WHAT IS YOUR GUT TELLING YOU?

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APDA TAKE CONTROL SERIES

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ABOUT ME

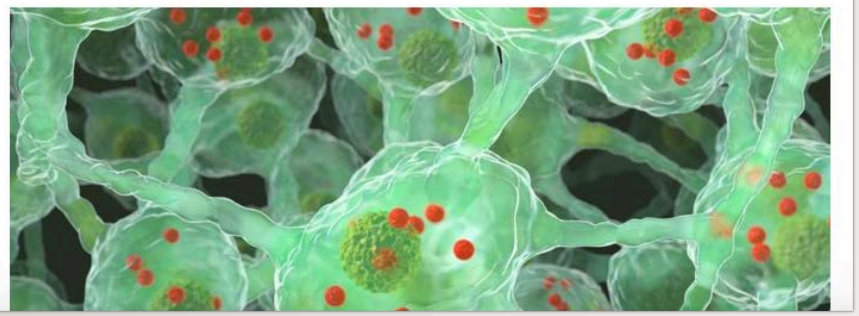
- Graduated Bastyr University
- Complementary and Alternative Medicine in PD Research Assistant
- Completed residency under Drs. Laurie Mischley & Marco Vespignani at Seattle Integrative Medicine
- Practice consists primarily of patients with PD – focus on gastrointestinal health

NEUROLOGICAL HEALTH

Does Parkinson's Begin in the Gut?

A growing body of evidence links the neurodegenerative disease to the gastrointestinal tract, opening new possibilities for treatment

By Diana Kwon on May 8, 2018



Does Parkinson's disease start in the gut?

Lionnet A[1,2], Leclair-Visonneau L[2,3,4], Neunlist M[2,3], Murayama S[5], Takao M[6], Adler CH[7], Derkinderen P[8,9,10], Beach TG[11].

⊕ Author information

Abstract

Parkinson's disease (PD) is pathologically characterized by the presence of intraneuronal inclusions, termed Lewy bodies and Lewy neurites, whose main component is alpha-synuclein. Based on the topographic distribution of Lewy bodies and neurites established after autopsy from PD patients, Braak and coworkers hypothesized that PD pathology may start in the gastrointestinal tract then spread through the vagus nerve to the brain. This hypothesis has been reinforced by the discovery that alpha-synuclein may be capable of spreading transcellularly, thereby providing a mechanistic basis for Braak's hypothesis. This 'gut to brain' scenario has ignited heated debates within the movement disorders community and prompted a large number of studies in both humans and animals. Here, we review the arguments for and against the gut as the origin of PD. We conclude that the human autopsy evidence does not support the hypothesis and that it is too early to draw any definitive conclusions. We discuss how this issue might be further addressed in future research.

Gut Microbiota Dysfunction as Reliable Non-invasive Early Diagnostic Biomarkers in the Pathophysiology of Parkinson's Disease: A Critical Review

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Recent investigations suggest that gut microbiota affects the brain activity through the microbiota-gut-brain axis physiological and pathological disease conditions like Parkinson's disease. Further dopamine synthesis in the brain is dopamine producing enzymes that are controlled by gut microbiota via the microbiota-gut-brain axis. Also alpha synuclei and the associated neurodegeneration in the enteric nervous system that increase intestinal permeability, oxidative stres inflammation, accounts for constipation in Parkinson's disease patients. The trigger that causes blood brain barrier leaka cell activation and inflammation, and ultimately neuroinflammation in the central nervous system is believed to be due to low-grade inflammation in the gut. The non-motor symptoms that appear years before motor symptoms could be r biomarkers, if they could be correlated with the established and reliable neuroimaging techniques or behavioral indices directions should therefore, focus on the exploration of newer investigational techniques to identify these reliable early and define the specific gut microbes that contribute to the development of Parkinson's disease. This ultimately should paw safer and novel therapeutic approaches that avoid the complications of the drugs delivered today to the brain of Parkins patients.

(J Neurogastroenterol Motil 2018;24:30-42)

Key Words

Biomarkers; Constipation; Gastrointestinal microbiome; Humans alpha synuclein; Parkinson disease

PARKINSONISM STARTING IN THE GUT!

GUT DISEASE BEFORE MOTOR SYMPTOMS

World J Gastroenterol. 2015 Oct 7;21(37):10609-20. doi: 10.3748/wjg.v21.i37.10609.

Brain-gut-microbiota axis in Parkinson's disease.

Mulak A[1], Bonaz B[1].

⊕ Author information

Abstract

Parkinson's disease (PD) is characterized by alpha-synucleinopathy that affects all levels of the brain-gut axis including the central, autonomic, and enteric nervous systems. Recently, it has been recognized that the brain-gut axis interactions are significantly modulated by the gut microbiota via immunological, neuroendocrine, and direct neural mechanisms. Dysregulation of the brain-gut-microbiota axis in PD may be associated with gastrointestinal manifestations frequently preceding motor symptoms, as well as with the pathogenesis of PD itself, supporting the hypothesis that the pathological process is spread from the gut to the brain. Excessive stimulation of the innate immune system resulting from gut dysbiosis and/or small intestinal bacterial overgrowth and increased intestinal permeability may induce systemic inflammation, while activation of enteric neurons and enteric glial cells may contribute to the initiation of alpha-synuclein misfolding. Additionally, the adaptive immune system may be disturbed by bacterial proteins cross-reacting with human antigens. A better understanding of the brain-gut-microbiota axis interactions should bring a new insight in the pathophysiology of PD and permit an earlier diagnosis with a focus on peripheral biomarkers within the enteric nervous system. Novel therapeutic options aimed at modifying the gut microbiota composition and enhancing the intestinal epithelial barrier integrity in PD patients could influence the initial step of the following cascade of neurodegeneration in PD.

KEYWORDS: Brain-gut-microbiota axis; Enteric nervous system; Gastrointestinal dysfunction; Gut microbiota; Parkinson's disease

PMID: 26457021 PMCID: PMC4588083 DOI: 10.3748/wjg.v21.i37.10609

CONSTIPATION IN PARKINSON'S DISEASE

- In 1971 6790 men between the ages of 51-75 were followed for 12 years
- What they found:
  - Men having <1 bowel movement increased their risk of developing PD 4 fold compared to men who had 2 BM per day
  - Men having <1 bowel movement increased their risk of developing PD 4.5 fold compared to men who had more than 2 BM per day
  - Even when adjusted for age, pack-years of cigarette smoking, coffee consumption, laxative use, jogging, and the intake of fruits, vegetables, and grains

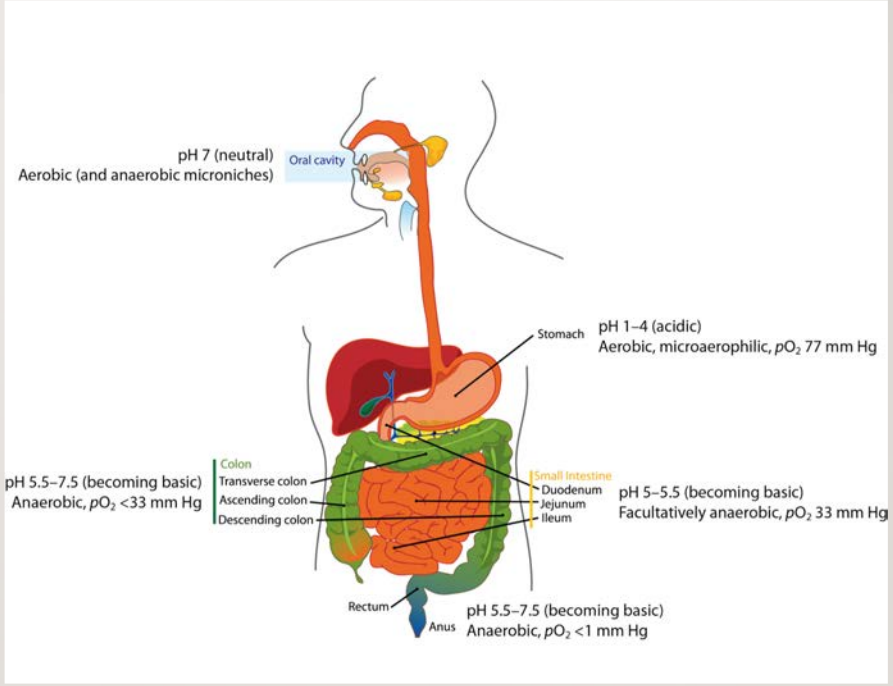
Aboott RD, 2001

WHAT IS YOUR GUT & WHY SHOULD I CARE?

The tube from your mouth to your anus

Non-Motor Symptoms are some of the most problematic symptoms in PD:

- Constipation
- Acid Reflux
- Nausea
- Weight Loss
- Abdominal Pain
- etc...



WHERE DIGESTION STARTS

- The mouth is NOT the first place that digestion starts
- You start the digestion process when you look at your food
- Your saliva has an enzyme called amylase that starts to break down starches before it gets to your stomach
- The pH of your stomach is ~2
- The Vagus Nerve stimulates digestion:

- stomach acid production -> gastrin -> pancreatic enzyme production

SMALL INTESTINES & COLON

- Most nutrients from food & medications are absorbed in the small intestines
- It has very small amounts of gut flora (10^4) compared to the large intestines (10^11)
- Most of the bugs in our gut – helpful and harmful – are in our colon

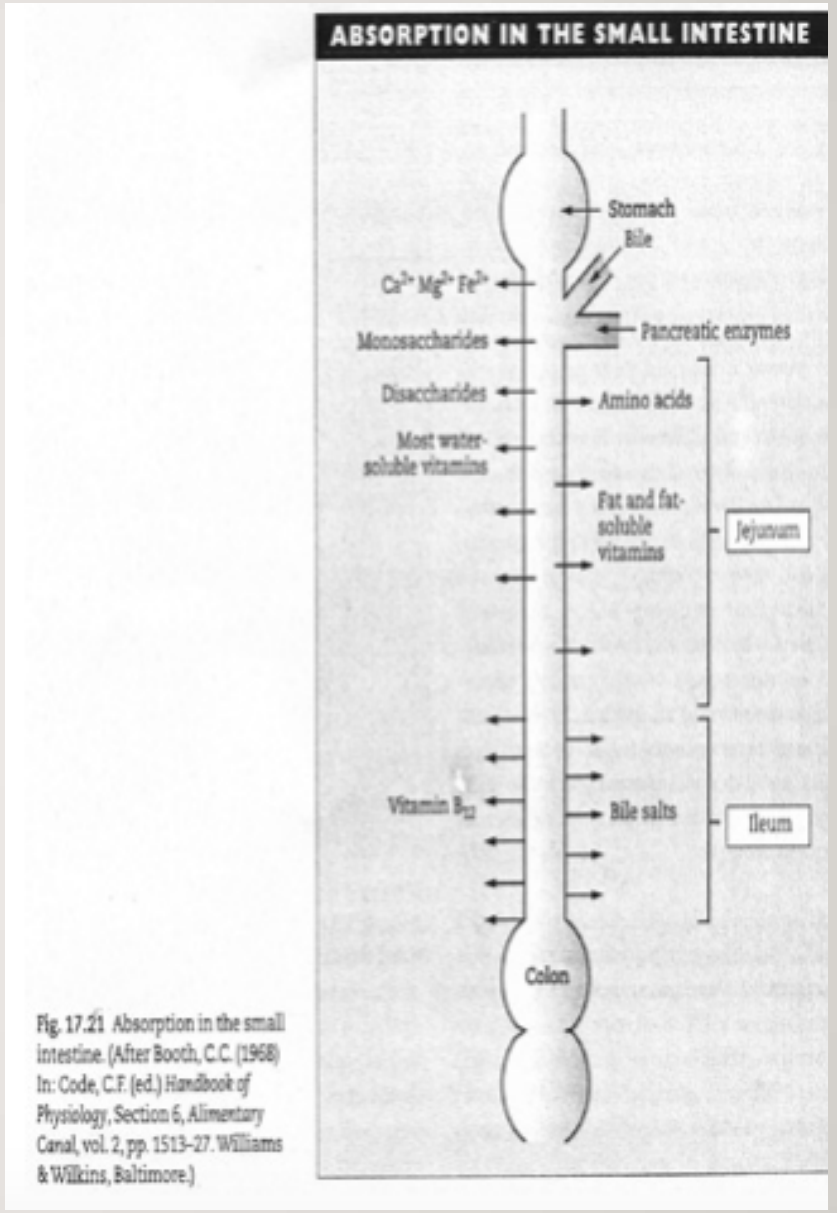
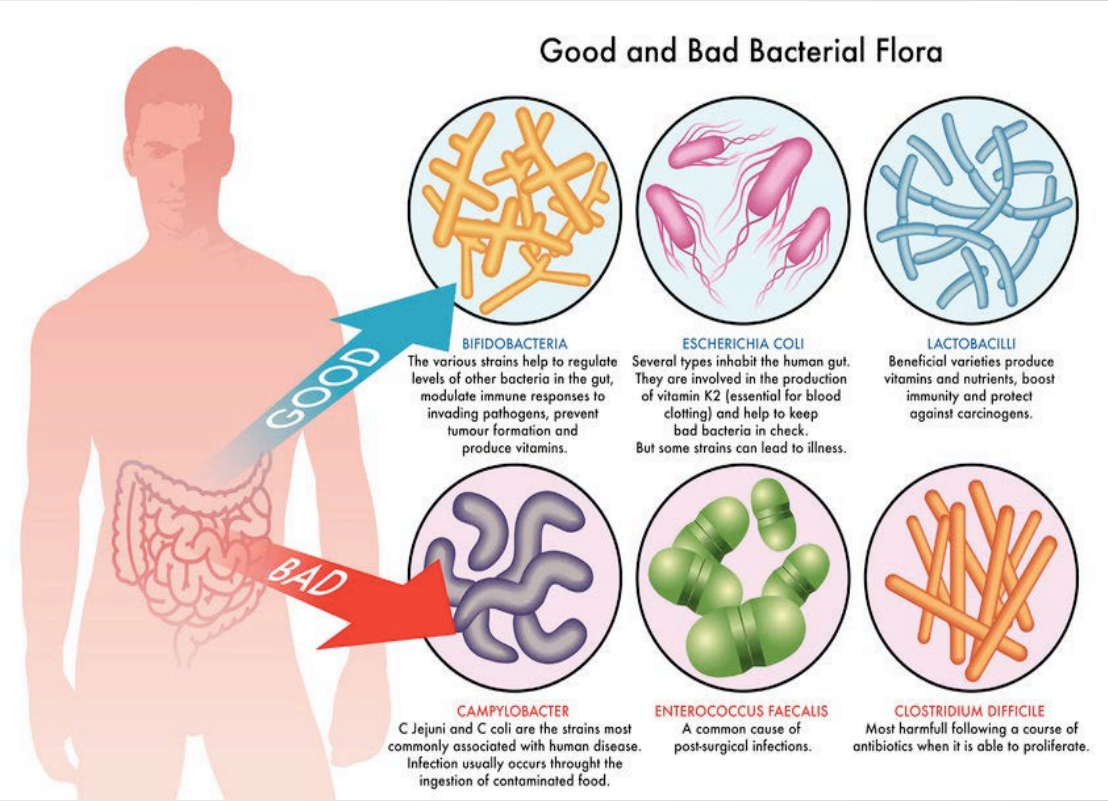


Fig. 17.21 Absorption in the small intestine. (After Booth, C.C. (1968) In: Code, C.F. (ed.) *Handbook of Physiology*, Section 6, *Alimentary Canal*, vol. 2, pp. 1513–27. Williams & Wilkins, Baltimore.)

Gorbach, 1996 Microbiology of Gastrointestinal Tract

GUT FLORA

- Role of the Gastrointestinal Flora:
  - Produce B12, Biotin, Folic Acid, B1
  - Ferment dietary fiber to be used for energy
  - More is being learned the more it is being researched



GI DISEASES ASSOCIATED WITH PD

1. Dysbiosis – AKA there is an imbalance in the bugs in your gut
2. H. Pylori
3. Small Intestinal Bacterial Overgrowth
4. Gastrointestinal Permeability
5. Low stomach acid
6. Celiac Disease
7. Lactose Intolerance/Dairy Allergy

Intestinal Health									
Permeability	Putrefecation	Infection				Immunological			
"Leaky Gut" (lactulose: mannitol)	(u) Indican	Increase in Hydrogen (H2)	Increase in Methane (CH4)	Increase in Combined H2 & CH4	H. pylori breath test	Antiparietal cell antibodies	anti-TTG	Gliadin	
>2 SD	>0	>20ppm	>3ppm	>15ppm	positive/ negative	>24.9 %	<6 U/mL	<20U	

DYSBIOSIS

- Recently it has been shown that individuals with PD are low in *Faecalibacterium* spp., *Coprococcus* spp., *Blautia* spp., *Prevotella* spp and/or have high amounts of in *Lactobacillus*, *Bifidobacterium*, *Verrucomicrobiaceae* and *Akkermansia*.
- One study compared the fecal microbiome of 72 patients with Parkinson's Disease to 72 controls
- It showed:
  - Prevotellaceae in feces of PD patients reduced by 77.6% compared to controls
  - an abundance of Enterobacteriaceae was associated with postural instability and gait difficulty

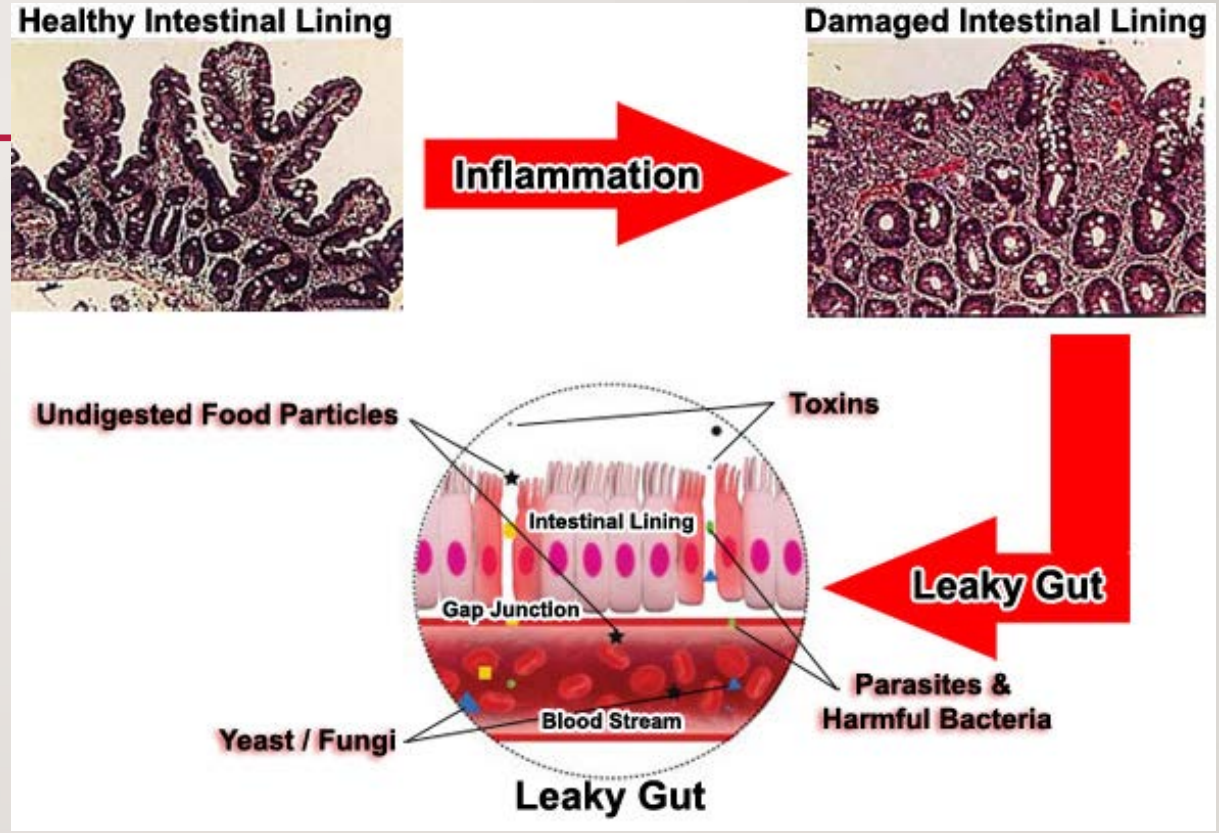
Bedarf et al, 2019; Gerhardt et al, 2018

WHAT CAN I DO ABOUT IT?

- Increase fiber
- Increase fresh fruits and vegetables!
- LESS MEAT
- No more artificial sweeteners! This also increases likelihood of leaky gut!

LEAKY GUT

- You can leaky gut even without gut symptoms!
- Inflammatory Processes are causing you to have leaky gut!
- *Causes of Leaky Gut:*
  - Diet
  - Food Allergens
  - Alcohol
  - Binge Alcohol Drinking
  - Dysbiosis



WHAT CAN I DO ABOUT IT

→ **MELATONIN!**
- One study showed that your gut produced 400-fold more melatonin than your pineal gland
- The melatonin produced in your gut decreases gastrointestinal permeability!

→ **PROBIOTICS**
- Prevotellaceae species in PD being low, increases gut permeability

→ **Glutamine?**
- A study showed intestinal permeability & inflammation improved in individuals after gastrointestinal surgery

→ **Dietary changes… Vegan, ketogenic, pescatarian…**

H. PYLORI

- A bacteria infection of the cells in your stomach that is associated with the following:
  - Peptic Ulcer Disease
  - Gastritis
  - Iron Deficiency Anemia
  - B12 Deficiency
  - Migraine
  - ……

AND…PARKINSON'S DISEASE!

H. Pylori is one of the most studied GI diseases in PD

The correlation between the two has been studied as well as the association between eradication and change in symptoms

H. PYLORI & ”ON” TIME

36 patients were tested for H. Pylori using serologic testing

- 50% were positive H. Pylori
- Duration of disease and L. Dopa dose were statistically significantly higher in H. Pylori positive individuals compare to seronegative
- Individuals without H. Pylori had longer “on” time; and seropositive patients had more off time according the UPDRS
- When treated for H. Pylori patients resulted in improved “on” time according to UPDRS

(Mridula KR 2017)

HOW DO YOU TREAT IT?

Conventional Therapy Prescription

→Triple Therapy: Clarithromycin, amoxicillin and a PPI

Alternative Therapies:

→ Combination of 8 botanical formulations Over the Counter:

- H. pylori formula, colloidal bismuth subcitrate, garlic, broccoli sprouts, probiotics cranberry juice, cinnamon tincture, thyme tea (Ayala G 2014)

HYPOCHLORHYDRIA

- Low Stomach Acid
- Need stomach acid for:
  - Nutrient absorption
  - Protection against bad microbes

WHAT DO I DO ABOUT IT??
Famous Answer…. It depends…

Anatomical?
→ **Injections of B Vitamins**
→ **Digestive Enzymes**

Medication
→ **Rhizinate** in place of your PPI?

Physiological
→ **Meditation, Mindful Eating**

SMALL INTESTINAL BACTERIAL OVERGROWTH

- Our small intestines is not supposed to have a measurable amount of bacteria
- This is being INCREASINGLY studied in Parkinson's disease
- If you have too many you can develop symptoms such as: constipation (or diarrhea), bloating, weight loss, nutritional depletion, decreased medication absorption!
- SIBO is associated with the following:
  - H. Pylori
  - Low Stomach Acid (Hypochlorhydria)/PPI Usage (Williams C, 2006)
  - Gastroparesis
  - Lactose Intolerance (Almeida JA 2008)
  - Leaky Gut (Intestinal Permeability) (Lopetuso LR, 2015)

THAT'S GREAT BUT WHY SHOULD I CARE?

- A study assessed 103 patients with PD via: breath test, UPDRS, quality of life questionnaire and objective measures of bradykinesia. Physicians were blinded to SIBO status
- 25.3% of PD patients were + for SIBO
- SIBO negative patients had a shorter duration of PD & lower Levodopa Equivalent dose
- SIBO + had increased abdominal pain, constipation
- Worse motor function

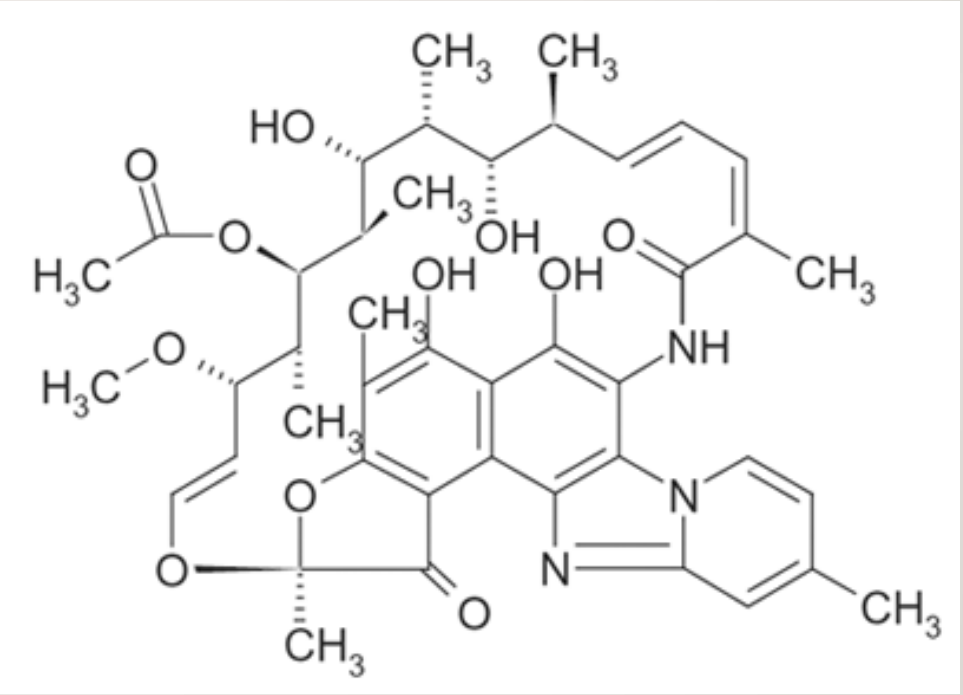
Another Study:

- 33 patients with PD were compared to 30 controls to assess SIBO & H. Pylori
- SIBO was statistically significantly higher in PD than controls (54.5% vs 20%); H. Pylori was not (33.3% vs 26.7)
- Patients with both SIBO and H. Pylori has significantly higher motor fluctuations than those without (87.5% vs 8.3%)
- SIBO + patients had longer "off" time

(Tan AH,

TREATMENT?

- The SIBO positive individuals in the study were treated with Rifaxamin 400mg three times daily for 7 days showed
- No side effects were reports
- 1 month later 77.8% of the patients were SIBO free & improved motor fluctuations
- However 6 months later 43% were SIBO + again



Fasano A, 2013

WHAT ARE SOME OF THE OPTIONS TO TREAT?

- Pharmaceutical:
  - Rifaximin with/without Neomycin (Pimentel M, 2011)
  - Lovastatin for methane positive individuals? (Muskal S, 2017)
- Botanical: (Chedid,V 2014)
  - FC-Cidal/Dysbiocide
  - Candibactin-AR/Candibactin-BR
  - Allysin+Berberine+Oregano Oil
- Elemental Diet (Pimentel M, 2004)
  - 14 days – 80% effective
  - 21 days - 85% effective

DIETARY MODIFICATIONS

If you look into dietary modifications to treat SIBO this is what you will find:

- SIBO Diet – Specific Carbohydrate Diet + Low FODMAP
  - No research and VERY restrictive
- SCD
  - Restrictive and research on IBD
- Low FODMAP
  - Research of its use in IBS; less restrictive
- Low Fermentation Diet
  - Used at Cedar Sinai by Dr. Pimentel – least restrictive

BUT…. these may not be appropriate

WHAT CAN I DO NOW?

SO MUCH!!!!!

Feed	Feed the good bugs in your gut
Eat	Eat lots of whole foods. Fresh fruits & vegetables to help diversify your microbiome
Chew	Chew your food!
Exercise	EXERCISE – this is the number one thing you can do to decrease progression AND when your body moves, so do your bowels!
Smell	Smell your food… yes even if you do not have your sense of smell
Stimulate	Stimulate digestion – lemon water with meds and before meals, bitter foods

DISCLOSURES

- None

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