Joint Webinar Presentation

The Physiological Roles of Intestinal Microbiota

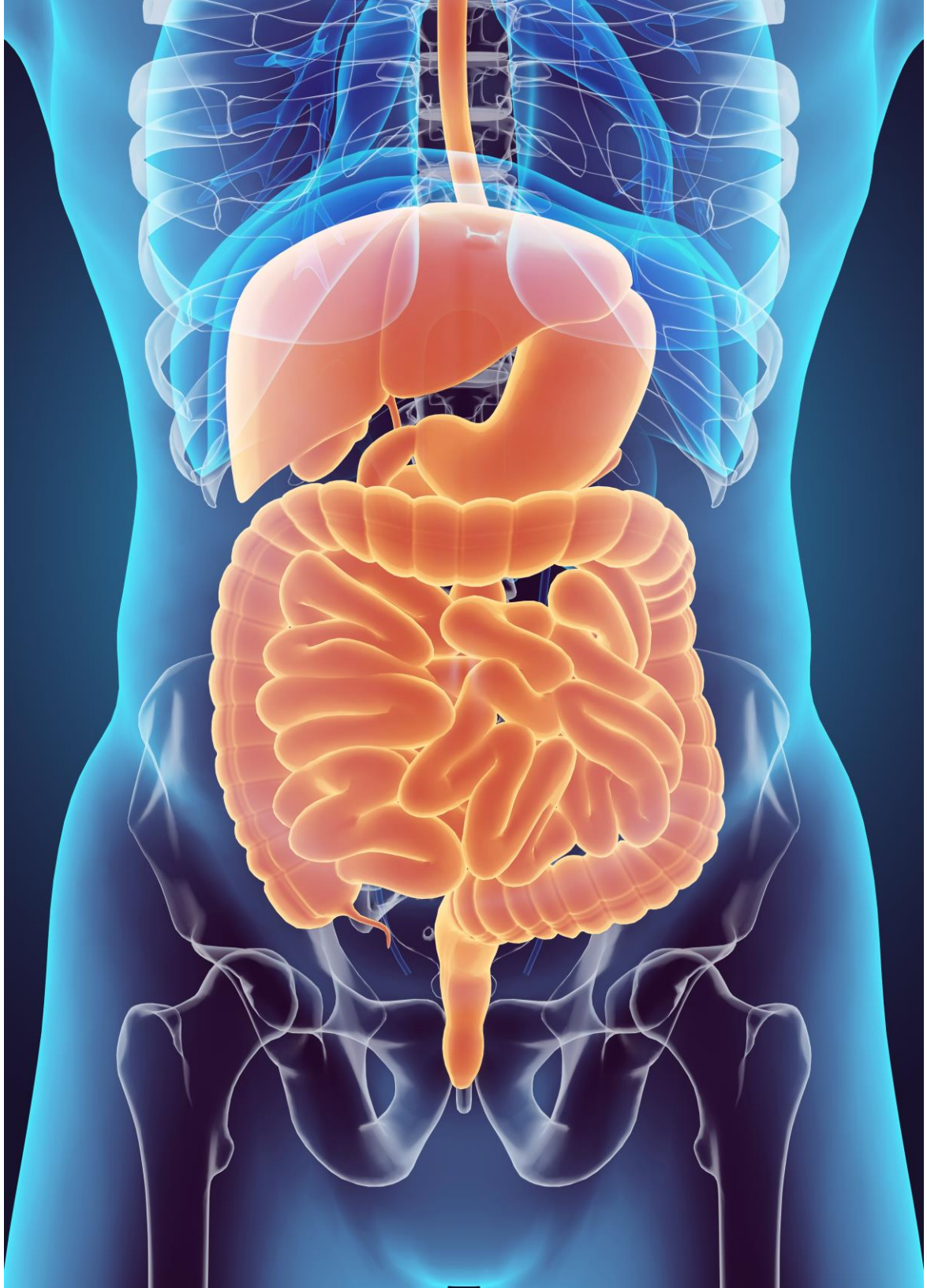
Earn **1.5** CPEUs

Presented by **Kelly Anne Tappenden**, PhD, RD, on Thursday,
September 20, 2018, **2:00-3:30pm** ET

Learning Objectives

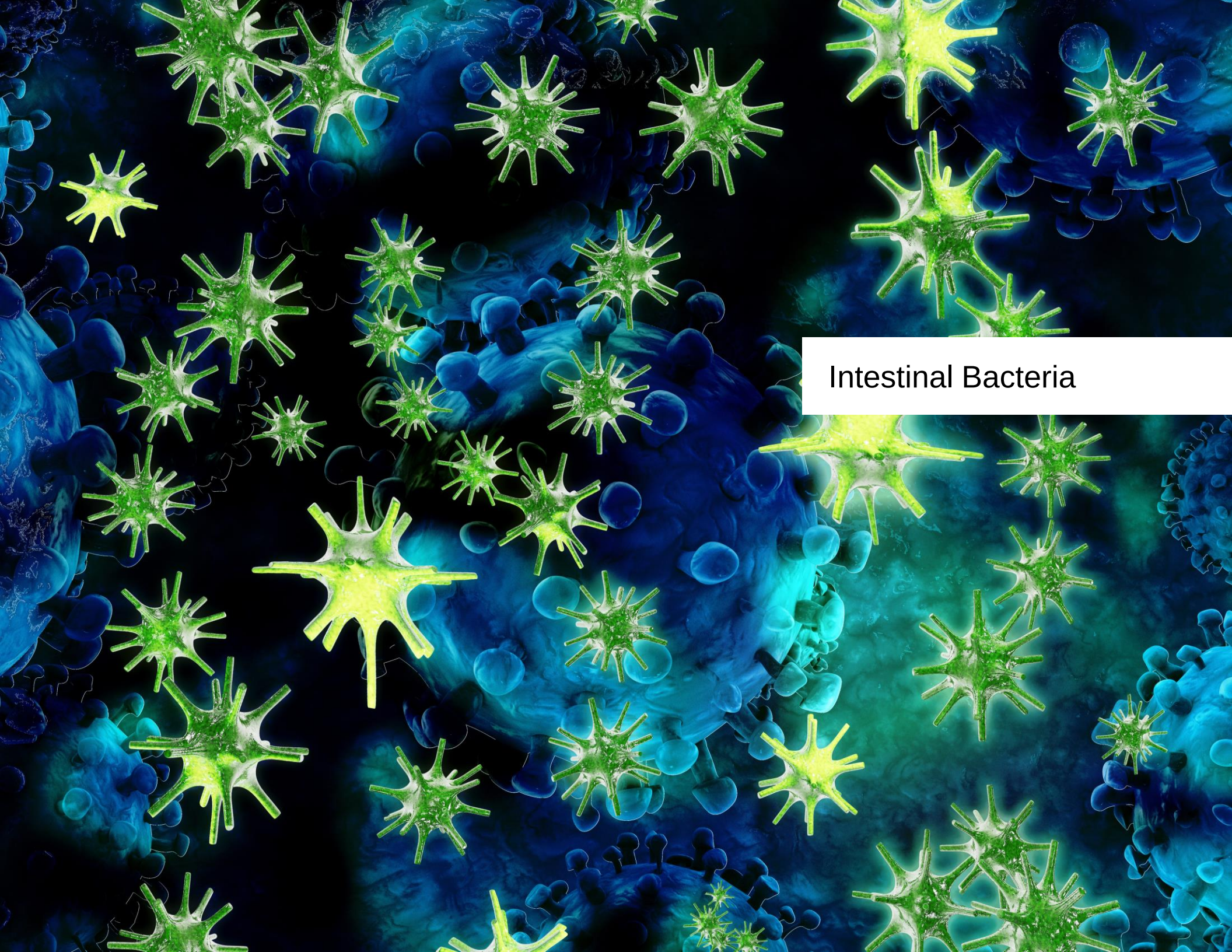
After completing this continuing education course, nutrition professionals should be able to:

- Articulate the many important physiologic functions of the intestinal microbiota
- Recognize signs and symptoms in individuals at high risk for dysbiosis
- Prescribe nutritional strategies, including the use of pre- and probiotics aimed at optimizing the intestinal microbial community



Specialized structure facilitates function

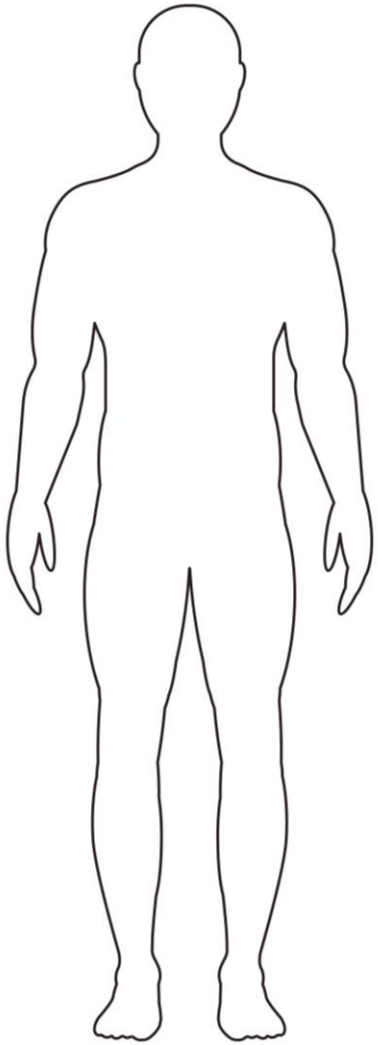
Multiple Epithelial Cell Types


Intestinal Bacteria

Who are we?

Microbial Cells
≈100 Trillion (≈70-90%)

Human Cells
≈30 Trillion



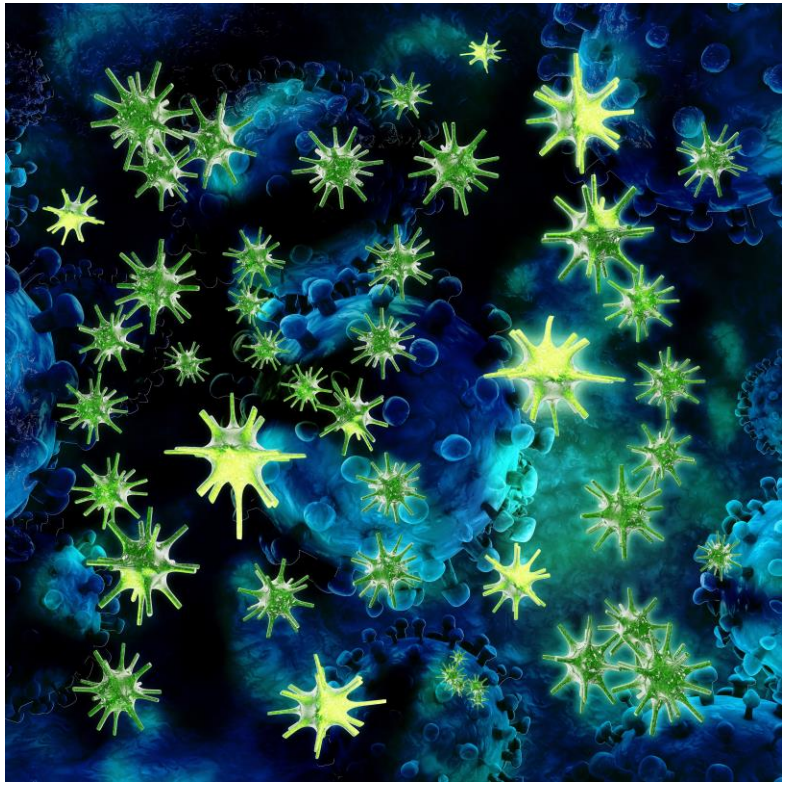
Microbial Genes
≈2,000,000 (≈99%)

Human Genes
≈23,000

Physiological Functions of the Commensal Microbiota

1. Prevent overgrowth of pathogenic organisms

- **Receptor competition**
- **Nutrient competition**
- **Antimicrobial substances**



Physiological Functions of the Commensal Microbiota

2. Stimulate intestinal immunity (GALT)

Physiological Functions of the Commensal Microbiota

3. Powerful anti-inflammatory activity

- **Bifidobacterium**
- **Lactobacillus**

Uninfected

Infection-induced inflammation

Infection + lactobacillus

Peña JA et al., Infect Immun 2005;73(2):912-920.

Physiological Functions of the Commensal Microbiota

4. Production of essential mucosal nutrients, such as short-chain fatty acids

Physiological Functions of the Commensal Microbiota

5. Control of epithelial cell proliferation and differentiation

Apoptosis

Signaling molecules

Villus Height

Proliferation

Physiological Functions of the Commensal Microbiota

6. Gut-brain axis

Factors affecting stability and complexity of gut microbiome in health and disease

Further stepwise microbiome development through life, modified by diet, genetics and the environment

Dysbiosis with childhood diseases

Disease	Microbiota composition changes
Celiac Disease	Lack of bacteria of the phylum Bacteroidetes along with an abundance of Firmicutes
IBD	↓ concs of Faecalibacterium prausnitzii and Bifidobacteria ↑ levels of Escherichia coli Reduced diversity of gut microbiota
IBS	Significantly ↑ % of the class Gammaproteobacteria Presence of unusual Ruminococcus-like microbes
NEC	Predominance of Gammaproteobacteria ↓ diversity of gut microbiota
Obesity	↑ Firmicutes at expenses of the Bacteroidetes group
CF	↓ counts of lactic acid bacteria, clostridia, Bifidobacterium spp., Veillonella spp., and Bacteroides-Prevotella spp.
Allergy	↓ counts of Lactobacilli, Bifidobacteria, and Bacteroides ↑ counts of Clostridium difficile ↓ diversity of gut microbiota

Buccigrossi et al., Curr Opin Gastroenterol 2013;29:31–38.

Microbe contact begins *in utero*

Human milk microbiome varies with stage of lactation, obesity and route of delivery

Human milk = the ultimate SYNbiotic!

Microbiota: breast vs bottle?

- Breast-fed infants
  - stable developing microbiota
  - dominated by bifidobacteria (‘bifidofactor’)
  - decreased pathogens
- Formula-fed infants
  - Less stable microbiota
  - assoc with higher incidence of pathogenic infections, pneumonia, diarrhea, and allergy

Harmsen et al., JPGN 2000:30;61-67

Dysbiosis with childhood diseases

Disease	Microbiota composition changes
Celiac Disease	Lack of bacteria of the phylum Bacteroidetes along with an abundance of Firmicutes
IBD	↓ concs of Faecalibacterium prausnitzii and Bifidobacteria ↑ levels of Escherichia coli Reduced diversity of gut microbiota
IBS	Significantly ↑ % of the class Gammaproteobacteria Presence of unusual Ruminococcus-like microbes
NEC	Predominance of Gammaproteobacteria ↓ diversity of gut microbiota
Atopy	↓ counts of Lactobacilli, Bifidobacteria, and Bacteroides ↑ counts of Clostridium difficile ↓ diversity of gut microbiota
Obesity	↑ Firmicutes a t expenses of the Bacteroidetes group
CF	↓ counts of lactic acid bacteria, clostridia, Bifidobacterium spp., Veillonella spp., and Bacteroides-Prevotella spp.

Buccigrossi et al., Curr Opin Gastroenterol 2013;29:31–38

Dysbiosis in adult disease

- Acute diarrhea
- IBD
- Functional bowel disorders
- Liver disease
- Energy regulation
- GI malignancy
- *C. diff* disease

Old Dancing Russians??

A story long in the making…

- First reported intakes being the injection of soured milks by Nomads >2000 years ago
- >100 years ago, Elli Metchinikoff, known as the pioneer of probiotics, observed complex microbial population of the colon
  - ‘Autointoxication’
  - Longevity in Bulgarians linked to consumption of fermented milk containing lactobacillus
  - Abandoned colectomy for probiotic use

What is a Probiotic?

Oral probiotics are living microorganisms that upon ingestion in specific numbers, exert health benefits beyond those of inherent basic nutrition

- Nonpathogenic
- Resistant to technological processing, storage and delivery
- Resistant to gastric acidity and lysis by bile
- Viable in the gastrointestinal environment
- May adhere to the epithelium
- Produces antimicrobial substances

Strong evidence supporting PRObiotic use

Clinical Condition	Organism
Diarrhea	
Infectious adult – treatment	Saccharomyces boulardii, LGG
Infectious childhood – treatment	LGG, Lactobacillus reuteri
Prevention of antibiotic-associated diarrhea	S. boulardii, LGG, L. casei, . Bulgaricus, S. thermophilus
Inflammatory Bowel Disease	
Pouchitis - Preventing and maintaining remission	VSL#3
Immune response	LGG, L. acidophilus, L. plantarum, B. lactis, L. johnsonii, VSL#3
Atopic eczema associated with cow's milk allergy	
Treatment	LGG, B. lactis
Prevention	LGG, B. lactis

Lactobacillus reuteri is effective therapy for acute rotavirus diarrhea in children

- PRCT with children (n=40) 6-36 months of age hospitalized with acute diarrhea (75% rotavirus)
- placebo or 10^{10}-10^{11} CFU *L. reuteri* for hospital stay of >5d
- duration of watery diarrhea after treatment was 1.7(sd1.6) days in the *L. reuteri* group and 2.9(sd2.3) days in the placebo group (p=0.07)
- By d2, only 26% of *L. reuteri* group had watery diarrhea, compared with 81% of placebo (p=0.0005)
- Stool cultures revealed good colonization of *L. reuteri* in those treated (>75% of *Lactobacilli* detected)

Shornikova et al., JPGN 1997;24:399-404.

Lactobacillus improves clinical outcomes in children with acute infectious diarrhea

Recommendation for Use of PRObiotics in Diarrhea in Children

Condition	Sample Size	Probiotics Studied	Efficacy
Prevention of day-care diarrhea	1700	B. lactis/S.thermophilus LGG	+
Prevention of nosocomial diarrhea	356	LGG B. lactis/S.thermophilus	+/-
Antibiotic-associated diarrhea	2000	LGG Saccharomyces boulardii	+++
Infectious diarrhea	3000	LGG Saccharomyces boulardii L. acidophilus LB	+++
Persistent diarrhea	235	LGG	++

Guandalini S. J Clin Gastro 2008;42(S2):S53-S57.

VSL#3 are beneficial for maintaining remission in patients with pouchitis.

- 23 RCTs (n=1763) comparing probiotics with controls in IBD
- Probiotics assoc with induction of remission in UC (P<0.01, RR=1.51)
    - VSL#3 (P<0.0001, RR=1.80)
- VSL#3 reduced the clinical relapse rates for maintaining remission in patients with pouchitis (P<0.00001, RR=1.18)

Shen et al., Inflamm Bowel Dis 2014;20:21–35

VSL#3 induced remission in patients with mild-to-moderately active ulcerative colitis

Probiotics and antibiotic assoc diarrhea

Objective – Evaluate the evidence for probiotic use in the prevention and treatment of antibiotic-associated diarrhea

Source – 82 RCTs, 11,811 subjects

Probiotic studied - *Lactobacillus, Bifidobacterium, Saccharomyces, Steptococcus, Enterococcus and/or Bacillus*

Results - probiotic administration with reduction in AAD (RR, 0.58; 95% CI, 0.50 to 0.68; *P*.001)

Interpretation - insufficient to determine whether this association varies systematically by population, antibiotic characteristic, or probiotic preparation.

Hempel et al., JAMA 2012;307:1959-1969.

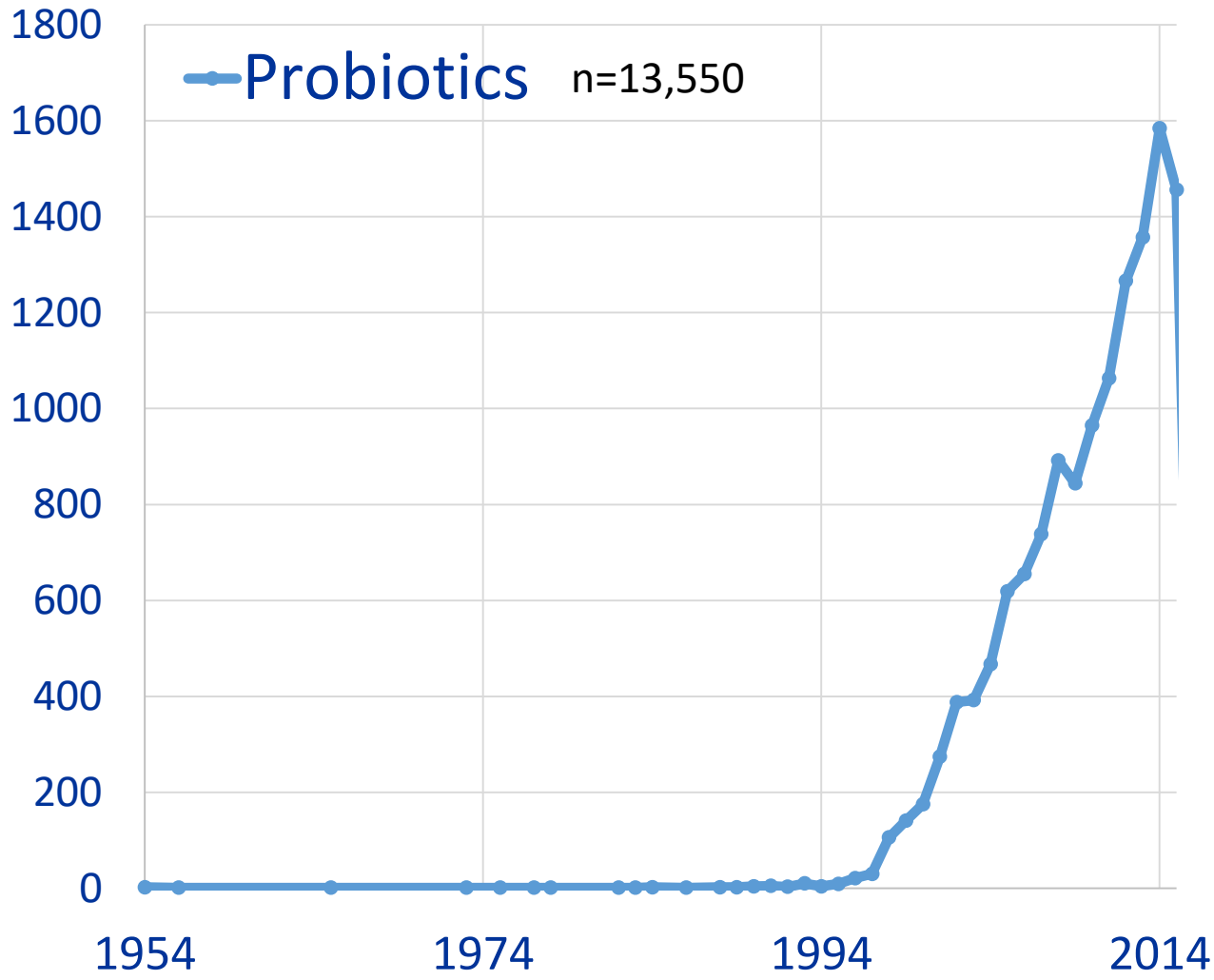
Moderate Evidence Supporting PRObiotic Use

Clinical Condition	Organism
Diarrhea	
Prevention of infection	Saccharomyces boulardii, LGG
Treatment of recurrent C. difficile-associated diarrhea	S. boulardii, LGG
Prevention of recurrent C. difficile-associated diarrhea	S. boulardii, LGG
Necrotizing Enterocolitis	B. infantis, S. thermophilus, B. bifidus
Irritable Bowel Syndrome	B. infantis

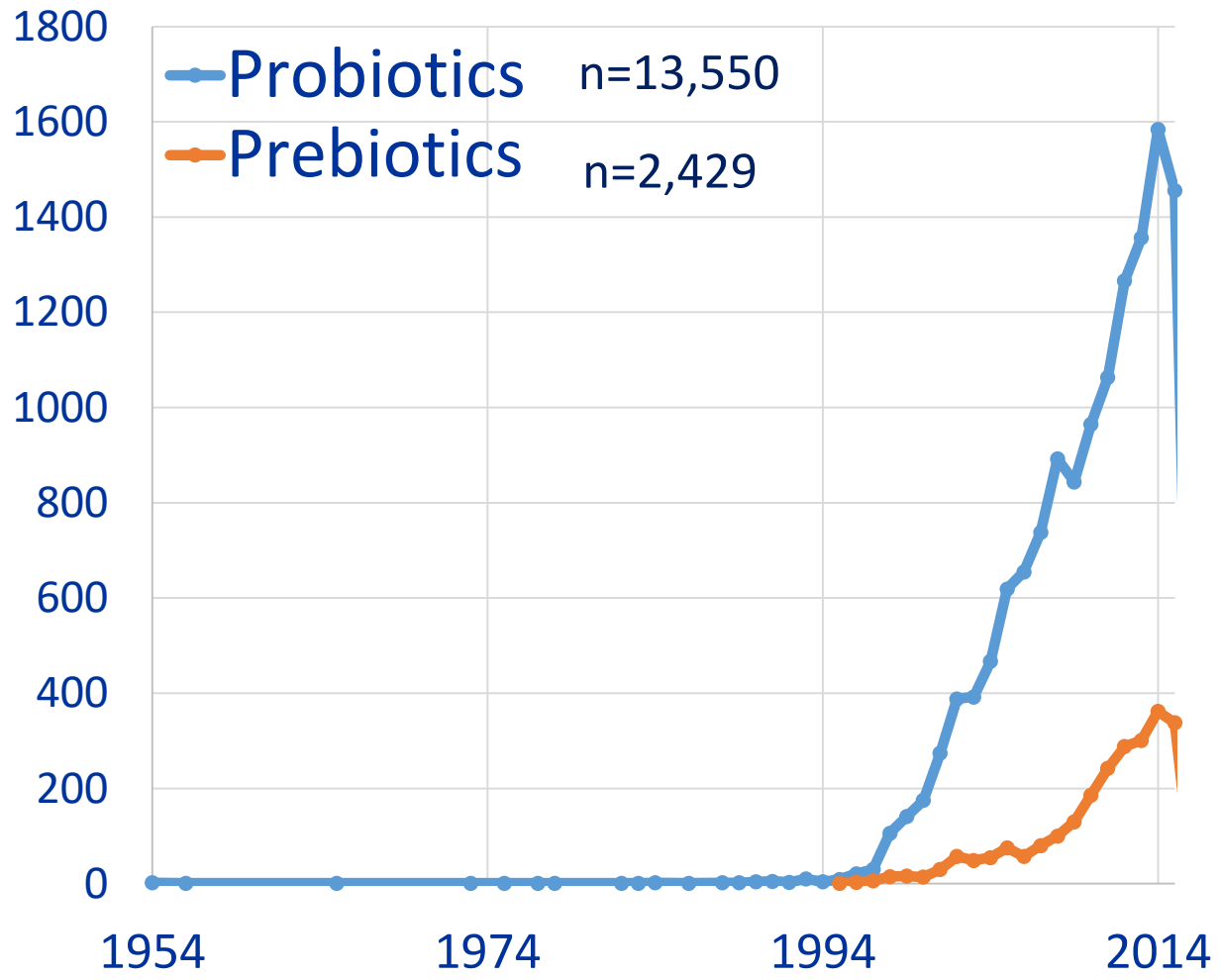
Irritable bowel syndrome symptoms alleviated by *B infantis* 35624

VSL#3 prevented ↑ fat diet-induced obesity and diabetes

PubMed Citations by Year



PubMed Citations by Year



What is a PREbiotic?

- A prebiotic is a non-digestible *food* ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one of a limited number of bacteria in the colon, and thus improves host health.

  (Gibson and Roberfroid,1995; Gibson et al., 2004)

- Many prebiotics are classified as a functional *fiber*





Compared to probiotics…

Prebiotics are:

~100 yr younger

5.6X ↓ studied

Less Exciting?

Top Reasons Why Prebiotics Should Not Be Overlooked

- ❑ Evoke similar benefit as probiotic interventions.
- ❑ Provide necessary substrate for microbiota.
- ❑ Lasting impact on microbiota and clinical outcomes.
- ❑ Safe, food-based strategy associated with wealth of data.

Proposed mechanisms of prebiotics on obesity

Short-term diet alters the intestinal microbiota

Animal-based diet:

- ↑ bile-tolerant microorganisms
- ↓ Firmicutes that metabolize dietary plant polysaccharides
- link between dietary fat, bile acids growth of microorganisms capable of triggering IBD

David et al., Nature 2014;505:559.

Infants consuming formula with prebiotic have microbiota more similar to that of breast fed infants.

Prebiotic formula reduces cumulative incidence of infections during first 6 months of life

Prebiotic formula reduces episodes of infections and fever during first 2 years of life.

Prebiotic formula reduces incidence of allergic manifestations during first 2 years of life

Prebiotics reduced occurrence of early atopic dermatitis among healthy infants at low risk

Galacto-oligosaccharide prevents incidence and symptoms of Traveler's Diarrhea

	Placebo (n=78)	B-GOS (n=81)
Subjects with diarrhea	30*	19
Diarrhea duration (d)	4.567* ± 3.026	2.368 ± 2.060
Duration of abdominal pain (d)	3.533* ± 2.583	2.000 ± 1.987
Duration of vomiting (d)	0.433 ± 0.675	0.526 ± 0.722
Duration of fever (d)	0.133 ± 0.581	0.210 ± 0.713
Duration of anorexia (d)	0.233 ± 0.466	0.157 ± 0.688
Duration of headache (d)	0.600 ± 1.695	0.578 ± 0.961
Duration of dizziness (d)	0.800 ± 1.763	0.663 ± 0.806
Quality of Life (score/d)	53.12 ± 3.96	62.37* ± 5.51

Drakoularakou et al., Eur J Clin Nutr 2010;64:146–152.

Prebiotics results in positive short- and long-term health economic benefits

Prebiotic cost = €51
Quality Adjusted Life Years = 0.108
Incremental cost-effectiveness ratio = € 472

Lenoir-Wijnkoop et al., Eur J Health Econ 2012;13:101–110.

Dietary inulin reduces inflammation associated with pouchitis

- Randomized, double-blind crossover trial on 20 subjects ileal pouch-anal anastomosis
- randomized to placebo or 24 g inulin for 3 wks with fecal analysis after each test period
- Inulin ↑ [butyrate], ↓ pH, ↓ # *Bacteroides fragilis*, and ↓ [secondary bile acids] in feces

	Placebo	Inulin	P-value
Clinical score	1.26 (0.29)	1.00 (0.27)	0.17
Endoscopic score	1.47 (0.32)	0.95 (0.22)	0.04
Histologic score	2.61 (0.26)	2.11 (0.14)	0.04
Total PDAI score	5.39 (0.62)	4.05 (0.44)	0.01

Welters et al. Dis Colon Rectum 2002;45:621-627.

Galacto-oligosaccharide stimulated bifidobacteria and alleviated IBS symptoms

- Subjects with IBS (n=44) completed 12-wk crossover RCT
- Randomized to 3.5 g GOS, 7 g GOS or 7 g placebo daily and symptoms assessed weekly
- Prebiotic ↑ faecal bifidobacteria (3.5, $P<0.005$; 7, $P<0.001$).
- 3.5 GOS: improved stool consistency ($P < 0.05$), flatulence ($P < 0.05$), bloating ($P < 0.05$), composite score of symptoms ($P < 0.05$)
- 7 GOS: improved anxiety scores ($P < 0.05$)
- Placebo without effect

Silk et al Aliment Pharmacol Ther 2009;29:508-518.

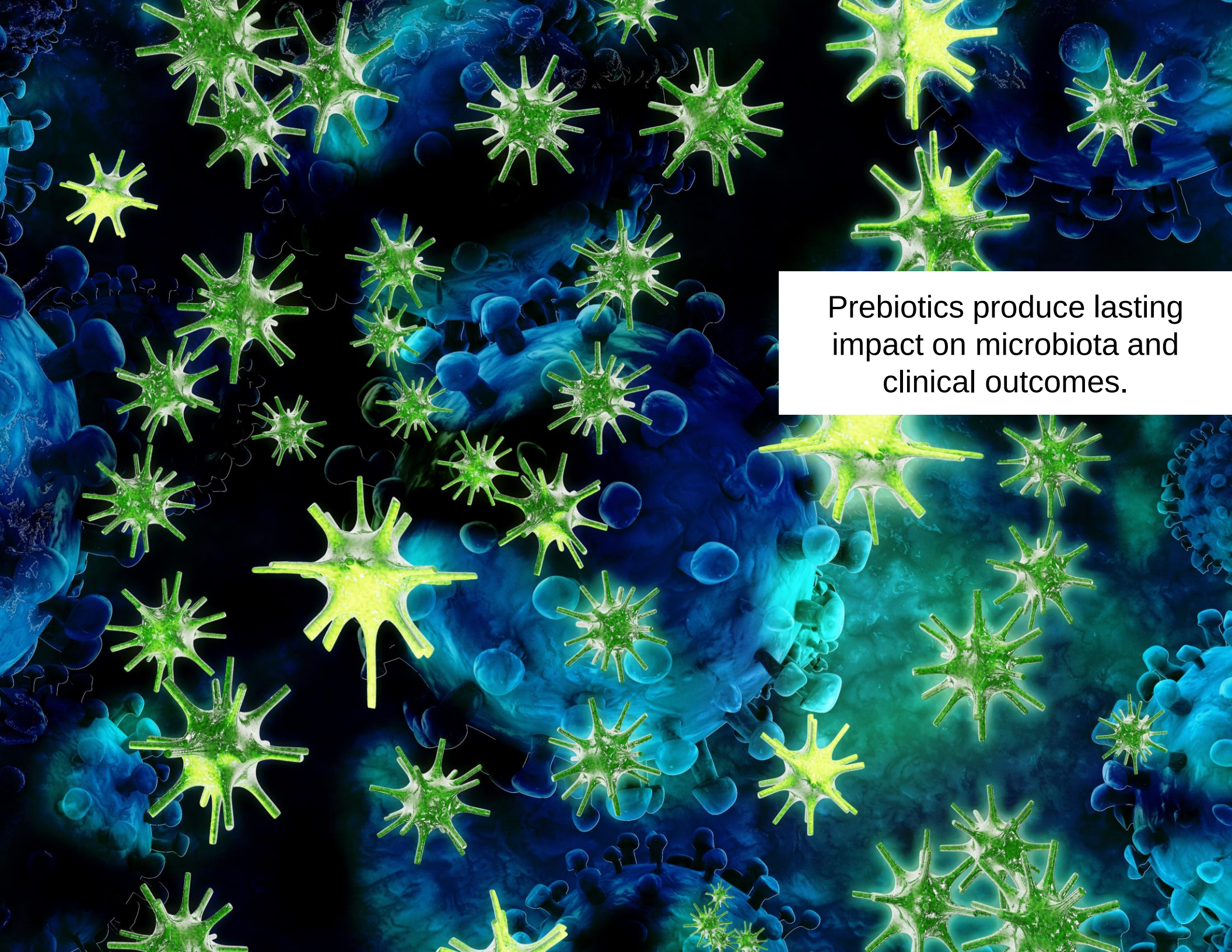
Prebiotic reduced recurrence of diarrhea in subjects with CDAD.

Objective - to determine if the prebiotic oligofructose could alter the fecal microbiota and, in addition to antibiotic treatment, reduce the rate of relapse from *C difficile* infection.

- n=142 patients
- stool culture confirmed oligofructose as prebiotic
- relapse of diarrhea more common in those taking placebo (8.3% prebio vs 34.3% placebo, *P < 0.001).*
- longer period of time from commencing antibiotic to diarrhea settling (6 vs 3 days; *P = 0*.007).
- patients who relapsed stayed in hospital longer than those who did not (53 vs 26 days, *P = 0.021)*

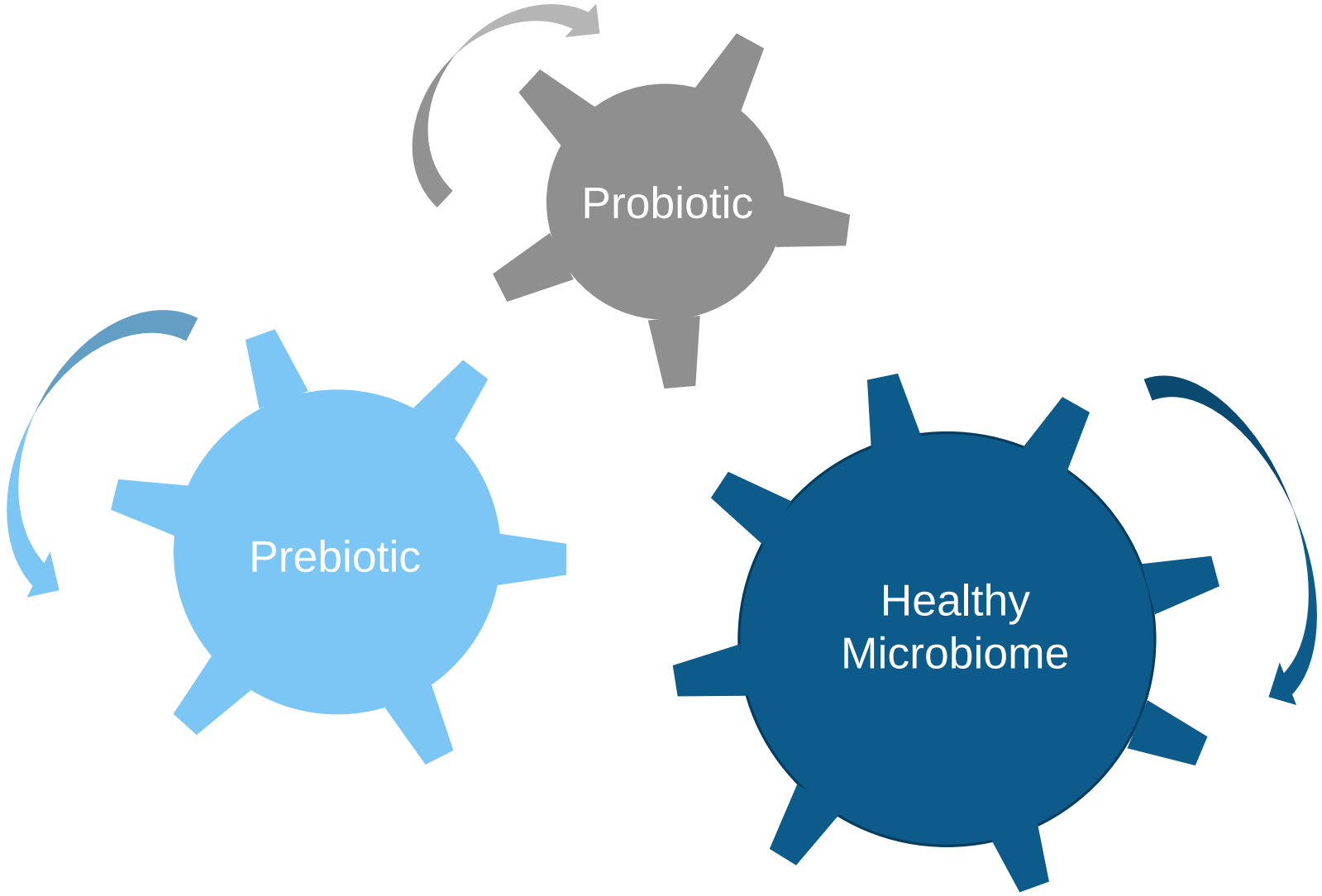
Lewis et al. Clin Gastroenterol Hepatol 2005;3(5):442-448.

Oligofructose intake improves physical characteristics in overweight and obese adults



Prebiotics produce lasting impact on microbiota and clinical outcomes.

We need to consider (and feed) this complex ecosystem



CREDIT CLAIMING

You must complete a brief evaluation of the program in order to obtain your certificate. The evaluation will be available for one year; you do not need to complete it on September 20, 2018.

Credit Claiming Instructions:

1. Go to CE.TodaysDietitian.com/Microbiota **OR** log on to CE.TodaysDietitian.com, go to "My Courses" and click on the webinar title.
2. Click "Take Course" on the webinar description page.
3. Select "Start/Resume Course" to complete and submit the evaluation.
4. Download and print your certificate.