Update in GI: What’s New and Useful

Walter J. Coyle, MD, FACP, FACG
Scripps Primary Care 2011

Movement of the Talk

- Eosinophilic esophagitis: What is it and how do I treat it?
- GERD: What’s New?
- Celiac Sprue: The epidemic
- Hepatitis B and C: Newer Rx
- Inflammatory Bowel Disease: Newer Rx
- CRC screening: Follow the guidelines
Movement of the Talk Part II

- Stool Transplants: The New Rage
- Rosacea and SIBO: New evidence
- Chronic nausea: a new link
- The Human Microbiome: Hot topic
  - Pro and Prebiotics: a rational approach
- C. difficile: It will not go away!
- Conclusions

Question Number 1

- 27 year old male presents with intermittent solid food dysphagia for years. He has had 2 food impactions. He had childhood asthma. The most likely diagnosis is?
  - A. Peptic stricture
  - B. Schatzki’s ring
  - C. Eosinophilic esophagitis
  - D. Adenocarcinoma of the distal esophagus
  - E. Achalasia
**Eosinophilic Esophagitis**

- Common, may be increasing
- Higher in males, younger pts with h/o atopy
- Strong association with food and aeroallergens
  - **THE ALLERGIC ESOPHAGUS**
- Adults: present with dysphagia, atypical GERD symptoms: Usually have years of symptoms
- Children: Failure to thrive, nausea or vomiting.

---

**Eosinophilic Esophagitis**

-Linear Furrows
- Rings

**Diagnosis:** Biopsy at endoscopy
Eosinophilic Esophagitis

- Eos. Abscesses
- Long, often complex strictures
- Careful dilation

Eosinophilic Esophagitis

- Mucosal tear after scope passage
- Try medical treatment first
**Eosinophilic Esophagitis: Treatment**

- PPIs have shown efficacy in up to 50% of pts
- Topical steroids useful but recent PC/Rand studies have shown less efficacy than open label studies
  - Fluticasone or budesonide: Swallowed (not inhaled)
- Allergy consultation: May be helpful in finding food or aeroallergen that is main culprit

*Am J Gastroenterol 2010; 105:747–756*

---

**GERD: What’s Hot**
Nighttime GERD and Sleep

- National GERD survey:
  - GERD pts reported lower quality of life (QOL) than unaffected subjects
  - Nocturnal GERD pts symptoms had lower physical and mental QOL scores than other GERD subjects and controls

- Another national survey:
  - 78% GERD pts have nighttime symptoms
  - 75% noted that nighttime heartburn affected their sleep
  - 63% of those with nighttime heartburn believed it negatively influenced their ability to sleep well

Arch Intern Med 2009;161:45-52
Am J Gastroenterol 2003;98:1487-1493

GERD and BMI: Women

An increase in BMI of 3.5 was associated with increased risk of frequent GERD symptoms, even in women with normal baseline weight

P<0.001
Multivariate odds in women with at least weekly GERD symptoms (n=2306) or no symptoms (n=3904)

GERD

- PPIs are no longer viewed as innocuous meds
  - Malabsorption of nutrients
    - Iron, calcium, Vitamin B12
  - Increase risk for fractures
  - Increase risk for infections including *Clostridium difficile*
  - Interaction with clopidogrel

PPI use and Hip fracture

- Case-control study of patients older than 50 years in a large UK database
  - PPI users had a 4/1000 risk for hip fx vs 1.8/1000 in non-users of acid related meds
  - Absolute risk still low
- Seven case control or cohort trials have shown a small absolute increased risk of fractures
- Recent meta-analysis (DDW abs only) showed a slight increase in hip fx with PPI therapy

*JAMA 2006;296:2947-29*
*Calcif Tissue Int. 2008;83:251-259*
Long term PPI use

- AGA now recommends Calcium / Vit D in long term users
- No guidelines for monitoring B12 or iron
  - Be aware, check when clinically indicated
- Be aware of meds that absorb better with acid
  - Digoxin, amoxicillin, ketoconazole, iron, calcium
  - Organic (heme derived) iron now available

PPIs and Infections

- Studies have linked acid suppression meds including PPIs with C. difficile infection
  - Higher recurrence of C diff if on PPI at time of Rx
- May increase risk for hospital acquired pneumonia

Arch Intern Med 2010;170:772-8
Proton Pump Inhibitors and Risk for Recurrent Clostridium difficile Infection

Amy Linsky, MD; Kalpana Gupta, MD, MPH; Elizabeth V. Lawler, DSc; Jennifer R. Fonula, MA; John A. Herms, MD

Arch Intern Med. 2010;170(9):772-778

Less is more

42% more likely to recur if on PPIs

PPIs and clopidogrel

US Food and Drug Administration: Drug Safety Information Nov 2009
PPIs: Walt’s Recs

- Right drug, right disease, right patient
  - If your patient needs the PPI for PUD, GI bleeding, Barrett’s esophagus, then use the PPI
    - Lowest dose that works
    - Use Calcium and Vit D in long term users
- If it is symptomatic GERD only, other options
  - Lifestyle changes, H2 blockers, antacids
  - Informed consent to patient until final data
  - NB. More GI bleeding in Cogent study in non-PPI users
Celiac Sprue: What’s New!

- Common gene: DQ2 and DQ8: Up to 25%
  - Predisposes you only to Celiac
- Actual disease in 1% in US: Iceberg analogy
- Gluten enteropathy VS Gluten intolerance
  - Gluten avoidance is in vogue!!!
- Diagnosis: Gold standard remains SB biopsy
- Serology: Tissue Transglutaminase and Endomysial antibody excellent sens/specificity
  - ALWAYS check serum IgA (IgA deficiency)

Celiac Burden

The Celiac Iceberg

- Symptomatic Celiac Disease
- Inflamed small intestine
- Silent Celiac Disease
- Normal small intestine
- Latent Celiac Disease

Genetic susceptibility: - DQ2, DQ8
Positive Serology
Celiac Issues and Dilemma

- Pt presents for Celiac testing on gluten free diet
- Pt has negative serology (maybe even normal SB biopsy) and insists they have celiac
  - Role for genetic testing
- Gluten intolerance vs Gluten enteropathy

Health Maintenance:
- Bone health
- Liver disease
- Vitamin and mineral deficiencies

*Am J Gastroenterol* advance online pub, 1 March 2011

Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease: A Double-Blind Randomized Placebo-Controlled Trial

Jessica R. Biesiekierski, B Appl Sci 1, Evan D. Newnham, MD, FRACP 1, Peter M. Irving, MD, MRCP 1, Jacqueline S. Barrett, PhD, BSc, MND 1, Melissa Haines, MD 1, James D. D'eeke, BSc, PhD 2, Susan J. Shepherd, B Appl Sci, PhD 1, Jane G. Muir, PhD, PG rad Dip(Dietetrics) 1 and Peter R. Gibson, MD, FRACP 1

*Am J Gastroenterol* advance online publication, 11 January 2011; doi: 10.1038/ajg.2010.487
Results

- Am J Gastroenterol advance online publication, 11 January 2011; doi: 10.1038/ajg.2010.487

- Figure 1. Recruitment pathway and reasons for screen failure and withdrawals.

Results

- Pain
- Breath
- Satisfaction with stool consistency
- Tiredness
Discussion

- No prior randomized controlled trials demonstrating that the entity of “gluten intolerance” does actually exist.

- This study supports the existence of non-celiac gluten sensitivity based on the following symptoms:
  - Bloating
  - Dissatisfaction with stool consistency
  - Abdominal pain
  - Tiredness

Future studies

- Gluten may have the following deleterious effects in non-celiac patients:
  - Increase fermentation, and thus, distension
  - Increase cholinergic activation, and thus, increased smooth muscle contractility
  - Increase enteric NS stimulation by gluten digestion creating neurally active peptides

- Symptoms may not be related to gliadin proteins of gluten
  - Carbohydrates – fructans (in wheat)
Novak Djokavic claims his energy improved on gluten-free diet and coincided with his winning streak.

“A gluten-free diet can have implications far beyond the physical, especially in tennis, which taxes the mind like few other sports.”

Hepatitis B Virus (HBV)

Transmission electron micrograph of HBV from blood of patient with hepatitis B

Image at left (18327): Courtesy of Centers for Disease Control and Prevention Public Health Image Library at: http://phil.cdc.gov/phil/home.asp
Question Number 2

**Most deaths from chronic hepatitis B are due to??**

A. Portal hypertension  
B. Glomerulonephritis  
C. Spontaneous bacterial peritonitis  
D. GI hemorrhage  
E. Hepatocellular Ca

Complications of CHB

- **Fibrosis**  
  - Consequence of ongoing liver injury and repair

- **Cirrhosis**  
  - Risk of progression to cirrhosis of untreated CHB is 2-6% per year

- **End-stage Liver Disease**  
  - Typically presents 3-5 years after a diagnosis of CHB with cirrhosis

- **Hepatocellular Carcinoma**  
  - 70% of deaths in patients with CHB are due to HCC, with or without cirrhosis

## Treatment Guidelines: Recommendations for Patients With Cirrhosis

### Compensated Cirrhosis

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Potential</th>
<th>Not Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF</td>
<td>Peg-IFN alfa-2a*</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Adefovir</td>
<td>Telbivudine</td>
</tr>
</tbody>
</table>

### Decompensated Cirrhosis

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Not Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF</td>
<td>Peg-IFN alfa-2a and alfa-2b†</td>
</tr>
<tr>
<td>Entecavir</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** therapies are approved for monotherapy only.

*Early cirrhosis only.
†Contraindicated.


## Treatment Guidelines: Recommendations for First-Line Therapy in Patients Without Cirrhosis

### HBeAg Positive or Negative Chronic HBV

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
<th>Not Preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF</td>
<td>Adefovir</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Telbivudine*</td>
<td></td>
</tr>
<tr>
<td>Peg-IFN alfa-2a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*HBV DNA must be undetectable at 24 weeks to continue (Keeffe).
AASLD guidelines: lamivudine and telbivudine not preferred due to relatively high rate of resistance. Adefovir not preferred due to weak antiviral activity and relatively high rate of resistance in HBeAg-negative studies.

Duration of Treatment for Chronic HBV

HBeAg(+)  
- 6 to 12 months after HBsAg seroconversion to reduce relapse rate

HBeAg(-)  
- Relapse common after cessation of therapy; long-term treatment currently recommended

Cirrhosis
- Long-term therapy required
- Combination therapy commonly used

Keeffe EB. Clin Gastroenterol Hepatol. 2006;4:936-962

New hope for hepatitis C, an often hidden disease  
Two strong drugs that promise to help cure the liver-threatening disease may be coming soon

Paul Pockros: The Last Great Hope
Question Number 3

Hepatitis C is found in what percentage of US citizens???

A. 1%
B. 2%
C. 3%
D. 4%
E. 5%

Predictions for 2010-2019

• 193,000 HCV deaths
  - 720,700 million years of advanced liver disease
  - 1.83 million years of life lost

• $11 billion in direct medical care costs

• $21.3 and $54 billion societal costs from premature disability and mortality

Wong Am J Pub Health 2000
HCV Testing Routinely Recommended

- Based on increased risk for infection
  - Ever injected illegal drugs
  - Received clotting factors made before 1987
  - Received blood/organs before July 1992
  - Ever on chronic hemodialysis
  - Evidence of liver disease

- Based on need for exposure management
  - Health care, emergency, public safety workers after needle-stick/mucosal exposures to HCV-positive blood
  - Children born to HCV-positive women

Screening for HCV

- 2010 IOM Recommendation
  - All patients born 1945-1964!

Targets of New Hepatitis C Antivirals

- **Capsid**
- **Envelope**
- **Protease/Helicase**
- **Polymerase**

### Proteases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir</td>
<td>Vertex</td>
<td>III</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Merck</td>
<td>III</td>
</tr>
<tr>
<td>TMC 435</td>
<td>Tibotec, Medivir</td>
<td>IIb</td>
</tr>
<tr>
<td>BI 1335</td>
<td>Boehringer Ingelheim</td>
<td>IIb</td>
</tr>
<tr>
<td>Vaniprevir (MK 7009)</td>
<td>Merck</td>
<td>II</td>
</tr>
<tr>
<td>Narleprevir</td>
<td>Merck</td>
<td>IIa (discontinued)</td>
</tr>
<tr>
<td>Danoprevir</td>
<td>Roche/ Genentech</td>
<td>II</td>
</tr>
<tr>
<td>BMS-850032</td>
<td>BMS</td>
<td>I</td>
</tr>
<tr>
<td>ACH 1625</td>
<td>Achillion</td>
<td>Ib</td>
</tr>
<tr>
<td>GS 9256</td>
<td>Gilead</td>
<td>Ib</td>
</tr>
<tr>
<td>ABT 450</td>
<td>Abbott/ Enanta</td>
<td>I</td>
</tr>
<tr>
<td>IDX 320</td>
<td>Idenix</td>
<td>I (FDA hold)</td>
</tr>
<tr>
<td>GS 9451</td>
<td>Gilead</td>
<td>I</td>
</tr>
<tr>
<td>ACH 2684</td>
<td>Achillion</td>
<td>I</td>
</tr>
<tr>
<td>MK 2170</td>
<td>Merck</td>
<td>I</td>
</tr>
</tbody>
</table>
Emerging HCV Treatment Paradigm

- 2011: Peg-IFN + RBV + protease inhibitor

↓

- 2014: Protease + polymerase +/- other agents ( +/- Peg-IFN +/- RBV)

Inflammatory Bowel Disease

- Newer Concepts

- Treatment

- Top down VS Step up
Current Model: Pathogenesis of Crohn’s Disease and UC

**Environmental Triggers & Modifiers**

**Genetic Susceptibility**

**Immune Response**


Environment and IBD

- Geographic distribution
  - Increase incidence in emigrants to North
- Smoking
- Germ free animals do not get IBD
  - Influence of the microbiome
- ? Infectious (M. paratuberculosis, E. coli, Measles) – Antibody testing
- Diet and Diversion of fecal stream
Environmental Triggers

Infections
Antibiotics
NSAIDs
Diet
Smoking
Stress

IBD

Normal Intestine vs. Intestine With IBD

Normal bowel: controlled inflammation

Environmental triggers (medications infections, diet?)

Normally: inflammation is down-regulated

Normal bowel: controlled inflammation

Inflamed bowel

IBD: failure to down-regulate inflammation

Chronic uncontrolled inflammation = IBD
Management Goals in IBD

- Define disease extent and severity and type
- Evaluate for extra-intestinal disease and complications
- **Induction of clinical remission**
  - Short term side effects balanced vs. disease severity
- **Maintenance of remission**
  - Medical vs. Surgical
  - **STEROID SPARING**
- Education and improvement of quality of life
- “Step up” vs “Top down therapy”

Therapeutic Options in IBD

**Crohn’s Disease**
- 5-Aminosalicylates
- Antibiotics
- Corticosteroids
- 6-MP/ AZA
- Methotrexate
- Biologics (TNFs)
- Tacrolimus
- Probiotics?
- Surgery

**Ulcerative Colitis**
- 5-Aminosalicylates
- Corticosteroids
- 6-MP/ AZA
- Cyclosporine
- Biologics (only infliximab to date)
- Probiotics?
- Surgery
Top down vs Step up Rx

Inverted pyramid in IBD treatment

(1) Current approach
- Biological agents
- AZA/6MP
- MTX
- Prednisone Budesonide
- 5-ASA
- Antibiotics

(2) Early treatment

Should we use TNFs earlier

Rationale for Top-down Approach: Top-down vs Step-up: Early Infliximab or Standard Therapy

Clinical remission (CDAI <150), off corticosteroids, and no intestinal resection

- Step-up
- Top-down

<table>
<thead>
<tr>
<th>Week</th>
<th>Step-up</th>
<th>Top-down</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>26</td>
<td>65</td>
<td>67</td>
</tr>
<tr>
<td>52</td>
<td>60</td>
<td>45</td>
</tr>
<tr>
<td>78</td>
<td>62</td>
<td>47</td>
</tr>
<tr>
<td>104</td>
<td>45</td>
<td>57</td>
</tr>
</tbody>
</table>

P<.001, P<.006, P<.028, P<.787, P<.431

Summary for IBD

- Pathogenesis remains obscure still
  - Role of Microbiome key
- Serology has limited role in diagnosis
  - Helpful in borderline cases
- Treatment options have increased
  - Individualized therapy best
  - Top down appropriate for some patients

Question Number 3

Which of the following extra-intestinal manifestations of IBD does not respond to treatment of the IBD???

A. Primary sclerosing cholangitis
B. Erythema nodosum
C. Sacroileitis
D. Acute arthritis
E. A and C
F. B and D
Colon Cancer Screening

- Review of the Guidelines

Question Number 3

- What is the lifetime risk for colon cancer in the United States?
  A. 2%
  B. 4%
  C. 6%
  D. 8%
  E. 10%
Colon Cancer

- Second most common cause of cancer death
- Prototypical disease for screening
  - Intermediate probability of disease
  - Significant impact on public health
  - Well defined, modifiable disease progression

Current Guidelines

<table>
<thead>
<tr>
<th>Test</th>
<th>USPSTF</th>
<th>ACS ACR USMSTFCC</th>
<th>ACG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50-75</td>
<td>50</td>
<td>50/45 AfAm</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>10 yrs</td>
<td>10 yrs</td>
<td>10 yrs</td>
</tr>
<tr>
<td>Flex Sig</td>
<td>5 yrs</td>
<td>5 yrs</td>
<td>5-10 yrs</td>
</tr>
<tr>
<td>FS/FOBT</td>
<td>5 yrs/3 yrs</td>
<td>5 yrs/3 yrs</td>
<td>5 yrs</td>
</tr>
<tr>
<td>DCBE</td>
<td></td>
<td>5 yrs</td>
<td></td>
</tr>
<tr>
<td>CT Colonography</td>
<td>Insuff Evid</td>
<td>5 yrs</td>
<td>5 yrs</td>
</tr>
<tr>
<td>FOBT</td>
<td>Yearly</td>
<td>Yearly</td>
<td>Yearly</td>
</tr>
<tr>
<td>FIT</td>
<td>Yearly</td>
<td>Yearly</td>
<td>Pt refuses</td>
</tr>
<tr>
<td>Stool DNA</td>
<td>Yearly</td>
<td>Yearly</td>
<td>Yearly</td>
</tr>
</tbody>
</table>

Stool DNA
Average Risk Screening: Recommendations

- ≥50 years old
- Stool cards (yearly); FIT?? AND Flexible sigmoidoscopy (every 3–5 years)
- OR Colonoscopy (every 10 years)
- OR Barium enema (every 5 years)
- Preferred: ACG and MSGITF
  Option: USPSTF, ACS, AGA

FUTURE?
- Stool DNA
- CT colonography
- Capsule Colonoscopy

New Recommendations for African-Americans

- Younger mean age at diagnosis (60–66 years)
- Higher incidence rates
- Higher mortality rates
- More proximal distribution of cancers and adenomas
- Recent American College of Gastroenterology recommendations to begin average-risk screening at age 45

Screening Compliance is Low

Figure 4D. Colorectal Cancer Test Within Recommended Time Intervals, Adults 50 and Older, US, 2005

Cancer Prevention and Early Detection, Facts and Figures 2008

Stool Transplants:
Everyone is doing it!
Stool Transplants: How To

- Stool transplants: “prepared” feces by NGT or enema or colonoscopy
  - Usually family member; 30-50 g fresh stool
  - Stool homogenized for delivery
  - No infectious complications to date
    - Screen for Hepatitis, HIV, etc...
  - 73-100% response reported in C Diff

Gastro 2006;130 Clin Infect Dis 2003;36

Stool Transplant: Evidence

- 2003 case series of refractory *C diff* patients
  - Stool via NG from healthy family member
  - 15 of 18 became recurrence-free

- 2009 case series of refractory *C diff* patients
  - 11 of 15 became recurrence-free

- 2010 case series of refractory C diff patients
  - Stool via colonoscopy
  - 12 of 12 with immediate and sustained response

Clin Infect Dis 2003;36: 540-544
QJM 2009;102:781-784
Yoon, J of Clin Gastro 2010, 44:562-66
Colonoscopy Stool Transplants

Coming to your neighborhood soon... .

Stool transplants done here.

Donations accepted.
Coyle’s Corollary

It is better to be a stool donor than a recipient.

Stool donor cards will be made available after this lecture.
Stool Donor Card

Share your stool; stop C diff

Clinical Gastrohepology 2008; 759-764

Small Intestinal Bacterial Overgrowth in Rosacea: Clinical Effectiveness of Its Eradication

ANDREA PARDOI, STEFANIA PAOLINO, ALFREDO GRECO, FRANCESCO DRAGO, CARLO MANISI, ALFREDO REBORA, AURORA PARDOI, and VINCENZO SAVARINO

*Department of Internal Medicine, Gastroenterology Unit, and †Department of Endocrine and Medical Sciences, Dermatology Unit, University of Genoa, Genoa, Italy

Clinical Gastro Hep 2008; 759-764
Methods

- Prosp. study; 113 pts with rosacea  60 controls
- Derm Assessment by two docs
  - 7 point scale
- All subjects completed global score
- Baseline labs, Urease BT, H2 Breath tests
  - Lactulose BT: 1st, + test if double peak seen
  - Glucose BT: 2nd (1 wk later), + test single peak
- Hp + pts, treated then re-tested by H2 BT
- If both Hp + and SIBO+: rx SIBO 1st

Results: SIBO pos and neg pts

![Graphs showing clinical outcomes](image)

*Figure 2. Clinical outcome in SIBO positive patients treated with rifaximin (eradicated patients) or placebo.*
*Figure 3. Clinical outcome in SIBO positive and SIBO negative patients treated with rifaximin.*
Rosacea and the Microbiome

SIBO common in Rosacea pts
- Esp those with papulopustules
- Rx of SIBO results in dramatic improvement of rash
  - 78% resolved/ 17% improved (95% total)
- Affect is sustained (9 months); relapse can be re-treated
- Hypothesis: SIBO increases intest absorption of bacterial products, esp endotoxin, proinflam cytokines
  - SIBO more important then colonic bacteria (SIBO neg rosacea pts did not respond as well)

Discussion
Question number 4. What is the cause of discoloration?

A. Strep toxic shock syndrome
B. Gray Turner sign from pancreatitis
C. Cannabinoid hyperemesis syndrome
D. Heparin-induced cutaneous hemorrhage

Cannabinoid Hyperemesis Syndrome

- First reported in Australia
- Chronic, heavy marijuana use
  - More common in males
- Recurrent episodes of abdominal pain and vomiting
- Compulsive hot bathing and showers for relief of symptoms
- Rx: Quit the Weed!

Singh E, Coyle W. Am J Gastro 2008;103:1048-49
The Microbiome and Probiotics

The Human Microbiome

- Definitions:
  - Microbiome: Aggregate of all gut species
  - Microbiota: Individual bacterial species in the biome
  - Over 100 trillion organisms ($10^{14}$)
    - Passengers in the mobile colonic petri dish
    - Over 500 species identified so far (70 divisions)
    - 90% of the cells in our body our microbial!
  - 100 fold more genes in our gut then in us
  - Our flora are an integral part of our genetic landscape and evolution
The Human Gut Flora

<table>
<thead>
<tr>
<th>Phyla</th>
<th>Representative genera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>Ruminococcus</td>
</tr>
<tr>
<td>Firmicutes</td>
<td>Clostridum</td>
</tr>
<tr>
<td></td>
<td>Peptostreptococcus</td>
</tr>
<tr>
<td></td>
<td>Lactobacillus</td>
</tr>
<tr>
<td></td>
<td>Enterococcus</td>
</tr>
<tr>
<td>Bacteroidetes</td>
<td>Bacteroides</td>
</tr>
<tr>
<td>Proteobacteria</td>
<td>Desulfobrio</td>
</tr>
<tr>
<td></td>
<td>Escherichia</td>
</tr>
<tr>
<td></td>
<td>Helicobacter</td>
</tr>
<tr>
<td>Verrucomicrobia</td>
<td>Bifidobacterium</td>
</tr>
<tr>
<td>Acidobacteria</td>
<td></td>
</tr>
<tr>
<td>Cytophagia</td>
<td></td>
</tr>
<tr>
<td>Synergisteta</td>
<td></td>
</tr>
<tr>
<td>Archaea</td>
<td>Methanobrevibacter</td>
</tr>
</tbody>
</table>

* Prokaryotic phyla were identified by using an alignment of the 16,348-sequence dataset from reference 18
* Not related to any known genera.


Microbes and Humans

Dethlefsen Nature 2007; 449:812-818
**Gut Flora and Metabolism**

- Microbial genomes enhance our metabolic activity
  - May indirectly or directly effect our metabolism
- The colon is very active metabolically
  - 20-70 gms of carbs and 5-20 gms of protein/day
  - Over 100 kcal per day!
- Mass of colonic microbiome = single kidney
  - Metabolically as active as the liver

*Hooper, et al. Annu Rev Nutr, 2002*

**Probiotics**

- **Definition:** Live microorganisms which when ingested in adequate amounts confer a health benefit on the host.
- **Majority of probiotics are Gram +, lactic acid producers** (ie. Firmacutes)
  - Bifidobacterial species and *Lactobacillus* species
  - Survive transit through stomach and duodenum
- **Others include:** non-pathogenic streptococci, enterococci, *E coli* Nissle 1917, *Saccharomyces boulardii* (yeast)

*Sheil, et al. In Gastrointestinal Microbiology, 2006*
**Question Number 5**

Which probiotic has been shown to decrease mucosal IL-6 levels?

A. *Lactobacillus acidophilus*
B. *Bifidobacter infantis*
C. *Saccharomyces boulardii*
D. *Lactobacillus rhamnosus*

---

**Probiotics**

- **VSL #3**
- **4 lactobacilli**
  - *L. plantarum, casei, acidophilus, debrueckii spp*
- **3 bifidobacteria**
  - *B. infantis, breve, longum*
- **1 streptococcus**
  - *Streptococcus salivarius ssp. thermophilus*

Rand, PC studies have shown efficacy in pouchitis and IBS. Some efficacy in mild/mod UC in new study.
Probiotics

- Digestive Advantage
  - Ganeden BC30
  - Bacillus coagulans
  - Erythritol
  - Cellulose
  - Other minor ingredients

- Some data for IBS
  - Mostly bloating


Probiotics

- Bifidobacterium infantis 35624 aka Bifantis
- “Patented” strain of probiotic in Align
- Decreased symptoms in two large trials in subjects with IBS*

O’Mahoney L, et al. Gastro 2005;128
Probiotics

- **Saccharomyces boulardii**
- Other minor ingredients
- Shown in Rand / PC trials to help prevent recurrent *C. difficile* infection
- Decreases antibiotic associated diarrhea

Am J Gastroenterol. 2006 Apr;101(4):812-22

Probiotics in Food (Actimel)

- *L. casei* Immunitas™
- Claim it is scientifically proven to be effective
- “Each bottle contains 10 billion live” bacteria that survive and remain active in the digestive tract.”
**Probiotics in Food (Activia)**

- Contains Bifidus regularis
- Bifidobacterium animus
- Scientific trials show increased transit time in adults and women
- “Helps with slow transit in women and the elderly”

_Bioscience and Microflora, 2001;20:43-48,
Aliment Pharn Ther 2002;16:587-93_

**Probiotics for Immune System**

- Lactobacillus rhamnosus GG (ATCC 53103)
- Patented by Gorbach and Goldin
- Various studies have shown it to be better than placebo for diarrheal illnesses
- Proven to survive the stomach, produces lactic acid and binds to human colonocytes

_BMJ 2007; 335 : 340-345_
# Probiotics and prebiotics in maintenance of remission in Crohn’s disease

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>n</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Dur</th>
<th>Intervention</th>
<th>Comparator</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guslandi (2000)</td>
<td>32</td>
<td>S. Boullardii + Mesalamine</td>
<td>Mesalamine</td>
<td>6</td>
<td>6</td>
<td>38</td>
<td>0.04</td>
</tr>
<tr>
<td>Campieri (2000)</td>
<td>40</td>
<td>VSL #3</td>
<td>Mesalamine</td>
<td>12</td>
<td>20</td>
<td>40</td>
<td>NR</td>
</tr>
<tr>
<td>Prantera (2002)</td>
<td>45</td>
<td>LGG</td>
<td>Placebo</td>
<td>12</td>
<td>17</td>
<td>11</td>
<td>0.3</td>
</tr>
<tr>
<td>Schultz (2004)</td>
<td>11</td>
<td>LGG</td>
<td>Placebo</td>
<td>6</td>
<td>60</td>
<td>67</td>
<td>NS</td>
</tr>
<tr>
<td>Bousvaros (2005)</td>
<td>75</td>
<td>LGG</td>
<td>Placebo</td>
<td>24</td>
<td>31</td>
<td>17</td>
<td>0.18</td>
</tr>
<tr>
<td>Marleau (2006)</td>
<td>98</td>
<td>L. johnsonii</td>
<td>Placebo</td>
<td>6</td>
<td>49</td>
<td>64</td>
<td>0.15</td>
</tr>
<tr>
<td>Van Gossum (2007)</td>
<td>70</td>
<td>L. johnsonii</td>
<td>Placebo</td>
<td>3</td>
<td>15</td>
<td>14</td>
<td>0.91</td>
</tr>
<tr>
<td>Chermesh (2007)</td>
<td>30</td>
<td>Synbiotic 2000</td>
<td>Placebo</td>
<td>24</td>
<td>25</td>
<td>20</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Clostridium difficile*
*Clostridium difficile* and altered microbiota

Confirmed BI NAP1 strain

Metronidazole failures

Leffler and Lamont in GASTRO 2009;136:1899-1912

New C Difficile Rx Guidelines

Infect Control Hosp Epidemiol 2010; 31(5):431-455
Burden Of CDI in US


Treatment

- DC offending antibiotic(s) if possible
- Avoid antiperistaltic agents (incl narcs)
- Supportive care (hydrate, electrolytes)
- Antimicrobial therapy:
  - Oral metronidazole: 250 mg qid or 500 mg TID for 10 days; low cost, effective
  - Oral Vancomycin: 125-250 mg QID for 10 days
    - High cost

Ann Intern Med 2006;145
Gastro 2009; 136:1913–1924
Recurrence: Probiotic Treatment of *C difficile*

- **Probiotics**
  - *Saccharomyces boulardii*: 500 mg bid for 4-6 wks
  - Best evidence of all probiotics
  - Several DB / PC trials show good efficacy
  - *Lactobacilli*: 1g qid for 4-6 weeks
    - Evidence not as convincing
  - PO nontoxicogenic *C Diff*: experimental
    - Effective but only case reports to date

Gastro 2006;130  Ann Intern Med 2006; 145

---

**Fidaxomicin**

**ORIGINAL ARTICLE**

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Muline, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and You-Keung Shue, Ph.D. for the OPT-80.003 Clinical Study Group


- **Macrocyclic antibiotic**
- Cure: 88.2% vs 85.8% vancomycin
- Recurrence Rate: 15.4% vs 25.3%
- FDA approved.
Fidaxomicin

- FDA approved May 2011
- Macrolide Ab: Aka Dificid
- Dose: 200 mg BID for 10 days
- Estimated cost: $2800 for full course

Walt’s Rec: Not first line, too expensive
  - Save for recurrent C. difficile infections

Figure 2. Rates of Primary and Secondary End Points.
For the primary outcome of clinical cure, the lower boundary of the 97.5% confidence interval for the difference in cure rates between fidaxomicin and vancomycin was -3.1 percentage points in the modified intention-to-treat (mITT) analysis and -2.4 percentage points in the pre-protocol (PP) analysis.
Probiotics and Diarrhea

- 135 hospitalized pts given antibiotics
- DB, PC, Rand trial
- Probiotic Yogurt (Actimel) or PC BID
- Diarrhea: 34% PC vs 12% active (NNT:5)
- C Diff: Less often in Rx arm (NNT: 6)
- First rand trial to show prevention of C diff with probiotics


Probiotics and Pancreatitis

Not all good news!

- 296 hospitalized pts with acute pancreatitis given probiotics
- DB, PC, Rand trial; Given in tube feedings
- Probiotic: Ecologic 642 (L. acidophilus, casei, salivarius, lactis and B. bifidum, lactis.)
- Morbidity: No difference in infections
- Mortality: 24 (16%) vs 9 (6%) in PC
  - 9 pts in Rx arm developed ischemic bowel

Prebiotics

- Ingested substances that selectively stimulate the proliferation and/or activity of desirable bacterial populations present in the host intestinal tract.
- Usually target bifidobacteria and lactobacilli
  - Bifidogenic or bifidus factors explored in the 50s
- Usually are non-digestible oligosaccharides (NDOs)
  - Lactulose, galacto-oligosaccharides, lactosucrose...

Prebiotics

- Inulin: plant polymers mainly comprising fructose units, use have a terminal glucose
- Indigestable fiber
- Gut flora produce H2, CO2, methane gas from inulin

"Breakfast of Flatulence"
Prebiotics

Is it possible to design a food, sugar, protein, or fat that would alter your gut flora to promote weight loss?

More likely possibility is to give a prebiotic that decreases your “Energy Harvest” of colonic bacteria

ie. lose weight by making your gut flora less efficient at digesting your left over food
Conclusions

- Future studies must focus on the mechanisms of influence of our gut flora.
- Studies must be placebo controlled and high quality.
- Truly need translational science to work at the levels of the petri dish, genomics, and clinical outcomes.
- Much more to come!
GI Update: Summary

- Longstanding dysphagia: Think EoE
- PPIs: Use them thoughtfully
- Be smart about Celiac disease: Know the tests
- Many new options for Hepatitis B and C
- TNFs will be used more often for IBD
- Colon cancer screening: DO IT!

GI Update: Summary

- Stool transplants: Not ready for prime time
- Think SIBO with Rosacea
- Pot and vomiting: Ask about hot baths
- Microbiome: research will explode
- C. difficile: the pest is here to stay
Questions

Break Time

THE CALL
First Rule: Never go to “check” a puppy out

The Visit

Review of Bloodline
Rule two: Never believe that parents have anything to do with the pup.

Rule Three: Never bring the puppy home.
The Infection
The Decision
Probiotics and *C. Difficile*

- 124 Adults with *C. difficile* (Rand, PC)
  - 64 1st episode, 60 recurrent CDAD
  - Standard Ab with *S. boulardii* or PBO
- Outcome: Recurrence of CDAD
  - 1st Episode: 19.3% vs 24.2% (P=.86)
  - Rec CDAD: 34.6% vs 64.7% (P=.04)
- *S. boulardii* reduces risk for recurrence in subjects with recurrent *C. difficile*

PPIs and Clopidogrel

- Most PPIs are metabolized partly via CYP 2C19
- CYP 2C19 critical for activation of clopidogrel
- Very mixed data whether PPIs decrease efficacy of clopidogrel: ie. **Concern is stent patency**
- Prompted FDA warning
- The only Rand/PC controlled study
  - Showed no effect from PPIs on stent occlusion
  - Study stopped due to funding shortage

**COGENT TRIAL**

- 3761 subjects
- CV Event Rate: 4.9% vs 5.7%

*N Engl J Med 2010;363:1909-17*
Gastroenterology for the Primary Care Physician

Walter J. Coyle, MD

COGENT TRIAL

-3761 subjects
-GI event rate: 1.1% vs 2.9%

End point | Placebo, n | PPI, n | p
---|---|---|---
All CV events | 67 | 69 | NS
MI | 37 | 36 | NS
Revascularization | 67 | 69 | NS
GI events | 67 | 38 | 0.007

Bhatt D. TCT 2009; Sept 24, 2009; San Francisco, CA.