Probiotics 2019
Fulfilling the Promise

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Objectives

• To define the proven GI uses of Probiotics
• To understand the difficulty in comparing strains, studies and results
• To describe how to best diagnose and treat CI difficile
• To discover how fecal transplants may be the ultimate Probiotic
• To describe the future uses of Probiotics

Conflict of Interest Disclosure

I have no conflicts and nothing to disclose
Microbiome Definitions

- Microbes
- Genetic Material

The Facts:
- 10X more microbes than we have cells
- 100X more genes than we have
- We carry 2 kg of bacteria
- Over 500 species

Factors Affecting the Microbiome

- Antibiotic use
- Infections
- High fat/high sugar diet
- Exercise
- Vegetarian diet
What is a Probiotic?

Definition

• Probiotic: live micro organisms that when administered in adequate amounts confer a health benefit to the host

What is a Prebiotic?
Prebiotic

- Non-digestible carbohydrate present in foods, which provides health benefits indirectly by promoting the growth of beneficial microorganisms

- Jerusalem artichoke
- Garlic
- Leeks

What is a Synbiotic?

Synbiotic

- A combination of Probiotic and Prebiotic

- Yogurt
- Whole grains
- Bananas
What is the most important characteristic of a Probiotic?

1. Number of live organisms
2. Bacterial strains
3. Longevity of the product

Common Probiotics

- VSL #3 a combination of several bacteria
- Align B infantis
- Culturelle Lactobacillus GG
- Dan Active L casei
- Florastor Saccharomyces boulardi

Fermented Milk Products

- Uses many strains of Lactobacillus
  - Kefir from Czech Republic
  - Sauermilch from Germany
  - Dadliah from Indonesia
  - Leben from the Middle East
  - Buttermilk in the US
Fermented Tea Product

• Kombucha

Probiotic Regulation

• U.S. Food products with no specific health claim. **None** yet submitted to the FDA for specific health claim.

• Europe: Health claims must be substantiated

Most Common Adult Probiotic Use

1. Irritable Bowel Syndrome
2. Ulcerative Colitis Adjuvant Therapy

3. Treatment of Pediatric Viral Diarrhea
   - Shortens diarrhea by 1 day
Antibiotic induced (Not Cl diff) diarrhea

Hempel S et al
Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis
JAMA 2012:307;1959

Cl difficile Prevention

Goldenberg JZ et al
Cochrane Database Syst Rev 2013 5;CD006095

Tung JM et al
Prevention of Clostridium difficile with Saccharomyces boulardii: a systematic review
Canadian Journal of Gastroenterology 2009:22;817

We Need More Data

Traveler’s Diarrhea prevention
Adjuvant treatment for H pylori infection
Doesn’t Work

• To treat C. difficile

Are There Any Risks of Probiotic Use?

Brandt LJ et al
Long-term follow-up of fecal microbiota transplantation for recurrent Clostridium difficile infection.
Am J Gastroenterol 2012;107;1079

Risks

• Infections in immunocompromised patients
• Development of autoimmune illnesses
What are the Research Difficulties in Studying Probiotics?

• Species and strain specific
• Dose
• Manufacturing standards
• Mechanism of action

Mechanisms??

• Antimicrobial
• Increase epithelial barrier
• Increased immunity
• Anti-inflammatory
• Modulation of pain in IBS
• Prevent harmful bacteria from attaching to the gut
• Modulating motility

Is it the Bacterium or its Metabolite?

Butyrate
Beneficial Properties of Butyrate

• Improves insulin sensitivity
• Signals the liver for less gluconeogenesis
• Butyrate is an energy source for colonic epithelial cells and maintains homeostasis

High Fiber May Increase Butyrate Production

Probiotics are useful in all these conditions except:

1. Ulcerative colitis
2. Crohn’s disease
3. Rotavirus infection in children
Irritable Bowel Syndrome

- Probiotics improve the global symptoms of bloating and flatulence (limited effectiveness)
- Hard to compare studies
- Different species, strains, preparations and doses in different patient populations


Ulcerative Colitis

- VSL #3 is the only probiotic studied for the prevention and relapse of ulcerative colitis when added to a standard regimen controlling ulcerative colitis
- According to the Cochrane analysis; no evidence for usefulness alone in the maintenance of remission


Probiotics and Acute Infectious (Viral) Diarrhea

- Safe
- Reduces duration of the diarrhea by 1 day
- 63 studies/8014 patients
- Not related to probiotic strain or number of organisms per capsule

What percentage of patients given antibiotics develop non specific diarrhea?

1. 10%
2. 30%
3. 50%

Newberry S
Probiotics can reduce risk of diarrhea caused by antibiotics
Rand Corp. Southern California Evidence-based Practice Center May 8, 2012

Probiotics may help reduce this number

Hempal, S, et al
Probiotics for the prevention and treatment of antibiotic associated diarrhea: a systematic review and meta analysis
JAMA 2012;309:1959

Todd

- Age 29 with a history of Irritable Bowel Syndrome has found several microbiome testing sites online and is asking for a recommendation.

- How do you answer?
Microbiome Based Tests

• Not yet ready for prime time
• Not yet validated
• Not yet proven of use for specific diseases
• More questions than answers

Khoruts A
A clinician's guide to microbiome testing
Gastro.org news/Nov 8, 2018

Ernie

• Is a 78 y.o recently diagnosed with a urinary tract infection
• He was given Septra DS for 10 days
• Unfortunately developed Cl difficile
• Then treated with Metronidazole 250 mg qid for 10 days
• Diarrhea recurred 2 weeks later
• Then given Vancomycin 125 mg qid
• Diarrhea returned 3 weeks later

What should we do now?
1. Fidaxomicin (Dificid)
2. Vancomycin AND Metronidazole
3. Repeat stool for Cl difficile
4. Fecal transplant
Should Metronidazole be a first line drug to treat Cl difficile?

• NO
  • The probability of Cl diff recurrences increased from 20 – 47% between 1991 and 2002


Why is Cl difficile Important?

• Increasingly causing deaths in the elderly, estimated to be 29,300 in 2011-

• From 2001 to 2012:
  42.7% increase in Cl diff
  188.8% increase in RECURRENT Cl diff**

• Sporadic outbreaks in healthcare facilities

• Virulent strain (NAP1/027)

** This increase was determined as the addition of the number of infections in the recurrent group, minus the sum total of all infections.
How Do We Test for Cl diff?

- PCR cannot distinguish asymptomatic carriers from true Cl difficile
- GDH antigen test (glutamate dehydrogenase) cannot distinguish between toxigenic and non toxigenic
- Nucleic Acid Amplification Test (NAAT)

Celeste

- Is a 50 y.o who had Cl diff 3 weeks ago treated with Vancomycin 125 mg qid for 10 days
- 3 weeks later, diarrhea returns
- Would you:
  1. Treat again for Cl diff?
  2. Do another stool test?

Martha C

- Is a 76 y.o female who had an unknown antibiotic exposure 2 weeks ago and now has Cl diff with:
  - T 101F
  - Diffuse abd pain
  - WBC 20,000 and shift to left
What is the ABX of choice?
How do you treat if she develops an ileus?
Is IV Vancomycin effective for Cl difficile treatment?

- Not effective
- Risk of: Red Man Syndrome, Nephrotoxicity, Ototoxicity

How Long After Antibiotic Use Can We Expect to See Cl diff?
What percentage of hospitalized asymptomatic patients are carriers of *Clostridium difficile*?

1. 1 - 5%
2. 5 – 20%

Mc Farland V et al
Nosocomial acquisition of *Clostridium difficile* infection

What percentage of asymptomatic extended care facility patients are carriers of *Clostridium difficile*?

Bender BS et al
Is *Clostridium difficile* endemic in chronic care facilities?
*Lancet* 1986 July 5:2(8497);11

Risk factors for recurrent *Clostridium difficile*

- PPI use
- Renal insufficiency
- Malnourished
- Elderly
- Long length of stay
- Serious illness/immunocompromised
Why stool transplants?

- 20-30% of patients treated for Clostridium difficile have a recurrence
- Many patients have multiple recurrences
- Fecal transplants break the cycle

Routes of Delivery

- Fecal Enemas
- Endoscopy
- Colonoscopy
- NG tube

Success Rates for Fecal Transplants

- 90% by colonoscopy
- Patients can feel better within hours of their transplant!!!
Fecal Transplants are Cost Effective

• More cost effective than other therapies for recurrent Cl difficile


What are the risks of stool transplants?

• Infections in immunocompromised patients?
• Development of autoimmune illnesses?
• Fecal Microbiota Transplant National Registry: actively collecting data

Tests for Stool Donor

• Hepatitis A,B,C
• HIV
• Stool O&P, C&S, Cl difficile
• MAY NOT BE COVERED BY HEALTH INSURANCE
OpenBiome – nonprofit stool bank

Should there be a standard donor pool?

Brown Cross

Choose Stool Wisely

• Case reports of fecal transplants from obese relatives causing significant wt gain in recipients
• No other causal factors

• Boggs, W
• Fecal transplants may up risk of obesity onset
• May 8, 2015
• Scientific American
Oral Capsule

- 116 patients
- Freeze dried stools placed in 40 capsules
- Non inferiority vs colonoscopy delivery


A Tale of an Isolated Village in Venezuela

- These Stone Age Villagers never had exposure to the outside world, especially not to antibiotics
- Stools showed 100 strains of bacteria unknown in North America

All of the following are risk factors for recurrent C. difficile except
1. Age
2. PPI use
3. Hospitalization
4. Diphenoxylate use
Which of the following are complications of Cl difficile:
1. Renal failure
2. Toxic megacolon
3. Death
4. All of the above

What is the Future of Probiotics?
- Obesity
- Non Alcoholic Fatty Liver Disease (NAFLD)
- Diabetes
- Autoimmune diseases
- Allergies
- Neurological probiotics for well being

The National Microbiome Initiative:
- Will probiotics ever overcome antimicrobial resistance?
- Microbiome relation to lipid levels
What is the future of fecal transplants?

- As of April 2019, there were 231 studies on fecal transplants (ClinicalTrials.gov)
  - Irritable Bowel Syndrome
  - Metabolic disease
  - Antibiotic resistance
  - Psychiatric disorders

Summary

- Probiotics have been shown to be helpful in treating:
  - Irritable Bowel Syndrome
  - Ulcerative Colitis
  - Acute Infectious Diarrhea in pediatrics, especially Rotavirus
- The role of Probiotics in treating many other diseases remains controversial
- The benefits of fecal transplants in recurrent Clostridium difficile far outweigh the risks

Thank You