogether
  - Natalizumab, ustekinumab, calcineurin inhibitors
- Nutrition
- Surgery

Adalimumab in pediatric CD

(Hyams et al, Gastro 2012; 143:365-74)

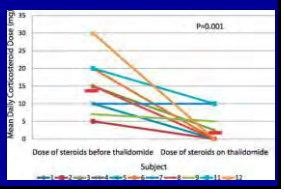
- 192 CD patients with active PCDAI (>30)
  - Approximately 60% on 'immunosuppressants"
  - Standard induction, then hi vs. low dose
- Results (clinical remission, high dose)
  - Week 26
    - 57% infliximab naïve, **17% if prior infliximab**
  - Week 52
    - 45% infliximab naïve, **19% if prior infliximab**

Infection rate about 5%, no lymphomas

Thalidomide for refractory CD

(Felipez et al 2012;JPGN 54:28-33)

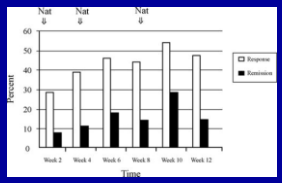
- 12 children, refractory to thiopurines and infliximab (between 3 and 21 infusions)
- Dosage 50-150 mg
- Takes 2-3 months to work



Natalizumab for pediatric CD

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

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



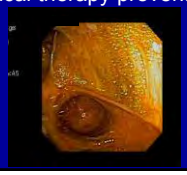
Surgery still important

Indications - stricture, abscess, fistula

Take out the worst, treat rest medically

Patient undergoing small bowel or colonic resection has 50% recurrence risk in 5 years

- Survey the anastomosis 9-12 months out
- Medical therapy prevents postop recurrence



Summary and current approach for treating moderate to severe CD

- Corticosteroid induction followed by an immunomodulator
  - 6-mercaptopurine or azathioprine usually
  - Methotrexate on occasion
  - Adjunct 5 ASA, antibiotics
- Consider follow-up assessment for mucosal healing at 6-12 months
- If not in complete remission in 6 months, I will recommend a biologic (infliximab)
  - Encourage continuing combination therapy

Summary and current approach

- I change from azathioprine or 6MP to low dose oral methotrexate after 6 months of dual therapy.
- If secondary loss of response:
  - Consider increasing dose or decreasing interval of infliximab
  - Consider adding azathioprine back
  - Change to a second anti-TNF agent (adalimumab)
- If fails second anti-TNF, change classes
  - Natalizumab
  - Thalidomide

Future research

- Efficacy of methotrexate as initial maintenance therapy in CD
- More data on antibodies to anti-TNF agents in children, and how they impact clinical response
- Can antibody formation and loss of response be reverse by adding immunomodulators back in?
- Better identification of high risk patients
- BETTER AND SAFER DRUGS

UPDATES ON IBD THERAPY

Athos Bousvaros MD, MPH, Children's Hospital, Boston

Board Style questions

1. A 16 year old patient with Crohn's of the ileum and colon was initially treated with prednisone, and has been maintained on mesalamine. She continues to have diarrhea, abdominal pain, fatigue, and intermittent rectal bleeding. According to data from the SONIC trial, which of the following medical regimens is most likely to induce remission?

A. Mesalamine and azathioprine

B. Azathioprine monotherapy

C. Infliximab monotherapy

D. Infliximab and Azathioprine

E. Infliximab and methotrexate

Correct answer: D

2. A 12 year old male with Crohn disease has been maintained on combination infliximab and azathioprine at a dose of 5 mg/kg every 2 months for the past 6 months. The family is concerned about the lymphoma risk in patients on combination therapy. You discuss the option of discontinuing azathioprine. Of the following, which is a TRUE statement about discontinuing azathioprine, and continuing with infliximab monotherapy?

A. Azathioprine discontinuation reduces the of mycobacterial infections

B. Azathioprine discontinuation increases the risk of antibodies to infliximab

C. Azathioprine discontinuation will result in higher likelihood of remission

D. Azathoprine is NOT associated with an increased risk of lymphoma

E. Azathioprine is ineffective as monotherapy for the treatment of Crohn disease

Answer: B

3. A 13 year old female with Crohn disease of the colon has maintained on mesalamine and mercaptopurine for 2 years. According to the family, she takes her medication regularly, and her last 6-thioguanine level was in the therapeutic range. She continues to have diarrhea, with 3-4 nonbloody BM per day. She is active, athletic, and has a normal physical examination. Laboratory studies demonstrate a hematocrit of 35%, esr of 22mm/hour, and albumin of 3.8 mg/dL. The family asks whether additional evaluation or treatment is necessary. Stool cultures, including C. difficile are negative.

Of the following, which is the most appropriate intervention:

A. Add infliximab

B. Change to methotrexate

C. Hospitalize for observation

D. Repeat colonoscopy

E. 72 hour fecal fat

Correct answer: D

MODULE D: IMAGING AND ACCESSING THE TUBES
Moderators: Sandeep Gupta MD and Marsha Kay MD

LOOKING DEEPLY INTO THE NOT SO SMALL INTESTINE
Victor Fox MD, Children's Hospital Boston

Learning objectives:

1. Understand the various modalities for intestinal visualization: push enteroscopy, SBE, DBE, spiral enteroscopy, and capsule endoscopy
2. Recognize the complimentary roles of capsule endoscopy and deep enteroscopy
3. Know new and emerging techniques including narrow-band imaging and confocal laser endomicroscopy

PUTTING TUBES WITHIN TUBES: ENTERAL THERAPEUTIC ACCESS
Robert Kramer MD, The Children's Hospital Colorado

Learning objectives:

1. Learn the various types of enteral access including G, GJ, J, and cecal tubes/buttons
2. Recognize the indications and appropriate usage for various access options
3. Know proper placement and care techniques to minimize complications

IMAGING THE PANCREATO-BILIARY TREE
Douglas Fishman MD, Texas Children's Hospital

Learning objectives:

1. Know who, when, and if to image beyond ultrasound
2. Pros/cons of various imaging techniques (MRCP, ERCP, EUS)
3. Describe potential therapeutic interventions with these techniques

UPDATE ON CRITICAL FOREIGN BODY INGESTIONS
Petar Mamula MD, Children's Hospital of Philadelphia

Learning objectives:

1. Be familiar with critical issues with foreign body ingestions
2. Understand evaluation and management of these ingestions
3. Learn about NASPGHAN's efforts highlighting this public health issue

Looking deeply into the not so small intestine

Victor L. Fox, MD
Boston Children's Hospital
Harvard Medical School
NASPGHAN Post-Graduate Course 2012

Photo by Bora Horza from Flickr.com

I have no financial relationships with any commercial entity to disclose

NASPGHAN

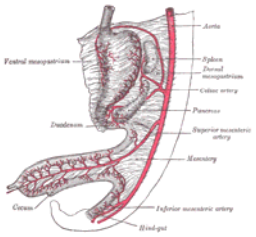
Learning Objectives

- Understand different forms of enteroscopy and their limitations (simple PE, DBE, SBE, spiral, operative, CE)
- Recognize complementary roles of CE and deep enteroscopy
- Learn about new imaging technologies (NBI, CLE)

Anatomy

- Mean length of adult human intestine 550 cm (range 350 – 700 cm)
  - ~450 – 500 cm between ages 5 and 10 years
- Mobility restricted by mesenteric attachments, congenital Ladd's bands, and post- operative adhesions

Weaver et al. Gut 1991;32:1321



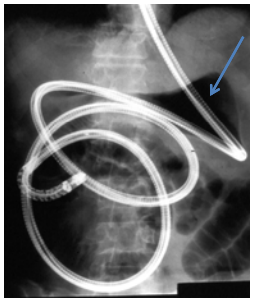
6 week embyro from Grey's Anatomy of the Human Body, 1918

Indications for Enteroscopy

- GI bleeding, inflammatory bowel disease, malabsorption, polyps, biliary obstruction
  - Crohn's disease, eosinophilic enteropathy, lymphoproliferative and GVHD disease
  - Celiac disease, lymphangiectasia, vascular anomalies
  - Polyps, tumors, congenital and acquired strictures
  - Bilary strictures, stones after Roux-en Y anastomosis

Simple Push Enteroscopy

- Slim colonoscope or enteroscope
- Technique
  - alternating advancement and withdrawal of scope
- Limitation
  - gastric loop formation resulting in limited depth of insertion (~100 cm)



From Swain et al. Gut 2004;53:1866

Intra-operative Enteroscopy

- Laparoscopy- and laparotomy-assisted
- Required for infants and young children
- Able to examine and treat entire small bowel
- Limitations
  - Invasive, costly, time-consuming, traumatic artifacts

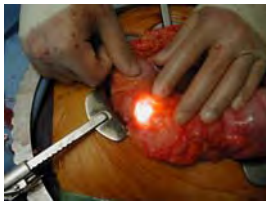


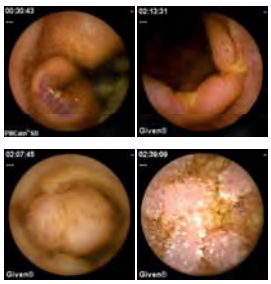
Photo: Courtesy of Steven Fishman, MD

Capsule Endoscopy

- 2001: Given Imaging released the M2A capsule
- "Disruptive technology" radically altered approach to diagnosis of SB disease
- First non-invasive, video endoscopy-quality imaging of entire small bowel

Capsule Endoscopy

- Revealed occult sources of GI bleeding
- Confirmed suspected Crohn's disease
- Found polyps and small tumors
- Mapped enteropathies



Capsule Endoscopy

- Advantages
  - Simple technique, non-invasive, ambulatory, high sensitivity and specificity, low risk, complete SB examination (> 80%)
- Limitations
  - Requires endoscopic placement for young child
  - Risk of retention or impaction (1-2%)
  - No therapeutic capability

SB Capsule Systems

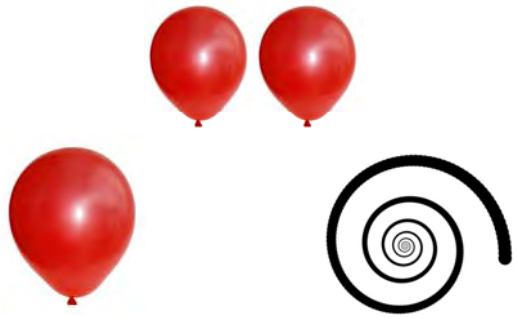
Product	Given SB2	Olympus EndoCapsule	Jinshan OMOM CE	IntroMedic MiroCam
Height	11 mm	11 mm	13 mm	11 mm
Width	26 mm	26 mm	28 mm	24 mm
Weight	3.7 g	3.8 g	≤6 g	3.4 g
Image rate	2/sec	2/sec	2/sec	3/sec
Depth of field	0-30 mm	0-20 mm	0-35 mm	0-35 mm
Field of view	156^0	145^0	140^0	150^0
Chip design	CMOS	CCD	CMOS	CMOS
Brightness control	Automatic	Automatic	Automatic	Automatic
Real-time viewing	Yes	Yes	Yes	Yes
Imaging duration	8 hr	8 hr	8 hr	11 hr

Pediatric Capsule Endoscopy

- >1,000 children studied worldwide
- Most common pediatric indication is evaluation of IBD followed by GI bleeding
- % yield of findings highly dependent on patient selection
- Cohen and Klevens 2011: meta-analysis of 740 CEs in 723 pts.
  - Overall yield = 65.4% where 54% performed for indication of suspected (34%) or known (16%) CD. Completion and retention rates were 86.2% and 2.6%. Rates of new Dx or change in Rx were 69.4% and 68.3%.

Cohen and Klevens. Clin Gastroenterol Hepatol 2011;9:490-6

Deep Overtube-assisted Enteroscopy



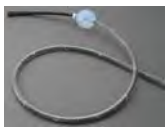
Deep Enteroscopy

- FDA approved first system, DBE (Fujinon) in 2004, SBE (Olympus) in 2007, and spiral device (Spirus) in 2008
- Achieves deep access (>200 cm) by pleating bowel over balloon-tipped or spiral overtube device
- Total SB examination feasible by antegrade and retrograde approach
- Depth limited by patient size, adhesions

Balloon Enteroscopy

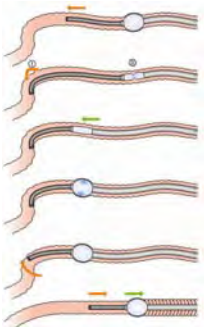
Fujinon: Double balloon enteroscope system

Olympus: Single balloon enteroscope system



(Images from Fujinon and Olympus)

Balloon Enteroscopy Technique



Insert scope deeply

Angulate scope tip and deflate balloon

Advance overtube

Inflate balloon

Release angulation

Pull back overtube and scope

Figure from Olympus

Overtube Specifications

	Fujinon		Olympus
Model No.	TS-13140	TS-12140	ST-SB1
Outer diameter	13.2 mm	12.2 mm	13.2 mm
Inner diameter	10.8 mm	10.8 mm	10 mm
Balloon diameter	40 mm	40 mm	40 mm
Working length	1350 mm	1350 mm	1320 mm
Total length	1450 mm	1450 mm	1400 mm
Balloon material	Latex	Latex	Silicone
Tube material	Polyurethane	Polyurethane	Silicone
Hydrophilic coating	yes	yes	yes
Balloon set pressure	5.6 kPa ± 2.0		5.4 kPa ± 2.6

Balloon Enteroscopy

- Advantages
  - Simultaneous diagnostic and therapeutic access to majority of small bowel
  - Antegrade and retrograde approach
- Limitations
  - Requires deep sedation or general anesthesia
  - Time intensive (60-90 min)
  - Limited to older children and adults
  - Usually incomplete SB examination

Spiral Enteroscopy (SE)

- Endo-Ease Discovery SB overtube*
  - 18.5 mm OD
- Enteroscope (SIF Q180 or EN 450T5)
- Patients = 75
- Mean depth beyond Treitz = 250 cm (50 – 400)
- Mean insertion time = 18 min (7 – 50)

Ackerman et al. Endoscopy 2008; 40:974-8

*Spirus Medical, Stoughton, MA

Spiral Enteroscopy

- Advantages
  - Simplicity of equipment and technique
  - Short duration of examination
- Limitations
  - Large diameter of overtube not suitable for most children

Pediatric Enteroscopy Series

Author	Year	Type	No. Pt	Age (range)	% Yield	Indications
Shen	2012	DBE	30	13 (6-17)	97	GIB 22, pain 4, diarrh 3, obstruction 1
de Ridder	2012	SBE	20	15 (11.3-18)	60	IBD
Di Nardo	2012	SBE	30	13 (7-18)	87	IBD
Barth	2010	SBE	7	12.8 (5-17)	43	IBD 2, polyps 2, Roux 2, abnl WCE 1
Lin	2010	DBE	11	15 (8-20)	46	GIB 4, polyps 2, pain 2, diarrh 2, abnl WCE 1
Thomson	2010	DBE	14	12.9 (8.1-16.7)	78	GIB 6, polyps 5, pain 2, obstruction 1
Nishimura	2010	DBE	48	12.2 (4-18)	65	Roux 23, GIB 10, polyps 5, pain 4, IBD 3, other 3

Complementary Roles of CE and Deep Enteroscopy

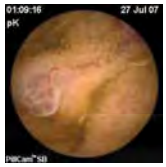
- CE performed to detect and localize lesions
- Proximal location suggests antegrade per-oral approach
- Distal location suggests retrograde, per-anal approach
- Multiple lesions, indeterminate location may require combined antegrade and retrograde or surgically-assisted approach

Case Example

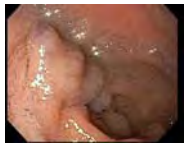
- 8 yr, 25 kg female with intermittent profound iron-deficiency anemia for 5 yrs, admitted for PRBC transfusion
- Prior negative examinations
  - EGD x 2, ileocolonoscopy, Meckel's scan

Case Example

CE positive for polypoid non-bleeding vascular lesion in mid-SB



Antegrade SBE used to successfully treat two jejunal lesions with injection sclerotherapy

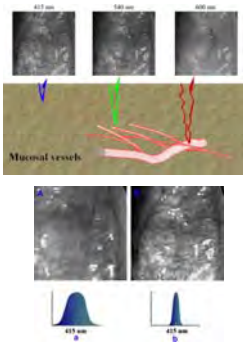


New Technologies

Robert Leighton, The New Yorker, Aug 13 & 20, 2012

Narrow Band Imaging

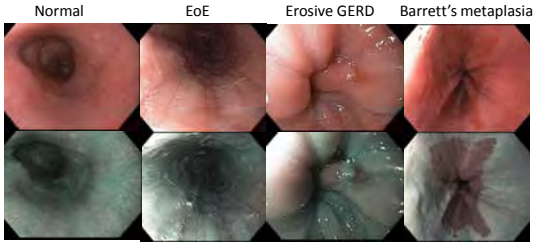
- Virtual chromoendoscopy technique
  - Narrowed bandwith blue-green light spectrum (415 nm and 540 nm) to enhance details of vascular and mucosal architecture
- Blue-green light is highly absorbed by hemoglobin (dark image)
- Narrow bandwidth increases contrast and resolution



Gono et al, Opt Rev 2003;10:1-5
Yao et al., GIE Clin N Am 2008, 18:415-33

NBI of Esophagus

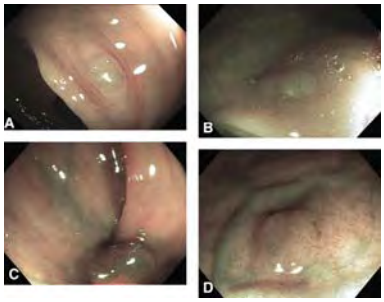
Normal EoE Erosive GERD Barrett's metaplasia



NBI of Colon Polyps

hyperplastic

adenoma



From Rastogi et al. Gastrointest Endosc 2011;74:593-602

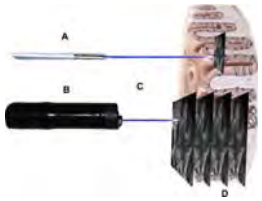
Clinical Impact of NBI

- Colon polyps
  - Rastogi et al 2011 found NBI had superior sensitivity (90%) and accuracy (82%) to predict adenoma histology
    - compared with SD-WL (52% and 69%) and HD-WL (67% and 73%)
    - 6 endoscopists, 630 subjects, prospective randomized trial
  - Nagorni et al 2012 found no significant difference between HD WLE and NBI for detection of colon adenomas or any polyps
    - 8 randomized trials with 3673 participants

Nagorni et al. Cochrane Database Syst Rev 2012;1:CD008361

Confocal Laser Endomicroscopy (CLE)

- Low power laser focused on defined field
- Same lens illuminates and detects in same focal plane = "confocal"
- Grey scale images constructed
- Endoscope and probe-based systems
- Live imaging at cellular level
  - 0.7 to 15 micrometer resolution
- Requires fluorophores
  - Fluorescein and acriflavine



Kiesslich, GIE Clin N Am, 2009;19:261-72

CLE Images

pCLE

eCLE

Normal duodenum

Celiac disease

Wallace et al. Endoscopy 2011;43:882-91

Venkatesh et al. JPGN 2010;51:274-9

Take Home Points

- Complete SB endoscopy is feasible in any child
- Start with non-invasive imaging (capsule or radiography)
- Choose invasive approach (simple push, operative, balloon) based on patient size, lesion location, and intended therapy
- New contrast and magnification technologies (NBI and CLE) offer potential application in pediatric practice but clinical benefit remains unproven

LOOKING DEEPLY INTO THE NOT SO SMALL INTESTINE

Victor Fox, MD, Children's Hospital, Boston

Board-style Questions

Question 1

The average length of the adult human intestine is which of the following?

A) 330 cm
B) 550 cm
C) 920 cm

Question 2

The small intestine may be examined by several different endoscopic techniques. Which of the following statements is incorrect?

A) Single-balloon enteroscopy and double-balloon enteroscopy are equivalent in their percentage yield of detecting small bowel lesions.
B) Simple per-oral push enteroscopy is generally limited to examination of the first 100 cm or less beyond the ligament of Treitz.
C) Pancreatitis is a rare complication of balloon overtube-assisted enteroscopy.
D) Capsule endoscopy offers both excellent sensitivity and excellent localization of detected lesions in the small bowel.

Question 3

An 8-year-old male with suspected Peutz-Jeghers syndrome is being seen for his first outpatient consultation and mentions intermittent cramping abdominal pain without vomiting or change in bowel pattern. Multiple small brown macules are seen along the vermillion border of the lips and a few are seen on the buccal mucosa of the mouth. His physical exam is otherwise normal.

Your next test should be which of the following:

A) Analysis of DNA for a mutation in the STK11 gene
B) Testicular ultrasound
C) MRI-enterography
D) Laparoscopy-assisted pan-enteroscopy
E) Balloon overtube-assisted enteroscopy
F) Capsule endoscopy

Question 4

Narrow band imaging and confocal laser endomicroscopy are two new endoscopic imaging technologies. Which of the following statement(s) is/are correct?

A) Narrow band imaging utilizes a narrow bandwidth of filtered light in the blue-green spectrum to make blood vessels appear bright against a darkened mucosal background.
B) Confocal laser endomicroscopy produces continuous real-time, color images at ~1,000 fold magnification.
C) Narrow band imaging improves the detection of colon polyps during screening colonoscopy and can distinguish adenoma from hyperplasia based on different surface patterns.
D) Confocal laser endomicroscopy requires the use of systemically injected fluorescein.
E) All of the above

Answer Key

Question 1
B
Explanation: The length of the adult small intestine ranges from 350 to 700 cm with a mean of 550 cm.

Question 2
D
Explanation: Capsule endoscopy offers excellent sensitivity but less reliable localization than contrast radiography or MRI enterography for detected small bowel lesions.

Question 3
F
Explanation: Although other causes should be considered, intermittent small bowel intussusception due to polyps is the most likely cause of intermittent cramping pain in this PJS patient. Both MRI enterography and capsule endoscopy would be helpful to confirm the presence and location of polyps but an 8 year old child would require anesthesia for this long duration MRI. Since large volume fluid ingestion is required just prior to MR enterography, anesthesia is not an option. Therefore, capsule endoscopy should be the next test. A prior patency capsule might be considered but is not offered as a choice here. The size and suspected location of detected polyps would guide decisions about enteroscopy and possible surgery.

Question 4
D
Explanation: NBI makes vessels appear dark against a bright background. CLE produces gray scale, not color, images. NBI has not been shown to improve the rate of polyp detection compared with conventional white light endoscopy.

Enteral Therapeutic Access:

"Putting tubes within tubes"

Robert E. Kramer, MD
Associate Professor of Pediatrics
Director of Endoscopy
Digestive Health Institute
Children's Hospital Colorado
University of Colorado

Disclosure

I have no financial relationships with any commercial entity to disclose

Objectives

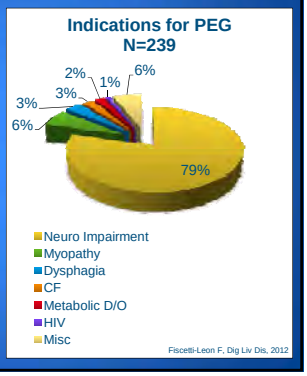
- Learn the various types of enteral access including G, GJ, J and ceccal tubes/buttons
- Recognize the indications and appropriate usage for various access options
- Know proper placement and care techniques to minimize complications

Background

- Wide variety of indications for enteral tube placement in children
- Determination of most appropriate device for is dependent on
  - Indication
  - Anticipated duration
  - Need for fundoplication
  - Current feeding device
  - Anatomic considerations

Feeding Tube Indications

- Developmental Feeding problems
- Allergy
- Inflammatory conditions
- Surgery
- Motility Disorders
- HIV/AIDS
- Short Bowel
- Aspiration/ Lung disease
- Chronic disease c FTT
- Pancreatitis



Timing

- No definitive guidelines for transition to more durable feeding device
- More than 8 weeks with NGT?
- Very difficult process for parents
- Most parents of developmentally delayed children very happy following procedure (91%)
  - Earlier placement (< 18 mos) associated with improved growth parameters
- 85% of parents report improved QOL and decreased stress

Feeding Tube Options

- Nasoenteral
  - NGT
  - NJT
- Gastrostomy
  - PEG/endoscopic
  - Surgical
  - Radiologic
- Transpyloric/ Gastrojejunostomy
  - Initial placement
  - Conversion from existing gastrostomy
- Enterostomy
  - PEJ
  - Surgical jejunostomy
  - cecostomy







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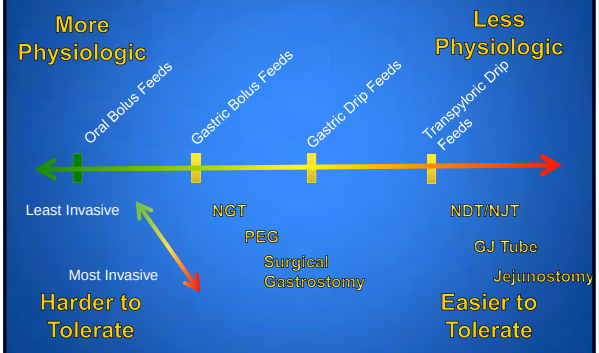
Feeding Spectrum



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Nasogastric/Nasojejunal

Pros

- Easy, most temporary
- Typically placed under fluoroscopic guidance
  - Endo placement for difficult anatomy or when diagnostic endoscopy needed
- Easily removed
- May use as trial

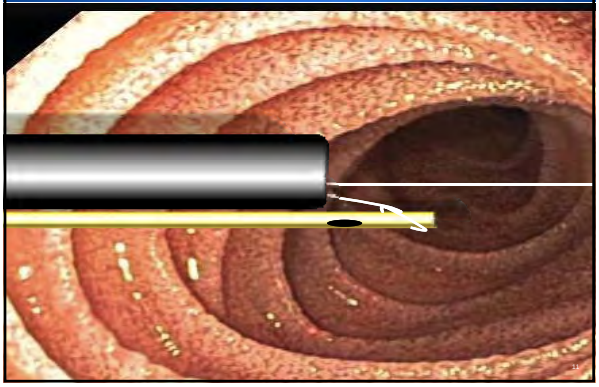
Cons

- Invasive to replace
  - Uncomfortable
  - Easily removed
  - Easily displaced by vomiting
- Long term Complications
  - Sinusitis
  - Esophageal/gastric erosions
  - Fatal hemorrhage from aorto-esophageal fistulae

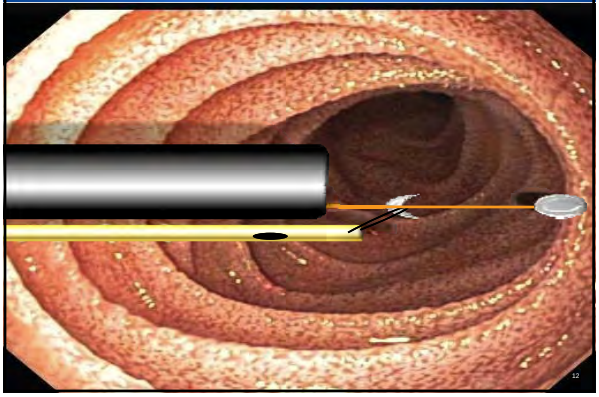
Methods: NDT Placement

- Primarily placed by Radiology under fluoroscopy
- Endo placement due to pt size or altered anatomy
- Generally use “drag method”
- Pitfall of drag method is removal of scope from duodenum without displacement of tube
  - Polyp snare vs clip method
  - Clip method: create suture loop at tip
    - Caution: loop tangling with clip

Polyp-Snare Method of NDT Placement



Endoclip Method of NDT Placement



PEG vs Surgical Gastrostomy

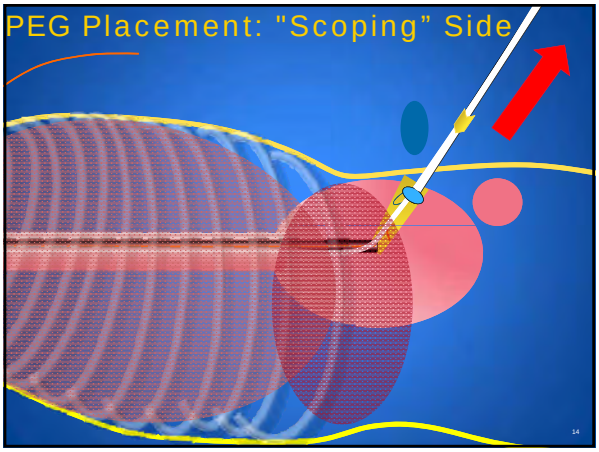
Pros

- Placed by GI
- Avoids surgical incision
- Shorter recovery time (d/c within 1-2 days)
- Less invasive, better tolerated by critically ill pts
- Able to use later that day
- Decreased medical costs
- Complication rate comparable to surgical method (19% vs 11%)

Cons

- Risk of perforation (2-3%)
- No antireflux protection
  - Most Neurologically impaired children, even with significant reflux, do well even w/o Nissen
- May increase risk of reflux
- Long tube, needs to be converted to button device
- Contraindicated if altered anatomy
  - severe scoliosis
  - malrotation
  - ? Prior abdominal surgery

PEG Placement: "Scoping" Side



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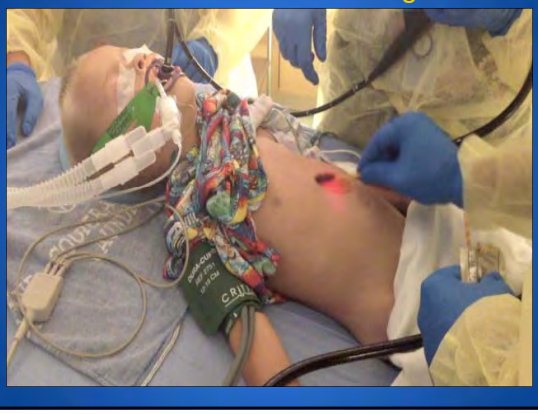
PEG Placement: "Poking" Side



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Post-PEG Care

- Cefazolin 20 mg/kg IV intraop, 6 hrs postop
- NPO x 4-6 hrs, then Pedialyte 60 cc bolus
- Can take bath after 7 days
  - May swim after 2 weeks
- Clean and rotate tube 180° 1-2 times per day
- Flush tube with 15 ml of water after each use
  - May try Club soda if clogged
- May still have “tummy time”, foam donut if irritated
- Change to button 8-12 weeks after PEG placement
  - Pull method versus endoscopic
  - Inadvertent removal before 6 weeks, confirm placement with film
- Granulation tissue: triamcinalone 0.5%, silver nitrate

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Gastrostomy Tube Types


MIC-Key Button


BARD Skin Level


Corpak Corflo Cubby


AMT Mini One


Kendall NutriPort

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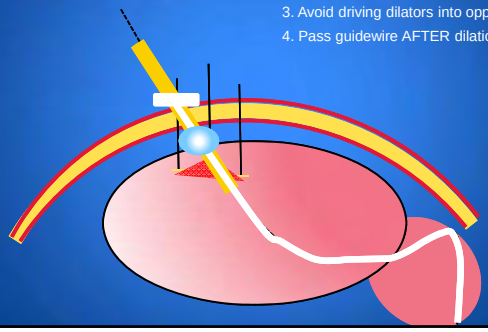
Gastrojejunostomy

- Conversion from GT can usually be done by Radiology (wt >10 kg)
- Endoscopically, easiest to pass scope through stoma (XP180, 5.6 mm, 16 Fr) and thread wire through scope and then tube over wire.
- Must choose appropriate length GJ. Too long and tube tends to loop in stomach from back-pressure.
- Angle scope toward pylorus
- Use Murray-lube and stiff guidewire
- Schedule replacement every 3 months by Radiology
  - Easier than starting from scratch if becomes dislodged

Initial Percutaneous GJ Placement

1. Stay sutures to anchor stomach
2. Angle insertion toward pylorus
3. Avoid driving dilators into opposing wal
4. Pass guidewire AFTER dilation



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Jejunostomy

- Indications: Direct access to small bowel, repeated loss of GJ placement
- Methods: PEJ vs Surgical
- Consider PEJ:
  - Smaller children (< 20 kg) when balloon may obstruct lumen
  - When more invasive surgery difficult to tolerate
  - History of multiple GI surgeries
- Technique:
  - Same premise as PEG, but anatomy not as defined
  - May do hybrid Lap-assisted PEJ with surgeon
- Published literature: Small series of 5 patients, with 2 minor complications

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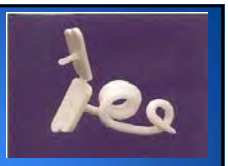
Cecostomy



- Indications: severe constipation, refractory to medical therapy
  - Anorectal malformation, Hirschsprung's, CP, idiopathic, spina bifida
- Methods: Surgical, percutaneous non-endoscopic, endoscopic (PEC), laparoscopic assisted (LAPEC)
- Technique
  - Similar to PEG technique
  - With LAPEC use single umbilical port to assist passage of scope and stabilization/visualization of cecum during trochar placement
- Complications: overall 16-30%
  - Chait: 6% site infection, 10% tube failure, 14% tube dislodgement
  - LAPEC: 2% hematoma, 12% fever, 6% dislodgement, 4% skin erosion

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Take-Home Points

- Variety of techniques available for endoscopic placement of enteral devices
- Complicated psychosocial aspects surrounding placement
- Choice of most appropriate device/technique depends on indication, anatomy, anticipated duration and size of patient
- Significant risks for placement, comparable to surgical placement

Future Directions

- Larger, randomized trials needed to compare surgical, endoscopic and radiologic methods for enteral access
- Development of hybrid laparoscopic/endoscopic procedures to minimize invasiveness and costs while maximizing safety
- Application of principles of Natural Orifice Transluminal Endoscopic Surgery (NOTES) to process of enteral device placement

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PUTTING TUBES WITHIN TUBES: ENTERAL THERAPEUTIC ACCESS

Robert E. Kramer, MD Children's Hospital Colorado/ University of Colorado

Board Style questions

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- Allergy
- Inflammatory conditions
- Surgery
- Motility Disorders
- HIV/AIDS
- Short Bowel
- Aspiration/ Lung disease
- Chronic disease c FTT
- Pancreatitis

Timing

- No definitive guidelines for transition to more durable feeding device
- More than 8 weeks with NGT?
- Very difficult process for parents
- Most parents of developmentally delayed children very happy following procedure (91%)
    - Earlier placement (< 18 mos) associated with improved growth parameters
- 85% of parents report improved QOL and decreased stress

- 87% recognized that they would have accepted an earlier placement of the GT had they anticipated the outcome
- Family dynamics improved considerably after placement as well
- Height improved significantly 6 months post-implantation (P = 0.045) and body mass index improved after 12 months (P = 0.041).

    When comparing nutritional outcome between children in whom the GT was placed before 18 months of age and those in whom it was placed later, height was found to improve significantly in the first group (P = 0.04).

Feeding Tube Options

- Nasoenteral
    - NGT
    - NJT
- Gastrostomy
    - PEG/endoscopic
    - Surgical
    - Radiologic
- Transpyloric/ Gastrojejunostomy
    - Initial placement
    - Conversion from existing gastrostomy
- Enterostomy
    - PEJ
    - Surgical jejunostomy
    - cecostomy

Feeding Spectrum

- PO bolus feeds: most physiologic, most difficult to tolerate
- Transpyloric Drip Feeds: least physiologic, least difficult to tolerate
- Must decide how much support and for how long a given patient needs it to determine most appropriate tube type

Nasogastric/Nasojejunal

- <u>Pros</u>
- Easy, most temporary
- Typically placed under fluoroscopic guidance
    - Endo placement for difficult anatomy or when diagnostic endoscopy needed
    - Easily removed
- May use as trial
- <u>Cons</u>
- Invasive to replace
    - Uncomfortable

Easily removed
Easily displaced by vomiting

- Long term Complications
  - Sinusitis
  - Esophageal/gastric erosions
  - Fatal hemorrhage from aorto-esophageal fistulae

Methods: NDT Placement

- Primarily placed by Radiology under fluoroscopy
- Endo placement due to pt size or altered anatomy
- Generally use “drag method”
- Pitfall of drag method is removal of scope from duodenum without displacement of tube
  - Polyp snare vs clip method
  - Clip method: create suture loop at tip
    - Caution: loop tangling with clip
- Polyp-Snare Method of NDT Placement
- Endoclip Method of NDT Placement

PEG vs Surgical Gastrostomy

- <u>Pros</u>
- Placed by GI
- Avoids surgical incision
- Shorter recovery time (d/c within 1-2 days)
- Less invasive, better tolerated by critically ill pts
- Able to use later that day
- Decreased medical costs
- Complication rate comparable to surgical method (19% vs 11%)
- <u>Cons</u>
- Risk of perforation (2-3%)
- No antireflux protection
  - Most Neurologically impaired children, even with significant reflux, do well even w/o Nissen
- May increase risk of reflux
- Long tube, needs to be converted to button device
- Contraindicated if altered anatomy
  - severe scoliosis
  - malrotation
  - ? Prior abdominal surgery

PEG Placement: "Scoping” Side

- Place patient with HOB slightly elevated to pull stomach downwards

- May use transillumination button to help identify best site for tube placement on skin surface
- Need sufficient insufflation of stomach to aid passage of trochar
- Extend polyp snare around trochar as it enters stomach so easier to grasp guidewire as stomach insufflation lost
- Pass scope into stomach to confirm proper positioning after pulling PEG into place

PEG Placement: "Poking" Side

- Identify site on skin surface. May need to angle slightly cephalad
- Inject tract with lidocaine. Apply negative pressure to syringe as advancing through tract to ensure no bubbles before needle visualized entering the stomach by scope.
- Make smooth, transverse skin incision in single stroke with scalpel, about 3-4 mm wider than diameter of tube to be placed
- Ensure that trochar tightly inserted into sheath before passing into stomach, otherwise may buckle edge and not pass through skin incision
-

After wire pulled out with scope, attach to PEG tube by passing through the wire loop at end of PED and then over the retention bumper ("Through the chrome, over the dome")

Pull ends of wires tight to create a small, square knot that will pass easily through the skin incision

Wrap fingers around wire as it is pulled through the incision, using wiggling technique to deliver PEG through the abdominal wall

Apply topical antibiotic and split gauze to site, adjust stabilizer allow slack and not be too tight, cut tube to 10 cm and attach feeding connectors

Post-PEG Care

- Cefazolin 20 mg/kg IV intraop, 6 hrs postop
- NPO x 4-6 hrs, then Pedialyte 60 cc bolus
- Can take bath after 7 days

  May swim after 2 weeks
- Clean and rotate tube 180° 1-2 times per day
- Flush tube with 15 ml of water after each use
  - May try Club soda if clogged
- May still have "tummy time", foam donut if irritated
- Change to button 8-12 weeks after PEG placement

  Pull method versus endoscopic

  Inadvertent removal before 6 weeks, confirm placement with film
- Granulation tissue: triamcinalone 0.5%, silver nitrate

Gastrostomy Tube Types

- MIC-Key button
- BARD Skin Level
- Corpak Corflo Cubby
- AMT Mini One
- Kendall Nutriport

Gastrojejunostomy

- Conversion from GT can usually be done by Radiology (wt >10 kg)
- Endoscopically, easiest to pass scope through stoma (XP180, 5.6 mm, 16 Fr) and thread wire through scope and then tube over wire.
- Must choose appropriate length GJ. Too long and tube tends to loop in stomach from back-pressure.
- Angle scope toward pylorus
- Use Murray-lube and stiff guidewire
- Schedule replacement every 3 months by Radiology
  Easier than starting from scratch if becomes dislodged

Initial Percutaneous GJ Placement

- Similar concept to PEG placement but uses “push” technique rather than pull
- Stay sutures to anchor stomach during serial dilation of tract
- Angle insertion toward pylorus to help avoid looping of GJ within the stomach
- Avoid driving dilators into opposing wall as advancing through tract
- Pass guidewire AFTER dilation to avoid dislodging during dilation process
- Measure stoma length with stoma measuring device to choose the correct size tube
- Pass tube over wire through largest dilator as dilator itself is “peeled away”

Jejunostomy

- Indications: Direct access to small bowel, repeated loss of GJ placement
- Methods: PEJ vs Surgical
- Consider PEJ:
  Smaller children (< 20 kg) when balloon may obstruct lumen
  When more invasive surgery difficult to tolerate
  History of multiple GI surgeries
- Technique:
  Same premise as PEG, but anatomy not as defined
  May do hybrid Lap-assisted PEJ with surgeon
- Published literature: Small series of 5 patients, with 2 minor complications

Cecostomy

- Indications: severe constipation,

refractory to medical therapy
    - Anorectal malformation, Hirschsprung's, CP, idiopathic, spina bifida
- Methods: Surgical, percutaneous non-endoscopic, endoscopic (PEC), laparoscopic assisted (LAPEC)
- Appendicostomy: oldest technique, still often performed
    Advantage: uses appendix as natural conduit into cecum, therefore no artificial device
    Disadvantage: stoma may become stenosed in 11-27%, difficult to access
- PEC Technique
    Similar to PEG technique
    May be difficult to ensure adequate cleanout and progression to cecum in dilated, tortuous colon
    With LAPEC use single umbilical port to assist passage of scope and stabilization/visualization of cecum during trochar placement
- Complications: overall 16-30%
    Chait (Radiologic): 6% site infection, 10% tube failure, 14% tube dislodgement
    LAPEC: 2% hematoma, 12% fever, 6% dislodgement, 4% skin erosion

Take-Home Points

- Variety of techniques available for endoscopic placement of enteral devices
- Complicated psychosocial aspects surrounding placement
- Choice of most appropriate device/technique depends on indication, anatomy, anticipated duration and size of patient
- Significant risks for placement, comparable to surgical placement

Future Directions

- Larger, randomized trials needed to compare surgical, endoscopic and radiologic methods for enteral access
- Development of hybrid laparoscopic/endoscopic procedures to minimize invasiveness and costs while maximizing safety
- Application of principles of Natural Orifice Transluminal Endoscopic Surgery (NOTES) to process of enteral device placement

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1. A GI consult is requested for placement of a gastrostomy tube in a 13 year old male with cerebral palsy, recurrent pneumonias and severe scoliosis. He is currently at 84% of ideal body weight and has recently been started on nasogastric tube feeds. The most appropriate recommendation among the options listed below regarding feeding tube placement in this patient would be:
   A. This is an appropriate candidate for percutaneous endoscopic gastrostomy placement.
   B. Gastrostomy placement is not indicated due to ethical concerns regarding his generally poor prognosis.
   C. This is an appropriate candidate for surgical gastrostomy placement.
   D. Gastrostomy is not indicated since he can be continued on nasogastric tube feeds.
   E. None of the above.

ANSWER: C

With clear evidence of malnutrition this patient is certainly a candidate for enteral support via tube feedings. There are no overt ethical concerns based on his medical history, as presented, that should preclude placement of a feeding tube if all caregivers and the family are in agreement. While nasogastric feeds are an appropriate short to mid-term option for delivery of enteral nutrition, for the patient who requires continued support a more durable option, such as gastrostomy, would be more appropriate. This would improve quality of life and avoid complications such as frequent tube dislodgement, nasopharyngeal irritation, esophageal erosions and sinusitis associated with long term NGT use. In this patient, given the concern for potential reflux as a cause for recurrent aspiration pneumonias, evaluation for Nissen fundoplication may be considered and, if deemed appropriate, would favor coupling this procedure with a surgical gastrostomy placement. In addition, with the potential for abnormal intestinal anatomy due to his scoliosis, percutaneous endoscopic gastrostomy placement would entail greater risk than a surgical gastrostomy.

2. An 18 month old female with chronic emesis, chromosomal abnormalities and developmental delay is referred to GI for further evaluation of suspected reflux. As part of that evaluation a liquid phase gastric emptying study is performed, showing severe delay with an emptying time of 300 minutes. She has not responded to medical therapy with a number of promotility medications and her weight-for-length has now fallen below the 3rd percentile. The most appropriate recommendation among the options listed below would be:
   A. A trial of nasogastric drip feeds to evaluate for tolerance.
   B. Referral to surgery for Nissen fundoplication.
   C. Placement of a surgical jejunostomy feeding tube.
   D. Placement of a gastrojejunostomy feeding tube, by either endoscopic or combined endoscopic/surgical approach.
   E. Referral to an Occupational or Speech Therapist to work on feeding skills

   ANSWER: D

   With severe delay in gastric emptying that has not responded to maximal medical therapy and evolving failure to thrive, provision of enteral support via a feeding tube is reasonable. Given the delay, however, intragastric feeds with a nasogastric tube are not likely to be tolerated, so a plan for transpyloric feeds should be considered. A trial of *nasojejunal* feeds would be reasonable to establish tolerance, but this option was not presented. Fundoplication in this setting, without placement of a gastrostomy for venting/drainage, would be likely to result in gas-bloat syndrome and would not address the need to provide for enteral supplementation. Conversely, transpyloric feeds with a surgically placed jejunostomy would be an option to provide for enteral nutrition but also has the disadvantage of not allowing for drainage/decompression of the stomach. A primary

gastrojejunonostomy, however, allows for both gastric and small bowel access. In addition to being able to decompress the stomach, gastric access allows for trials of intragastric feeds in the future to assess for improved tolerance, while the jejunal port can be used as the primary source of nutrition. In contrast, feeding therapy is not likely to result in any improvement in tolerance of PO feeds in the face of severely delayed gastric emptying.

3. An 11 year old male with severe developmental delay and chronic idiopathic constipation with encopresis and fecal impactions is referred for consideration of cecostomy placement. In counseling the parents regarding the potential risks and benefits of this procedure, all of the following are true except:

   A. The most common complication of surgical appendicostomy placement is stomal stenosis.
   B. Percutaneous endoscopic cecostomy can be performed, with or without laparascopic assistance.
   C. Overall rate of complications for cecostomy placement is less than 5%
   D. The primary advantage of tube cecostomy over appendicostomy is the ease of accessing the stoma.
   E. All of the above are true.

   ANSWER: C

   Appendicostomy was the first technique used to access the cecum for antegrade enema therapy of intractable constipation and is still often used. The most common complication of this technique, however, is stenosis of the stoma, which may occur in 11-27% of patients, especially if the tract is not routinely accessed. Catheterizing the stoma remains one of the primary disadvantages of this method, which can be even more difficult in developmentally delayed children. In contrast, tube cecostomies are much easier to access and avoid complications of stomal stenosis, though cosmetically may be less appealing due to the presence of the percutaneous device. Tube cecostomies can be performed via open surgery, laparoscopically, radiologic guidance or via endoscopy. Newer methods combining percutaneous endoscopic cecostomy techniques with laparoscopic guidance have been described, with complication rates similar to surgical placement but advantages in terms of navigating the dilated and tortuous colon and placement of the most appropriate sized tube. Complication rates for all of these techniques, however, range between 16 and 30% in a number of series.

Imaging the Pancreaticobiliary Tree

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I HAVE NO DISCLOSURES

Objectives

- Know who, when and if to image beyond ultrasound
- Pros/cons of various imaging techniques (MRCP, ERCP, EUS etc)
- Describe potential therapeutic interventions with these techniques

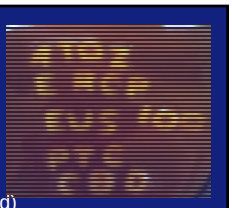
Care directed questions?

- Does ultrasound provide sufficient information?
  - To make clinical decision? (eg. acute pancreatitis)
  - Does an additional study add information for providers? (GI, surgeons, other consultants)
- How quickly do you need your information?
- Is the technology available locally?

Pitfalls of ultrasound

- Sensitivity of common bile duct stones ~40%
- Distal bile duct poorly visualized
- Abnormal bile duct diameter not well established in pediatrics
- Findings in acute pancreatitis may be normal
- Pancreatic duct difficult to visualize

Alphabet Soup in Pancreaticobiliary Imaging



- CBD (Common Bile Duct)
- HIDA (Hepatobiliary iminodiacetic acid)
- ERCP (Endoscopic Retrograde Cholangiopancreatography)
- PTC (Percutaneous Transhepatic Cholangiography)
- EUS (Endoscopic Ultrasound)
- Choledochoscopy (via ERCP or PTC)

Patient Selection

- Inflammatory
  - -Gallstone related disease
  - -Acute, recurrent and chronic pancreatitis
  - -Primary sclerosing cholangitis (PSC)
- Anatomic
  - -Choledochal Cyst
  - -Anomalous Biliopancreatic Union (ABPU) and pancreas divisum
- Motility (SOD and Biliary dyskinesia)

Hepatobiliary iminodiacetic acid (HIDA)

- Tc-99m labeled
- Same uptake, transport and excretion pathways as bilirubin
- Useful for functional gallbladder disease
- Post-operative issues (eg. bile leak)

HIDA scan for acute cholecystitis

- Acute cholecystitis= Non-filling of GB by 3-4 hours
  - -30 minutes with IV morphine
  - -Should have excretion into bowel unless obstructing stone
- False positives:
  - -Fasting < 4 hours or > 24 hours
  - -Small, contracted GB
  - -Chronic cholecystitis
  - -Hepatic dysfunction
  - -TPN usage

HIDA

- Pro
  - High sensitivity/specificity
  - Newer analogs with improved uptake and clearance
  - Disopropyl IDA and bromotriethyl IDA can be used with bilirubin as high as 20 to 30 mg/dL
  - Can assist in CBD obstruction
  - Excellent for bile leaks
- Con
  - Amount of time
  - Availability
  - Poor image quality with bilirubin >5 mg/dL
  - >24 hours NPO, high false positive

HIDA for biliary dyskinesia

- Emptying fraction < 35% with CCK
- Careful patient selection
- Query for pain during CCK
- Caution in patients with gastroparesis

Chumpitazi et al. JPGN 2012

Sphincter of Oddi Dysfunction (SOD)

- Type 1: Abnormal imaging and labs
  - Represents stenosis of the papilla
  - Dilated bile duct
  - Delayed excretion on HIDA or ERCP
  - Abnormal liver or pancreatic biochemistry during episode
- Type 2: Abnormal imaging
  OR
  Labs
- Type 3: Normal labs, Normal imaging

Reported use of MRCP in children

Study, year	Year	Enrollment	Blinding	Indication	Total (no.)	TP (no.)	FP (no.)
Hirohashi et al (9)	1997	Retrospective	Unblinded	Acute pancreatitis	6	5	0
Miyazaki et al (18)	1998	Prospective	Unblinded	Suspected PB disease	45	22	0
Shimizu et al (20)	2001	Prospective	Not stated	Acute pancreatitis	16	6	0
Arcement et al (14)	2001	Prospective	Not stated	Known PB disease	33	13	5
Ferrara et al (15)	2002	Prospective	Blinded	Suspected PSC	21	13	0
Manfredi et al (17)	2002	Prospective	Blinded	Chronic pancreatitis	15	7	2
Schaefer et al (19)	2006	Prospective	Unblinded	Suspected PB disease	7	7	0
Suzuki et al (21)	2006	Retrospective	Not stated	Choledochal cyst	33	33	0
Kamisawa et al (16)	2006	Retrospective	Not stated	Known PB disease	32	23	0
Tipnis et al	2008	Retrospective	Unblinded	Suspected PB disease	32	13	1
Summary					240	142	8

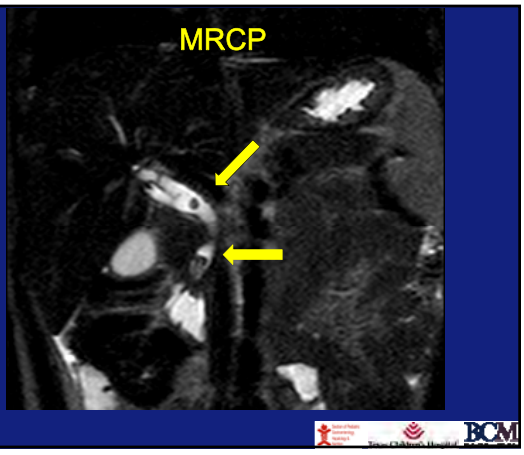
PB, pancreatobiliary; TP, true positive; TN, true negative; FP, false positive; FN, false negative.

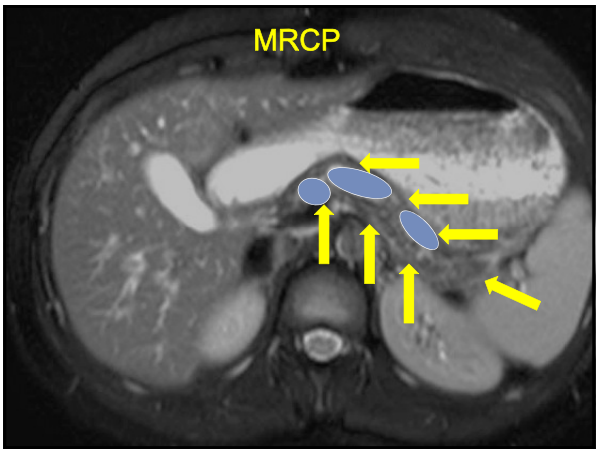
Tipnis et al. JPGN 2008

MRCP

- Pro
  - Non-invasive
  - Evaluate both biliary and pancreatic anatomy
  - Contrast not required for all studies
  - Differentiate between stones and tumors
  - MRCP comparable sensitivity and specificity to ERCP
- Con
  - Cost
  - Availability
  - Anesthesia for young children
  - Ductal changes in acute pancreatitis
  - Poor small duct differentiation
  - Ascites

Varghese et al. Clin Radiology; 2000: 155





ERCP usage in children

- ERCP allows for Therapeutic >>>> Diagnostic
  - -detection and removal of CBD stones
  - -Drainage, lithotripsy
  - -outline anatomy/variants
  - -can be performed in infants
- Major risks: Pancreatitis, Bleeding, Infection, and Perforation
- 10-60% of stones identified (can miss up to 20% of clinically significant stones)

Detection of CBD Stones

- High probability (>50% likelihood of stone at ERCP)
- ANY ONE → MAJOR
  - -Common Bile Duct Stone on Abdominal Ultrasound
  - -Total Bilirubin >4 mg/dL
  - -Clinical Ascending Cholangitis
- BOTH → MINOR
  - -Dilated Common Bile Duct (>6 mm) with gallbladder in situ
  - -Total Bilirubin 1.8-4 mg/dL

Pediatric CBD Detection

- ASGE criteria identified the majority of children
- When conjugated bilirubin substituted for total bilirubin in a "modified " criteria, more likely to have a stone (if ≥ 0.5 mg/dL) 25-fold
- Conjugated bilirubin was the most sensitive laboratory indicator of common bile duct stones (still only 68%)

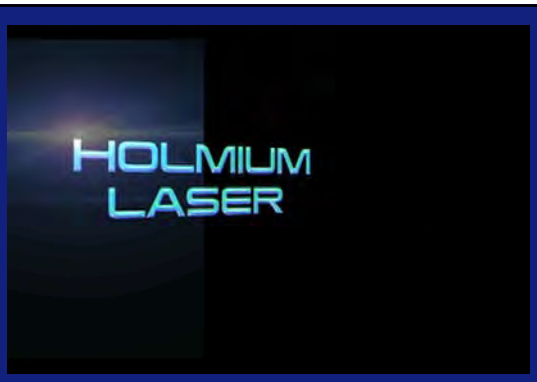
Fishman et al Gastroint Endosc 2011; 73(4), Suppl. Page AB117

Choledochoscopy

Harpavat et al. GIE 2012 (in press)
Fishman et al. World J Gastroenterol 2009

Choledochoscopy Usage

- Biliary strictures (benign or malignant)
- Filling defects mimicking large stones or tumor
- Evaluation of pancreatic stones or lesions
- Electrohydraulic lithotripsy (EHL) and Yg-Holmium laser destruction of bile duct stones
- Infectious and anastomotic lesions in liver transplant patients



Harpavat et al. GIE 2012 (in press)
Fishman et al. World J Gastroenterol 2009

EUS for Pancreaticobiliary Disease

- Biliary obstruction: Indications
  - Inaccessible trans-papillary approach
  - Altered anatomy (surgical, acquired, tumor)
- Acute pancreatitis (suspected CBD stone)
- Recurrent pancreatitis
  - Anatomic variants (ABPU, pancreas divisum)
  - Microlithiasis
- Chronic pancreatitis

Endoscopic Ultrasound

- Pro
  - Use in all age groups
    - Mini-probe (2.5 mm)
  - Growing experience in pediatrics
  - Useful in most PB disease
  - Therapeutic usage with FNA
  - Combine with ERCP

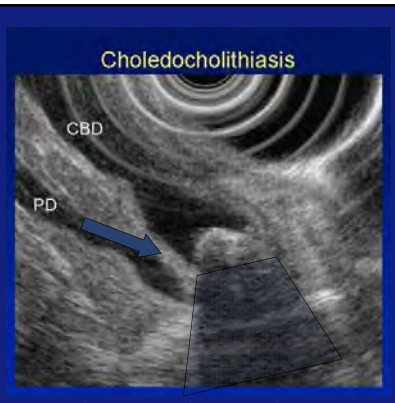
J Pediatr Surg 37:1370-1373
JPGN 2008 May;46(5):551-4

- Con
  - Endoscope size
    - Linear (12.8-13.8 mm)
    - Radial (12.1-12.7 mm)
  - Cost
  - Training
  - Requires anesthesia/sedation
  - Adverse events:
    - Bleeding, Infection, Perforation, Pancreatitis

Microlithiasis and biliary sludge

- Microlithiasis refers to stones or concretions ~2-3 mm
- Crystal analysis can be performed (direct or duodenal aspiration
- EUS may identify gallbladder sludge in up to 75% of patients with acute unexplained pancreatitis
- Cholecystectomy decreases rate of pancreatitis

Evans and Draganov, Nature 2006
Lee et al. NEJM 1999



www.ddc.musc.edu/professional/education/atlases/EUSatlas/index.cfm

Percutaneous Transhepatic Cholangiography/Cholecystography

- Interventional radiology
- Catheter based
- Can combine with:
  - Liver biopsy
  - ERCP (rendezvous)
  - choledochoscopy

Percutaneous Transhepatic Cholangiography/Cholecystography

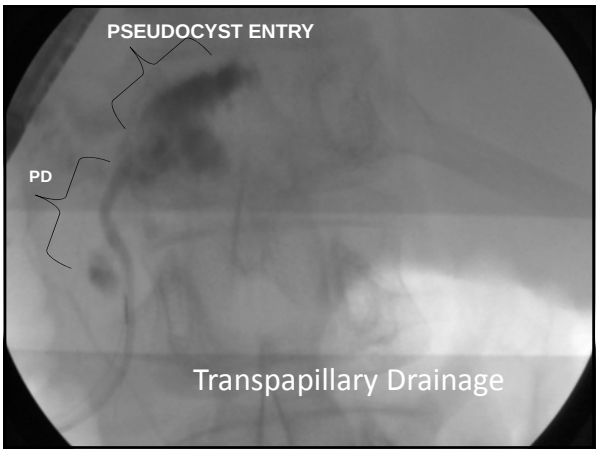
- Pro
  - Diagnostic and therapeutic
  - Highly effective for drainage
  - Combination therapy possible
  - Difficult anatomy or failed ERCP
- Con
  - Patient comfort
  - Requires external drain
  - Requires staged therapy
  - Adverse events:
    - Bleeding
    - Infection
    - Perforation

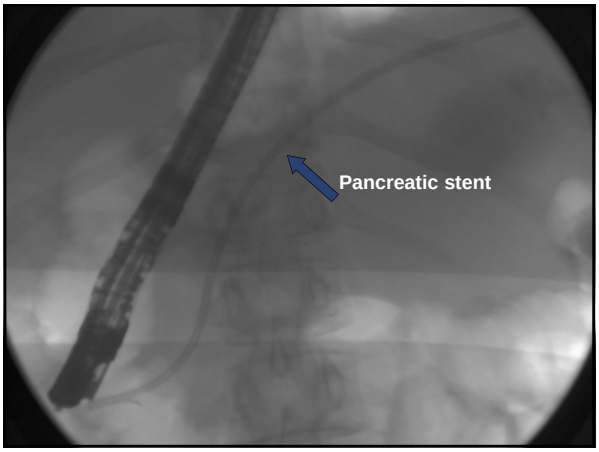
Therapeutic Endoscopy in Pancreatitis

- Acute pancreatitis (only in protracted cases)
  - ? Ductal stricture
- Recurrent pancreatitis
  - Sphincterotomy and/or stent placement
  - Manometry
- Chronic pancreatitis
  - Staged stent therapy
  - Stone removal and lithotripsy

Management of Pancreatic Pseudocyst

- Percutaneous Drainage (Interventional Radiology)
- Endoscopic
  - Transpapillary
  - Cystgastrostomy (Standard or EUS)
- Surgical drainage
  - Laparascopic cystgastrostomy
  - Tail pancreatectomy with drainage





COMPUTERIZED TOMOGRAPHY (CT)

CT

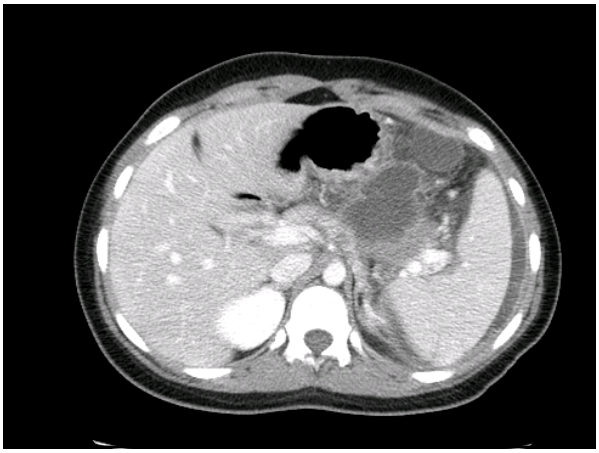
- Limited utility for gallbladder disease
  - Expense
  - Radiation exposure
  - Helical CT/CT cholangiography (CBD detection up to 88% sensitivity)
- Useful in acute deterioration
  - Evaluate other disorders with similar presentation
  - Fluid collections and leaks

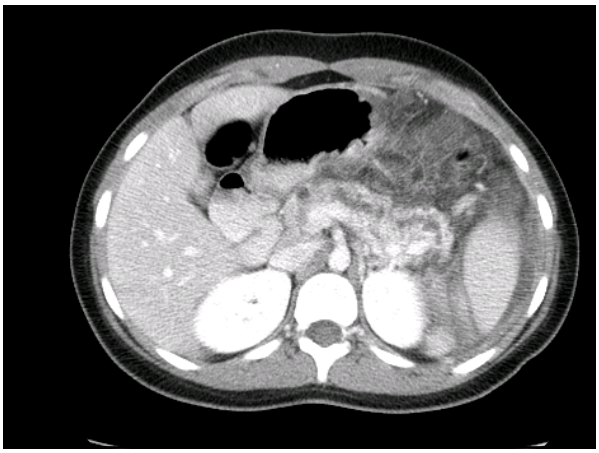
Maple et al. GIE 2010
Grand et al. AJR 2004

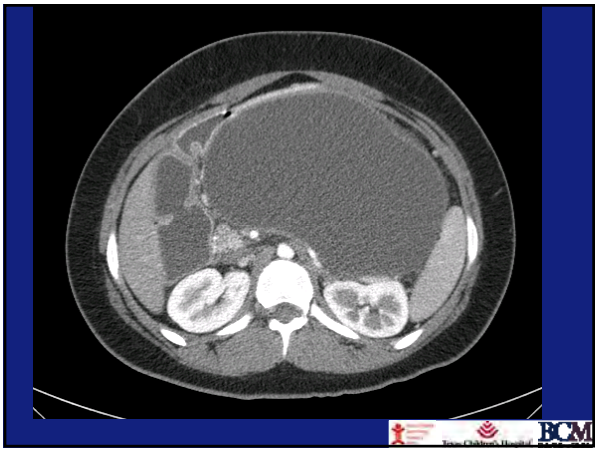
CT

- High sensitivity for pancreatic fluid collections/cysts
  - Compared to ultrasound
  - With ascites likely better than MRCP
- Able to identify necrosis, abscess, thrombosis
- Balthazar score in adults predictive of severity
- Typically not useful for pancreatic duct anatomy

Maple et al. GIE 2010
Grand et al. AJR 2004





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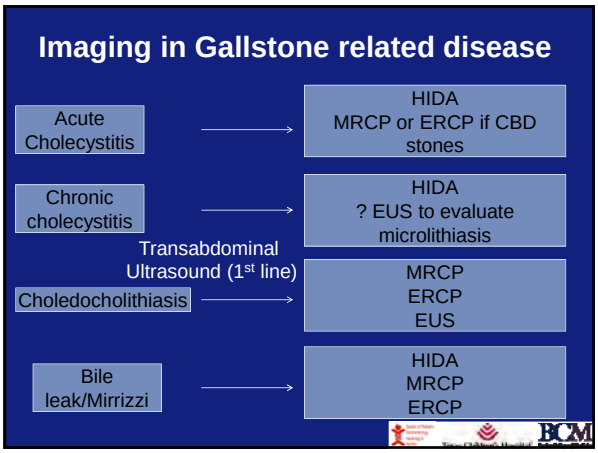
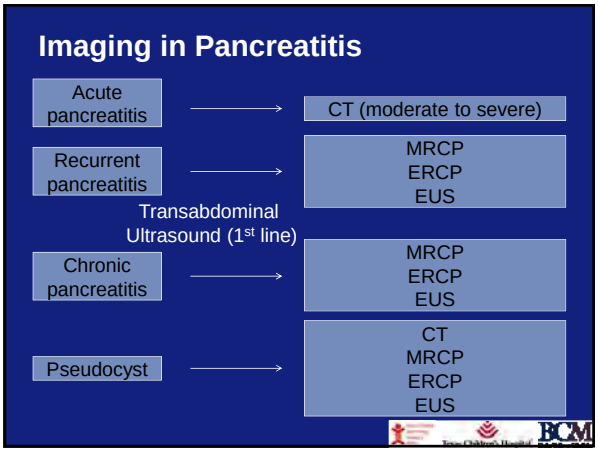
Endoscopic View
Pancreatic Pseudocyst

Imaging in Gallstone related disease



Imaging in Pancreatitis



Take home points

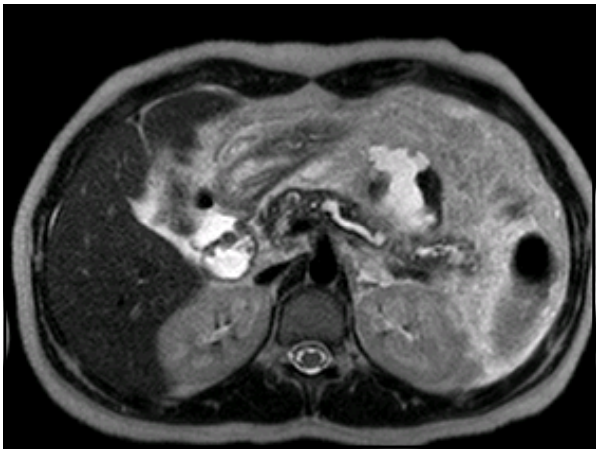
- Ultrasound is excellent for first-line diagnosis and management of pancreaticobiliary disease
- Array of imaging modalities available beyond US: HIDA, MRCP, ERCP, PTC and EUS
- Available therapeutic options include:
  - ERCP
  - EUS with FNA
  - PTC
  - Choledochoscopy

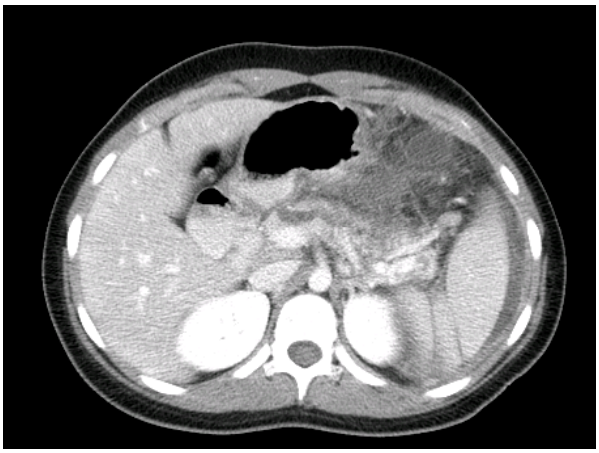
Future Directions

- Guidelines for CBD stone management in children
- Increased usage of pancreaticobiliary EUS in children
- Advancement of endoscopic therapies for recurrent and chronic pancreatitis in children

THANK YOU

dougfishman@gmail.com





IMAGING THE PANCREATO-BILIARY TREE

Douglas Fishman MD, Texas Children's Hospital

Board Style Questions

1. 14 y/o male with first episode of pancreatitis (mild) is discharged from the hospital. Six weeks later returns to emergency room with left upper quadrant pain. Liver panel is normal, but lipase is 1000 U/L. You suspect a pseudocyst. The first imaging to consider is:

A) KUB
B) Abdominal ultrasound
C) MRCP
D) HIDA
E) CT scan

2.. In the above patient, a pseuodcyst is confirmed by imaging to be 10 x 10 x 10 cm. Follow-up imaging 6 weeks later shows persistent pseudocyst. Best option to consider for drainage is:

A) Endoscopic cystgastrostomy
B) Laparascopic cystgastrostomy
C) ERCP with transpapillary drainage
D) Percutaneous drainage
E) All of the above

3. 15 year old Chinese-American girl presents to the emergency room with her 2nd episode of acute pancreatitis in 5 years. Abdominal U/S shows an enlarged hypoechoic pancreatic head and a tortuous dilated extrahepatic bile duct measuring 13mm and bilateral dilated intrahepatic bile ducts. No stones are visualized in the gallbladder or bile duct.

Labs: Bilirubin total: 1.1
Bilirubin conjugated: 0
AST: 27
ALT: 25
Alk Phos 62
Lipase 7,144

4. Which of the following is the most likely cause of her acute episode of pancreatitis?

A) Choledocholithiasis
B) Anomalous pancreaticobiliary junction
C) Auto-immune pancreatitis
D) Hereditary pancreatitis
E) CFTR mutation

4. 15 y/o female 92 kg (95% BMI) with RUQ pain. Labs notable for AST 400 U/L, ALT 400 U/L, GGT 400 U/L, Conjugated Bilirubin 0.6 mg/dL, Lipase 100 U/L Abdominal ultrasound notable for gallstones without wall thickening. The common bile duct is 6.5 mm without a visualized stone in the bile duct. The following morning, pain persists the AST, ALT, and GGT are unchanged U/L, but the conjugated bilirubin is 1.5 mg/dL and lipase is 10,000.

Appropriate management option for this patient include: (MAY CHOOSE MORE THAN ONE)

A) Repeat US
B) MRCP
C) ERCP
D) Laparascopic cholecystectomy with or without intraoperative cholangiogram
E) EUS

5. If in the same patient as above, labs notable for AST 400 U/L, ALT 400 U/L, GGT 400 U/L, Conjugated Bilirubin 1.5 mg/dL, Lipase 100 U/L Abdominal ultrasound notable for gallstones without wall thickening. The common bile duct is 6.5 mm without a visualized stone in the bile duct. The following morning, pain has resolved, the AST improved to 150 U/L, ALT 250 U/L, GGT 250 U/L, Conjugated bilirubin 0.0 mg/dL.

Appropriate management option (s) for this patient include: (MAY CHOOSE MORE THAN ONE)

A) Repeat US
B) MRCP
C) ERCP
D) Laparascopic cholecystectomy with or without intraoperative cholangiogram
E) EUS

6. 16 yr old boy with 2 episodes of pancreatitis over the last 4 months. Abdominal U/S showed a 2 x 2.5 cm. head of the pancreas mass. EUS with FNA and core-needle biopsy was non-diagnostic and did not show malignancy. Auto-immune pancreatitis is suspected. What test would be most helpful to confirm the diagnosis?

A) Sedimentation rate
B) Serum total IgG level
C) Serum IgG4 level
D) Endoscopic retrograde pancreaticogram
E) IgG4 stain of pancreas tissue

Answers.

1. B Although not most sensitive, US should identify pseudocyst if present. It may also identify reason for pancreatitis (eg. sludge) not seen on first hospitalization

2 E All are possible. Endoscopic approaches may be preferable to an open procedure, and similar to laparoscopic. Percutaneous drainage is more likely to re-accumulate and risk of fistula greater. IgG4 stain of pancreas tissue

3. B

4. C. Patient with gallstone pancreatitis. Bilirubin of 0.6 mg/dL suggestive of obstruction. ERCP provides treatment of obstructing common bile duct stones.

5. B. All of the above could be considered, however low to medium risk patient so MRCP, EUS or Laparascopic Cholecystectomy with IOC are likely preferred based on available adult data.

6. E. IgG4 stain of pancreas tissue

Update on Critical Foreign Body Ingestions

Petar Mamula, M.D.
The Children's Hospital of Philadelphia
University of Pennsylvania School of Medicine
Philadelphia, PA

I have no financial relationships with any commercial entity to disclose

Learning objectives

- Be familiar with critical issues with foreign body ingestions
- Understand evaluation and management of these ingestions
- Learn about NASPGHAN's efforts highlighting these public health issues

Background

- The challenge for the clinician is to predict which objects will not pass, or pose risk of a serious complication that would warrant removal
- American Association of Poison Control Centers - 116,000 cases of foreign body ingestion in 2010 (86,426 ≤5 year old)

Background

- Most pass spontaneously- 80-90%
  - Endoscopic removal - 10-20%
  - Surgical removal rare - ~1%
- Perforation rate <1%
  - Increased in symptomatic patients 5%
- Accounts for ~1500 deaths/year in US

Risks Factors for Complications

- Size
  - Greater than 2 cm diameter or 5 cm long unlikely to pass spontaneously
- Location
  - Esophagus
- Type
  - Sharp objects, magnets, batteries

Magnet ingestion chronology

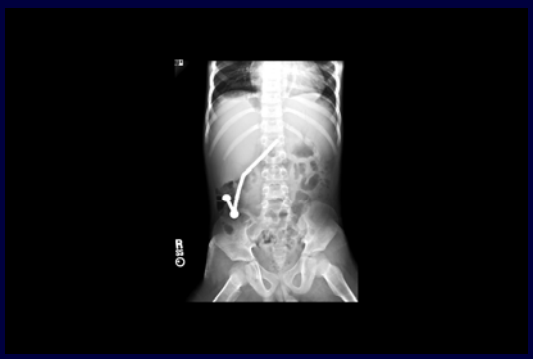
- 2002 - isolated case reports
- 2006 - 20 cases of magnet ingestion and injury in children were reported in the Center for Disease Control's Morbidity & Mortality Weekly Report
- 2007 - The U.S Consumer Products Safety Commission (USCPSC) issued the first warning after the death of a 20-month-old-child, as well as 33 other cases of ingestion
- 2008 - USCPSC had documented more than 200 reports

NASPGHAN

Magnets

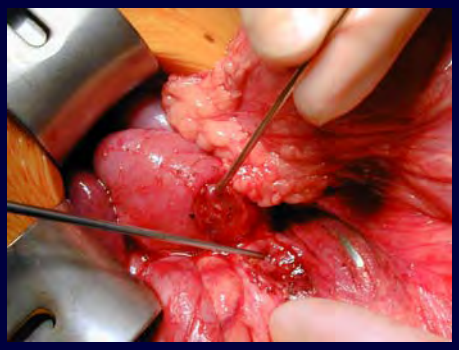
- 2012 - 39 pediatric gastroenterologists responding to an informal survey reported 93 cases of magnet ingestion (age 1-13 years, at least 372 magnets ingested)
  - 37 (83%) endoscopies with successful intervention/ 8 endoscopies with unsuccessful interventions
  - 30 (32%) surgeries (30 bowel perforations or fistulas, 11 reported near perforations or areas of pressure necrosis, 5 bowel resections)

NASPGHAN



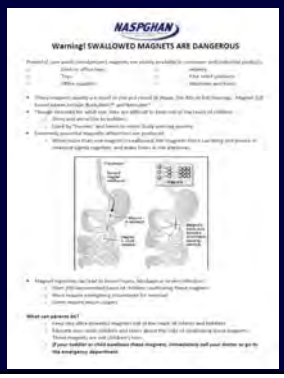
Liu, S. et al. JPGN, 2005.

NASPGHAN



NASPGHAN efforts

- Patient education
  - Patient brochure



NASPGHAN efforts

- Professional education
  - Action Alert
  - Podcast
  - Survey
  - Letter to the Editor (Chandra, S. et al., JPGN 2012)
  - Management of Ingested Magnets in Children (Hussain, S. et al., 2012 JPGN)
  - AAP Newsletter
  - To report a magnet ingestion using the Commission's online submission form, go to http://www.cpsc.gov/

NASPGHAN efforts

- Advocacy
  - Meeting with the U.S. Consumer Product Safety Commission (USCPSC)
  - Outreach to other societies (AAP, AGA, ACG, ASGE, etc.)
  - Media alert (spokespersons)
  - July 2012- USCPSC came to an agreement with most manufacturers regarding voluntary recall except for Maxfield & Oberton, which resulted in legal action

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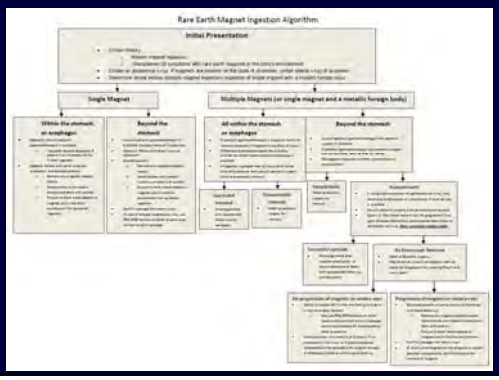
Magnet Algorithm



Initial Presentation

- Obtain History
  - oKnown magnet ingestion
  - oUnexplained GI symptoms with rare earth magnets in the child's environment
- Obtain an abdominal x-ray. If magnets are present on flat plate of abdomen, obtain lateral x-ray of abdomen
- Determine single versus multiple magnet ingestion

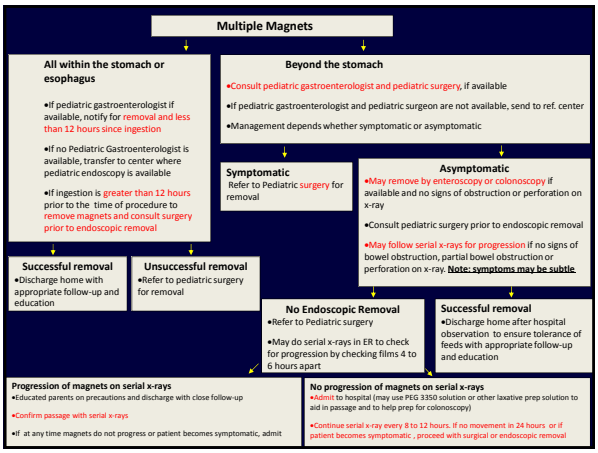
Single Magnet

Within the stomach, or esophagus

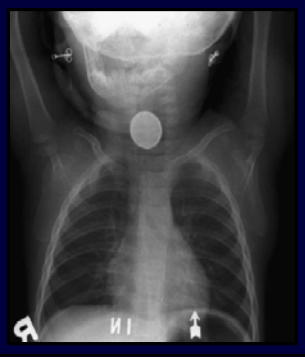
- Option 1: Consult pediatric gastroenterologist if available.
  - o Consider removal especially if patient is at increase risk for further ingestion.
- Option2: Follow with serial x-rays as outpatient and educate parents:
  - oRemove any magnetic objects nearby
  - oAvoid clothes with metallic buttons and belts with buckles
  - oEnsure no other metal objects or magnets are in the child environment for accidental ingestion

Beyond the stomach

- Consult pediatric gastroenterologist if available. Consider removal, if accessible
- Follow with serial x-rays as outpatient
- Educate parents :
  - oRemove any magnetic objects nearby
  - oAvoid clothes with metallic buttons and belts with buckles
  - oEnsure no other metal objects or magnets are in the child environment for accidental ingestion
- Confirm passage with serial x-rays



Battery ingestion



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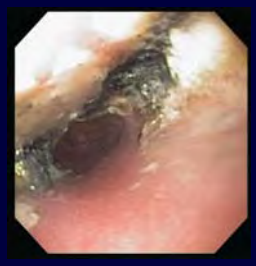
Battery ingestion major outcomes

Litovitz et al. Emerging battery-ingestion hazard: clinical implications. *Pediatrics*. Jun 2010;125(6):1168-77.

Batteries

• Esophageal damage can occur in a relatively short period of time- 2-3 hours when a disk battery is lodged in the esophagus



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Mechanism of injury

- Generation of an external electrolytic current that hydrolyzes tissue fluids which produces hydroxide at the battery's negative pole
- Leakage of alkaline electrolyte
- Physical pressure on adjacent tissue
- Heat production

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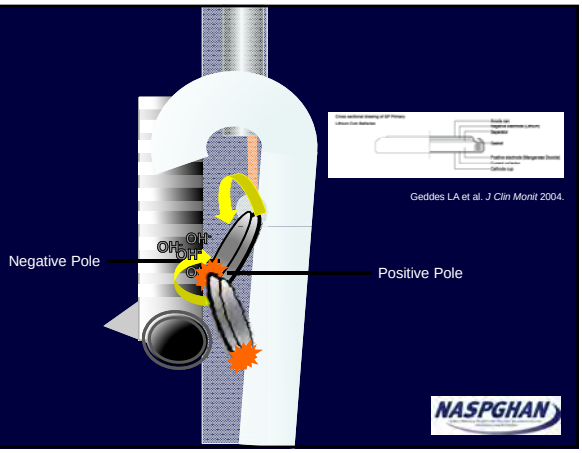
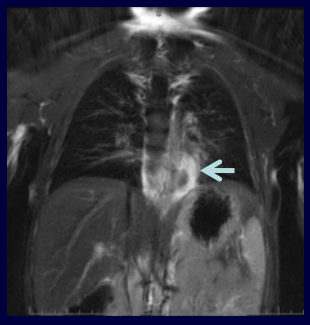


Geddes LA et al. *J Clin Monit* 2004.

NASPGHAN

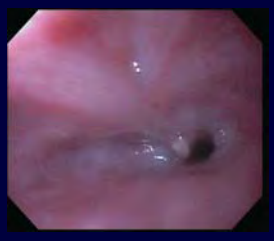


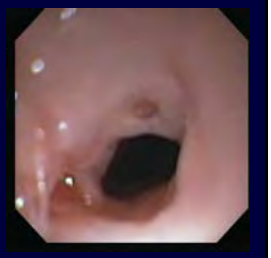
MRI- Fluid collection measuring 1.0 x 2.0 cm in para-esophageal soft tissues

Complications of battery ingestion

- Vocal Cord Paralysis
- Esophageal Perforation
- Esophageal Stricture
- Tracheal Stenosis
- Tracheomalacia
- Tracheo-Esophageal Fistula
- Hemorrhage from Arterial Fistula
- Infection
- Death

Stricture





Algorithms

Type of Ingestion	Esophagus	Stomach	Small intestine
Button batteries	Emergent endoscopic removal	Endoscopic removal if present > 48 hours	Surgical removal if x-rays show failure to progress
Large diameter (>15 mm) batteries	Emergent endoscopic removal	Endoscopic removal if present > 48 hours	See general rules
Sharp-pointed objects	Emergent endoscopic removal with sharp end trailing	Immediate endoscopic removal with sharp end trailing Straight pins can be left to pass spontaneously	If within reach, then immediate endoscopic removal with sharp end trailing Straight pins can be left
Large objects (longer than 5 cm or wider than 2 cm)	Immediate endoscopic removal	Endoscopic removal	See general rules
Multiple magnets	Immediate endoscopic removal	Immediate endoscopic removal	If within reach, then immediate endoscopic removal. Otherwise, see general rules

Summary

- Risk factors for complications include location, sharp, long (>5 cm), or large objects (>2 cm), multiple magnets and large disc batteries
- True emergency- remove esophageal battery within 2 hours
- Magnet algorithm (location, duration, symptoms, involve surgeons early)

UPDATE ON CRITICAL FOREIGN BODY INGESTIONS

Petar Mamula MD, Children's Hospital of Philadelphia

Board Style questions

1. A 3-year old boy swallowed four neodymium magnets 3 days ago. You have obtained abdominal x-ray which shows the magnets grouped in the right lower quadrant, but no other abnormalities. The patient is asymptomatic. The appropriate approach is to:

    a) Perform enteroscopy/colonoscopy to remove the magnets
    b) Obtain series of x-rays to monitor the magnet progression
    c) Obtain surgical consult
    d) All of the above

2. You are seeing a 2-year old girl who swallowed a 2 cm disc battery 6 hours ago. The x-ray obtained in the emergency room shows the battery lodged in the distal esophagus. The patient's vital signs are normal, and she is asymptomatic. Your NEXT step is to:

    a) Recommend administration of IV glucagon
    b) Obtain surgical consultation
    c) Admit for observation with a repeat x-ray
    d) Perform urgent upper endoscopy to remove the battery

3. A 4-year old boy has swallowed a single magnet ball 2 days ago. The magnet is from a set of high-powered neodymium balls that are approximately 4 mm in diameter. The patient is asymptomatic. The abdominal x-ray reveals the magnet to be located in the small bowel. You recommend the following:

    a) Admit for observation
    b) Enteroscopy to remove the magnet
    c) Follow with series of x-rays as outpatient
    d) Administer a laxative

4. What is the estimated number of deaths/year in the United States due to foreign body ingestion?

    a) 15
    b) 150
    c) 1,500
    d) 15,000

Answers:
1. D 2. D 3. C 4. C

MODULE E: WHEN ALL ELSE FAILS: LIVER, INTESTINE AND POUCH
Moderators: Melanie Greifer MD and Stanley Fisher MD

THE KID IS ON THE LIST: KEEPING COMPLICATIONS AT BAY FOR THE NON-TRANSPLANT HEPATOLOGIST
Simon Ling MB, ChB, The Hospital for Sick Children

Learning objectives:

1. Initial management of hepatorenal syndrome
2. Medical versus surgical management of ascites
3. Evaluation and management of encephalopathy

TRICKS OF THE TRADE FOR INTESTINAL FAILURE
Valeria Cohran MD, Children's Memorial Hospital, Chicago

Learning objectives:

1. How to optimize enteral nutrition
2. Tricks with parenteral nutrition
3. List newer surgical techniques and procedures

GASTROINTESTINAL AND LIVER COMPLICATIONS OF BONE MARROW TRANSPLANT
Ghassan Wahbeh MD, Seattle Children's Hospital

Learning objectives:

1. Know evaluation of liver complications in bone marrow transplant
2. Learn evaluation of gut complications in bone marrow transplant
3. Describe management of these complications in bone marrow transplant patients

POUCH DYSFUNCTION AND SURVEILLANCE: WHAT ARE MY OPTIONS?
Marla Dubinsky MD, Cedars-Sinai Medical Center

Learning objectives:

1. Learn how to recognize pouch dysfunction
2. Describe medical versus surgical options for pouch dysfunction
3. Know routine surveillance for cancer in patients with pouch

The kids on the list: Keeping complications at bay for the non-transplant hepatologist

Simon C Ling, MBChB
The Hospital for Sick Children
University of Toronto

I have the following financial relationships to disclose:

Bristol Myers Squibb	Research support
Gilead	Consultancy
Isis Pharmaceuticals	Consultancy

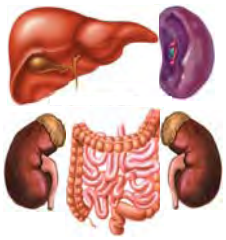
** No products or services produced by these companies are relevant to my presentation.*

Objectives

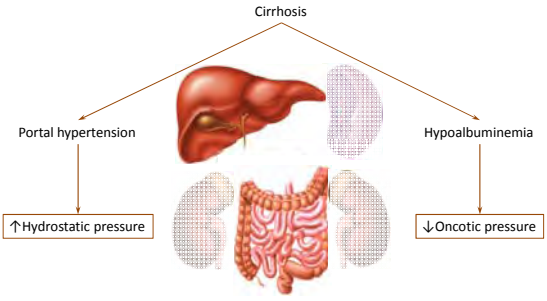
Understand the evaluation and management of:

- Ascites
- Hepatorenal syndrome
- Hepatic encephalopathy

How does ascites develop?



How does ascites develop?



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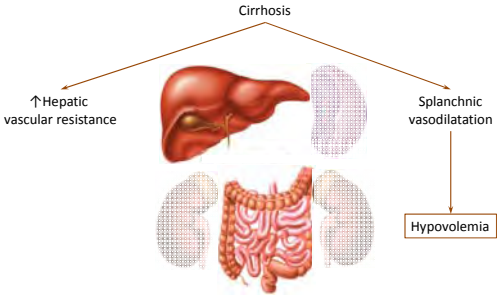
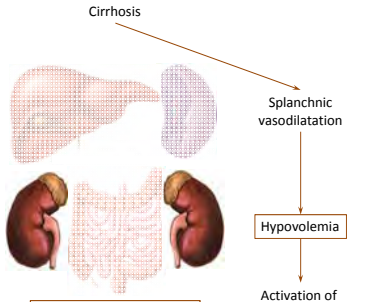
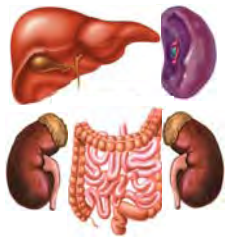


How does ascites develop?



How does ascites develop?

↑Hydrostatic pressure | ↓Oncotic pressure | Hypovolemia | Sodium & water retention

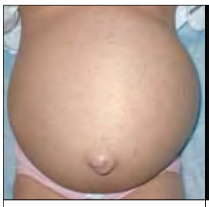


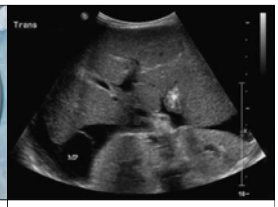
Sodium restriction | Diuretics | Albumin infusion | Paracentesis | TIPS

What is the impact of effective management of ascites?

- Symptoms ☑
- Spontaneous bacterial peritonitis ?
- Survival ?

Detection of mild ascites by physical examination is unreliable





	Fluid thrill	Shifting Dullness
Sensitivity	20-80%	60-88%
Specificity	80-100%	56-90%

USS = reference standard

Ascites is managed by a stepwise medical approach

1. Low sodium intake
   - aim for 1 mmol/kg/d (23 mg/kg/day)

Gatta, Hepatol 1991
Bernardi, Liver 1993
Gauthier, Gut 1986

2. Add spironolactone
   - Start at 2 mg/kg/day
3. Add frusemide
   - Start at 1 mg/kg/day

Angeli, Gut 2010
Santos, J Hepatol 2003

4. 25% albumin infusion 1 g/kg

Large volume or refractory ascites require additional measures

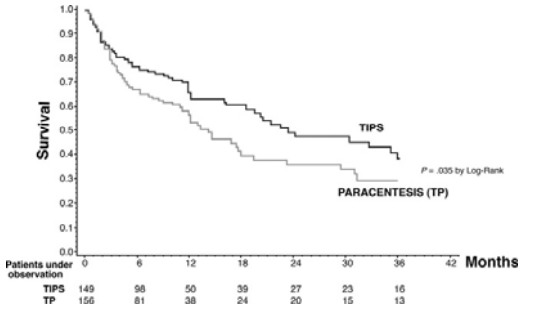
- Tense, large volume ascites
  - Large volume paracentesis
  - With 25% albumin infusion 1g/kg or 6-8g/liter

Kramer, JPGN 2001
Runyon (AASLD), Hepatology 2009
EASL, J Hepatol 2010

- Refractory ascites
  - Serial therapeutic paracentesis *vs.* TIPS
    - Less recurrence with TIPS
    - Less encephalopathy with paracenteses

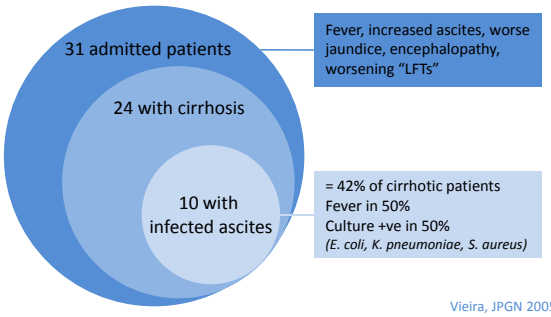
Saab, Cochrane Database 2009

TIPS may improve survival in cirrhotic adults with ascites



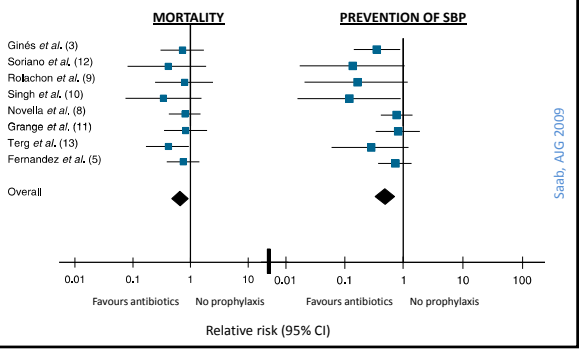
Solano, Gastroenterology 2007

Consider sampling ascites in cirrhotic children admitted to hospital



Vieira, JPGN 2005

Antibiotics prevent recurrent SBP and improve survival in cirrhotic adults



Saab, AJG 2009

Summary – the S's of ascites

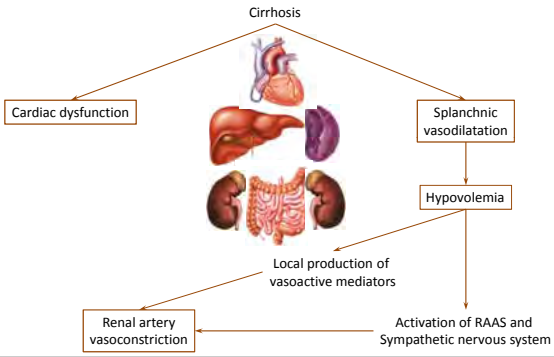
Sodium – restrict intake, measure in urine

Spironolactone ± frusemide

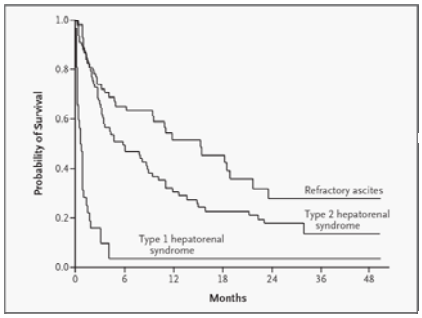
TIPS or paracentesis for tense ascites

Seek SBP

Hepatorenal syndrome arises from circulatory dysfunction



Outcomes of HRS are poor in adults



Ginès, NEJM 2004

Diagnostic criteria for HRS are clearly defined for adults

- Cirrhosis with ascites
- Creatinine > 1.5 mg/dl (> 133 µmol/l)
- No shock, no hypovolemia
  - 2 days diuretic withdrawal and volume expansion with albumin
- No nephrotoxic drugs
- No parenchymal renal disease
  - proteinuria <0.5g/day, <50 red cells/hpf
  - normal renal USS

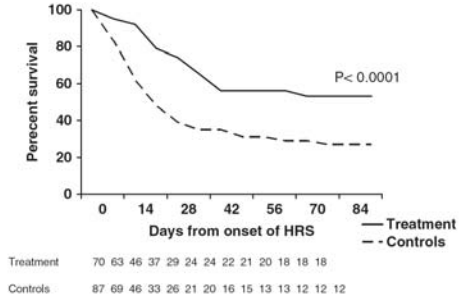
Salerno, Gut 2007

Treatment of HRS requires volume and vasoconstriction

- Stop diuretics
- Vasoconstriction + expand circulating volume
  - Norepinephrine + albumin
  - Octreotide + midodrine + albumin (+TIPS)
  - Terlipressin + albumin
- Hemodialysis
- Liver transplantation

Gluud, Hepatology 2010 Runyon (AASLD), Hepatology 2009 EASL, J Hepatology 2010

Midodrine + octreotide + albumin improves survival in adults with HRS



Skagen, J Clin Gastroenterol 2009

Summary – hepatorenal syndrome

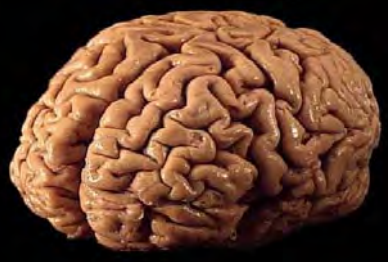
Volume

Vasoconstrictors

Dialyze

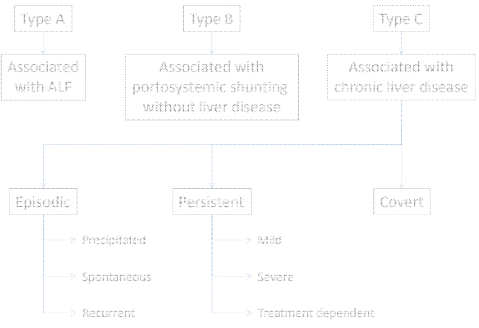
Transplant

Hepatic encephalopathy



- Key pathogenic factors include ammonia and GABA neurotransmission

Classification of hepatic encephalopathy



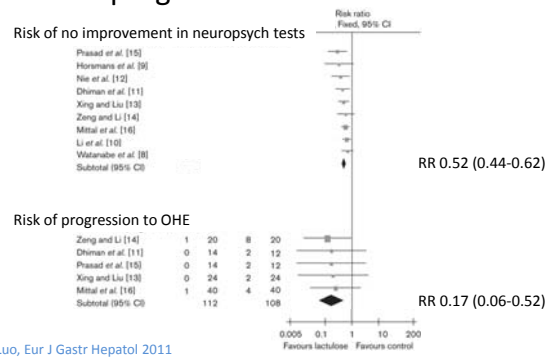
Covert hepatic encephalopathy is diagnosed with…

- Neuropsychological tests — Srivastava, JPGN 2010; Mack, Pediatrics 2006; Yadav, J Hepatol 2010
- Imaging
  - MRI/MRS — Foerster, AJNR 2009
- Electrophysiology
  - EEG
  - Evoked potentials — Nora, JPGN 2000

Management of hepatic encephalopathy

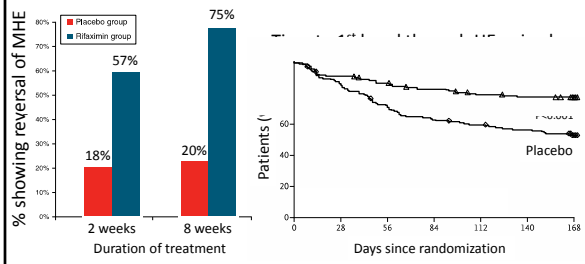
- Prevent or treat precipitating factors
- Correct nutritional deficiencies
  - Zinc? — Takuma, Aliment Pharm Ther 2010
  - Branch-chain amino acids? — Als-Nielson, Cochrane 2003
- Reduce ammonia and/or change microflora
  - Lactulose — Luo, Eur J Gastr Hepatol 2011
  - Rifaximin — MacLayton, Ann Pharmcother 2009
  - Probiotics? — McGee, Cochrane 2011

Lactulose improves test results and reduces progression to overt HE in adults



Luo, Eur J Gastr Hepatol 2011

Rifaximin reverses HE and prevents recurrence



Sidhu, Am J Gastro 2011

Bass, NEJM 2010

Summary – hepatic encephalopathy

- The significance of HE in children is poorly defined
- Diagnosis of MHE requires careful neuropsychiatric testing
- Effective therapies for HE in adults require studying in children

Future directions…


Ascites


Hepatorenal Syndrome


Hepatic Encephalopathy

How much of a problem are these in pediatrics?

What diagnostic criteria for MHE and HRS in children?

What therapies work?

Who should be treated?

THE KID IS ON THE LIST: KEEPING COMPLICATIONS AT BAY FOR THE NON-TRANSPLANT HEPATOLOGIST

Simon Ling, MD, ChB, The Hospital for Sick Children

Board Style questions

1. In children with cirrhosis, factors contributing to the development of ascites may include:
    a. Renal resistance to aldosterone effects
    b. Splanchnic vasoconstriction
    c. Sodium intake of 160-180 mg/kg/day (7-8 mmol/kg/day)
    d. Increased plasma oncotic pressure
    e. Elevated bilirubin levels

2. Hepatorenal syndrome in children
    a. Should be diagnosed only after discontinuing all diuretic therapy
    b. Only occurs in the presence of ascites
    c. Should prompt evaluation for liver transplantation
    d. May be treated by hemodialysis
    e. All of the above

3. Covert or minimal hepatic encephalopathy in children with cirrhosis and portal hypertension
    a. Is characterized by drowsiness or reduced level of consciousness
    b. Is always associated with elevated ammonia levels measured in blood
    c. May be reversed by performing a surgical porto-systemic shunt
    d. May progress to overt encephalopathy if septicemia occurs
    e. Is not associated with changes on MRI brain scan

Answers

1. c
2. e
3. d

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Intestinal Failure: Tricks of the Trade

Valeria Cohran M.D.
Ann & Robert H. Lurie
Children's Hospital of Chicago
Division of Gastroenterology
October 18, 2012

Ann & Robert H. Lurie
Children's Hospital of Chicago™

Disclosures

- **I have the following financial relationships to disclose:**

  Speakers Bureau for Nutricia *

** Products produced by this these companies are included in my presentation.*

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Objectives

- **1: How to optimize enteral nutrition and avoid nutritional deficiencies**
- **2: Reveal new and improved methods of parenteral nutrition**
- **3: Discuss up to date surgical procedures to maximize bowel function**

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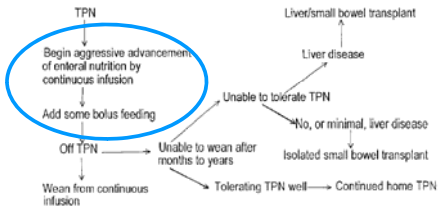
Optimizing enteral nutrition and avoid nutritional deficiencies

Progressive Therapies



Gastro 1997;113:1767–1778

Enteral route

- Continuous feedings are beneficial!
- Shorter the remnant bowel, the less likely to tolerate bolus or oral feedings
  - Diarrhea
  - Malabsorption
- Small amounts of oral feedings to prevent oral aversion
- GER or motility disorders are common
  - Nasojejunal
  - Gastrojejunal
- ↑ 600-700 Kcal/day in adult sbs patients receiving tube feedings vs patients taking only oral feedings

Gastro 2009;136:824–831

Enteral Nutrition

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- Duration of TPN dependence
  - Amino-acid based formulas or breast milk
  - Shorter time without a stoma
  - Percentage of enteral calories by 6 weeks of age
- Elemental formulas
  - Lack the optimal calcium:phosphorus ratios for preterm infants
  - Expensive

J Pediatr 2001: 139:27-33
JPGN 1998: 27(5):614-616

7

Duocal® Microlipid®

- **Duocal Powdered carbohydrate**
  - Hydrolyzed cornstarch 73% Fat supplement 22% (35% MCT)
  - Added to formulas to increase the caloric density
  - 42 kcal/Tablespoon
- **Microlipid**
  - 100% Fat LCT
    - Safflower oil
  - Added to tube feedings
  - 67.5 kcal/Tbsp

Fiber

- **Pectin®**
  - Nondigestible plant polysaccharides
  - Liquid
  - Relatively Inexpensive
  - Canning additive
  - < 6 months of age
- **Benefiber®**
  - Wheat Dextrin
  - 15 kcal/serving
  - 3 grams/serving

Anti-diarrheal agents

- **Imodium®**
  - Opioid receptor agonist lead to decreases in
    - Activity of the myenteric plexus
    - Colonic peristalsis
    - Gastrocolic reflex
    - Avoid in children < 6 months

- **Clondine patch**
  - Jejunostomy/ileostomy
  - Alpha adrenergic agonist that decreases intestinal transit
  - Short bowel syndrome and s/p small bowel transplant
  - Titrate up from 0.1 mg to max 0.3 mg

JPEN 2006 Nov-Dec;30(6):487-91
JPEN 2004 Jul-Aug;28(4):265-8

Pedialyte®

Ann & Robert H. Lurie Children's Hospital of Chicago

- Hydration fluid
- Contents
  - 250 mOsm/kg
  - Na 45 mEq/L
  - K 20 mEq/L
  - Cl 35 mEq/L
- Add to enteral feedings in lieu of IV fluids

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Vitamin and mineral deficiencies in SBS

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- 30 patients tapered from TPN
  - Mean age 5 years (range 2 to 9)
  - Median TPN duration 23 weeks
- Transition period
  - 33% ≥1 vitamin, 77% ≥1 mineral deficiency
- Full EN (Median transition 12 weeks)
  - 70% ≥ 1 vitamin deficiency, 77% ≥1 mineral deficiency
- Deficiencies
  - **vitamin D** (68%)
  - **zinc** (67%)
  - **iron** (37%)
- Multivitamin supplement (P=.004)
- Intact ileocecal valve (P=.02)
  - Independent of bowel length, gestational age, and days on PN

J Pediatr 2011 Jul;159(1):39-44

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Reveal new and improved methods of parenteral nutrition

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Intravenous lipids

- 10% or 20% lipid
- Phytosterols
  - Elevated in patients receiving TPN
  - Increases oxidative stress
  - Displacing cholesterol
  - Pediatric and adult data
    - Cholestasis is affected by lipid amount
    - > 1 gm/kg/day

JPEN 2000 Nov-Dec;24(6):345-50

Ann Intern Med. 2000 Apr 4;132(7):525-32

14

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Omegaven®

- Omega -3 fatty acid or Fish Oil
- Immunomodulatory effects on the liver
- Less impairment of biliary secretion
- Increase the Omega-3 FA to Omega-6 FA in the red blood cell
  - Reduced inflammatory effect
- Requires permission from the FDA
- Expensive

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Omegaven®

- 42 patients treated vs 49 historical cohort
  - Outcome serum D bili < 2 mg/dl
  - Reversal of cholestasis approximately 6 times faster than controls who received intralipid
- Outcomes
  - Intralipid group 12 deaths 6 transplants
  - Omegaven group 3 deaths 1 transplant (p<0.05)
- No hypertriglyceridemia, coagulopathy, or essential fatty acid deficiency
- Omegaven is safe and effective for therapy in patients with TPN associated liver disease

Annals of Surgery 2009;250:295-402

16

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Lipid Minimization

- N=31 in a multidisciplinary team
- Similar decline in bilirubin as in the Omegaven studies
- 8/13 had mild essential fatty acid deficiency
- Unclear effect of lower essential fatty acids on neurodevelopment
- More of the low lipid group received bowel decontamination
- Large randomized trials are needed.

J Pediatr 2012;160:421-7

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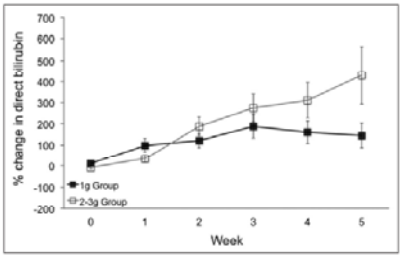
Lipid reduction to 1 gm/kg/day does not prevent cholestasis

- Neonates >21 days of TPN
  - n=29
  - n=32
  - No di ons



J Parenter Enteral Nutr. 2012 Jul 5. [Epub ahead of print]

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Enteral Fish Oil

- n=6 patients with Intestinal Failure requiring TPN > 6 months
- Intestinal length 24-95 cm (median 40 cm)
- 4/6 Enteral fish oil 250 mg/kg/day
- Total bilirubin normalized within 1.8-5.4 months
- Enteral supplementation and elimination of intralipids improved cholestasis
- Limitations
  - Small sample size,Retrospective study, serial EFAS were not followed
  - ?Alternative in some patients with some enteral tolerance

Nutr Clin Practice 2010; 25:199-204

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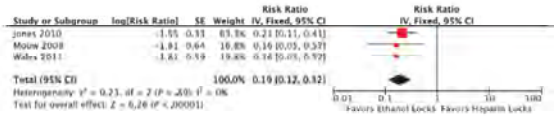
Ethanol locks prevent blood stream infections

(b) Pooled relative risk of CRBSI rate



(d) Pooled relative risk of catheter replacements

Pediatrics 2012; 129:318-329

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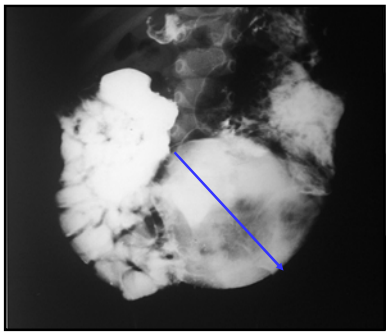
Discuss up to date surgical procedures to maximize bowel function

Bianchi, STEP, and Beyond!

Dilated Segments



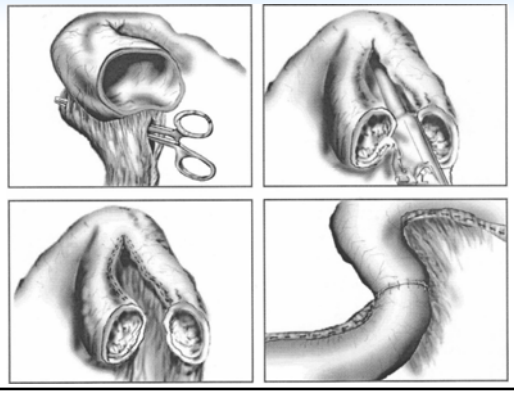
Indications for Intestinal lengthening

- Dilated loops of bowel >2 cm
  - UGI series
- Complications from the dilated loops of bowel
  - Recurrent bacterial infections
  - Plateau in enteral tolerance
  - TPN associated liver disease, not cirrhosis
  - Vomiting
  - Refractory D-lactic acidosis
- Goals
  - Enhance enteral tolerance
  - Restore normal bowel caliber and function
  - <40 cm Bianchi first choice*
    - Requires expertise

Journal of Pediatric Surgery (2012) 47, 931–937

JPGN (2012) 54, 505-9 *

Bianchi Procedure



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Serial Tapering Enteroplasty (STEP)

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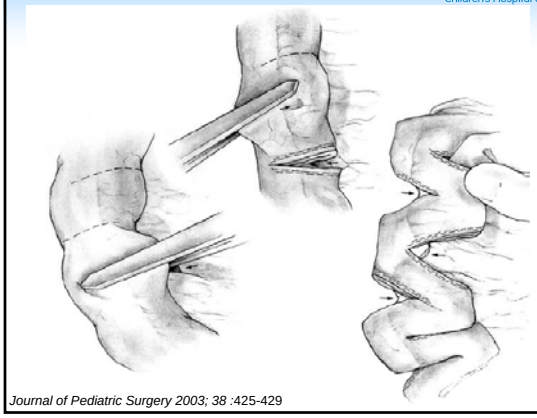
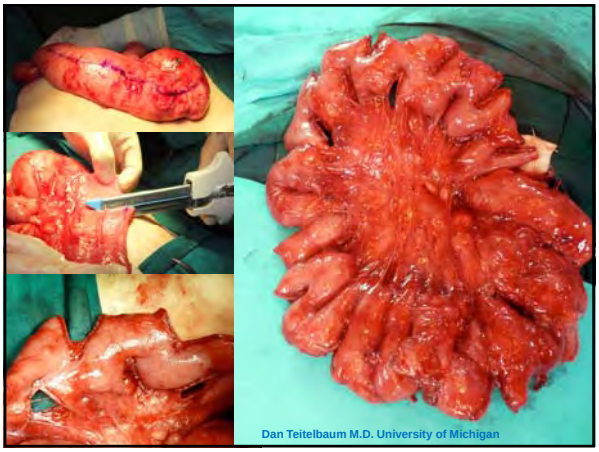


*Journal of Pediatric Surgery 2003; 38 :*425-429

25



Dan Teitelbaum M.D. University of Michigan

5 year outcomes after STEP

- Overall small bowel length increased by 46 ± 40%
- 4/12 had poor outcomes
  - 2 underwent combined liver intestinal transplant
  - 2 died from liver failure
- 7/8 patients tapered from TPN
  - Weight 30-40th %
  - Citrulline 18 ± 8 umol/L to 48 ± 15 umol/L 5 years
  - D-xylose increased to 3.4 ± 0.7mmol/L at 5 year mark
  - Fat malabsorption fell from 40% to 20%

Journal of Pediatric Surgery 2012; 47, 931–937

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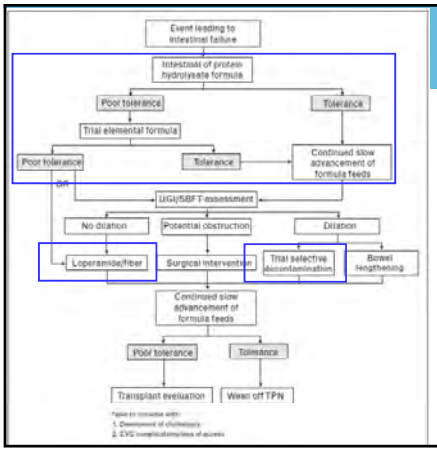
Surgical Outcomes

Table 3 Outcomes grouped by redilation status

	Redilated (n = 8)	No redilation (n = 6)	P
LILT	4	3	1.0
STEP	6	3	
Death	2	0	.46
Postoperative bowel length (cm)	70 ± 28	60 ± 36	.39
Weaned off PN	1	5	.03
Age	3.1 ± 3.5	2.8 ± 3.2	.69
BO	4	5	.30
GI bleed	5	2	.59
Reoperation	7	0	.005

Journal of Pediatric Surgery 2011; 46, 145–149



Current Opinion in Organ Transplantation 2010; 15:324–329

Summary/Take Home Points (1)

- Tailoring enteral therapy to the underlying physiology
  - Intestinal length 120 cm vs 30 cm of small intestine
  - Oral vs continuous
  - Gastric vs jejunal feedings
- Motility agents to decrease stool output
  - Fiber, imodium®, clonidine®
- Assessment of vitamin and mineral status is important
  - Vitamin B_{12}, Vitamin D, iron, zinc

Summary/Take home Points (2)

- TPN associated cholestasis
  - Lipid minimization
  - Omegaven®
  - Serial essential fatty acid levels
- Ethanol locks have been shown to decrease blood stream infections and catheter replacements
- Intestinal lengthening procedures
  - Improved enteral tolerance with improved absorption
  - Tapering from TPN
  - Redilation, GI bleeding, transplant
  - Patients still require intestinal rehabilitation after surgery

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Future Directions

- Investigate the use of growth factors including glucagon like peptide-2 (glp-2) to enhance intestinal adaptation
- Randomized trials evaluating the use of lipid alternatives such Omegaven® (Fish oil) and SMOF® (soy/MCT/olive/fish oil) in children
- Establishing multi-center consortium similar to Studies in Pediatric Liver Transplantation (SPLIT) and Childhood Liver Disease Research and Education Network (ChiLDREN) for pediatric intestinal failure

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TRICKS OF THE TRADE FOR INTESTINAL FAILURE

Valeria Cohran MD, Children's Hospital of Chicago

Board Style questions

Which of the following route/method is not commonly used in short bowel patients with poor enteral tolerance?

A. Bolus
B. Continuous
C. Nasogastric
D. Gastrojejunal

Sodium content of gastric fluid is approximately equal to

A. 140 meq/L
B. 75 meq/L
C. 60 meq/L
D. 45 meq/L

Bacterial overgrowth has been related to

A. Strictures
B. Poor peristalsis
C. Absence of the Ileocecal Valve
D. Blood stream infections
E. All of the above

Which of the following is not a common deficiency in patients with short bowel syndrome?

A. Zinc
B. Vitamin D
C. Iron
D. Manganese
E. Selenium

Answer Key
A, A, E, D

GASTROINTESTINAL AND LIVER COMPLICATIONS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

Ghassan Wahbeh MD
Associate Professor
Director, Inflammatory Bowel Disease Program
Seattle Children's Hospital
University of Washington

I have the following financial relationships to disclose:

Johnson & Johnson*
Abbott
UCB

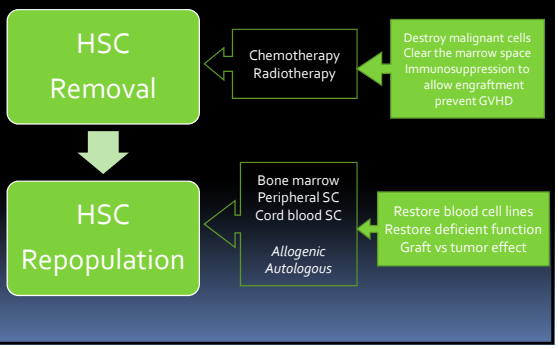
** Products or services produced by this company are relevant to my presentation*

Objectives

- Overview of HSCT
- Discuss HSCT gastrointestinal complications
  - Medication & radiation related
  - Infections
- Describe liver complications in HSCT patients
  - Medication & infection related
  - Veno-occlusive disease
- Review Graft vs. Host Disease of the gastrointestinal tract and liver

Overview of HSCT

Hematopoietic Cell Transplantation



Matching

- HLA
  - A/B/C/DR/DQ
- 25% patients may have a matched sibling
- 50% patients have a matched donor through donor programs
- Alternatives
  - Partial matching
  - Cord blood

Graft Rejection
GVHD

General Complications of HCT

- Chemotherapy toxicity
- Radiotherapy toxicity
- Infections
- **Acute & chronic Graft vs Host disease**
- Recurrent malignancy or other primary disease

Gastrointestinal complications of HSCT

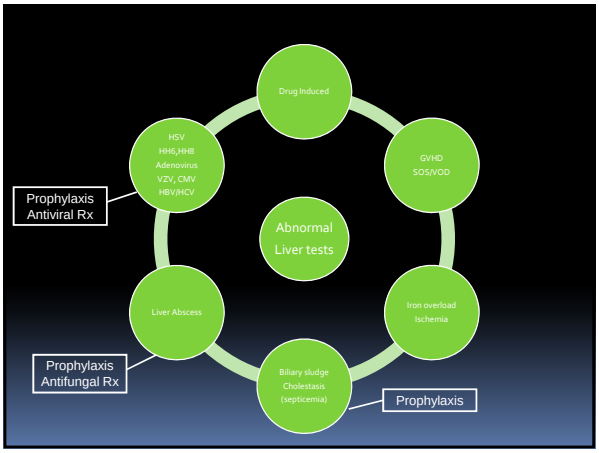
Medication induced symptoms

- Nausea/ vomiting
- Anorexia (<20 days)
- Mucositis
  - Dysphagia
  - Gagging
  - Odynophagia
  - Diarrhea, bleeding
- Diarrhea
  - Mg, MMF, Tacrolimus, Abx
  - Diet
- Narcotic bowel syndrome
  - Constipation
  - Nausea, bloating
  - Ileus
  - Abdominal pain

Other

- GI Infections
  - CMV, Adenovirus C diff, Cryptosporidium
- Typhlitis
- Perianal infections (less likely abscess)
- Pneumatosis intestinale
- GI bleeding
  - GVHD
  - Esophageal, GE trauma
  - Infectious
  - Gastric antral vascular ectasia (busulfan)

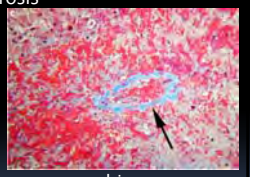
Liver complications of HSCT



Sinusoidal Obstruction Syndrome
Veno-occlusive disease

Jaundice
Hepatomegaly

- Risk factors
  - Existing liver disease & fibrosis
  - Medications
    - Cyclophosphamide
    - Radiation
- Diagnosis
  - Clinical picture
  - Doppler U/S, hepatic wedge pressure, biopsy



Choi et al. BMT (2005) 36, 891–896

SOS / VOD

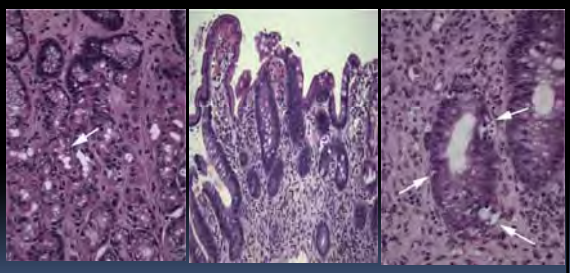
- Prognosis
  - 80% recovery
- Treatment
  - Supportive measures
  - Defibrotide
- Prevention
  - Ursodiol
  - Alternative regimen

Graft vs. Host Disease

GVHD Background

- Describes in 1955 in mice
- Common
- Significant morbidity & mortality
- Affects mainly "exposed" organs
- Rare in solid organ transplant
- Can occur in autologous transplant
  - Pseudo GVHD

Features



Human Pathology (2009) 40, 909–917

GVHD Classification

Acute

- Day 21-100
- 10-20% allograft recipients
- Symptoms
  - Rash, nausea, vomiting, anorexia, diarrhea, ileus, cholestatic hepatitis
- Liver GVHD usually follows skin and gut

Chronic

- >100 days
- 20-50%
- Symptoms
  - Variable
- Criteria
  - Sclerotic skin lesions
  - Oral or genital lichenous lesions
  - Bronchiolitis obliterans
  - GI webs, strictures

GVHD Complications

- Symptoms
  - Vary from acute to chronic
- Gastrointestinal inflammation & ulceration
  - Bleeding

GVHD Management

- Diagnosis
  - Clinical
  - Endoscopy
    - EGD, Proctoscopy
    - Biopsy
      - Gastric, avoid duodenum
      - Rectal biopsy
- Treatment
  - Prednisone
  - Beclomethasone
  - Budesonide
  - Tacrolimus
  - Sirolimus
  - MMF
  - Extracorporal photophoresis
  - Anti-TNF antibodies

GVHD Prevention

- Better matching
- Regimen selection
- Medications (depends on regimen)
  - Ursodiol, tacrolimus, mycophenolate mofetil, rapamycin, cyclosporine and methotrexate, cyclophosphamide
    - Wean with immunologic tolerance
- Graft T-cell depletion
  - ↑ disease relapse
  - ↑ infection

Summary

- Gastrointestinal and liver complications are relatively common after HSCT
- Complications are related to the underlying disease, chemotherapy, radiotherapy and graft vs host disease
- Aside from supportive measures, specific therapies may offer help in VOD & severe GVHD

Take Home points

- Early HSCT complication are caused by underlying disease, chemotherapy and radiotherapy
- Past 20 days from HSCT, GVHD accounts for the majority of gastrointestinal complications
- Gastrointestinal biopsies are risky in HSCT and should be limited in number & location

Future directions

- Conditioning regimen with less (no?) toxicity
  - E.g. tumor specific therapy "cancer vaccine"
- Better donor matching
  - Expanded donor pool
  - "Tolerant" stem cells

GASTROINTESTINAL AND LIVER COMPLICATIONS OF BONE MARROW TRANSPLANT

Ghassan Wahbeh MD, Seattle Children's Hospital

Board Style questions

1. What is the mostly likely cause of anorexia day 25 after HSCT?

a) Prednisone
b) Tumor cell lysis syndrome
c) Graft vs host disease
d) Biliary sludge
e) Radiotherapy

Answer C. Beyond day 20, GVHD is the most common cause of anorexia after GVHD. The side effects of the conditioning chemotherapy seem to last 2-3 weeks.

2. The following medications can cause diarrhea in a patient undergoing HSCT except:

a) Piperacillin
b) Tacrolimus
c) Mycophenolate
d) Magnesium
e) Dilaudid

Answer E. Conditioning medications and antibiotics commonly cause diarrhea in the HSCT patient. Narcotic pain medications can cause significant intestinal hypomotility and reduce stool output

3. Which of the following symptoms/sign should raise concern for perianal infection

a) Perianal pain
b) Purulent perianal discharge
c) Subcutaneous fluctuation
d) Rectal bleeding

Answer A. Given the neutropenia, it is uncommon for patients to have a frank abscess despite having a serious perianal infection. Perianal pain should prompt need to assess and treat a developing infection. Invasive anal exams should be avoided.

4. The following are associated with higher risk of veno occlusive disease except:

a) Cyclophosphamide
b) Ursodiol
c) Radiotherapy
d) Hepatitis C
e) Congenital hepatic fibrosis

Answer B. Ursodiol is used as prophylaxis for VOD. Preexisting liver disease and fibrosis, cyclophosphamide and radiotherapy are associated with higher VOD risk.

5. Which of the following is the microscopic hallmark of graft vs host disease

a) Lymphocytic infiltrate
b) Neutrophilic infiltrate
c) Eosinophilic infiltrate
d) Cell apoptosis

Answer D. Cellular apoptosis is the hallmark histologic finding of GVHD. Typically the lamina propria does not show significant inflammatory infiltrate although mononuclear cells, eosinophils and neutrophils can be seen.

Pouch Dysfunction and Surveillance: What are My Options?

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I have the following financial relationships to disclose:

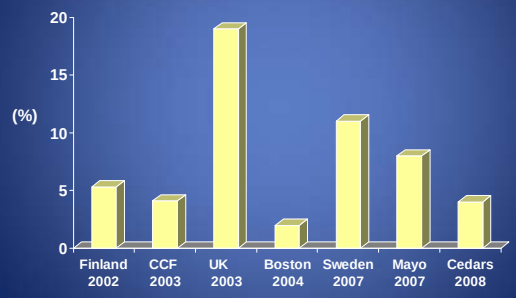
Prometheus Labs: consultant *
Abbott Consultant*
Jannsen Research Support

** Products or services produced by this (these) company (companies) are relevant to my presentation.*

Objectives

1. Discuss evaluation and recognition of pouch dysfunction
2: Describe medical vs. surgical options for the pouch
3: Cancer surveillance for patients with pouch

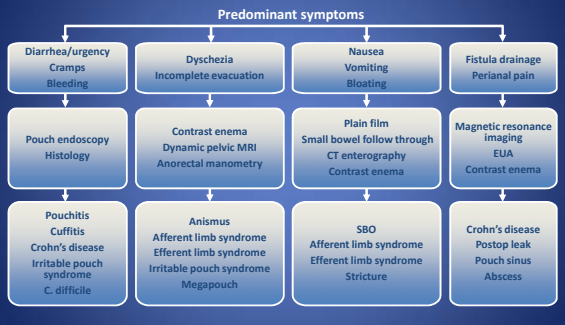
Overall Incidence of Pouch Failure



Evaluation and Recognition of Pouch Dysfunction Key points

- Establish baseline pouch function
- Scope early
- Need pouch and afferent limb visualization
- Pouchogram may be helpful
- Small bowel imaging for obstruction
- Video capsule endoscopy for proximal small bowel disease
- Stool cultures to rule out C.Diff

Evaluation of Pouch Symptoms

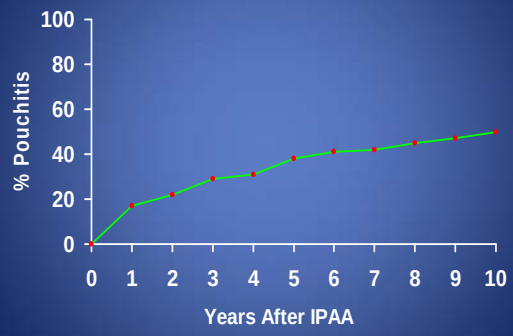


CT, computed tomography; SBO, small-bowel obstruction; EUA, examination under anesthesia

Shen B et al. *Clin Gastroenterol Hepatol.* 2008;6:145.

Describe medical vs. surgical options for the pouch

Pouchitis is Common After IPAA



Adapted from Penna et al.. 1996

Time to Pouchitis after IPAA

	Months	Range
Pouchitis	6	1-116
Acute	9	1-116
Chronic	5 *	1-28

* p<0.03 *vs* acute pouchitis

Acute pouchitis: antibiotic responsive

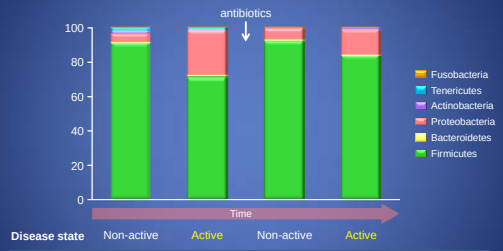
Chronic pouchitis: antibiotic dependent or refractory to antibiotic treatment

Fleshner et al., CGH (2007)

Treatment of Pouchitis

- **Acute pouchitis:**
  - 10-14 day course of antibiotics: ciprofloxacin plus or minus flagyl.
  - Alternatives include Rifaximin but data not convincing
  - No significant role of probiotics
- **Chronic Pouchitis**
  - Recurrent or maintenance course of antibiotics.
  - Can we associated with resistance and cycling antibiotics may be helpful
  - Limited replication of probiotic data
  - Unknown role of biologics and immunomodulators
  - Diversion may be needed

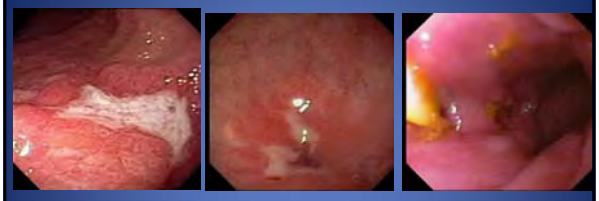
Pouch Inflammation is Associated with CD-Like Dysbiosis and May Be Predicted by Microbiota Analysis and Follow-Up



- Dysbiosis (microbial imbalances on or within the body) precedes and correlates with clinical and endoscopic course (ie. can predict pouchitis based on microbiome).
- Immunomodulators and biologics reverse dysbiosis, while antibiotic treatment does not.

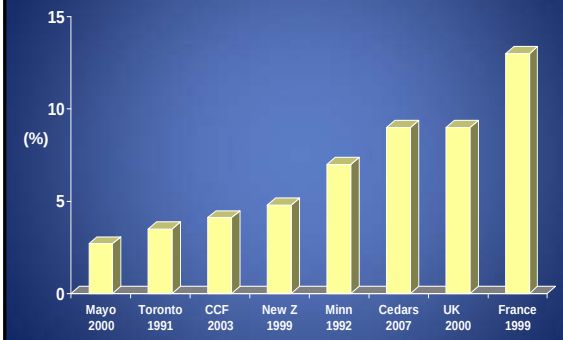
Kovacs A, et al. Presented at DDW; May 19, 2012. Abstract 46.

Classification of Crohn's Disease of Pouch



Inflammatory | Fibrostenotic | Fistulizing

Incidence of CD after IPAA



Association Between Disease Class and Outcome after IPAA

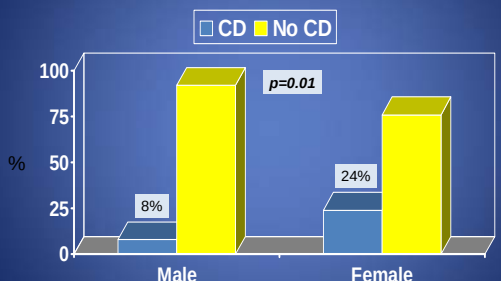
Disease Class	Acute Pouchitis (n=53)	Chronic Pouchitis (n=37)	Crohn's Disease (n=40)
Preoperative			
UC	39 (16%)	26 (11%)	24 (10%)
IBDU	14 (14%)	11 (11%)	16 (16%)
Postoperative			
UC	39 (17%)	24 (10%)	26 (11%)
IC	14 (14%)	13 (13%)	14 (14%)

No difference in AP, CP, CD regardless of Pre op or Post op Diagnosis

Murrell et al., DCR (2009)

Risk Factors for Denovo CD after IPAA

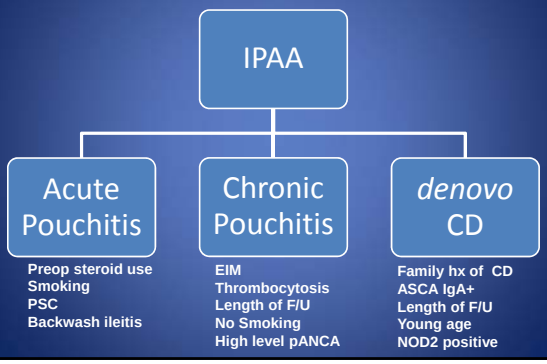
Female Gender



'Crohn's disease was diagnosed definitively based on clinical, radiographic, or histologic criteria'.

Alexander et al., J Ped Surg (03)

Risk Factors and IPAA Outcomes



Treatment of De Novo CD post IPAA

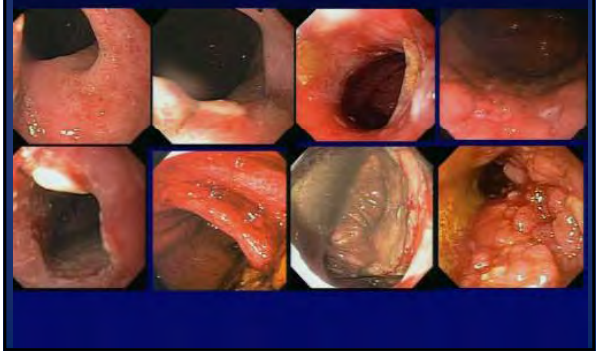
- Antibiotics
- Immunomodulators
- Biologics
- Diversion
- Pouch Excision

Adalimumab for Crohn's Disease of Pouch

Factor	Short term	Long term
Clinical response (N=48)		
None (%)	14(29.2)	22(45.8)
Partial (%)	10(20.8)	10(20.8)
Complete (%)	24(50.0)	16(33.3)
Clinical response inflammatory or fibrostenotic disease (N=23)		
None (%)	7(30.4)	12(52.2)
Partial (%)	6(26.1)	4(17.4)
Complete (%)	10(43.5)	7(30.4)
Clinical response in fistulizing disease (N=25)		
None (%)	7(28.0)	10(40.0)
Partial (%)	4(16.0)	6(24.0)
Complete (%)	14(56.0)	9(36.0)
Mucosal healing (%)	20(41.7)	13(27.1)
Pouch failure (%)	NA	9(18.8)

Li Y, Shen B. IBDJ 2012 [Epub ahead of print]

Cuffitis



Cuffitis

- Endoscopic and histologic inflammation of the rectal columnar cuff (short-strip pouchitis)
- Symptoms similar to those of pouchitis
- High incidence of associated arthralgias
- Overall symptomatic incidence about 4%
- Factors associated with cuffitis
  Younger age (OR=1.16; p=0.04)
  Arthralgias (OR=4.1; p=0.003)

Fichera et al., (07)
Shen at al, CGH (06)

Treatment of Cuffitis

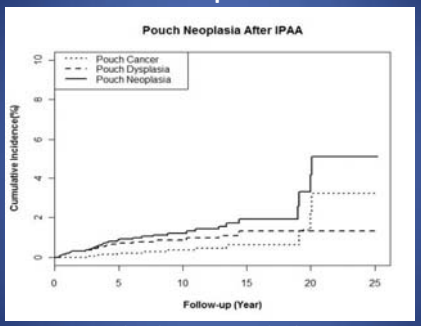
- Mesalamine suppositories *(Shen et al.,2004)*
  500 mg BID
  >90% improvement in bleeding
  70% improvement in arthralgias
- Antibiotics are generally not effective
- ? Immunomodulators
- Mucosectomy with ileal pouch revision but 10% risk of loss of pouch

Clostridium Difficile Infection in Pouch

Authors	Year	N	Prevalence	Outcome
Mann/ *DCR*	2003	1	-	Recovered
Shen/ *DDS*	2006	1	-	Recovered
Shen/ *CGH*	2008	115	18%	Risk factors: Male (OR=5.0)
Shen/*NR GH*	2009	1	-	Fatal
Li/*IBDJ*	2012	196	11% (PCR for toxin B)	Refractory/Recurrence to vancomycin

Cancer surveillance for patients with pouch

Pouch Neoplasia: Cleveland Clinic Experience N=3203



adenocarcinoma 11; lymphoma 1; SCC 3; dysplasia 23

Kariv R, et al. *Gastroenterology* 2010;139:806-812.

Cox Model for Risk Factors for Pouch Neoplasia

	Adjusted HR (95%CI)	*P*
Male gender	1.16 (0.56-2.39)	0.686
Age at pouch	1.01 (0.98-1.04)	0.586
Duration of UC	1.01 (0.97-1.05)	0.547
PSC	0.41 (0.05-3.19)	0.394
Chronic pouchitis	0.69 (0.24-2.00)	0.497
Extensive colitis	1.53 (0.53-4.39)	0.430
Colectomy for cancer	13.43 (3.96-45.53)	<0.0001
Colectomy for dysplasia	3.62 (1.59-8.23)	0.002
Mucosectomy	0.78 (0.34-1.8)	0.559

Kariv R, et al. Gastroenterology 2010;139:806-812.

The Facts on Pouch Neoplasia

- The cumulative incidence of pouch cancer (including lymphoma and squamous cell cancer) has been reported to be 2.4% and 3.4% at 20 and 25 years post-IPAA, respectively
- We should be attempting to identify patients at relatively high risk for pouch cancer and enrolling them in a surveillance program.
- Evaluation 1 year after IPAA, as it appears chronic inflammation should be evident after approximately 6 months.
- Optimal schedule and technique for surveillance endoscopy is unclear

Take Home Points

- "Novel" disease entities can develop, largely due to the change of bowel anatomy

  Reset of "immune thermostat"
- Endoscopy plays a major role in diagnosis and differential diagnosis of pouch disorders
- Cancer can occur in patients after colectomy
- Multidisciplininary approach with a medical, endoscopic, and surgical team

Future Directions

- Refining UC vs UC like CD classification pre IPAA
- Role of microbiome and genetics at predicting post IPAA outcomes
- Role of fecal transplant
- Refining denovo CD classification

POUCH DYSFUNCTION AND SURVEILLANCE: WHAT ARE MY OPTIONS?

Marla Dubinsky MD, Cedars-Sinai Medical Center

Board Style questions

1) Incidence of pouch failure has been reported at:

A. Greater than 25%
B. 5-10%
C. No risk of pouch failure

Answer is B: Most cohorts reported rates of 5-10%. Only one group reported higher than that.

2) The most common pouch complication seen after IPAA is:

A. Acute pouchitis
B. Chronic pouchitis
C. Bowel obstruction
D. Crohn's disease

Answer is A: more than 50% of patients will experience acute pouchitis

3) The most effective treatment for cuffitis is:

A. Prednisone
B. Anti-TNF therapy
C. Local Mesalamine
D. Oral mesalamine

Answer is C. Local mesalamine is the best therapy for cuffitis

4) Although rare, dysplasia of the pouch is increased in patients who underwent IPAA for:

A. Colonic dysplasia or cancer
B. Colonic pseudopolyposis
C. Treatment refractory disease
D. Pancolitis

Answer is A: Cox modeling suggest that pouch dysplasia is increased most in patients who underwent colectomy for dysplasia or cancer