Update in GI: What’s New and Useful

Walter J. Coyle, MD, FACP, FACG

October 2012
Disclosures

- I have no disclosures related to this talk

- Specifically, I have no interests in any probiotic or pre-biotic brands
Movement of the Talk

- Eosinophilic esophagitis: What is it and how do I treat it?
- GERD: What’s New?
- Celiac Sprue: The epidemic
- CRC screening: Follow the guidelines
  - What’s new?
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 Pre biotics: a rational approach
- *C. difficile*: It will not go away!
- Conclusions
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
Visceral Adiposity Increases the Risk of GERD

Subcutaneous adiposity

Visceral adiposity

Courtesy of Brian Jacobson
Obesity-Separation of the LES and Diaphragmatic Crus

HRM

Inspiration

LES

Crural Diaphragm

Intragastric Pressure

Normal

Obese

Intragastric Pressure

Visceral Adiposity

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)
## Obesity as a Risk Factor: Barrett’s Esophagus

Risk of Barrett’s Esophagus in Obesity with GERD Symptoms

<table>
<thead>
<tr>
<th>Obesity</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>With GERD Symptoms</td>
<td>34.4</td>
<td>6.3-188.0</td>
</tr>
<tr>
<td>Without GERD Symptoms</td>
<td>0.7</td>
<td>0.2-2.4</td>
</tr>
</tbody>
</table>

n = 167 with histologically confirmed Barrett’s esophagus

EAC in the Danish Population

- General population: n = 2602 (92.40%)
- BE Population: n = 197 (7.60%)

- Total general population = 5.4 million
- Total BE population = 11,028
- Risk of EAC for BE: 0.12% per 1000 patient yrs. (1/833 BE cases)

Hvid-Jensen et al., NEJM 2011;365(15):1375-1385
Lower Incidence of EAC with Larger Studies

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 (less an issue now)
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 at risk for osteoporosis
- 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

Am J Gastro 2007;102:2047-56
CMAJ  2004;171:33-38
JAMA. 2004;292:1955-60
Arch Intern Med 2010;170:772-8
LESS IS MORE

Proton Pump Inhibitors and Risk for Recurrent Clostridium difficile Infection

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

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

42% more likely to recur if on PPIs

Figure 2. Recurrence-free survival in those exposed vs unexposed to proton pump inhibitors (PPIs) during treatment for incident Clostridium difficile infection. Time to recurrence started from the incident toxin finding or the start of antibiotic treatment (=3 days after the diagnosis).
**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 Disease: What’s New!

- Common gene: DQ2 and DQ8: Up to 25%
  - ONLY predisposes one 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

Silent Celiac Disease

Latent Celiac Disease

Inflamed small intestine

Normal small intestine

Genetic susceptibility: - DQ2, DQ8
Positive Serology
Varying Forms of Celiac Disease

- Classical celiac disease of childhood
- Late onset, non-specific GI symptoms
- Dermatitis herpetiformis
- Extra-intestinal presentations (many)
- Associated conditions (many)
- Silent or asymptomatic celiac disease (relatives)
- Latent or potential celiac disease
Dermatitis Herpetiformis

- Pruritic papulovesicular lesions
  - IgA deposits at dermal-epidermal junction
- Almost all have abnormal intestinal biopsies
  - Few have GI symptoms
- Treatment directed against skin doesn’t help gut lesions (e.g., dapsone)
- Gluten free diet helps both gut and skin
Associated Autoimmune Conditions

- Diabetes mellitus - Type I
  - ~3 to 8% have celiac disease
- Autoimmune thyroid disease (~5%)
- Addison’s disease
- Alopecia areata
- Sjogren’s syndrome
- Others
Associated Hepatobiliary Conditions

- Primary sclerosing cholangitis
- Autoimmune cholangitis
- Primary biliary cirrhosis
- Elevated transaminases (up to 5 X normal)
  - Nonspecific histologic changes
  - Normalize on GFD within a year in 75-95%
  - Evaluation of unexplained elevated AST, ALT includes testing for celiac disease

Changing Picture of Disease

- Classical form less prevalent now
- Average age of diagnosis in 5th decade
- Many are overweight
- Seroprevalence M=F, diagnosis M<F
- Other presentations are being increasingly recognized:
  - Anemia
  - Osteoporosis
  - Obstetrical problems
  - Neuropsychiatric manifestations
  - Related autoimmune conditions
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. Doecke, BSc, PhD 2, Susan J. Shepherd, B Appl Sci, PhD 1, Jane G. Muir, PhD, PGrad Dip (Dietetics) 1 and Peter R. Gibson, MD, FRACP 1

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

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

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

Pain

Bloating

Satisfaction with stool consistency

Tiredness

Gluten
Placebo
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
Gluten: The new bad boy

“I have no idea what gluten is, either, but I’m avoiding it, just to be safe.”
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 Djokovic 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.”
Colon Cancer Screening

- Review of the Guidelines
- What’s new?
- How are we doing?
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 USMSTF</th>
<th>ACG</th>
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<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>
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<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></td>
<td></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>
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<tr>
<td>Stool DNA</td>
<td></td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Group</td>
<td>Colo</td>
<td>FSig</td>
<td>FOBT</td>
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<td>-----------------------</td>
</tr>
<tr>
<td><strong>USPSTF 2008</strong></td>
<td>Q10yr; Age 50-75</td>
<td>Q5yr; Age 50-75</td>
<td>Annually; Age 50-75</td>
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<tr>
<td><strong>ACS-MSTF 2008</strong></td>
<td>Q10yr; Age ≥ 50</td>
<td>Q5yr; Age ≥ 50</td>
<td>Annually; Age ≥ 50</td>
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<tr>
<td><strong>ACG 2009</strong></td>
<td>ACS/MSTF</td>
<td>Q5-10yr; Age ≥ 50</td>
<td>Annually; Age ≥ 50</td>
</tr>
<tr>
<td><strong>AAFP 2010</strong></td>
<td>USPSTF</td>
<td>USPSTF</td>
<td>USPSTF</td>
</tr>
<tr>
<td><strong>NCCN 2010</strong></td>
<td>ACS/MSTF</td>
<td>ACS/MSTF</td>
<td>ACS/MSTF</td>
</tr>
<tr>
<td><strong>Kaiser</strong></td>
<td>Avg risk adults</td>
<td>Avg risk adults</td>
<td>Avg risk adults</td>
</tr>
<tr>
<td><strong>United</strong></td>
<td>ACS/MSTF</td>
<td>ACS/MSTF</td>
<td>ACS/MSTF</td>
</tr>
</tbody>
</table>
Recent Evidence: Colonoscopy Reduces Mortality

- National Polyp Study (2012)
  - Removal of adenomas resulted in 53% lower risk of CRC related death within 10 years (up to 23 years)

- Canadian studies
  - CRC related deaths decreased with gastroenterologist performed colonoscopy complete to cecum (even right sided)

- German study
  - Diminished CRC incidence after colonoscopy

Zauber AG et al. NEJM 2012
FIT

- Antibody tests for the globin product
  - Test performance can be modified/adjusted
- Better compliance than FOBT
  - Easier (brush stool in toilet water)
  - Not impacted by diet
  - One, two, or three samples required
- Any positive test = colonoscopy
- Cannot make a class recommendation
  - Individual tests vary considerably; similar sensitivity to HS FOBT and better specificity
Colonoscopy versus Fecal Immunochemical Testing in Colorectal-Cancer Screening

Enrique Quintero, M.D., Ph.D., Antoni Castells, M.D., Ph.D., Luis Bujanda, M.D., Ph.D., Joaquín Cubiella, M.D., Ph.D., Dolores Salas, M.D., Ángel Lanas, M.D., Ph.D., Montserrat Andreu, M.D., Ph.D., Fernando Carballo, M.D., Ph.D., Juan Diego Morillas, M.D., Ph.D., Cristina Hernández, B.Sc., Rodrigo Jover, M.D., Ph.D., Isabel Montalvo, M.D., Ph.D., Juan Arenas, M.D., Ph.D., Eva Laredo, R.N., Vicent Hernández, M.D., Ph.D., Felipe Iglesias, R.N., Estela Cid, R.N., Raquel Zubizarreta, M.D., Teresa Sala, M.D., Marta Ponce, M.D., Mercedes Andrés, M.D., Gloria Teruel, M.D., Antonio Peris, M.D., María-Pilar Roncales, R.N., Mónica Polo-Tomás, M.D., Ph.D., Xavier Bessa, M.D., Ph.D., Olga Ferrer-Armengou, R.N., Jaume Grau, M.D., Anna Serradesanferm, R.N., Akiko Ono, M.D., José Cruzado, M.D., Francisco Pérez-Riquelme, M.D., Inmaculada Alonso-Abreu, M.D., Mariola de la Vega-Prieto, M.D., Juana Maria Reyes-Melian, M.D., Guillermo Cacho, M.D., José Díaz-Tasende, M.D., Alberto Herreros-de-Tejada, M.D., Carmen Poves, M.D., Cecilio Santander, M.D., and Andrés González-Navarro, M.D., for the COLONPREV Study Investigators*
Colonoscopy versus FIT in Colorectal-Cancer Screening

- 26,703 colo invites; 26,599 FIT invites
  - Male and females, randomized, prospective
  - 24.6% had colo vs 34.2% had FIT (P<.001)
  - CRC: 30 pts (0.1%) vs 33 (0.1%)
  - Adenomas: 514 (1.9%) vs 234 (0.9%)  P<.001

- FIT test may compare well to colo for cancer detection. Poor for detection of polyps.

N ENGL J MED 2012; 366:697-706
Average Risk Screening: Recommendations

≥50 years old

OR

Flexible sigmoidoscopy (every 3–5 years)

AND

Stool cards (yearly); FIT??

OR

Colonoscopy (every 10 years)

Option: USPSTF, ACS, AGA

Preferred: ACG and MSGITF

OR

Barium enema (every 5 years)

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

*Either a fecal occult blood test within the past year or sigmoidoscopy in the past 5 years or colonoscopy within the past 10 years. Total rates are age-adjusted to the 2000 US standard population.


American Cancer Society, Surveillance Research

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

Last-ditch method at fighting intestinal superbug

By LAURAN NEERGAARD, AP Medical Writer – Mon Dec 13, 9:34 pm ET

WASHINGTON – A superbug named C-diff is on the rise, a germ that so ravages some people’s intestines that repeated tries of the strongest, most expensive antibiotic can’t conquer their disabling diarrhea.

Now a small but growing number of doctors are trying a last-ditch treatment: Using good bacteria to fight off the bad by transplanting stool from a healthy person into the sick person’s colon.

Yes, there’s a yuck factor. But reports of several dozen cases in a medical journal and at a meeting of the nation’s gastroenterologists this fall suggest that with no more inconvenience than a colonoscopy, people who have suffered C-diff for months, or longer, can rapidly improve.

"This is the ultimate probiotic," says Dr. Lawrence Brandt of New York’s Montefiore Medical Center, who has performed 17 of the procedures.
Coming to your neighborhood soon....

Stool transplants done here.
Donations accepted.
BRIEF COMMUNICATION

Success of Self-Administered Home Fecal Transplantation for Chronic Clostridium difficile Infection

MICHAEL S. SILVERMAN,*† IAN DAVIS,§ and DYLAN R. PILLAI*‖

*Department of Medicine, University of Toronto, Toronto, Ontario; †Lakeridge Health Corp, Oshawa, Ontario; ‡Department of Medicine, Dalhousie University, Halifax, Nova Scotia; and §Ontario Agency for Health Protection and Promotion, Toronto, Ontario, Canada

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:471–473
Fecal Transplant Workgroup

Good review and provides “cookbook” recipe for performing fecal transplant
Coyle’s Corollary

It is better to be a stool donor than a recipient.
Stool donor cards will be made available after this lecture.
NHS Organ Donor Register

I want to help others to live in the event of my death

Stool Donor Card

Share your stool; stop C diff
Small Intestinal Bacterial Overgrowth in Rosacea: Clinical Effectiveness of Its Eradication

ANDREA PARODI,* STEFANIA PAOLINO,† ALFREDO GRECO,* FRANCESCO DRAGO,‡ CARLO MANSI,* ALFREDO REBORA,‡ AURORA PARODI,† and VINCENZO SAVARINO*

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

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.

Clinical Gastro Hep 2008; 759-764
Rosacea and the Microbiome
Discussion

- 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)
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
Cannabinoid Hyperemesis: A Case Series of 98 Patients

Douglas A. Simonetto, MD; Amy S. Oxentenko, MD; Margot L. Herman, MD; and Jason H. Szostek, MD
### TABLE 3. Clinical Manifestations of Cannabinoid Hyperemesis in 98 Patients

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>98 (100)</td>
</tr>
<tr>
<td>Emesis</td>
<td>98 (100)</td>
</tr>
<tr>
<td>Time of symptoms (n=75)</td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>53 (71)</td>
</tr>
<tr>
<td>Postprandial</td>
<td>16 (21)</td>
</tr>
<tr>
<td>During defecation</td>
<td>6 (8)</td>
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<tr>
<td>Abdominal pain</td>
<td>84 (86)</td>
</tr>
<tr>
<td>Location of pain (n=75)</td>
<td></td>
</tr>
<tr>
<td>Epigastric</td>
<td>46 (61)</td>
</tr>
<tr>
<td>Periumbilical</td>
<td>17 (23)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Description of pain (n=48)</td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td>13 (27)</td>
</tr>
<tr>
<td>Crampy</td>
<td>14 (29)</td>
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<tr>
<td>Sharp</td>
<td>11 (23)</td>
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<tr>
<td>Other</td>
<td>10 (21)</td>
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<td>Bowel habits (n=95)</td>
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<tr>
<td>Diarrhea</td>
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<td>Constipation</td>
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<tr>
<td>Both</td>
<td>2 (2)</td>
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<tr>
<td>Normal</td>
<td>64 (67)</td>
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<tr>
<td>Relief with hot showers (n=57)</td>
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<tr>
<td>Yes</td>
<td>52 (91)</td>
</tr>
<tr>
<td>No</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Other symptoms</td>
<td></td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Bloating</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Flushing</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Chills</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

### TABLE 4. Proposed Clinical Criteria for Cannabinoid Hyperemesis

**Essential for diagnosis**
- Long-term cannabis use

**Major features**
- Severe cyclic nausea and vomiting
- Resolution with cannabis cessation
- Relief of symptoms with hot showers or baths
- Abdominal pain, epigastric or periumbilical
- Weekly use of marijuana

**Supportive features**
- Age less than 50 y
- Weight loss of >5 kg
- Morning predominance of symptoms
- Normal bowel habits
- Negative laboratory, radiographic, and endoscopic test results
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 Microbiome: Who’s there?

- Early gut colonization has four phases
  - Phase 1: Sterile gut
  - Phase 2: Initial acquisition: vagina, feces, hospital
  - Phase 3: Breast feeding or bottle-feeding (different)
    - Breast fed more bifidobacteria (up to 90% of flora)
    - Bottle fed more diverse; more *Bacteroides*, and Clostridial species
  - Phase 4: Start of solids; move to adult flora
    - Bifidobacteria remain key flora into adulthood

Ley, Peterson, Gordon. Cell 2006;124:837
Ley, et al. PNAS. 2005, 102: 11070
C-Section and Gut Flora

- Danish Registry: C-section vs NVD in 2.1 mil Danes
  - 32 million person years of follow-up
  - 1.29 RR for IBD (most notable < age 14)

- Scottish study on rising incidence of IBD
  - C-section associated with increased risk of IBD
  - 1.26 RR (boys only)
  - More UC than CD

Andersen et al. Inflam Bowel disease, 2012;18:999-1005
Breastfeeding and IBD

- Systemic review: Found 8 articles related
- Children who are breast fed protected from IBD
  - Decreased risk for IBD (OR .69, CI .51-.94, P=02)
  - Only protective in early years
  - Is it microbiome or some factor in breast milk?

Barclay et al. J Pediatrics, 2009;155:421-426
# The Human Gut Flora

<table>
<thead>
<tr>
<th>Phyla</th>
<th>Representative genera</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
</tr>
<tr>
<td><em>Firmicutes</em></td>
<td><em>Ruminococcus</em></td>
</tr>
<tr>
<td></td>
<td><em>Clostridium</em></td>
</tr>
<tr>
<td></td>
<td><em>Peptostreptococcus</em></td>
</tr>
<tr>
<td></td>
<td><em>Lactobacillus</em></td>
</tr>
<tr>
<td></td>
<td><em>Enterococcus</em></td>
</tr>
<tr>
<td>Bacteroidetes</td>
<td><em>Bacteroides</em></td>
</tr>
<tr>
<td>Proteobacteria</td>
<td><em>Desulfovibrio</em></td>
</tr>
<tr>
<td></td>
<td><em>Escherichia</em></td>
</tr>
<tr>
<td></td>
<td><em>Helicobacter</em></td>
</tr>
<tr>
<td>Verrucomicrobia(^{b})</td>
<td></td>
</tr>
<tr>
<td>Actinobacteria</td>
<td></td>
</tr>
<tr>
<td>Cyanobacteria(^{a})</td>
<td></td>
</tr>
<tr>
<td>Synergistes(^{b})</td>
<td></td>
</tr>
<tr>
<td><strong>Archaea</strong></td>
<td></td>
</tr>
<tr>
<td>Euryarchaeota</td>
<td><em>Methanobrevibacter</em></td>
</tr>
</tbody>
</table>

\(^{a}\) Prokaryotic phyla were identified by using an alignment of the 18,348-sequence dataset from reference 18.

\(^{b}\) Not related to any known genera.

Infant antibiotic exposures and early-life body mass

Studied 11,532 children in Avon, UK (91-93)
Mapped antibiotic use (<6m, 6-14m, 15-23m)
Body mass documented at 6wks, 10m, 20m, 38m and 7 yrs
Multivariate analysis: role of tob, mother’s BMI, other medications, etc…
Antibiotics in children and obesity

Proposed Mechanisms in Obesity

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

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 GG
Probiotics

- VSL #3
- 4 lactobacilli
  - *L. plantarum, casei, acidopholus, delbrueckii* spp
- 3 bidifobacteria
  - *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

- 12 different species
- Mostly Lactobacillus and Bidifobacter species
- Clinical data with these combinations lacking
Probiotics

- **Digestive Advantage**
  - Ganeden BC\(^{30}\)
  - *Bacillus coagulans*
  - Erythritol
  - Cellulose
  - Other minor ingredients

- **Some data for IBS**
  - Mostly bloating

*Postgrad Med, Vol. 121, Issue 2, March 2009*
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: E. coli Nissle 1917

- Discovered in 1917 by Professor Alfred Nissle
- Well studied
- Some data for use in IBD, IBS, and Ab associated diarrhea
- Excellent safety profile
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>Relapse Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Guslandi</td>
<td>32</td>
</tr>
<tr>
<td>(2000)</td>
<td></td>
</tr>
<tr>
<td>Campieri</td>
<td>40</td>
</tr>
<tr>
<td>(2000)</td>
<td></td>
</tr>
<tr>
<td>Prantera</td>
<td>45</td>
</tr>
<tr>
<td>(2002)</td>
<td></td>
</tr>
<tr>
<td>Schultz</td>
<td>11</td>
</tr>
<tr>
<td>(2004)</td>
<td></td>
</tr>
<tr>
<td>Bousvaro</td>
<td>75</td>
</tr>
<tr>
<td>s (2005)</td>
<td></td>
</tr>
<tr>
<td>Marleau</td>
<td>98</td>
</tr>
<tr>
<td>(2006)</td>
<td></td>
</tr>
<tr>
<td>Van Gossum</td>
<td>70</td>
</tr>
<tr>
<td>(2007)</td>
<td></td>
</tr>
<tr>
<td>Chermeshan</td>
<td>30</td>
</tr>
<tr>
<td>(2007)</td>
<td></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

**Table 3. Recommendations for the Treatment of *Clostridium difficile* Infection (CDI)**

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, mild or moderate</td>
<td>Leukocytosis with a white blood cell count of 15,000 cells/µL or lower and a serum creatinine level less than 1.5 times the premorbid level</td>
<td>Metronidazole, 500 mg 3 times per day by mouth for 10–14 days</td>
<td>A-I</td>
</tr>
<tr>
<td>Initial episode, severe*</td>
<td>Leukocytosis with a white blood cell count of 15,000 cells/µL or higher or a serum creatinine level greater than or equal to 1.5 times the premorbid level</td>
<td>Vancomycin, 125 mg 4 times per day by mouth for 10–14 days</td>
<td>B-I</td>
</tr>
<tr>
<td>Initial episode, severe, complicated</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete ileus, consider adding rectal instillation of vancomycin</td>
<td>C-III</td>
</tr>
<tr>
<td>First recurrence</td>
<td>...</td>
<td>Same as for initial episode</td>
<td>A-II</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>...</td>
<td>Vancomycin in a tapered and/or pulsed regimen</td>
<td>B-III</td>
</tr>
</tbody>
</table>

* The criteria proposed for defining severe or complicated CDI are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

*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:** 1 g 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

- Macrocyclic antibiotic
- Cure: 88.2% vs 85.8% vancomycin
- Recurrence Rate: 15.4% vs 25.3%
- FDA approved.
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 −2.6 percentage points in the per-protocol (PP) analysis.
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
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
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
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

Feed your flora!!!
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

  - i.e. lose weight by making your gut flora less efficient at digesting your left over food
Designing Probiotics: The Future?

Understand traits that underlie probiotic function

Drug

- Identify genes responsible
- Derive robust mutants
- "Designer strains" or genetically modified organisms (GMOs)

Food

- Compare strains at gene level and in vitro
- Select natural strains for specific genes/gene products to improve probiotic function
- Optimal natural strains

Clinical documentation
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
- Colon cancer screening: DO IT!
  - Colonoscopy saves lives
  - New role for FIT testing
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%

Figure 2. Kaplan–Meier Estimates of the Probability of Remaining Free of Primary Cardiovascular Events, According to Study Group.

The event rate for the primary cardiovascular end point at day 180 was 4.9% in the omeprazole group and 5.7% in the placebo group.

COGENT TRIAL

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

Figure 1. Kaplan–Meier Estimates of the Probability of Remaining Free of Primary Gastrointestinal Events, According to Study Group.

The event rate for the primary gastrointestinal end point at day 180 was 1.1% in the omeprazole group and 2.9% in the placebo group.
### COGENT Trial

**COGENT event rates**

<table>
<thead>
<tr>
<th>End point</th>
<th>Placebo, n</th>
<th>PPI, n</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CV events</td>
<td>67</td>
<td>69</td>
<td>NS</td>
</tr>
<tr>
<td>MI</td>
<td>37</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>Revascularization</td>
<td>67</td>
<td>69</td>
<td>NS</td>
</tr>
<tr>
<td>GI events</td>
<td>67</td>
<td>38</td>
<td>0.007</td>
</tr>
</tbody>
</table>

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

Follow-Up to the January 26, 2009, Early Communication about an Ongoing Safety Review of Clopidogrel Bisulfate (marketed as Plavix) and Plavix (marketed as Plavix and Plavix)

US Food and Drug Administration: Drug Safety Information Nov 2009
Clopidogrel with or without Omeprazole in Coronary Artery Disease

Deepak L. Bhatt, M.D., M.P.H., Byron L. Cryer, M.D., Charles F. Contant, Ph.D., Marc Cohen, M.D., Angel Lanas, M.D., D.Sc., Thomas J. Schnitzer, M.D., Ph.D., Thomas L. Shook, M.D., Pablo Lapuerta, M.D., Mark A. Goldsmith, M.D., Ph.D., Loren Laine, M.D., Benjamin M. Scirica, M.D., M.P.H., Sabina A. Murphy, M.P.H., and Christopher P. Cannon, M.D., for the COGENT Investigators*

Inflammatory Bowel Disease

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

Genetic Susceptibility

Environmental Triggers & Modifiers

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
- NSAIDs
- Stress
- Smoking
- Antibiotics
- Diet

Inflammatory Bowel Disease (IBD)
Normal Intestine vs. Intestine With IBD

Normal bowel: controlled inflammation

Environmental triggers (medications, infections, diet?)

Normally: inflammation is down-regulated

IBD: failure to down-regulate inflammation

Inflamed bowel

Normal bowel: controlled 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
Inverted pyramid in IBD treatment

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

(2) Early treatment
- Surgery
- 5-ASA
- Antibiotics
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

<table>
<thead>
<tr>
<th></th>
<th>wk 14</th>
<th>wk 26</th>
<th>wk 52</th>
<th>wk 78</th>
<th>wk 104</th>
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</thead>
<tbody>
<tr>
<td>Step-up</td>
<td>33</td>
<td>36</td>
<td>42</td>
<td>47</td>
<td>50</td>
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<tr>
<td>Top-down</td>
<td>65</td>
<td>60</td>
<td>62</td>
<td>45</td>
<td>57</td>
</tr>
</tbody>
</table>

With permission from Elsevier.
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