

Pharmacological Issues with Bacterial Overgrowth: Causes and Treatment Strategies

Kathleen M. Gura PharmD, BCNSP, FASHP, FPPAG, FASPEN
Center for Advanced Intestinal Rehabilitation (CAIR)
Boston Children's Hospital

Disclosures

- B.Braun – advisory board, consultant
- Fresenius Kabi – consultant, research support
- Pronova/BASF – advisory board, research support
- Sancilio & Company -advisory board, research support

I will be speaking on the off label use of medications.

Learning Objectives

1. Discuss the impact of acid suppression on the development of bacterial overgrowth
2. List several commonly used treatment strategies to prevent the recurrence of bacterial overgrowth.
3. Understand the limitations of using cyclic anti-infectives to manage bacterial overgrowth.

Small Intestinal Bacterial Overgrowth (SIBO)

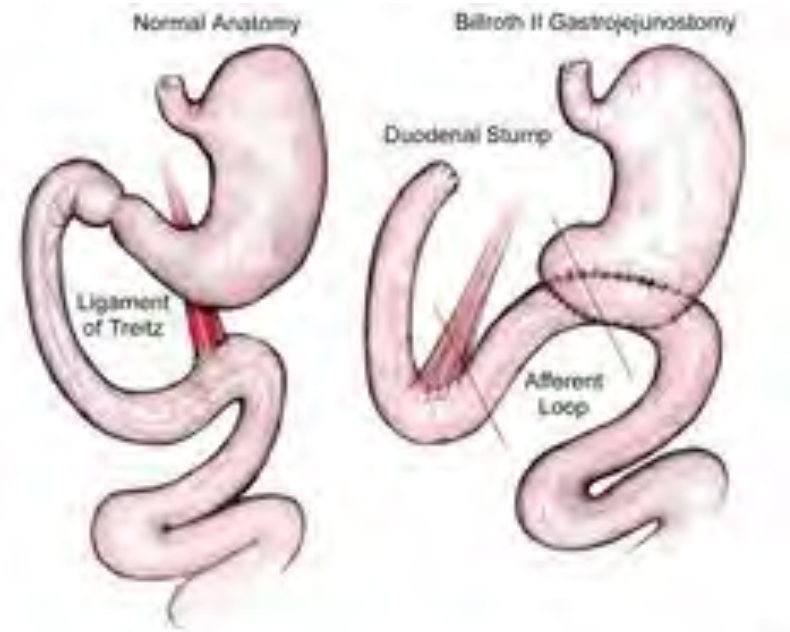
- Not the same as SIBO syndrome
- Commonly accepted definition:
 - $>10^5$ CFU/mL small intestinal fluid minimum number of bacteria

SIBO Syndrome

- Increased number of colonic bacteria
 - Coliforms
 - *Enterococci*
 - Gram positive anaerobes
- Associated with nutrient malabsorption
 - Due to bacteria itself or bacterial metabolites
 - D-lactate
 - Ammonia
 - Ethanol

Background

- SIBO described with use of Bilroth 2 procedure for ulcers
 - Blind loops created
 - Allowed for bacterial overgrowth/steatorrhea



<http://media-cache-ak0.pinimg.com/originals/13/f0/35/13f035b03393be9d20ad35bfab533a87.jpg>

Pathogenesis

- Infection
- Autoimmune inflammation
- Surgical alterations
- Intestinal dysmotility
- Inhibition of gastric acid production
 - PPIs
 - H-2 blockers
- Also associated with:
 - Cirrhosis
 - NASH
 - Crohn's Disease
 - IBS
 - Acute pancreatitis
 - Intestinal fistula
 - Hypochloryhydria
 - Pancreatic insufficiency
 - Short bowel syndrome



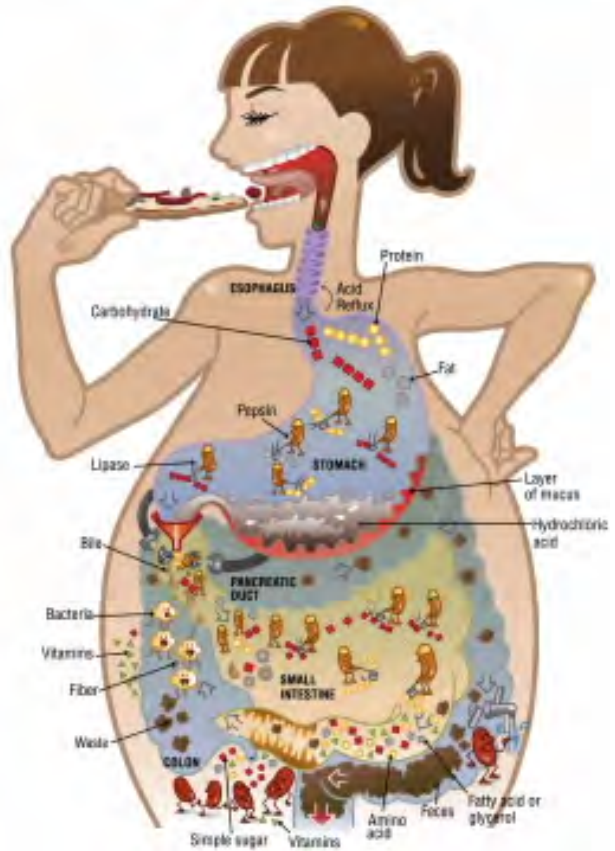
Symptoms

- Bloating
- Early satiety
- Cramping
- Steatorrhea



What is “normal”?

- Upper intestinal tract
 - 10^3 - 10^5 CFU/g bacteria
- Lower intestinal tract (TI/ cecum/colon)
 - 10^{12} CFU/g anaerobic bacteria
- Intestinal flora closely resembles GI epithelial cells
 - Regulates metabolic functions
 - Nutrient absorption
 - Bile acid conjugation
 - Vitamin metabolism
 - Gut integrity



<http://movingtowardhealth.files.wordpress.com/2013/06/digestion-image.jpeg>

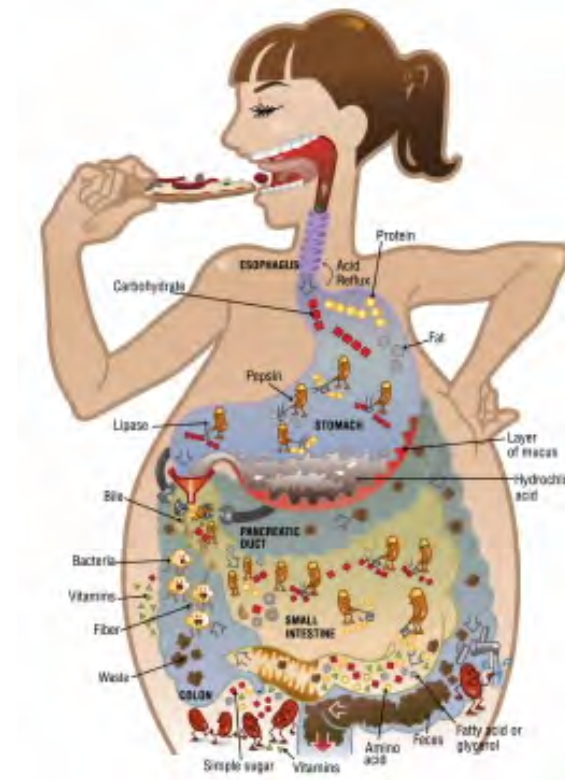


Distribution of Bacteria within the GI Tract

Mouth 10^{7-8} /mL

Duodenum $10-10^3$ /mL

Jejunum 10^{3-5} /mL



Stomach $0-10^3$ /mL

Ileum 10^{7-8} /mL

Cecum/colon 10^{10-12} /mL

What happens in SIBO...

- Competition for nutrients
- ↑ unabsorbed substances
- Malabsorption 2^o mucosal damage
- Steatorrhea 2^o fat malabsorption & ↑ bile acid deconjugation
- Vitamin deficiencies

SIBO Complications

- Malnutrition
- Anorexia/weight loss/poor growth
- Bacterial translocation
- Bowel inflammation
- Failure to wean from PN
- Neurologic complications
 - D-lactic acidosis
 - Hyperammonemia
 - Ethanol “autointoxication”

D-Lactic Acidosis

- D-lactate encephalopathy
- Due to overgrowth of anaerobes in small intestine or malabsorption of carbohydrates/starches in the colon instead of small intestine
- Neurologic symptoms include:
 - altered mental status
 - slurred speech
 - ataxia
- Onset of neurologic symptoms is accompanied by metabolic acidosis and elevation of plasma D-lactate concentrations



<http://www.nature.com/ki/journal/v77/n3/thumbs/ki2009437f1th.jpg>

Mucosal Damage

- Intestinal epithelial integrity destroyed
- 2^o up-regulation of inflammatory cytokines
- ↑ bacterial penetration
- Alters immune regulation

Diagnosis of SIBO: 3 Approaches

- Direct aspiration and culture of jejunal contents
- Breath tests
- Response to empiric therapy

Jejunal Aspirate Cultures

“gold standard”

- $>10^5$ CFU/mL organisms from aspirated fluid
- Identification of colonic-type flora
- More reliable than duodenal aspirate cultures

Breath Tests

- Rationale

- Bacteria produce hydrogen following CHO fermentation
(↑bacteria ↑fermentation ↑H production)

- Limitations

- Altered transit time
 - Colonic acidity
 - Wide variations in sensitivity and specificity

- **Glucose breath test**

- Fasting breath H >10ppm greater than baseline after ingesting 50g glucose on 2 consecutive samples abnormal
 - Inaccurate in patients with cirrhosis
 - False positives can occur if intestinal transit time too rapid

- Xylose

- Measures radio labeled carbon dioxide (¹⁴ C-D xylose)
 - Improved sensitivity and specificity
 - Cannot be use in pregnant patients or children

Other Non-invasive Diagnostic Methods for SIBO

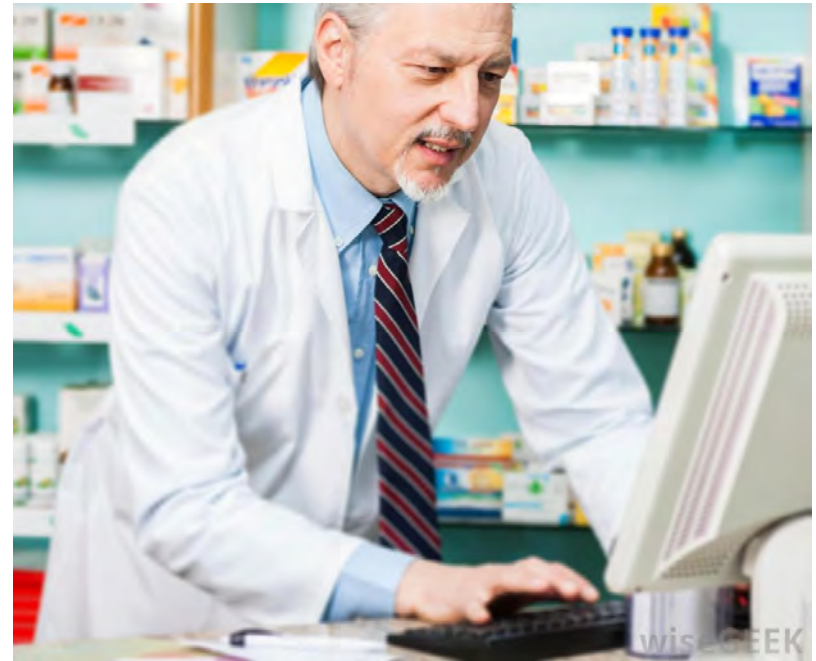
- Urine indican test
 - Indican
 - By product of tryptophan metabolism by bacteria
 - Not useful in patients with rapid transit times
 - Has not been validated against jejunal aspirate cultures
- Empiric antibiotic therapy
 - If symptoms diminish or tests normalize, diagnosis is made

Treatment of SIBO

- Treat the underlying disease
- Dietary manipulation
- Antibiotics
- Probiotics /prebiotics/synbiotics
- Motility medication
- Bowel flushes
- Avoidance strategies

Review the Medication List!

- Drugs associated with intestinal stasis:
 - Narcotics
 - Benzodiazepines
- Eliminate or substitute with alternative agents



Dietary Manipulations

- Simplest solution
- Goal: provide a diet of readily absorbable nutrients
 - ↓ calories available for bacterial metabolism
- Examples
 - ↓ nonabsorbed carbohydrates
 - Switch to high fat, low carbohydrate, low fiber diet
 - Fat not significantly metabolized by bacteria
 - Substituting fat for carbohydrate may ↓ SIBO symptoms
- Adults prone to developing lactase deficiency
 - Avoid lactose containing foods in patients with a positive breath test for lactose intolerance

Other Nutritional Considerations....

- Patients with SIBO are prone to a variety of nutrient deficiencies including:
 - Calcium
 - Magnesium
 - Iron
 - Vitamin B12
 - Fat soluble vitamins
- Nutritional deficiencies in SIBO often subtle sign overgrowth is present

Antibiotics

- Rationale: eradicate symptoms of SIBO
- Typically initiated when bowel dilates or transit time is slow
- Often done to manage comorbidities of SIBO
 - Malabsorption
 - Flatulence
 - Diarrhea
 - Neurologic symptoms
- May also be used to ↓ bacterial translocation
 - ? ↓ bloodstream infections
- Therapeutic goal: to eradicate symptoms
 - Unrealistic to completely eradicate enteric flora

Antibiotic Selection

- Goal symptom control
- Should target anaerobes
- Effect temporary
- Limited spectrum antibiotic preferred over broad spectrum
- Typically cyclically prescribed (7-14 days) followed by 14-21 days off
- Typical overgrowth dose is 50% of therapeutic dose
- Metronidazole preferred empiric agent

Metronidazole

- nitroimidazole antibiotic
- Dose: 20mg/kg/day
- Side effects
 - Neurologic (headache, peripheral neuropathy)
 - Di-sulfiram reaction when taken with ethanol
 - Taste aversion
- Drug interactions
 - **ethanol**
 - may enhance the QTc-prolonging effect of Highest Risk QTc-Prolonging Agents
 - Avoid such combinations when possible
 - Use should be accompanied by close monitoring for evidence of QT prolongation or other alterations of cardiac rhythm
 - Examples:
 - naratriptan, sumatriptan, zolmitriptan
 - **cisapride**, dolasetron, granisetron, ketanserin, ondansetron
 - azithromycin, clarithromycin, **erythromycin**



Alternative Agents

- Nitazoxanide (Alinia)
 - Similar spectrum as metronidazole
- Rifaximin (Xifaxan)
 - Non absorbable form of rifampin
 - Affects only the gastric flora
 - Broad aerobic and anaerobic spectrum
 - Bacteriostatic not bacteriocidal
 - Dose 1650mg/day x 7-10 days
 - Limitation: \$\$\$\$\$\$\$\$ (\$28.28 1 500mg tablet!)

Alternative Agents

- Amoxicillin/clavulanic acid (Augmentin)
 - Bactericidal against both aerobes and anaerobes
 - Prokinetic properties
 - ↑amplitude and duration of propagated small intestinal contractions during the fasting state
 - MOA unknown ? Motilin agonist or GABA inhibition
 - May increase risk multidrug resistance
 - Diarrhea limits usefulness
 - Dose: 30mg/kg/day

Other Antibiotics Used in SIBO Management

- Neomycin
- Doxycycline
- Ciprofloxacin
- Trimethoprim- sulfamethoxazole
- Gentamicin (oral)
- Norfloxacin
- Cephalexin

Selective Decontamination

- May reduce bloodstream infections
- Goal ↓ gram negative aerobic bacteria
 - ↓ bacterial translocation
 - Doesn't impact gram positive anaerobic bacteria
- Ideal antibiotics possess broad anti-coliform and anti-Enterococcal properties
 - Example: ciprofloxacin

Comparison of Agents Used for Treatment of Bacterial Overgrowth

(Typical course 7-10 days)

All meds given orally!

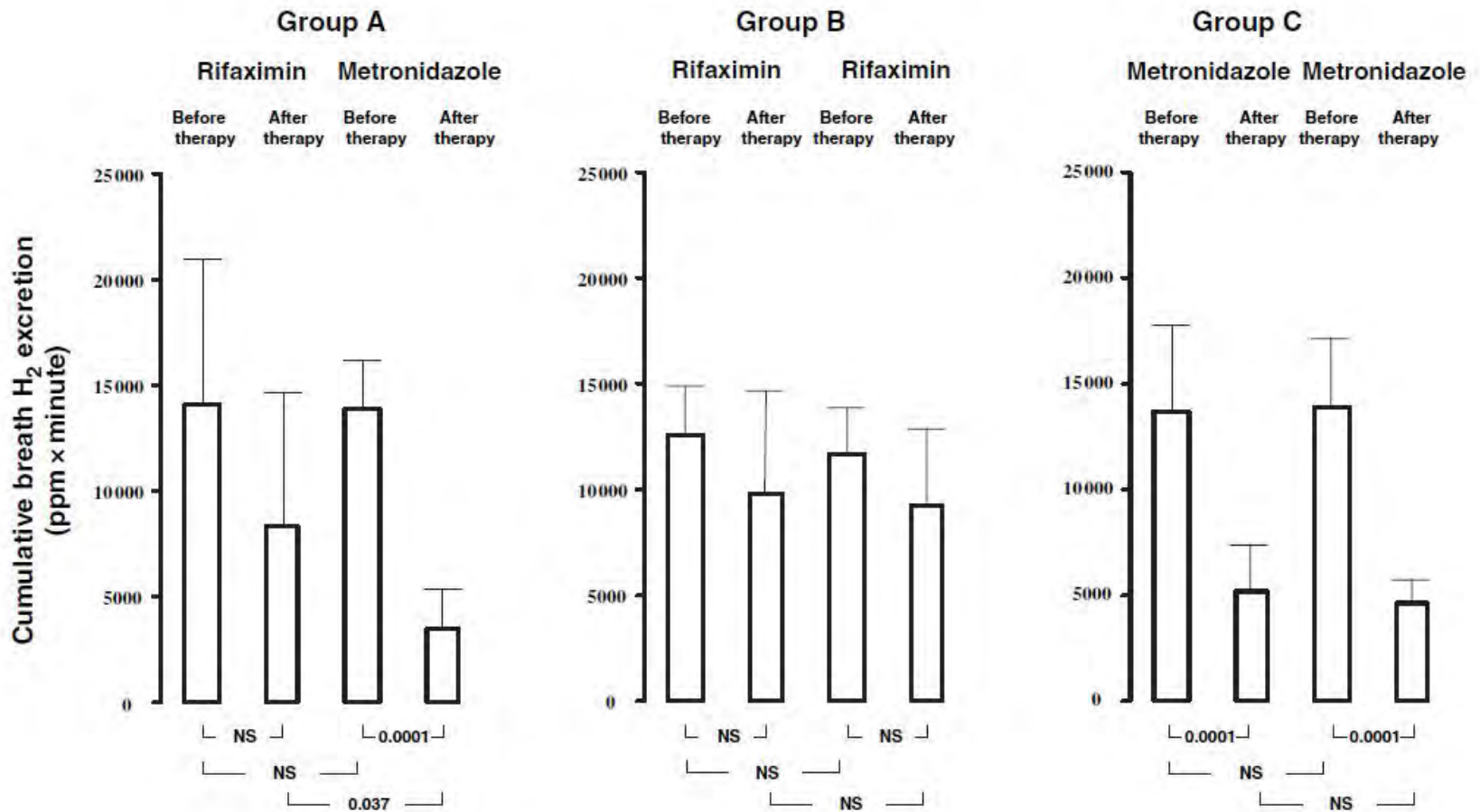
Medication	Pediatric dose	Adult dose	Comments	% orally Absorbed	% renally excreted	Cisapride Yes/No
Amphotericin	< 5 years: 100mg bid 5-12 years: 250mg bid	500mg bid	Injection given orally	0	40% (2-5% active)	yes
Augmentin	10mg/kg/dose bid	500mg bid		Complete (amoxicillin)	30-40%	yes
Bactrim (TMP/SMX)	2 mg TMP/kg/dose daily	1 SS tablet daily Each tablet: Sulfamethoxazole 400 mg / trimethoprim 80 mg		Almost completely, 90% to 100%	Sulfamethoxazole, 10% to 30%; Trimethoprim, 50% to 75%	NO
Ciprofloxacin	20-40mg/kg/day bid	500 mg bid		50-80%	30-50%	NO
Clindamycin	10-30 mg/kg/day Divided tid /qid	300mg tid		90%	10%	Yes
Colistin	<5 years: 25 mg 2-4 times/day 5-12 years: 50 mg 2-4 times/day	100 mg 2-4 times/day	Injection given orally	insignificant	75% in 24 hours	Yes
Doxycycline	children > than 8 yrs 100mg bid	100mg bid		100%	23%	NO
Gentamicin	2mg/kg/dose bid Others: 2.5mg/kg/dose tid not to exceed 300mg/day	2-2.5 mg/kg/dose tid Not to exceed 300mg	Injection given orally	None	100%	Yes
Metronidazole	10mg/kg/dose bid others: 5mg-10mg/kg/dose bid - tid	250mg -500mg tid-qid		90%	10%	NO
Neomycin	50mg/kg/day Divided every 6 hours	500 mg bid 500mg -2gm every 6-8 hrs	Available as tablets only	3%	0.9-1.5%	Yes
Tetracycline	Children >8 years: 25-50 mg/kg/day in divided doses every 6 hours	500mg tid		75%	60%	NO
Tobramycin	< 5 years: 10mg 2-4 times/day 5-12 years: 40mg 2-4 times/day	80mg 2-4 times/day	Injection given orally	Poor	90-95%	Yes
Rifaximin	Not established 20 to 30 mg/kg/day has been used	400mg tid	Non formulary at Children's	<0.4%	<1%	Yes
Vancomycin	125mg every 6 hours (10mg/kg/dose qid) Max total daily dose 2gram/day	125mg - 500mg every 6 hrs Max total daily dose 2gram/day		Poor	Oral doses primarily via feces	Yes

Metronidazole vs Rifaximin

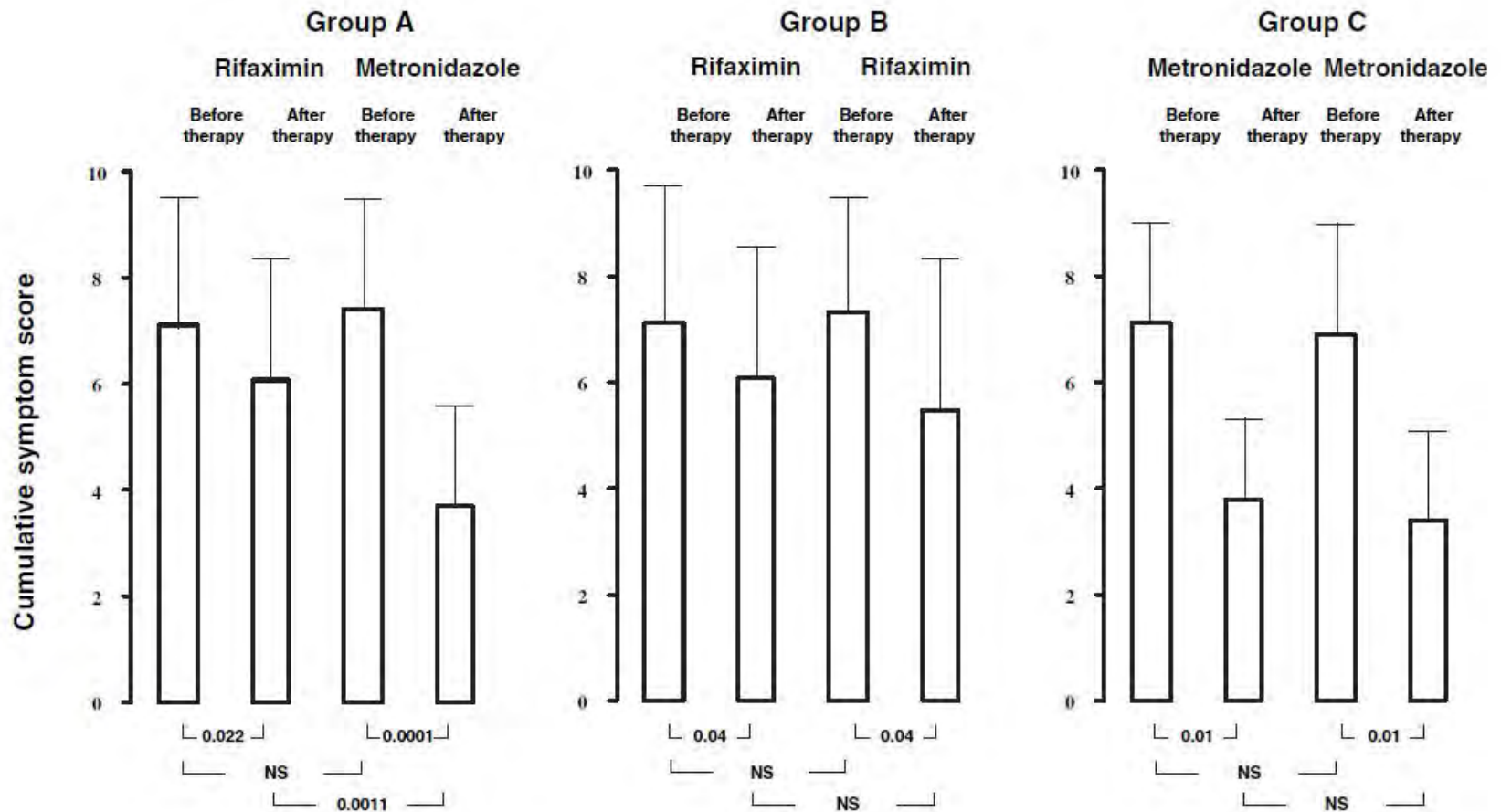
(Aliment Pharmacol Ther 2005;21:985-92)

- OBJECTIVE
 - Evaluate the efficacy of absorbable versus non-absorbable antibiotics in treatment of small intestinal bacterial overgrowth
- POPULATION
 - 21 patients with SIBO due to gastric cancer or gastrojejunostomy, or peptic ulcer disease
 - SIBO diagnosis made with breath hydrogen test
- INTERVENTION
 - Rifaximin then metronidazole
 - Rifaximin then rifaximin
 - Metronidazole then metronidazole

Metronidazole vs Rifaximin



Metronidazole vs Rifaximin



Metronidazole vs Rifaximin

Table 1. Effect of therapy on severity of symptoms and abdominal girth.

Symptom	Group A				Group B				Group C			
	Rifaximin		Metronidazole		Rifaximin		Rifaximin		Metronidazole		Metronidazole	
Pain	9 ± 2	8 ± 2	9.3 ± 1	6 ± 1*	9 ± 1	8 ± 1	9 ± 1	7 ± 1	8.7 ± 1	5.8 ± 1*	8.6 ± 1	5.3 ± 1*
Flatulence	4.1 ± 1	3.2 ± 1	5 ± 1	3.6 ± 1*	4.1 ± 1	3.3 ± 1	5 ± 1	3.6 ± 1	4.6 ± 1	3.1 ± 1*	4.6 ± 1	3.1 ± 1*
Bloating	9 ± 1	8 ± 1	9.3 ± 1	4.4 ± 1*	9 ± 1	8 ± 1	9.3 ± 1	7 ± 1	9.1 ± 1	4.1 ± 1*	8.6 ± 1	4.3 ± 1*
Diarrhoea	6.1 ± 1	5.1 ± 1	6 ± 1	1 ± 1*	6.1 ± 1	5.1 ± 1	5.9 ± 1	4.4 ± 1	6.1 ± 1	2 ± 1*	6 ± 1	1 ± 1*
Abdominal girth	77 ± 5	74 ± 6	76 ± 5	70 ± 5*	78 ± 4	76 ± 4	77 ± 5	75 ± 6	77 ± 5	71 ± 5*	78 ± 5	72 ± 4*

* $P < 0.01$ vs. before therapy.

Metronidazole vs Ciprofloxacin

(Aliment Pharmacol Ther 2003;18:1107-12)

- **OBJECTIVE**

- Compare efficacy of metronidazole and ciprofloxacin in the treatment of bacterial overgrowth in patient with Crohn's disease

- **POPULATION**

- 29 patients with bacterial overgrowth, diagnosed by glucose breath test

- **INTERVENTION**

- Group A: metronidazole 250mg TID
- Group B: ciprofloxacin 500mg BID
- Both are taken orally for 10 days

Metronidazole vs Ciprofloxacin

- ENDPOINTS
 - Glucose breath test normalization occurred in 13/15 patients in metronidazole group and in all patients treated by ciprofloxacin ($P=ns$)

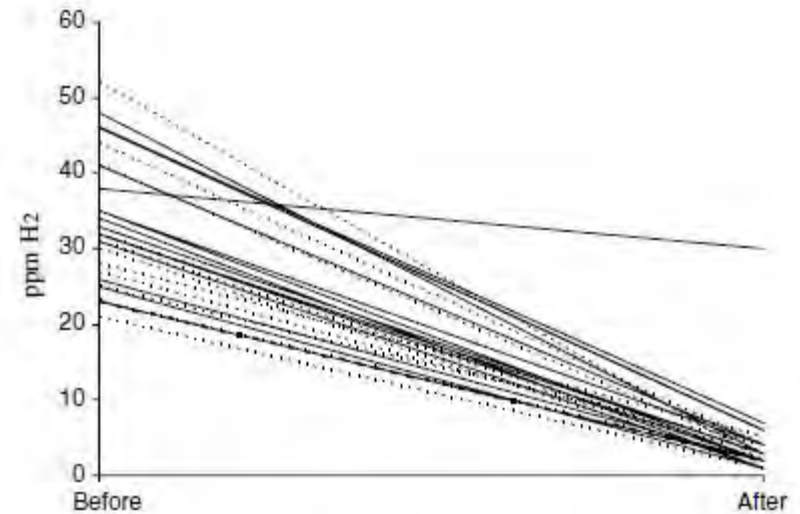


Figure 1. Expiratory H₂ level at glucose breath test before and after therapy with metronidazole (continuous line) and ciprofloxacin (dotted line).

Metronidazole vs Ciprofloxacin

Symptom	Group A (n = 15)			Group B (n = 14)		
	Basal	After treatment	P	Basal	After treatment	P
Bloating	2.3 ± 0.7	0.7 ± 0.9	< 0.001	2.3 ± 0.4	1.3 ± 0.4	< 0.001
Stool softness	2.3 ± 0.4	1.3 ± 0.4	0.02	1.8 ± 0.6	1.6 ± 0.5	0.04
Abdominal pain	1.8 ± 0.6	1.5 ± 0.6	0.04	1.9 ± 0.7	1.6 ± 0.5	0.04

Data are presented as mean ± standard deviation.

Symptom	Before therapy			Improvement after therapy		
	Group A n (%)	Group B n (%)	P	Group A n (%)	Group B n (%)	P
Bloating	14/15 (93)	12/14 (86)	ns	12/14 (85)	10/12 (83)	ns
Soft stools	9/15 (60)	8/14 (57)	ns	4/9 (44)	4/8 (50)	ns
Abdominal pain	8/15 (53)	7/14 (50)	ns	4/8 (50)	3/7 (43)	ns

Table 3. Modification in clinical scores induced by antibiotic therapy in 29 patients treated with metronidazole 250 mg t.d.s. (Group A) or ciprofloxacin 500 mg b.d. (Group B)

Table 4. Clinical response to therapy in 29 patients treated with metronidazole 250 mg t.d.s. (Group A) or ciprofloxacin 500 mg b.d. (Group B)

Antimicrobial Cocktails

- Non-absorbable antibiotics
- Alters GI flora without impacting other organ systems
- Examples
 - Colistin/tobramycin/nystatin (or amphotericin)

Probiotics

- Alters composition of flora using live non-pathogenic bacteria
- Minimizes adverse effects seen with antibiotics
- Have been used for centuries in food
- Use in IF limited
- Concerns of ↑ sepsis risk in patients with CVCs
- Examples:
 - Lactobacillus acidophilus;
 - Lactobacillus bulgaricus
 - Lactobacillus rhamnosus
 - Saccharomyces boulardii

Prebiotics

- Non-digestible fermentable foodstuffs
- Enhance growth of desirable bacteria
 - Bifidobacteria
 - Lactobacillus
- Not absorbed in small intestine; fermented by colonic bacteria
- Examples:
 - Oligosaccharides
 - Inulin-type fructans
 - Fruto-oligosaccharides

Synbiotics

- Combination of probiotic and prebiotic
 - net health benefit is synergistic
- Probiotic bacteria colonize the small intestine while the prebiotic stimulates the microflora in the large intestine
 - Combination works separately but synergistically as they increase the overall gut health
- Trend toward improved symptom relief when combined with an antibiotic
- Examples:
 - Bifidobacteria and fructo-oligosaccharides (FOS)
 - Lactobacillus rhamnosus GG and inulins
 - Bifidobacteria or lactobacilli with FOS or inulins or galactooligosaccharides (GOS)

Motility Agents

- Dysmotility can occur as bowel dilates
- Prokinetics may improve slow motility
- Examples:
 - Amoxicillin/clavulanic acid
 - Erythromycin
 - Metoclopramide
 - Cisapride
 - Tegaserod

Erythromycin

- Motilin agonist
- Improves small intestine motility in both fed and fasting state; enhances gastric emptying
- Low doses used (1-2mg/kg/dose)
- High doses associated with antral spasm/vomiting
- Tachyphylaxis requires used drug holidays

Metoclopramide

- Dopamine antagonist in the CNS
- Increases acetylcholine release by presynaptic neurons
- Accelerates esophageal clearance, improves gastric emptying, enhances small bowel motility
- CNS side effects (i.e., dystonia) limit usefulness
- Has FDA black box warning

Cisapride

- Available only via limited access protocol
- PRA International 1-877-795-4247
- accelerates gastric emptying by stimulating 5-HT₄ receptors that results in the release of acetylcholine from the neurons in the myenteric plexus
- no dopamine receptor blocking activity, no EPS side effects

↑ LES pressure

↑ amplitude of peristalsis

↑ gastric emptying,

↑ colonic motility



Cisapride

- Dosing:
 - neonates: 0.15-0.2 mg/kg/dose 3-4 times/day
(max. 0.8 mg/kg/day)
 - infants/children: 0.15-0.3 mg/kg/dose 3-4 times/day
(max. 10 mg/dose)
 - adults: 10mg po qid
- Reduce dose by 50% in hepatic dysfunction
- Monitoring: baseline EKG, lytes if also on diuretics

Cisapride

- Adverse reactions
 - cardiac arrhythmias
 - QT prolongation
 - torsades de pointes
- Interactions – CYP3A3/4 substrate
 - grapefruit juice
 - ketoconazole, fluconazole, erythromycin
 - ritonavir, saquinavir
 - metronidazole

Tegaserod (Zelnorm)

- Serotonin 5-HT₄ Receptor Agonist
- Approved indication: emergency treatment of irritable bowel syndrome with constipation (IBS-C)
- Available in U.S. under an emergency investigational new drug (IND) process (druginfo@fda.hhs.gov)
- <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103223.htm>

Bowel Flushes

- Done if medication ineffective or severe symptoms
 - Performed daily or weekly
- Involves mechanically flushing excess bacteria from the bowel
 - Example: daily low dose magnesium citrate or Miralax (osmotic laxatives)
- Encourage patient to pass stool every several hours
 - may be enough to decrease symptoms

Avoidance Strategies: Role of Excessive Acid Suppression

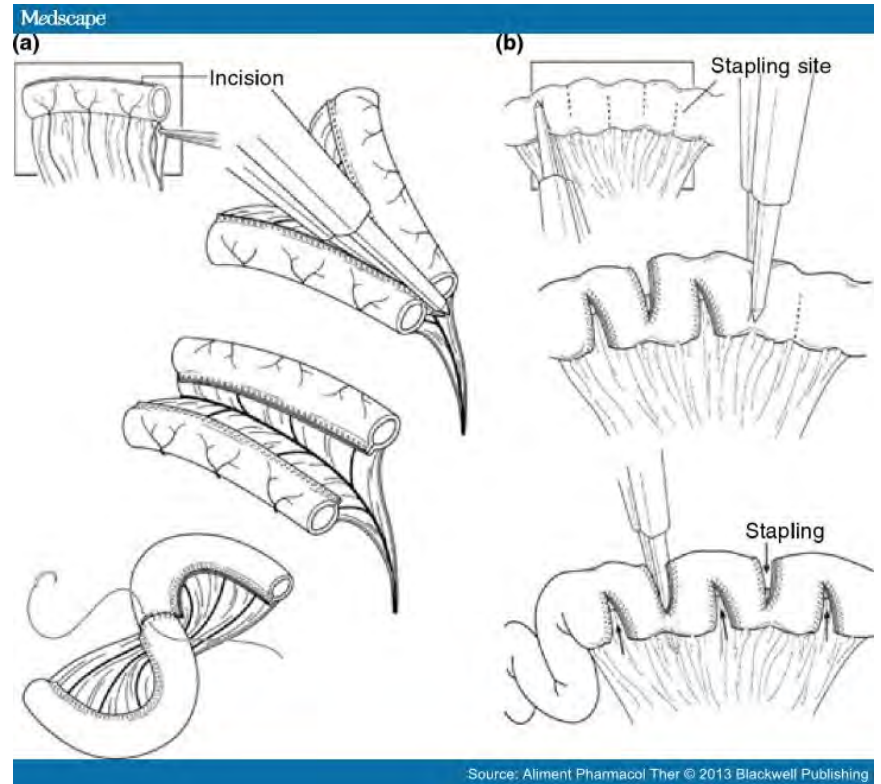
- Minimize use of acid suppression agents
 - H-2 antagonists
 - Proton pump inhibitors
- Increased pH can increase bacterial load
 - Decreases normal intestinal flora
- Use lifestyle changes to manage GERD whenever possible
- Use lowest possible dose for the shortest duration of time

Steroids

- Colitis can occur 2° inflammation due to SIBO
- Symptoms include bloody stools
- In addition to antibiotics and dietary changes aminosalicylates or steroids often used
 - Sulfasalazine
 - Enteral budesonide
 - Reduces inflammation caused by excess bacteria
 - Used only in extreme cases & on very short term basis

Surgical Options

- In severe cases of SIBO unresponsive to conventional measures
- Include:
 - Temporary colostomy placement
 - Intestinal tapering
 - Bowel lengthening (i.e., Bianchi, STEP)





Key Points

- SIBO is a condition due to excessive colonization of the small intestine by bacteria (typically coliform)
 - Associated with mucosal inflammation & nutrient malabsorption
- Management consists of treating the underlying cause, dietary manipulation and antibiotic therapy
- SIBO due to dysmotility should be treated with prokinetics to enhance motility to eliminate and prevent relapse of SIBO
- Consider diets of high fat/low carbohydrate and low fiber to reduce symptoms
 - Avoid lactose containing foods as lactose deficiency can develop in adult patients with SIBO
- Recurrence is common after treatment
 - Patients may require chronic cyclic antibiotic therapy
 - Rotating antibiotic regimens may help prevent the development of resistance
- Severe cases of SIBO may result in colitis and ileitis, mimicking a Crohn's flare

