



EMERGING APPLICATIONS OF PROBIOTICS IN GUT HEALTH

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- The growing interest in gut health is not merely hype.
- According to a report published [by Schieberg research](#): “gut health” is one of the popular search terms when it came to understanding the connection between nutrition and healthy living.
- Google Trends analysis also highlighted this trend, showing a 350% increase in searches for “best foods for gut health” between 2012 and 2017 in the U.S.

History of Probiotics

Elie Metchnikof (1845-1916)

Lactic acid bacteria can render a great service in the fight against intestinal putrefaction'

'Postpone and ameliorate old age'

The Prolongation of Life (1908)



Ilya Ilich Metchinicov
1845-1916

Probiotics: definitions

- ***World Health Organization:***
 - ***“live microorganisms which when administered in adequate amounts confer a health benefit on the host”***
- **A bacterial strain that:**
 - **Survives the stomach acid and bile**
 - **Adheres to intestinal lining**
 - **Grows and establishes temporary residence in the intestines**
 - **Imparts health benefits**

Probiotics

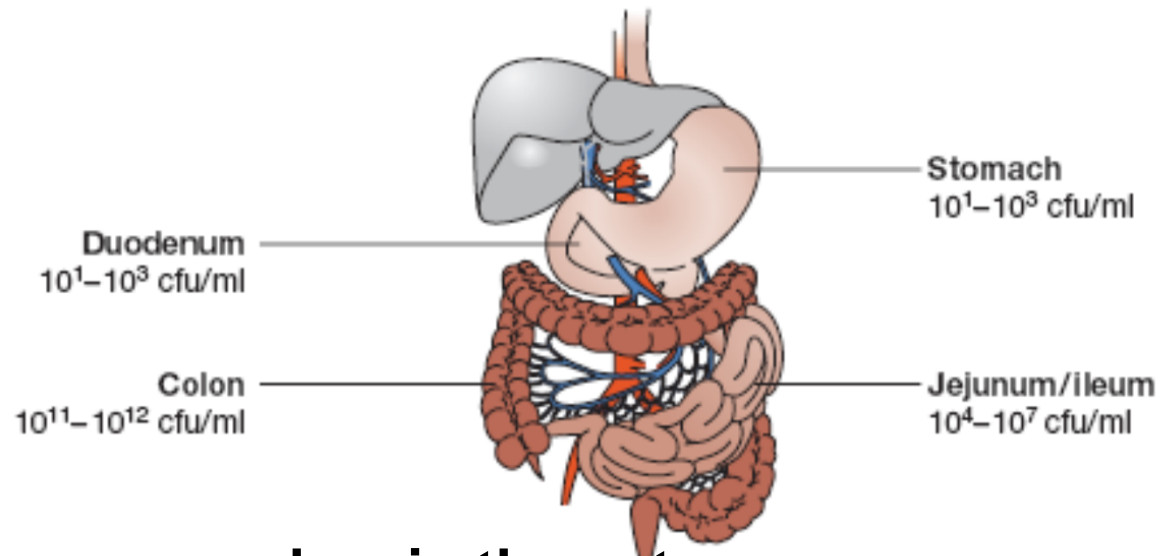
- **Colonization at birth(?PLACENTA)**
- **Similar to maternal species(diff. for Caeserian vs Vaginal delivery)**
- **Breast milk not sterile**
- **Specific organisms vary by age in first year but become established by 1 year**
- **No. of bacteria in gut 10 times the total no. of body cells.70% of immune system is in the intestine.**
- **Composition of each individuals microbiota is so distinctive.....it could be used as an alternative to fingerprints..!**
- **Composition also influenced by age,socio-economic srroundings & use of antibiotics**

Distribution of microbes in the gut

Present in all parts of the intestinal tract

Increase from esophagus to colon

- ✓ acid production
- ✓ bile
- ✓ motility
- ✓ ileocecal valve

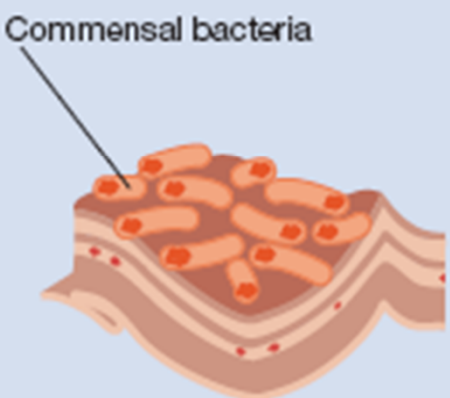
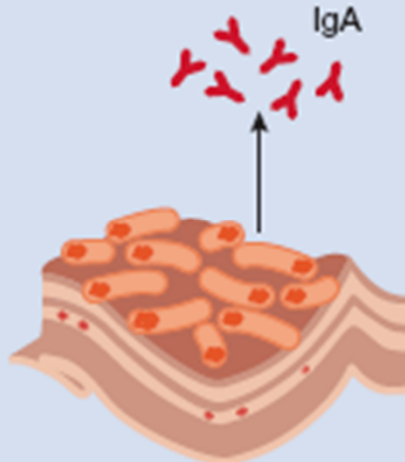
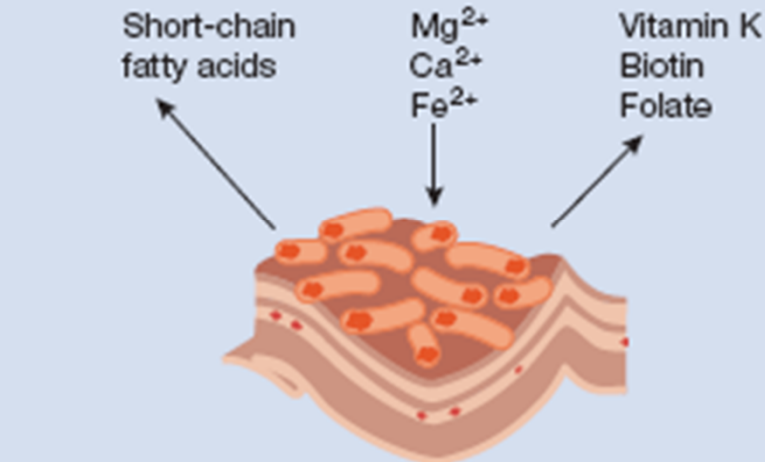


Surface-lumen axis: more anaerobes in the outer mucus

Bacteria are not in direct contact with the mucosa – at least, in healthy subjects

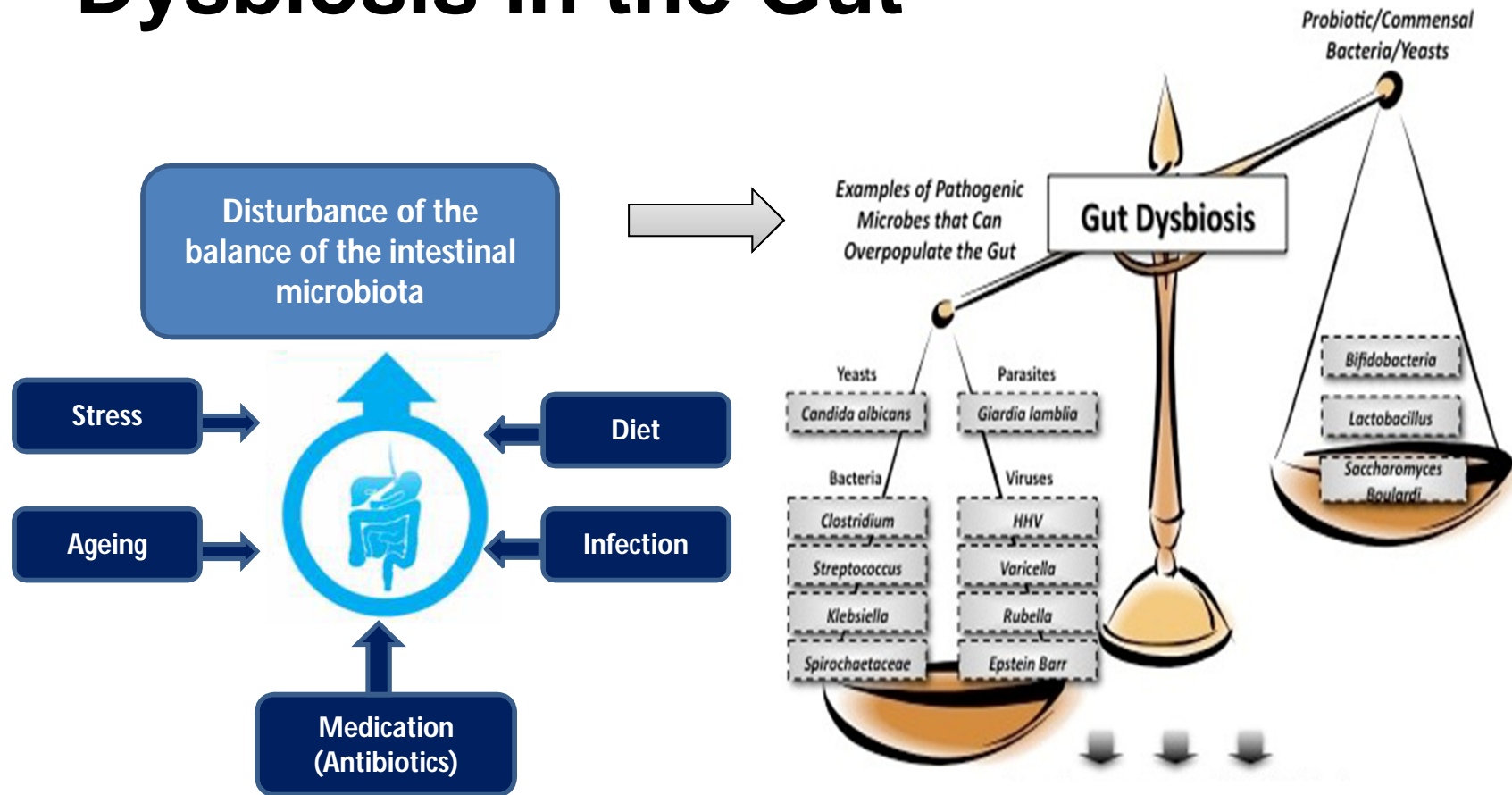
Microbes in Intestinal Health and Disease; A.S. Neish *Gastroenterology* 2009;136:65-80

The Gut Micro biota and its influence on health

Protective functions	Structural functions	Metabolic functions
<p>Pathogen displacement</p> <p>Nutrient competition</p> <p>Receptor competition</p> <p>Production of anti-microbial factors e.g., bacteriocins, lactic acids</p>	<p>Barrier fortification</p> <p>Induction of IgA</p> <p>Apical tightening of tight junctions</p> <p>Immune system development</p>	<p>Control IEC differentiation and proliferation</p> <p>Metabolize dietary carcinogens</p> <p>Synthesize vitamins e.g., biotin, folate</p> <p>Ferment non-digestible dietary residue and endogenous epithelial-derived mucus</p> <p>Ion absorption</p> <p>Salvage of energy</p>
<p>Commensal bacteria</p> 	<p>IgA</p> 	<p>Short-chain fatty acids</p> <p>Mg²⁺ Ca²⁺ Fe²⁺</p> <p>Vitamin K Biotin Folate</p> 

O'Hara A.M. *et al.* EMBO reports 2006; 7: 688-693.

Dysbiosis in the Gut



Increasingly recognized as a risk factor for human disease: Infections, Obesity, Diabetes, NEC, IBS, IBD

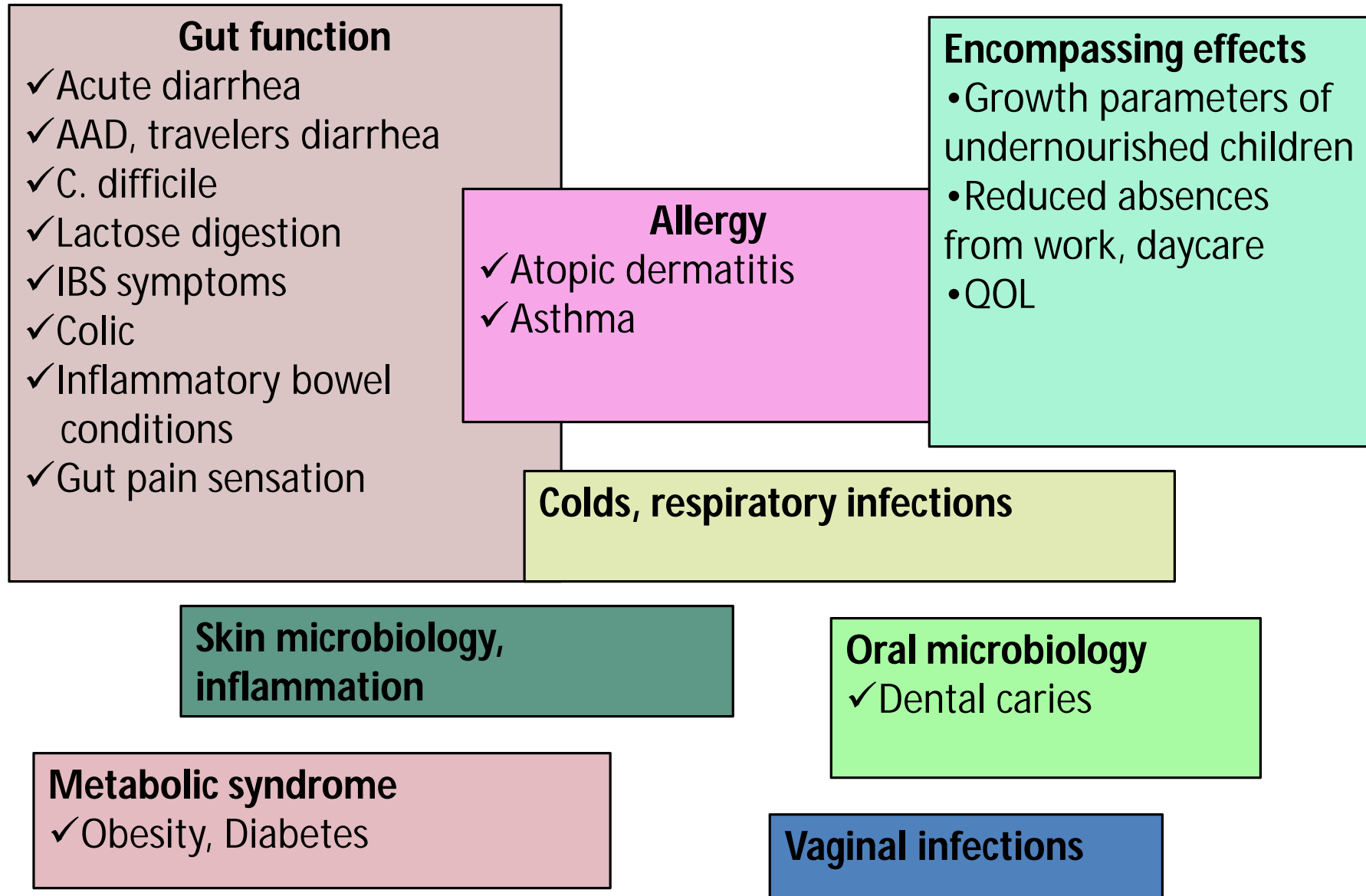
PNAS March 15, 2011 Suppl.



Scientific Evidence for Probiotics

- ✓ *In vitro* studies, *In vivo* animal studies, Human observational/epidemiology studies ,Human experimental studies, Randomized Double Blind Placebo Controlled studies with validated biomarkers
- ✓ In 2017, there were around 2000 articles: in high ranking peer-reviewed journals; increasing DBPCRTs
- ✓ Meta-analyses are usually based on a generic probiotic benefit
- ✓ Reviews and meta-analyses will include relevant trials with different strains but generic conclusions may not be true for individual strains
- ✓ Each Probiotic strain to be supported by its own dossier of scientific evidence...

Diverse Targets for Probiotics

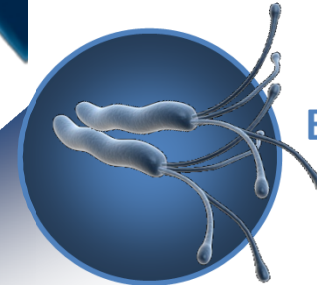


Probiotics in the Treatment of Gastrointestinal Disorders

Diarrhea
Acute infectious
Antibiotic-associated
C. difficile



H. pylori
Eradication



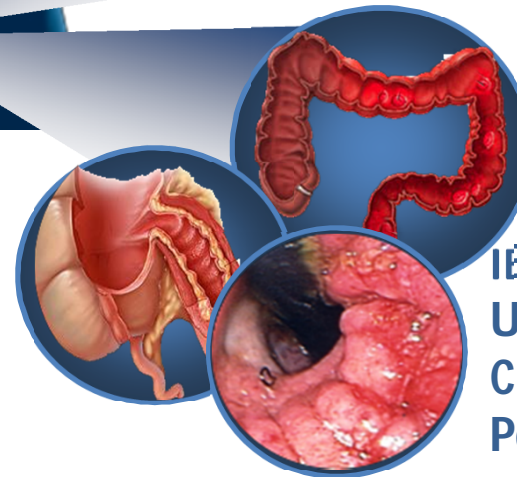
Lactose
Intolerance



Constipation



IBD
Ulcerative colitis
Crohn's disease
Pouchitis



Probiotics in Diarrhoea

- *Allen et al (2010) Cochrane Systematic Review*
- Used alongside rehydration therapy, probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhoea.

Probiotics in Diarrhoea

- Children(Rotavirus) PCTs results using Lactobacillus sp.
 - Decreased diarrhoea duration
 - decreased number of stools
 - decreased virus shedding in stools
- Prophylactically beneficial in malnourished children & children in developing countries(Sur et al ,Kolkata,2010-LcS)
- Efficacy of Vibrio Cholera vaccine better when combined with probiotics

Probiotics in Antibiotic associated Diarrhoea

- LcS 6.5×10^9 live spores daily lowers incidence of AAD in hospitalised pts having spinal cord injuries (17% vs 54.9% Wong et al 2013 BJN)
- Decrease duration of AAD
- Decrease recurrence rate
- **Increasing evidence that Lactobacillus probiotic strains reduce risk AAD & CDAD**
- **Also role in SIBO is established**

Probiotics in Constipation

- In slow transit constipation(STC) improvement of colonic transit time by acceleration of transit in Rectum & Sigmoid(Krammer et al Mannhiem 2011 used LcS)
- Mechanism:
 - LcS consumption increased bacterial cell mass & hence stool wt. causing dilated intestinal walls which increased peristalsis.
 - LcS led to formation of organic acids which stimulated ileal & colonic motility

Probiotics in IBS

- Benefit only in a sub group of patients with evidence of decreased pain abdomen, flatulence, stool frequency & consistency.

Probiotics in IBD

Still evolving and contentious..microbiota as cause??

Pouchitis: positive reports (in adults), with a mixture of bacterial strains(VSL3)-85% remission vs 6%(Mimura et al 2004 GUT) & decreased relapse(15% vs 100%)(Gionchetti et al 2000)

Ulcerative Colitis: some positive effects

- maintenance of remission
- induction of remission in mild-mod flare ups

Crohn disease:minimal- no benefit

Choice of strain, dosing, and disease activity severity might well account for variable results

Conclusion?: more high quality data (RCT's) are required!

Eamonn et al Nutr clin Pract 2012

Helicobacter pylori Infections

Chronic gastritis, Peptic ulcers, Gastric adenocarcinoma, and a number of non-gastrointestinal disorders.

Bifidobacteria and B. subtilis may inhibit the growth or attachment of H. pylori.

Possible mechanisms by which L. salivarius eradicates H. pylori include the ability of the former to bind to gastric epithelial cells, to produce a high quantity of lactic acid, and to proliferate rapidly.

Microbiota & Liver disease

- **Functions of Intestinal microflora:**
 - Maintain the microbial barrier against established as well as potential pathogens.
 - Influence motility & perfusion of int. wall
 - Stimulate intestinal immune system
 - Decrease bacterial translocation
 - Produce Vitamins
- In CLD impairment of above happens with colonization of small intestine by colonic bacteria(**bacterial overgrowth**) & increased **bacterial translocation**.

Microbiota & Liver disease

- **Bacterial Overgrowth + Portal HT**(causing vasodilatation of int. mucosa & edema of lamina propria)+**Intestinal integrity loss**(due to toxins-alcohol,abberent bile secretion,malnutrition)+**defective Intestinal immune system**→→**Translocation of Intestinal bacteria** into mesenteric LN,blood & other organs.

Probiotics in CLD

- Improve the microbial barrier & hence **decrease the intestinal wall permeability** → Reduce Translocation.
- Limit oxidative & inflammatory liver damage (decrease pro-inflammatory enzymes & TNF).

Probiotics In HE

- Gut produced ammonia + bacterial overgrowth + delayed GI transit time + inability of liver to remove toxins are key factors in the pathogenesis of HE.
- Probiotics decrease ammonia by reducing bacterial Urease activity (similar action as non absorbable antibiotics & lactulose).
- Probiotics improve bowel transit time
- Decrease fecal pH thus lower NH_3 & other toxin absorption

Probiotics In HE

- **WGO practice Guidelines say Probiotics in hepatology are indicated for MHE & in prevention of episodes of Overt HE .**
- Lactobacillus sp., Enterococcus, Bifidobacterium or Symbiotics all effective in MHE /HE.
- As effective as Lactulose in decreasing Blood Ammonia levels (Changing gut pH by SCFA, decreasing Bacterial urease activity & decreasing intestinal permeability to ammonia)- Shukla et al Aliment Pharmacol Ther 2011

Probiotics in ALD

- In liver cirrhosis of alcoholic etiology, the alcohol itself may play a role, such as increased gut permeability, endotoxemia, and TNF- α production. In rats, *Lactobacillus* GG has been shown to reduce alcohol induced gut leakiness and steatohepatitis. The same group also found that the mucosa-associated microflora was altered in rats on a high alcohol diet, and this dysbiosis could be counteracted by *Lactobacillus* GG or oat supplementation.

Probiotics in NASH

- Bacterial overgrowth & increased proinflammatory cytokines are important factors in pathogenesis of NASH.
- Probiotics work by
 - Lowering TNF leading to decreased FA in hepatocytes
 - Increases NK cells thus reducing inflammatory signalling
 - Limit oxidative & Inflam. liver damage

Probiotics in reduction of infection in liver cirrhosis patients

- Life threatening infective complications by bacteria originating from GI tract common(SBP)
- 50-70% have small intestinal overgrowth of colonic bacteria.
- Bacterial translocation & impaired mucosal membrane barrier
- Probiotics or Symbiotics decreased endotoxemia/bacterial translocation(Lactobacillus sp..E coli,VSL-3).
- VSL-3 reduces Cytokines & TNF
- Improvement in CP score

Probiotics in Prophylaxis of infections after liver transplantation

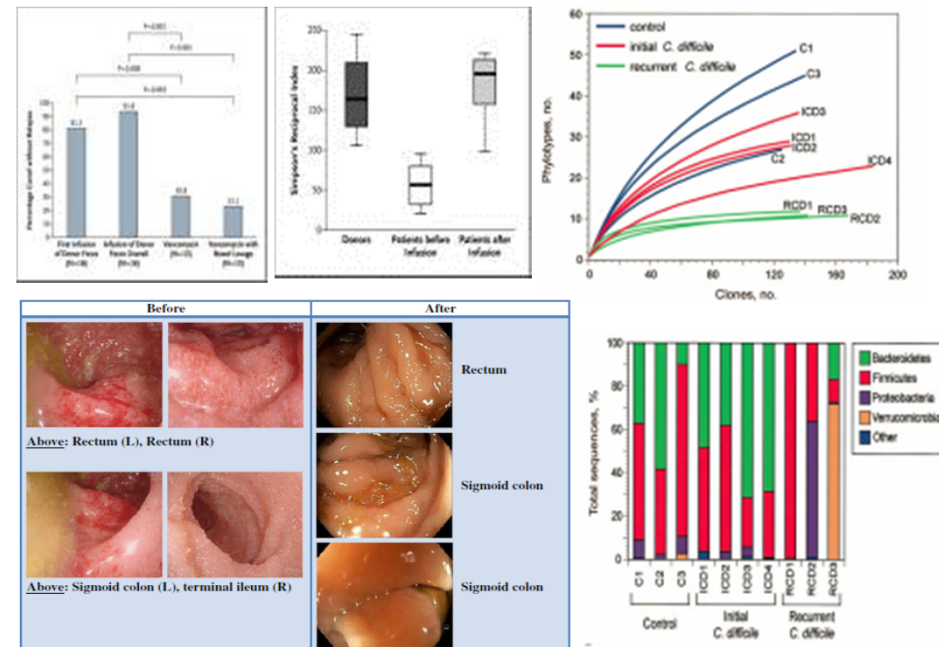
- Patients in the postoperative period after a liver transplant are mainly at risk of infection by organisms, coming in most cases from the digestive tract.
- A prospective, randomized, double-blind study was published on 66 patients after liver transplantation, whereas half of the patients received a combination of 4 *Lactobacillus spp.* together with the standard enteral nutrition. In the probiotic group, a significant reduction in postoperative bacterial infection (3% against 48%) was observed and the length of the antibiotic therapy was substantially reduced [[60](#)]

Fecal Microbiota Transplantation (FMT)

- also named as fecal transplant,
fecal bacteriotherapy
- used primarily to treat *Clostridium Difficile*-associated infection (CDI) and IBD
- its cure rate is up to 90% in CDI
- the mechanism underlying the procedure is to correct the intestinal dysbiosis by introducing donor-fecal microbiota
- indicating it's potential in treatment of other microbiota-associated diseases, such as sepsis.



Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*



What is FMT?

- Transfer of stool and bacteria from the colon of a healthy person to the colon of a person ill with a CDI

How Are Donors Screened?

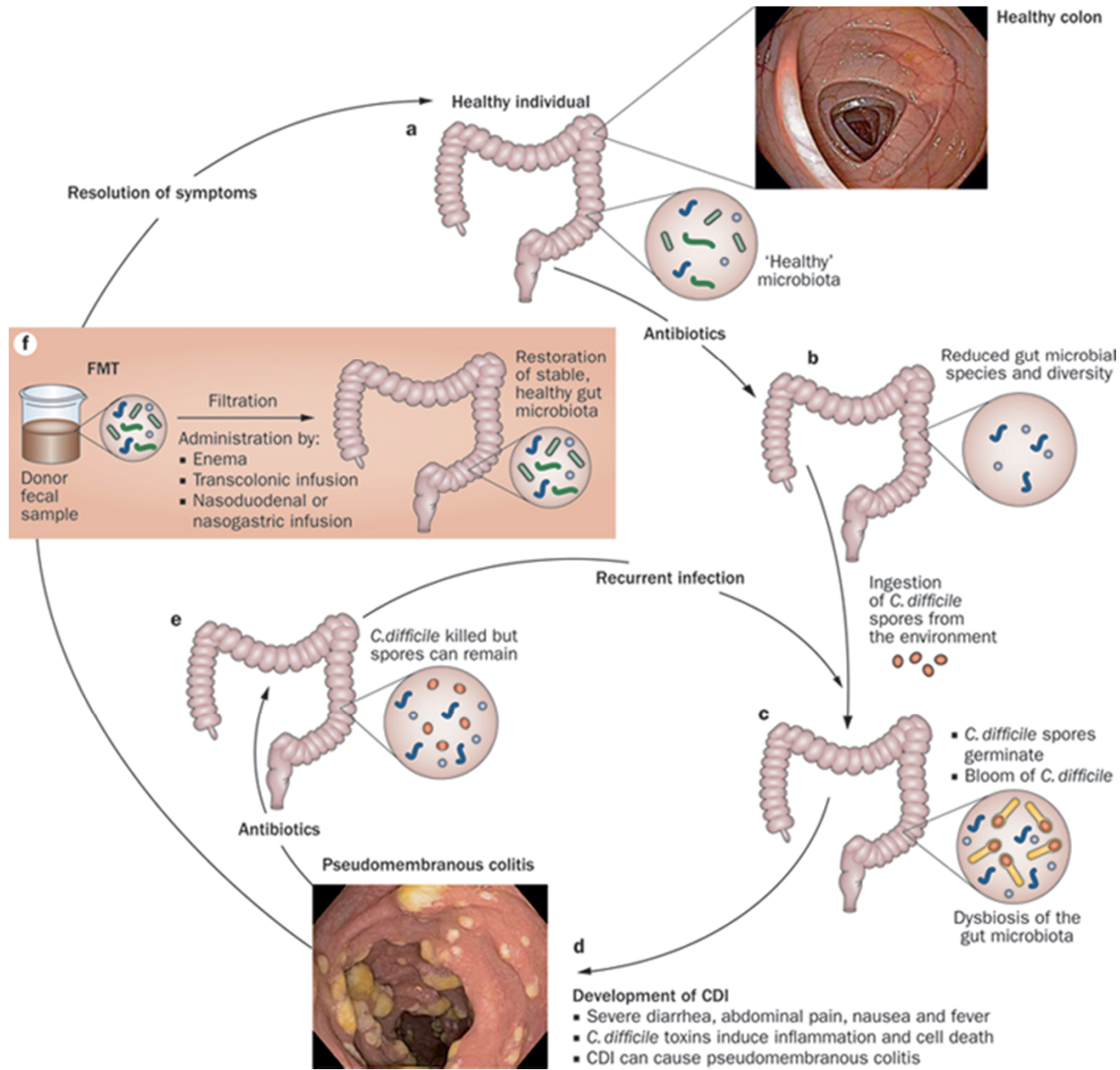
- Use same exclusions as for blood product donation
- Screen donor for any illness – generally want someone who is healthy and on no medications
- Screen for hepatitis A, B, C, HIV, H.pylori, syphilis, C.difficile, Giardia, E.coli, Salmonella, Shigella, Campylobacter infections
- Can be an individual familiar to the patient or familiar to the MD

What is the process?

- Stool is collected from the donor, processed to create a liquid suspension in water, filtered for large particulates
- Stool can be frozen and used later with similar efficacy

How is the FMT Administered?

- Small bowel upper endoscopy to the jejunum
- Nasojejunal tube placement
- Colonoscopy
- Retention enemas
- Oral capsules



Results of FMT(CDI)

- Success rates depend slightly on route of delivery
- Enema → 80-85%
- Upper GI → 80-85%
- Colonoscopy to the right colon → 90-95%
- Usually see control of diarrhea symptoms within 48-96 hours

Risks of FMT

- Risk of aspiration if not delivered deep into upper small intestine
- Risk of acquiring infection from donors – rare, single case reports
- Risk of complications from sedation and endoscopy – bleeding, perforation, transmission of other infections: 1/1000-1/10,000
- DOES NOT IMPACT LIVER TRANSPLANTATION SCREENING OR STATUS

Studies Underway for IBD Treatment

- Studies in IBD, IBS require intense regulatory oversight by the FDA.
- Single study of 16 patients with IBD
 - Improved frequency of flares – 63%
 - Remission of flares over 21 months in 19%
 - No increased risk of flares
 - Average reduction in stool frequency from 8.2 to 3.6 per day
 - Some patients able to stop IBD meds (25%)
- CDI in IBD responds well to FMT (90% cure rate)

FMT for IBS Patients

- Small study showed 70% improvement in bloating, constipation, diarrhea in 13 IBS patients

FMT for PSC?

- May help with control of associated UC
- No studies on treatment of PSC reported or underway
- Certainly has a role in treatment of CDI in PSC patients, pre-transplant, during transplant evaluation, and post-transplantation

FMT Current status

- FMT is safe and effective for CDI and may play a role in controlling IBD and IBS
- Colonoscopy/Enema delivery has better cure rates than NG route.
- Currently all uses for FMT outside of CDI treatment are considered investigational and must take place in the setting of a clinical trial(Alcoholic hepatitis,ALF,NASH,HE)
- FMT does NOT alter liver transplant status, may resolve recurrent infections that delay transplantation.

Future perspectives

- ❖ **Extent of influence of probiotics in human health using human feeding studies**
- ❖ **Studies on human populations for colon cancer or cancer recurrence**
- ❖ **Validate markers used for assessing probiotic function. Testing of predictions based on biomarker studies with actual results in human clinical evaluation is needed. Biomarker validated in the areas of immune system, cancer and gut microbiology is especially important. Once validated biomarkers will be useful tools to assess the dose dependence and strain specific responses.**
- ❖ **Assess effects of probiotics on populations and activity of gut microbes. The application of gene based methods holds much promise in this field.**
- ❖ **Improve reliability and ease of taxonomic classification of probiotic bacteria. Improve strain performance and activity.**
- ❖ **Elucidate the physiological role and mechanism of action probiotics**

CONCLUSIONS

- **Role of Probiotics well established in Infective & antibiotic ass. diarrhoea.**
- **Positive Role of Probiotics in Pouchitis & also in UC/Crohn's??**
- **Possible role in IBS & Constipation**
- **Role in vaccination efficacy (Cholera)**
- **Adjuvant therapy for H.pylori eradication**

Conclusions

- **Probiotics are becoming part of numerous therapeutic modalities in hepatology, as their effect on intestinal microflora can positively influence many liver diseases(NASH,ALD,Liver Tx)**
- **However, verification of the efficiency of this treatment from the perspective of evidence-based medicine will be difficult, as different probiotics can be expected to have different effects in different diseases.**
- **FMT is the “new mantra”**
- **With respect to the increasing number of studies on probiotics, the future prospects in this field are optimistic.**



• Thank You