Probiotics 2017: Fulfilling the Promise
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Disclosure:
• Speaker’s Bureau AbbVie
  Synergy Pharmaceuticals

Objectives
• To learn about the proven GI uses of Probiotics
• To understand the difficulty in comparing strains, studies, potency and results
• To understand how fecal transplants may be the ultimate Probiotic
• To review the potential future uses of Probiotics
“When you come to a fork in the road, take it”

AMERICAN GUT

- Crowd sourced from UC San Diego
- Sample kit and questionnaire about diet
- Developing a database

Microbiome Definitions

- Microbes
- Genetic Material
The Facts:

• 10 X 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

Probiotic

• Live micro organisms that when administered in adequate amounts confer a health benefit to the host
Prebiotic

• Usually non-digestible carbohydrate present in foods which provide health benefits indirectly by promoting the growth of beneficial microorganisms
  Jerusalem artichoke
  Garlic
  Leeks

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. Shelf life 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

Probiotic Regulation

- U.S. Food products with no specific health claim.
- None yet submitted to the FDA for specific health claim
- No viable cell counts required
- No shelf life/storage required

Probiotics in 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

Allen SJ et al
Probiotics for treating acute infectious diarrhoea
Controversial Use

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 L et al
Cochrane Database Syst Rev. 2013;5:CD006205
We need more data

• Traveler’s Diarrhea prevention
• Adjuvant treatment for H pylori infection

Doesn’t Work

• To treat Cl difficile

Are There Any Risks of Probiotic Use?

Brandt, LJ et al. Long term follow up of volunteers used to introduce bacteria for recurrent Clostridium difficile infection. Am J Gastroenterology 2012; 107:1275
Risks

• Infections in immunocompromised patients?

What are the Research Difficulties in Studying Probiotics?

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

Another Clinical Factor

• Probiotics are susceptible to die off during prolonged storage
Mechanisms??

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

Is it the Bacterium or its Metabolite?

Butyrate
What is Butyrate???

Beneficial Properties of Butyrate

• Lowers pH
• Inhibits pathogens
• Improves gut immunity
• Improves Insulin sensitivity
• Signals the liver for less gluconeogenesis
• Is an energy source for colonic epithelial cells
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

Shen, R et al
Effect of probiotic on inducing and maintaining therapy in ulcerative colitis, cohen's disease and pouchitis meta analysis of randomized controlled trials
Inflammatory Bowel Disease 2014:20:21

Probiotics and Acute Infectious (Viral) Diarrhea

- Safe
- Reduces the duration of the diarrhea by 1 day
- 63 studies/8014 patients
- Includes infants and children
- NOT related to probiotic strain, number of organisms per capsule or type of infection

Allen SJ et al
Probiotics for treating acute infectious diarrhoea
Cochrane Database Syst Rev 2010 CD003048

What percentage of patients given antibiotics develop non specific diarrhea?

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

• Do you recommend probiotics to your patients who have had antibiotic induced diarrhea (NON Cl difficile) previously related to the SAME antibiotic?

Probiotics may reduces this number


Questions

• Are Probiotics useful to prevent Cl difficile?

• What is the standard of care?
What’s the Data on Probiotic Prevention of Cl difficile?

- 3818 patients in 20 trials
- Probiotics reduced Cl difficile by 66%
- (Lactobacillus and Saccharomyces boulardii)


Cl difficile Prevention??

- 23 RCTs N 4213
- Cl diff infection 5.5% Probiotic cohort 2%
- Probiotics MAY prevent Cl diff

Goldenberg JZ et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea. Cochrane Database Syst Rev 2013:5;CD006095

We need more data

- Specific antibiotics matched to specific Probiotics
- Use in different populations; in and out patient; very sick; mildly ill
- Which probiotics are most efficacious?
- Studies don’t start Probiotics at the same time

Rao K and Young V. Probiotics for the prevention of Clostridium difficile infection in hospitalised patients: is the jury still out? Gastroenterology 2017:152;1817
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
- The treated with Metronidazole 250 mg qid for 10 days
- Diarrhea recurred 2 weeks later
- Then given Vancomycin 125 mg qid
- Diarrhea returned 2 weeks later

What should we do now?

1. Fidaxomicin (Dificid)
2. Vancomycin AND Metronidazole
3. Fecal transplant

Which of the following are true regarding Fidaxomicin?

1. Reduces recurrence rates for Cl difficile
2. More effective than Vancomycin
3. No adjustment is needed for renal compromise
Why is Cl difficile Important?

- Three times more prevalent than in 2000*
- Increasingly causing deaths in the elderly, estimated to be 29,300 in 2011 *
- Sporadic outbreaks in healthcare facilities
- Virulent strain (NAP1/027)

Fernanda, C et al. The Burden of Cl diffic Infection in the US. MMWR 2015: 64; 1045

Celeste

- Is a 50 y.o who had Cl diff 3 weeks ago treated with Vancomycin 125 mg qid for 10 days
- Now diarrhea again
- 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?
How Long After Antibiotic Use Can We Expect to See Cl diff?

What percentage of hospitalized asymptomatic patients are carriers of Cl difficile?
1. 5%
2. 10%
3. 20%
4. 50%

What percentage of asymptomatic extended care facility patients are carriers of Cl difficile?
Risk factors for recurrent Cl difficile

- PPI use
- Renal insufficiency
- Malnourished
- Elderly
- Long length of stay
- Serious illness/immunocompromised

Why stool transplants?

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

Routes of Delivery

- Fecal Enemas
- Endoscopy
- Colonoscopy
- NG tube
- Freeze dried capsules
Success Rates for Fecal Transplants

• 90% by colonoscopy
• Patients can feel better within hours of their transplant!!!

Tests for Stool Donor

• Hepatitis A,B,C
• HIV
• Stool O&P, C&S, CI difficile
• MAY NOT BE COVERED BY HEALTH INSURANCE

Openbiome™
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 13, 2015
- Scientific American

Synthetic Stool

- “RePOOPulate”
- Has only 30 strains of bacteria

- Petrof, EO
- Stool substitute transplant therapy for the eradication of Clostridium difficile infection: “RePOOPulating the gut”
- Microbiome 2013
### All of the following are risk factors for recurrent Cl 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
- Antimicrobial resistance
- Autoimmune diseases
- Allergies
- Neurological probiotics for well being
Summary

• Probiotics have been shown to be helpful in treating: Irritable Bowel Syndrome
  Ulcerative Colitis
  Acute Infectious Diarrhea in peds, especially Rotavirus
• The role of Probiotics in treating many other diseases remains controversial
• Fecal transplants prevent recurrence of Cl difficile