Health Benefits of Probiotics by Impacting the Intestinal Barrier Function

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Introduction

Background
Scope of the review
The GI barrier: a complex multilayer system designed to prevent translocation of microbes, antigens & toxins from the lumen inside the body

GI BARRIER

Chemical
Digestive secretions, antimicrobials

Immunological
Immune structures (PP, lymph nodes), cells (macrophages, dendritic cells, lymphocytes), molecules (IgA, cytokines)

Microbiota
Bacteriocines, antibiotics, pH reduction, competition for resources

Physical
Motility, water efflux, mucus layer, epithelium (tight junctions)

Gastro-intestinal barrier

Mucosal barrier
Leaky gut barrier and disease


Heyman et al. (2012) Intestinal permeability in coeliac disease: insight into mechanisms and relevance to pathogenesis, Gut 61, 1355-64.


Camilleri et al. (2012) Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome, Am J Physiol Gastrointest Liver Physiol 303, G775-85.


Roxas JL, et al. (2010) Enterohemorrhagic E. coli alters murine intestinal epithelial tight junction protein expression and barrier function in a Shiga toxin independent manner. Lab Invest 90, 1152-1168
Probiotics & barrier mechanisms

Commensal microbiota
- Colonization resistance
- Antimicrobial compounds (metabolites, bacteriocins)
- Inhibition of toxin production/toxin degradation

Mucosal barrier
- Mucin, antimicrobials & SIgA secretion
- Epithelial integrity
- Gut motility
- Immunomodulation
Probiotics and disease


Metabolic syndrome

GI infections

IBS

Probiotics
Prebiotics
Synbiotics

NEC

IBD
Scope

Impact of probiotics on mucosal barrier* integrity and commensal microbiota as mediating factors of their beneficial effects on model disorders

* Studies on mucosal immunity not included
Results

Probiotics, barrier & management of model disorders
Probiotics and enteric infection


- “Moderate quality evidence suggests that probiotics are both safe and effective for preventing Clostridium difficile-associated diarrhea” Goldenberg J.Z. et al. (2013) Cochrane Database Syst Rev. 31;5:CD006095

Probiotics & pathogen challenges to the barrier

Direct effects on pathogens

- Colonization resistance
  - *B. longum* Bar33 and *L. helveticus* Bar13
    - ↓ *C. difficile, C. perfringens, E. faecium, Campylobacter* in elderly volunteers (Rampelli 2013)
- Antimicrobial compounds
  - Reuterin (*L. reuteri*) inhibits enteric pathogens (Cleusix 2007)
  - Abp 118 (*L. salivarius* UCC118) inhibits *L. monocytogenes* translocation (Corr 2007).
- Inhibition of toxin production/toxin degradation
  - *B breve* Yakult ↓ STEC Shiga toxin *in vitro and in vivo* (Asahara 2004)
  - *S. boulardii* protease degrades Toxin A from *C. difficile* (Castagliuolo 2014)

Mucosal barrier modulation

- Mucin expression
  - Adherent *Lactobacillus* spp ↑ mucin expression and prevent EPEC adherence *in vitro* (Mack 1999)
- Inhibition of pathogen-induced disruption of epithelial integrity
  - *L acidophilus* (Sherman 2005), *L plantarum* (Mangell 2002), *L casei* (Parassol 2005), reduce the EHEC and EPEC increase in permeability *in vitro*
- SIgA production
  - *L. plantarum* P8 ↑ fecal SIgA in middle-age and elderly humans (Wang 2014).
Probiotics and NEC


- “Supplementation with prebiotic oligosaccharides was safe and did not result in decreased incidence of NEC” Srinivasjois R. et al. (2013) Clin Nutr. 32(6):958-65

- “In VLBW infants, probiotic (Bifidobacterium lactis) and synbiotic (Bifidobacterium lactis plus inulin) but not prebiotic (inulin) alone decrease NEC” Dilli D. et al. (2015) J. Pediatr. 166:545-51
Probiotics, immature barrier & NEC

Microbiota modulation

- **Beneficial effects**
  - *L. rhamnosus* LGG (Manzoni 2006; Romeo 2011), *L. reuteri* ATCC 55730 (Romeo 2011) and *L. reuteri* DSM 17938 (Oncel 2015) prevent *Candida* colonization

- **Inconsistent effects**
  - No effects of LGG+BB536 (Rougé 2010)
  - LGG ↑ Gram + and anaerobic species diversity in preterms under 1500 g but not in more mature infants (Agarwal 2003)

Mucosal barrier modulation

- **In preterm infants**
  - *B. lactis* BB12 ↓ permeability (Stratiki 2007), ↑ fecal SIgA, ↓ fecal calprotectin (Mohan 2008)
  - Heat-inactivated *B. breve* C50/S. *thermophilus* 065 ↑ fecal SIgA in partially breast-fed infants, but not in exclusively formula-fed (Campeotto 2011)

- **In animal models**
  - ↓ permeability to small solutes, macromolecules and endotoxin, ↓ bacterial translocation to extraintestinal tissues
  - Restored expression and localization of TJ and adherens junctions proteins
  - ↑ enterocyte proliferation, migration, ↓ apoptosis
  - Normalized expression of TLRs, mucins antimicrobials
Probiotics and IBD

“There is insufficient data to recommend probiotics for use in CD. There is evidence to support the use of (some) probiotics for induction\(^1\) and maintenance of remission in UC\(^2\) and pouchitis\(^3\). Future quality studies are needed to confirm whether probiotics, prebiotics, and synbiotics have a definite role in induction or maintenance of remission in CD, UC, and pouchitis”


\(^1\) VSL\#3, \(^2\) E. coli Nissle 1917 & L. rhamnosus GG, \(^3\) VSL\# 3
Probiotics, barrier & IBD

Microbiota modulation

VSL#3 \textit{Lactobacillus}, \textit{Bifidobacterium} and \textit{S. salivarius} in UC (Venturi 1999); \uparrow total bacterial numbers, richness and diversity of the bacterial microbiota & \downarrow diversity of fungal flora (Kuhbacher 2006)

Mucosal barrier modulation

- \textbf{Increased epithelial integrity}
  - Probiotics protect against cytokine-driven epithelial barrier dysfunction (multiple \textit{in vitro} studies)
  - P40 component of \textit{L rhamnosus} GG prevents cytokine-induced hyperpermeability and ameliorates DSS-induced colitis in mice (Yan 2011)
  - Soluble factor from \textit{B infantis} increases ZO-1 and occludin in epithelial cell lines and improves colitis in IL10 Ko mice (Ewaschuk 2008)
  - \textit{L. plantarum} duodenal perfusion in healthy individuals results in structural changes in ZO-1 and occludin, associated with reduced permeability (Karczewski 2011)

- \textbf{Stimulation of antimicrobial production by the mucosa}
  - \textit{B. breve} NCC 22950 normalized RegIII-$\gamma$ expression (not permeability) and decreased susceptibility to DSS colitis in Nod1(-/-); Nod2(-/-) mice (Natividad 2012)
Probiotics and IBS

“Probiotics are effective treatments for IBS, although which individual species and strains are the most beneficial remains unclear. Further evidence is required before the role of prebiotics or synbiotics in IBS is known.”

Probiotics, barrier & IBS

Microbiota modulation

- Multispecies probiotic: Microbiota stabilization (Kajander 2008); increased *Clostridia* and *Enterococcus* (Lyra 2010)
- Multispecies probiotic: no effect (Brigidi 2001)
- *B. animalis* subsp. lactis CNCM I-2494 reduced *B. wadsworthia* and increased the butyrate-producing potential of the commensal microbiota (Veiga 2014)

Mucosal barrier modulation

- Increased epithelial integrity
  - Lactibiane Tolerance® ↑ occludin expression, prevented hyperpermeability and ↓ visceral hypersensitivity induced by LPS, stress or IBS luminal metabolites (Nebot-Vivinus 2014)
  - *B. longum* HB55020 and *L. acidophilus* HB56003 ↑ claudin-1 and occludin expression, reduced inflammatory markers and prevented hypersensitivity in a model of PI-IBS (Wang 2014)
  - *B. lactis* CNCM I-2494 prevented hyperpermeability and endotoxemia induced by stress and restored occludin and JAM-A expression (Agostini 2012)

- Mucus layer
  - *L. farciminis* prevented stress-mediated alterations in mucin O-glycosylation and mucus physical properties. It also prevented hyperpermeability and hypersensitivity (Da Silva 2014)
Probiotics and metabolic disease

Probiotics

- VSL#3 improved insulin sensitivity and reduced total cholesterol, triglyceride, LDL, and VLDL and increased HDL in overweight adults (Rajkumar, H. et al. (2014) Mediators Inflamm. 2014, 8)

Pre- and Synbiotics

- Reduced endotoxemia, insulin resistance, steatosis and metabolic inflammatory markers by *B longum* + FOS in NASH patients (Malaguarnera M. et al. (2012) Dig. Dis. Sci. 57:545-53)
Probiotics, barrier & metabolic disease

Microbiota modulation

- **L. salivarius** Ls-33 ATCC SD5208: ↑ *Bacteroides-Prevotella-Porphyromonas/Firmicutes* ratio in obese adolescents (Larsen 2013), but no effects on metabolic outcomes.

- VSL#3: ↑ total aerobes, total anaerobes, *Lactobacillus, Bifidobacterium, Streptococcus* in overweight adults (Rajkumar, 2014).

Mucosal barrier modulation

- **L. casei** Shirota ↓ insulin resistance and endotoxemia in diet-induced obese mice (Naito 2011).

- **B. longum** ↓ endotoxemia, fat mass, insulin resistance, blood pressure in diet-induced obese rat (Chen 2011).

- **B. animalis** subsp. *lactis* 420 supressed bacteremia and reduced insulin resistance and inflammation in high fat diet-fed mice (Amar et al. 2011).
Conclusions & Gaps
Conclusions & Gaps

✓ (Some) Probiotics have the potential to prevent and/or treat multiple disorders. Evidence ranges from good/fair (AGE, NEC, UC, pouchitis, IBS) to emerging (metabolic disease)
✓ (Some) Probiotics positively modulate microbiota composition and barrier integrity, which possibly explains their impact on health and disease (at least partially)

? Good quality, clinical trials in well-defined populations comparing the effect of different doses and/or strains on both clinical and barrier outcomes are required
Thank you!

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Effect of Formula Containing *Lactobacillus reuteri* DSM 17938 on Fecal Microbiota of Infants Born by Cesarean-Section

*Bifidobacterium* abundance

**Phylogenetic similarity**

V=vaginal, C=C-section; Ct=control formula; Lr=*L. reuteri* formula