Everyone Goes…

Update on IBS Pathophysiology and Treatment Options

Ann Hays, MD
Division of Gastroenterology and Hepatology
University of Virginia College of Medicine

Disclosures

- I have no financial interests or relationships to disclose other than that
- The information in this presentation should not be used as a substitute for clinical judgment
- Non-FDA approved therapy will be discussed

Objectives

1. Review Rome III criteria for IBS
2. Recognize the four basic subsets of IBS including classic post-infectious IBS
3. Review Post-Infectious IBS as an archetype for IBS pathophysiology
4. Treatments for IBS: what is and isn't in 2008 BMJ Meta-analysis on Rx for IBS

ROME III CRITERIA

- ASSOCIATED WITH 2 OF 3:
  - IMPROVEMENT W DEFECATION
  - ONSET ASSOCIATED W CHANGE IN FREQUENCY
  - ONSET ASSOCIATED W CHANGE IN FORM

  OCCURING:
- 3 DAYS / MONTH OVER 3 MONTHS
- SYMPTOMS PRESENT X 6 MONTHS

Rome III focus on stool form rather than defecation frequency as in Rome II

LONGSTRETH, ET AL, GASTROENTEROLOGY, 2006; 130: 1480

IBS Subclasses

1. IBS-A or M: alternating diarrhea and constipation

2. IBS-D: diarrhea predominant

3. IBS-C: constipation predominant

4. PI-IBS: post-infectious IBS, usually diarrhea predominant

Alarm/DDX features

- **Weight loss**
- **Progressive**
- **Older age at onset**
- **Nocturnal symptoms**
- **Fever**
- **Blood**
- **Recent onset**
- **----------**
- **Recent antibiotics**
- **Family h/o CRC, IBD, autoimmune dz, celiac dz**
- **Abnormal physical findings**
- **Association w menstrual cycle**

Abuse history-UNC Study

- Abuse history common in IBS
- Associated w reporting more pain, more psychosocial distress, and poorer outcomes
- 20 pt: 10 w IBS Looked at MRIs and pain reporting during rectal distention
- Both groups w activation of dorsal ingulate regions but enhanced in those w h/o abuse who also reported greater pain
- UNC Ringel and Drossman et al Gastroenterology 2008; 134(2): 296

ACG Position Task Force

- Routine diagnostic testing (CBC, CMP, TSH, O&P, abd imaging) is not recommended in pt w typical IBS (1C strong recommendation, weak evidence)
- Literature review reveals accuracy of alarm features to be poor (low yield)
- IBS-D and IBS-A test for celiac dz (1B strong recommendation, moderate evidence)

Celiac dz MAY present w osteopenia, seizures, IDA, arthritis, bloating, constipation

AJG 2009, suppl 1: S1-35

ETIOLOGY

Emerging theories for the etiology of IBS include one or all:

Alteration of intestinal biomata

Alteration of intestinal immune cells

Alteration of intestinal hormones and neurotransmitters

Disordered motility

Post infectious IBS

- Example of imbalance in biomata, intestine, immune & nervous systems causing dis-ease
- "irritable colon syndrome"
  - Stewart 1950, Chaudary & Truelove 1962
  - Described in ~ 25% of their bacillary and amebic patients
- IBS-PI : 3-30% of severe bacterial GE, 1st described after Giardia

PI-IBS: Walkerton & Bergen Outbreaks

- Walkerton Outbreak 2000
  - f/u reports q 2-3 yr through 2008
  - study of 904 pt that began 2 yr after they were infected
  - Muni water contamination primarily E Coli, campylobacter
  - New onset IBS in 28% of infected @ 2-3 yr, 14 % @ 6 and 8 yr

Marshall, Gastro 2003;124:1662, 2006;131:445, 2011;140:726

PI-IBS: Bergen Outbreak (Giardia)

Bergen Norway 2004 1500 cases Giardia

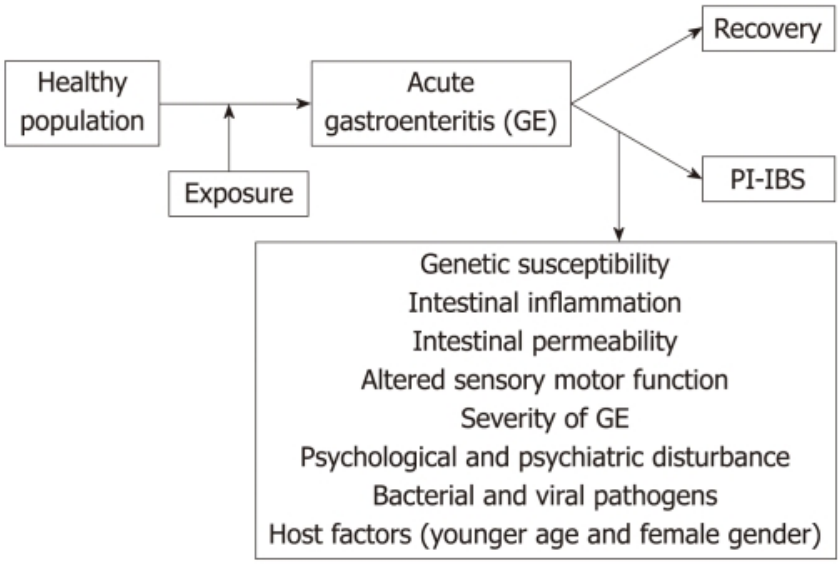
- 10% still had GI sx 1 year later
- 10 rx live fecal flora & 8 antibiotics
- Sx recurred 1 yr later in all those who initially improved

Morken Scand J GE 2009;44:1286

- PI-IBS
  - females w h/o anxiety/depression
  - Severe dysentery (cramps, fever, weight loss, bloody, prolonged > 7d)
  - Camphylobacter : most common preceding infection

Grover. Clin Gastro Hept 2009;7:48
Verdu and Riddle. Chronic Gastrointestinal Consequences of Acute Infectious Diarrhea: AJG 2012: 981
Braak et al. Mucosal Immune Cell Numbers and Visceral sensitivity in Patients w IBS. AJG 2012: 715

Post Infectious IBS Sequence of Events



Question

- 35 yo female w 5 yr h/o intermittent crampy abd pain, episodes of diarrhea and no weight loss. Fhx negative for CRC, IBD, celiac. PE including rectal exam is normal, CBC and ESR normal.

Which of the following is most appropriate:

1. Abdominal US
2. Glucose hydrogen breath test
3. Colonoscopy with bx
4. Explain nature of IBS to her and offer prn anti-spasmodic

Drug Treatment IBS

- No great meds
- Strong placebo response 30-70% in DB, RCT
- Frequent SE (try to stop a med, before starting another in order to keep your pt out of medical vortex)
- Lubiprostone: GCC activator increases intestinal secretion and colon transit
- TCA: low dose, no good studies, high incidence of SE, ~20% better than placebo
- Tegaserod (5-HT_4 agonist) for IBS-C recalled b/c CNS/CV SE
- Alosetron (5-HT_3 antagonist) restricted b/c promoted to decrease abd pain, useful in IBS-D but in IBS-C pt developed ischemic colon, several deaths
- Antibiotics rare, check GBT, don't expect much, risk of resistance,
  - Rifaxamin
  - Neomycin (methane producers)

IBS Question 2

- 44 yo woman with IBS-D is started on imipramine 10mg daily but she c/o fatigue, disorientation and palpitations. Her IBS sx are unchanged.

The most appropriate course of action is:

a. Continue the drug for 2 wk as she will gradually adapt to the side effects

b. Stop it and prescribe nortriptyline 10 mg daily

c. Stop it and prescribe lubiprostone 24 mcg bid

d. refer her for hypnosis

IBS Question 3

- 35 teacher develops diarrhea on trip to Mexico. Takes Cipro and loperamide x 3 d. Three months later she presents w loose BM and bloating. No weight loss, fever, bleeding. Fatigued. Heme negative. Stool for Giardia Ag is negative.
- Which of the following statements re: this condition is true?

a. It is more likely to develop in females w anxiety
b. It is best to get a colonoscopy with random bx to look for subepithelial band of collagen
c. It is less likely if antibiotics are taken

IBS Question 4

- Which of the following treatments for IBS exhibits the greatest benefit over placebo in randomized trials?

a. Lubiprostone
b. Hypnosis
c. Psyllium
d. a good physician-patient relationship

Pharmacotherapy in IBS: Should be Directed to the Individual's Dominant Symptom(s) and Setting of Those Sx

Leave your drugs in the chemist's pot if you can cure the patient with food. - Hippocrates, 420 BC

Reassurance 40%
Diet

He cures most in whom most have faith. – Galen

Placebo or Hawthorne effect in IBS

Consistently around 40%

Meaning that if a study report 60% improvement for a particular RX, only 20% who received the active medication are likely to have improved

Also, that no matter what you rx for any one individual, you have a 40% chance of success.

BMJ meta-analysis 2008

- Ford et al. BMJ 2008; 337: a2313 (for ACG position statement) --Studies w poor quality scores excluded)
- **Fibre** unspecified: 7 studies, no significant effect, NNTT 11
- **Bran**: no benefit
- **Ispaghula** (a soluble fibre): 4 studies, marginal benefit, NNTT 6
- **Anti-spasmodics:** 12 studies,
  - Hyosysamine 400 pt, NNTT 3.5
- **Peppermint oil:** 3 studies, NNTT 2.5 (smooth musc. relaxant), not a current ACG recommended therapy
- *Most studies were before ROME, did not differentiate subsets*

IBS-Constipation

Reassurance/Diet

Peppermint oil: 1-2 caps tid (NNT 3) (Altoids ? alternative)
Vitamin C (no NNT): 500 mg 1-2/d
Psyllium: 2-4 gm w meals & adjust
Lactulose: 10-20 gm bid
PEG: 17 g in ¼ liter water daily
Magnesium hydroxide: 20-40 cc daily
Lubiprostone: 8 mcg bid
Linaclotide: FDA approved,

Linaclotide for Chronic Constipation

- Minimally absorbed guanylate cyclase receptor activator
- Increases CGMP ➔cystic fibrosis tranducer ➔secretion of Cl^- and HCO_3 into intestinal lumen
- Released 2012 for chronic constipation; under study for IBS-C
- NEJM 8/2011 (Lembo and Ironwood)

Two 12 wk randomized, placebo controlled trials 1276 pt

3 spontaneous BM/wk ($p<0.01$, Diarrhea 4% linaclotide)

145 mcg 21%, 16% (NNTT 5.6, 6.2)

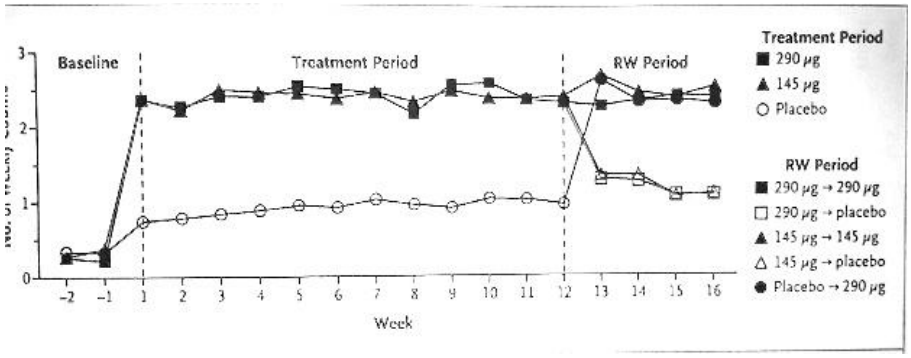
Placebo 3 %, 6%

290 mcg 19%, 21% (NNTT 10, 6.6)

Linaclotide

NEJM 8/2011

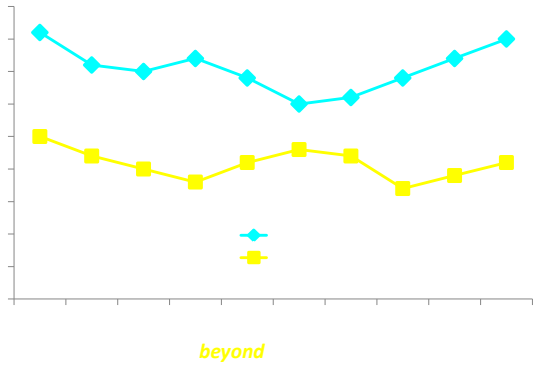
- # complete spontaneous BM per week
- IBS Rome III patients excluded



FDA APPROVAL chronic constipation 2012

Probiotics and IBS

- Evidence points toward profound effect of alterations in biomata on physiologic functions
- DNA based molecular "biomata-grams" reveal significant differences in the biomata of normal and IBS patients
- Manipulation of the biomata with antibiotics, prebiotics, probiotics are reported to decrease IBS symptoms

Small Intestinal Bacterial Overgrowth in IBS?

- Pimentel et al. reported an abnormal LHBT in 84% of IBS subjects vs. 20% of healthy controls[1]