Complex Chronic Diseases

Small Intestinal Bacterial Overgrowth and the Gut

A Clinical Prospect

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Presentation

i. Background
ii. Clinical Manifestations in Complex Chronic Diseases, a link
iii. Complex Chronic Diseases, paths and possible etiologies
iv. Microbiome, An Overview
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viii. Diagnosis and Testing
ix. Management of SIBO
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    ii. Herbal Therapies
    iii. Prokinetics and probiotics
    iv. Elemental diet
x. Last Words

Complex Chronic Diseases

(Central Sensitivity Syndromes)

Disease Focus

1.Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

2. Fibromyalgia

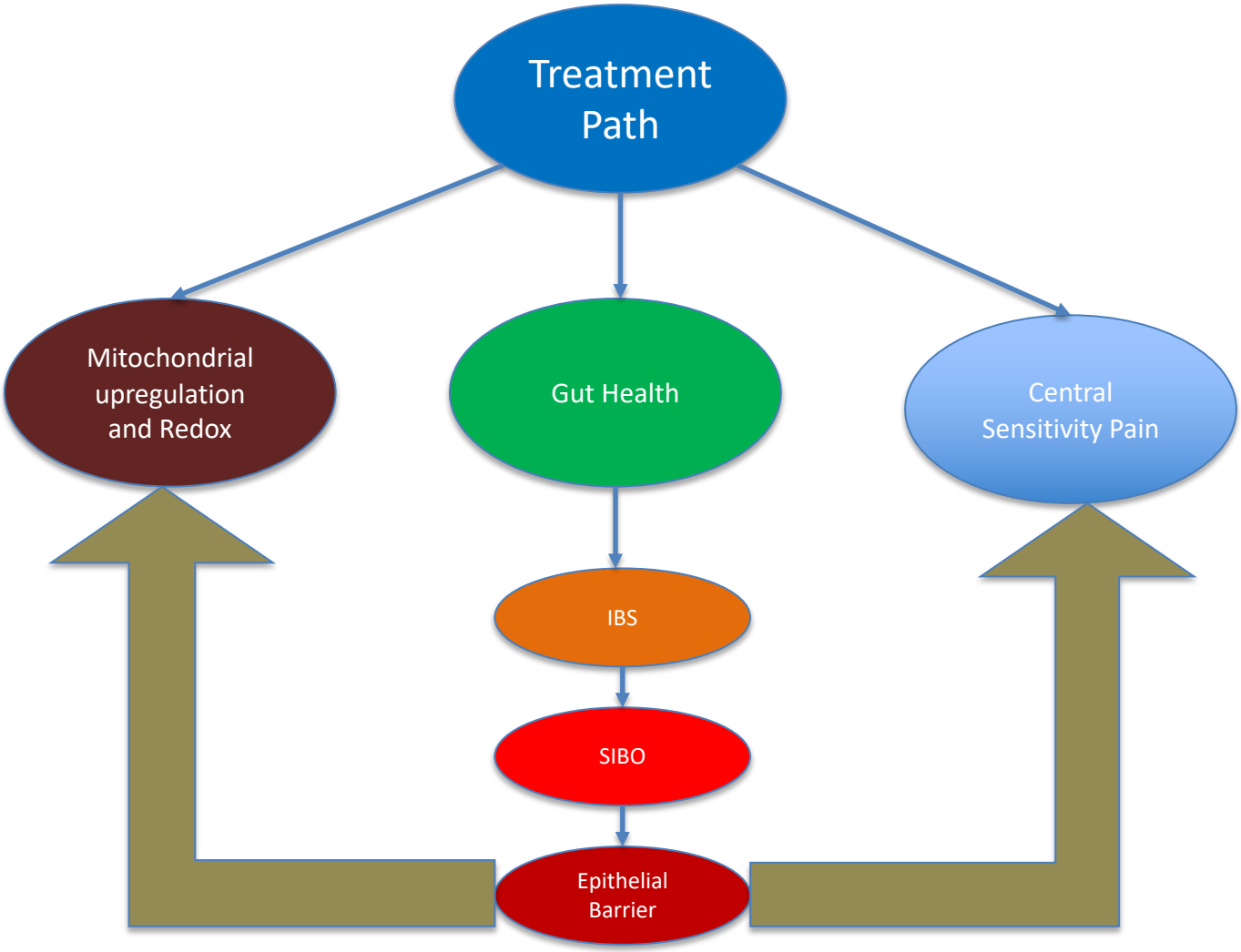
3. Chronic Lyme

4. MS

Symptoms

1. Fatigue
2. Post exertion malaise
3. Cognitive Dysfunction (concentration, brain fog, memory)
4. Pain
5. IBS- bloating, gas, constipation/diarrhea, GERD
6. Sleep

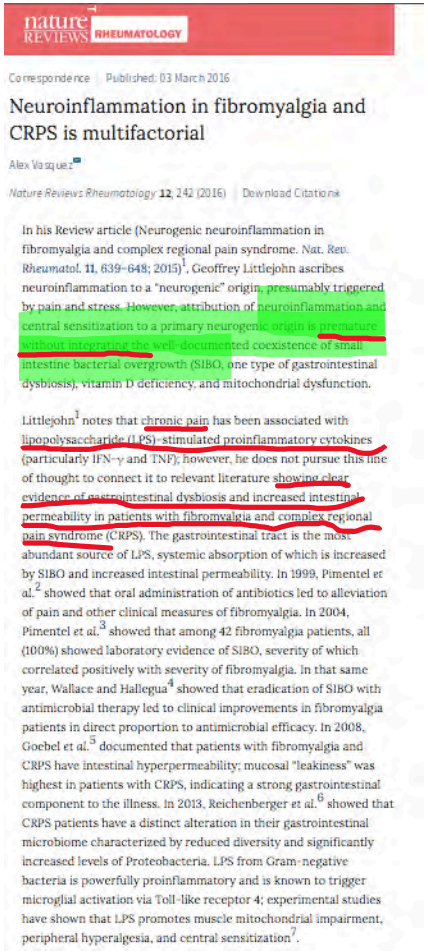
Complex Diseases



Chronic Pain associated with LPS (IFN and TNF)

Positive correlation SIBO and FM pain (antibiotics)

Reichenberger showed that CRPS (complex regional pain syndrome) have distinct alteration in microbiome (reduced diversity levels of Proteobacteria



nature REVIEWS RHEUMATOLOGY

Correspondence | Published: 03 March 2016

Neuroinflammation in fibromyalgia and CRPS is multifactorial

Alex Vasquez

Nature Reviews Rheumatology **12**, 242 (2016) | Download Citation

In his Review article (Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome. *Nat. Rev. Rheumatol.* **11**, 639–648; 2015)[1], Geoffrey Littlejohn ascribes neuroinflammation to a "neurogenic" origin, presumably triggered by pain and stress. However, attribution of neuroinflammation and central sensitization to a primary neurogenic origin is premature without integrating the well-documented coexistence of small intestine bacterial overgrowth (SIBO, one type of gastrointestinal dysbiosis), vitamin D deficiency, and mitochondrial dysfunction.

Littlejohn[1] notes that chronic pain has been associated with lipopolysaccharide (LPS)-stimulated proinflammatory cytokines (particularly IFN-γ and TNF); however, he does not pursue this line of thought to connect it to relevant literature showing clear evidence of gastrointestinal dysbiosis and increased intestinal permeability in patients with fibromyalgia and complex regional pain syndrome (CRPS). The gastrointestinal tract is the most abundant source of LPS, systemic absorption of which is increased by SIBO and increased intestinal permeability. In 1999, Pimentel et al.[2] showed that oral administration of antibiotics led to alleviation of pain and other clinical measures of fibromyalgia. In 2004, Pimentel et al.[3] showed that among 42 fibromyalgia patients, all (100%) showed laboratory evidence of SIBO, severity of which correlated positively with severity of fibromyalgia. In that same year, Wallace and Hallegua[4] showed that eradication of SIBO with antimicrobial therapy led to clinical improvements in fibromyalgia patients in direct proportion to antimicrobial efficacy. In 2008, Goebel et al.[5] documented that patients with fibromyalgia and CRPS have intestinal hyperpermeability; mucosal "leakiness" was highest in patients with CRPS, indicating a strong gastrointestinal component to the illness. In 2013, Reichenberger et al.[6] showed that CRPS patients have a distinct alteration in their gastrointestinal microbiome characterized by reduced diversity and significantly increased levels of Proteobacteria. LPS from Gram-negative bacteria is powerfully proinflammatory and is known to trigger microglial activation via Toll-like receptor 4; experimental studies have shown that LPS promotes muscle mitochondrial impairment, peripheral hyperalgesia, and central sensitization[7].

Microbiome. 2017 Apr 26;5(1):44. doi: 10.1186/s40168-017-0261-y.

Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome.

Nagy-Szakal D[1], Williams BL[1], Mishra N[1], Che X[1], Lee B[1], Bateman L[2], Klimas NG[3,4], Komaroff AL[5], Levine S[6], Montoya JG[7], Peterson DL[8], Ramanan D[9], Jain K[1], Eddy ML[1], Hornig M[1], Lipkin WI[10].

⊕ Author information

Abstract

BACKGROUND: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterized by unexplained persistent fatigue, commonly accompanied by cognitive dysfunction, sleeping disturbances, orthostatic intolerance, fever, lymphadenopathy, and irritable bowel syndrome (IBS). The extent to which the gastrointestinal microbiome and peripheral inflammation are associated with ME/CFS remains unclear. We pursued rigorous clinical characterization, fecal bacterial metagenomics, and plasma immune molecule analyses in 50 ME/CFS patients and 50 healthy controls frequency-matched for age, sex, race/ethnicity, geographic site, and season of sampling.

RESULTS: Topological analysis revealed associations between IBS co-morbidity, body mass index, fecal bacterial composition, and bacterial metabolic pathways but not plasma immune molecules. IBS co-morbidity was the strongest driving factor in the separation of topological networks based on bacterial profiles and metabolic pathways. Predictive selection models based on bacterial profiles supported findings from topological analyses indicating that ME/CFS subgroups, defined by IBS status, could be distinguished from control subjects with high predictive accuracy. Bacterial taxa predictive of ME/CFS patients with IBS were distinct from taxa associated with ME/CFS patients without IBS. Increased abundance of unclassified Alistipes and decreased Faecalibacterium emerged as the top biomarkers of ME/CFS with IBS; while increased unclassified Bacteroides abundance and decreased Bacteroides vulgatus were the top biomarkers of ME/CFS without IBS. Despite findings of differences in bacterial taxa and metabolic pathways defining ME/CFS subgroups, decreased metabolic pathways associated with unsaturated fatty acid biosynthesis and increased atrazine degradation pathways were independent of IBS co-morbidity. Increased vitamin B6 biosynthesis/salvage and pyrimidine ribonucleoside degradation were the top metabolic pathways in ME/CFS without IBS as well as in the total ME/CFS cohort. In ME/CFS subgroups, symptom severity measures including pain, fatigue, and reduced motivation were correlated with the abundance of distinct bacterial taxa and metabolic pathways.

CONCLUSIONS: Independent of IBS, ME/CFS is associated with dysbiosis and distinct bacterial metabolic disturbances that may influence disease severity. However, our findings indicate that dysbiotic features that are uniquely ME/CFS-associated may be masked by disturbances arising from the high prevalence of IBS co-morbidity in ME/CFS. These insights may enable more accurate diagnosis and lead to insights that inform the development of specific therapeutic strategies in ME/CFS subgroups.

KEYWORDS: Chronic fatigue syndrome; Irritable bowel syndrome; Metabolic pathway; Metagenomic; Microbiota-gut-brain axis; Myalgic encephalomyelitis; Topological data analysis

Microbiome and Virome

Clinical Science (2018) **132** 523–542
https://doi.org/10.1042/CS20171330

PORTLAND PRESS

Review Article

Does the microbiome and virome contribute to myalgic encephalomyelitis/chronic fatigue syndrome?

Fiona Newberry[1,2], Shen-Yuan Hsieh[1,2], Tom Wileman[1,2] and Simon R. Carding[1,2]

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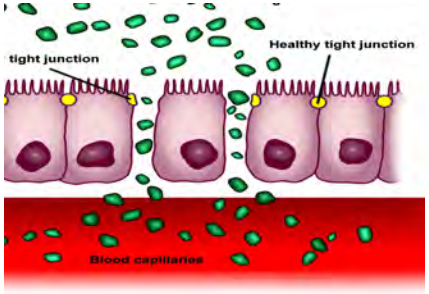
OPEN ACCESS

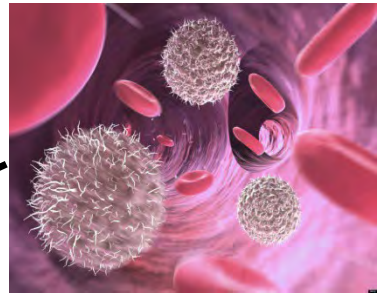
Myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) (ME/CFS) is a disabling and debilitating disease of unknown aetiology. It is a heterogeneous disease characterized by various inflammatory, immune, viral, neurological and endocrine symptoms. Several microbiome studies have described alterations in the bacterial component of the microbiome (dysbiosis) consistent with a possible role in disease development. However, in focusing on the bacterial components of the microbiome, these studies have neglected the viral constituent known as the virome. Viruses, particularly those infecting bacteria (bacteriophages), have the potential to alter the function and structure of the microbiome via gene transfer and host lysis. Viral-induced microbiome changes can directly and indirectly influence host health and disease. The contribution of viruses towards disease pathogenesis is therefore an important area for research in ME/CFS. Recent advancements in sequencing technology and bioinformatics now allow more comprehensive and inclusive investigations of human microbiomes. However, as the number of microbiome studies increases, the need for greater consistency in study design and analysis also increases. Comparisons between different ME/CFS microbiome studies are difficult because of differences in patient selection and diagnosis criteria, sample processing, genome sequencing and downstream bioinformatics analysis. It is therefore important that microbiome studies adopt robust, reproducible and consistent study design to enable more reliable and valid comparisons and conclusions to be made between studies. This article provides a comprehensive review of the current evidence supporting microbiome alterations in ME/CFS patients. Additionally, the pitfalls and challenges associated with microbiome studies are discussed.

An Overview of Response Leading To Chronic Inflammatory Diseases

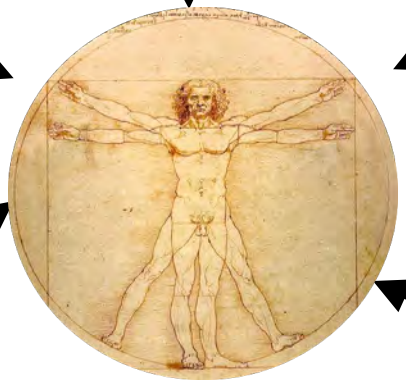


Increased Gut Permeability

Human Genome



Immune Response



Environmental Factors

Clinic Outcome

Microbiome

GUT PERMEABILITY – CHRONIC INFLAMMATION

Stress induces endotoxemia and increasing barrier permeability

Karin de Punder* and Leo Pruimboom
Frontiers in Immunology published: 15 May 2015

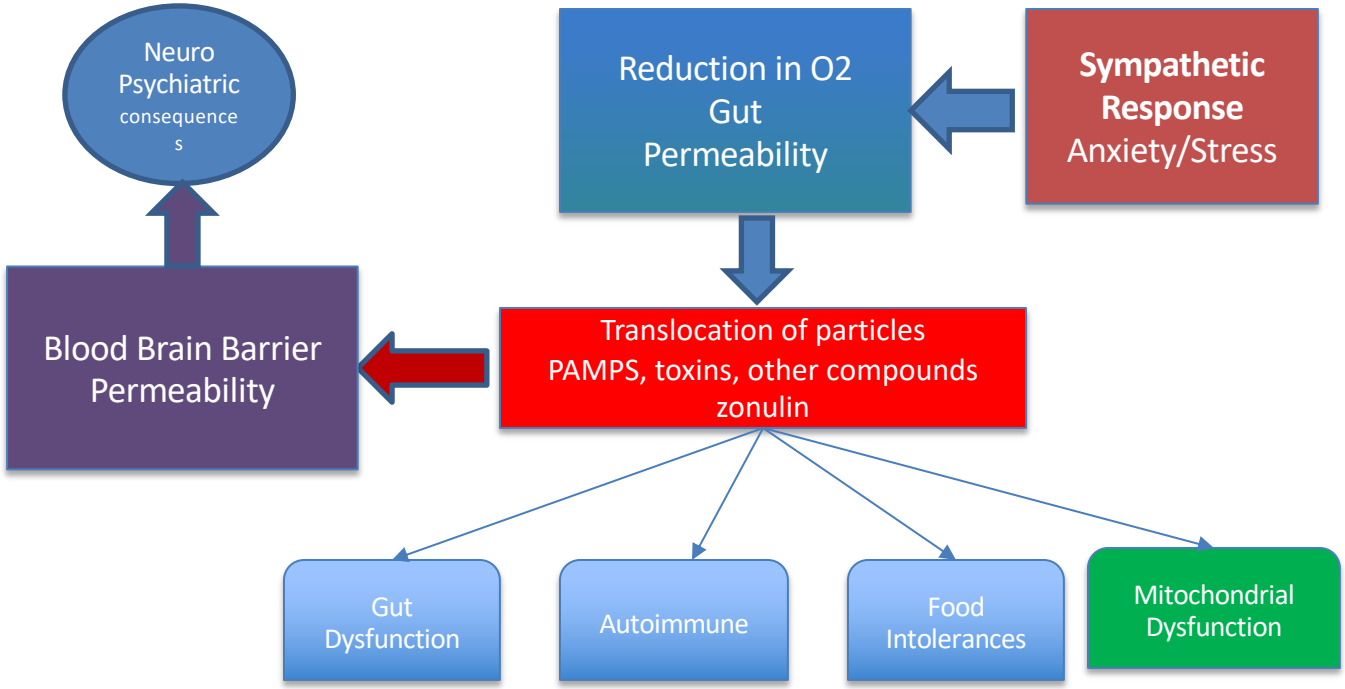
"Chronic non-communicable diseases (NCDs) are the leading causes of work absence, disability, and mortality worldwide. Most of these diseases are associated with low-grade inflammation."

"In combination with modern life-style factors, the increase in **bacteria/bacterial toxin translocation** arising from a more **permeable intestinal** wall causes a low-grade inflammatory state. We support this hypothesis with numerous studies finding **associations with NCDs and markers of endotoxemia**, suggesting that this process plays a pivotal and perhaps even **a causal role** in the development of low-grade inflammation and its related diseases."

GROUND ZERO OF MOST HEALTH DISORDERS

Etiology of Systemic Conditions

GUT-BRAIN-Mitochondria



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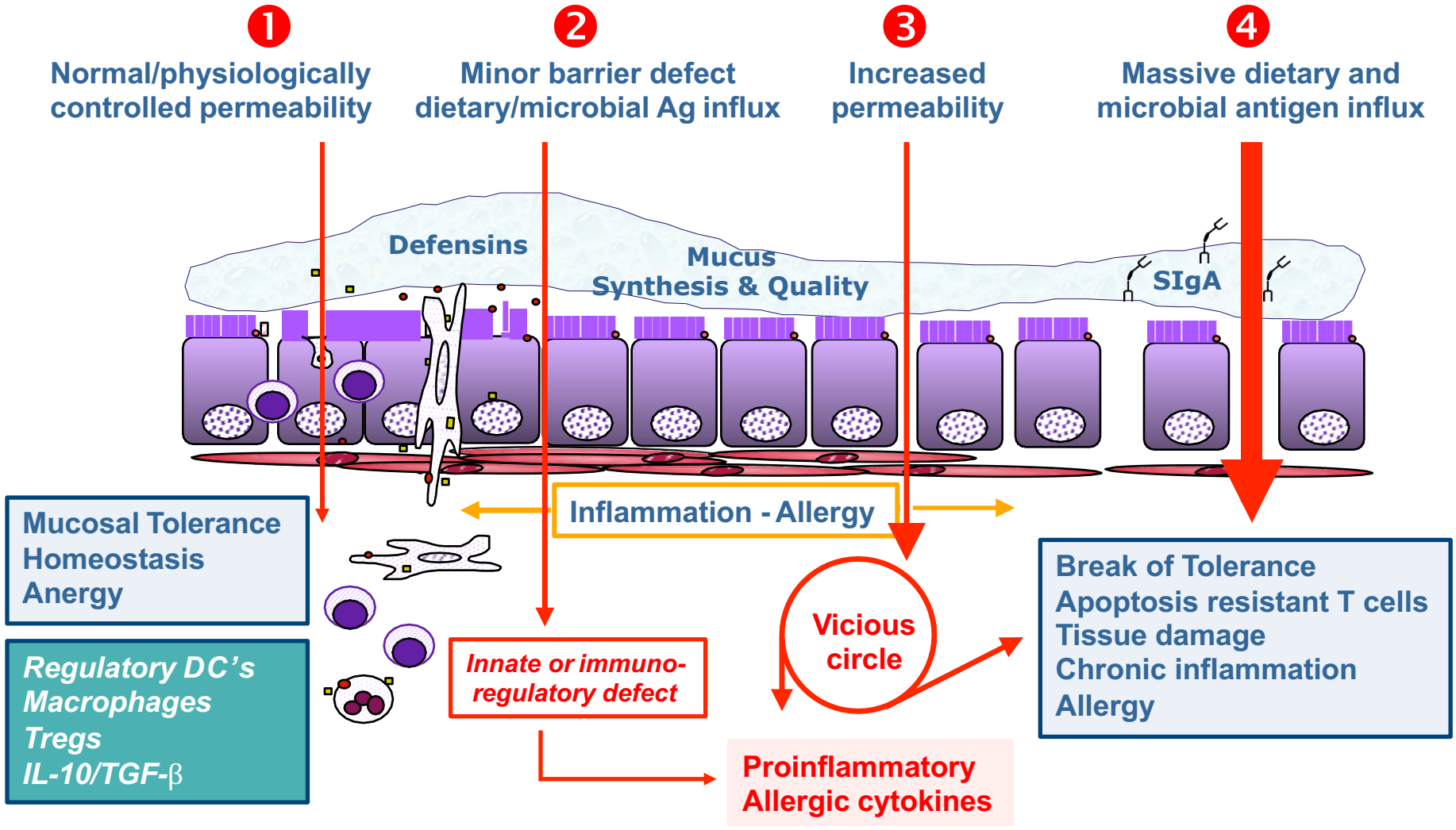
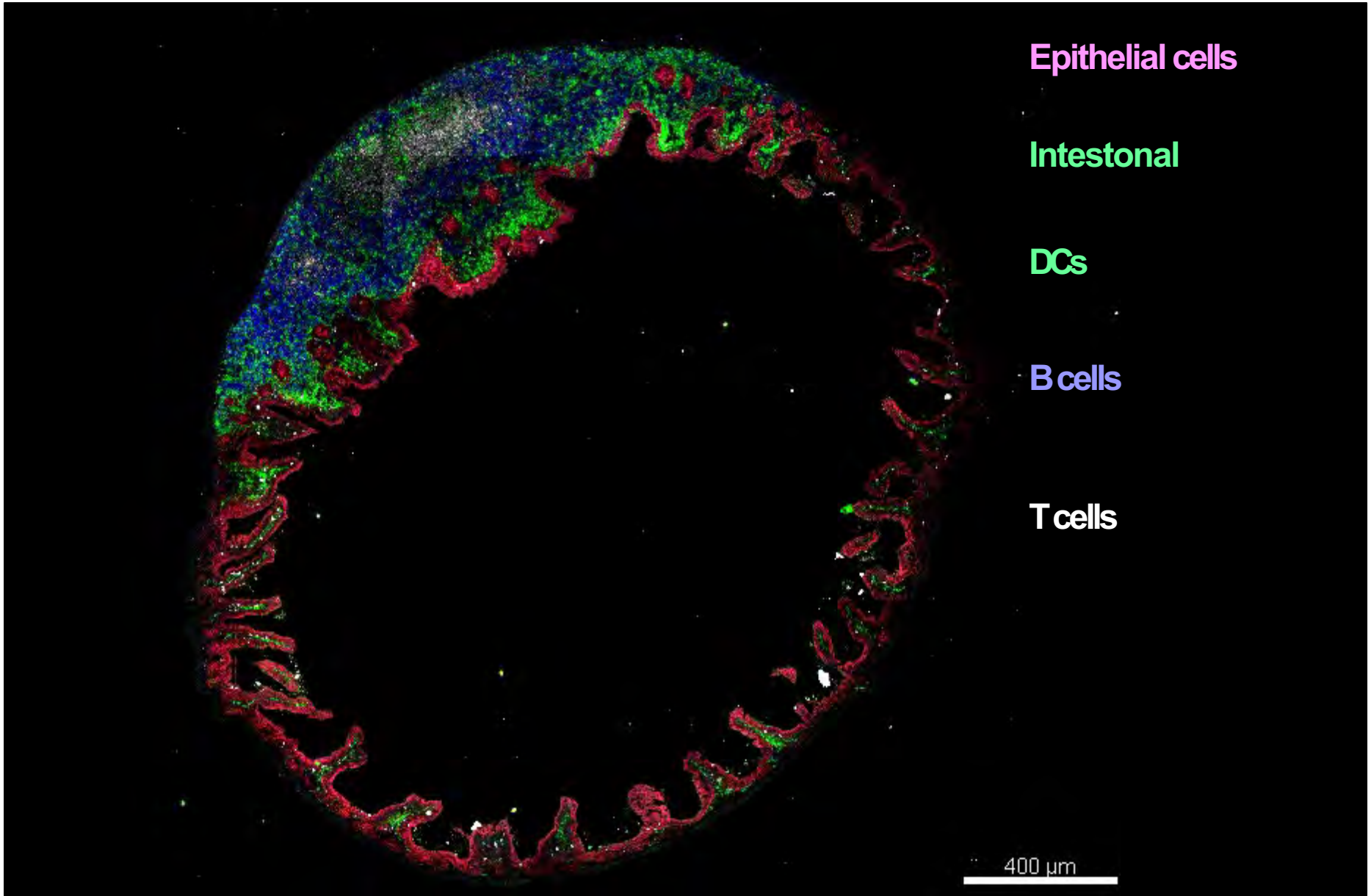
Loss of Mucosal Immune Homeostasis

Chronic Inflammation-Allergy

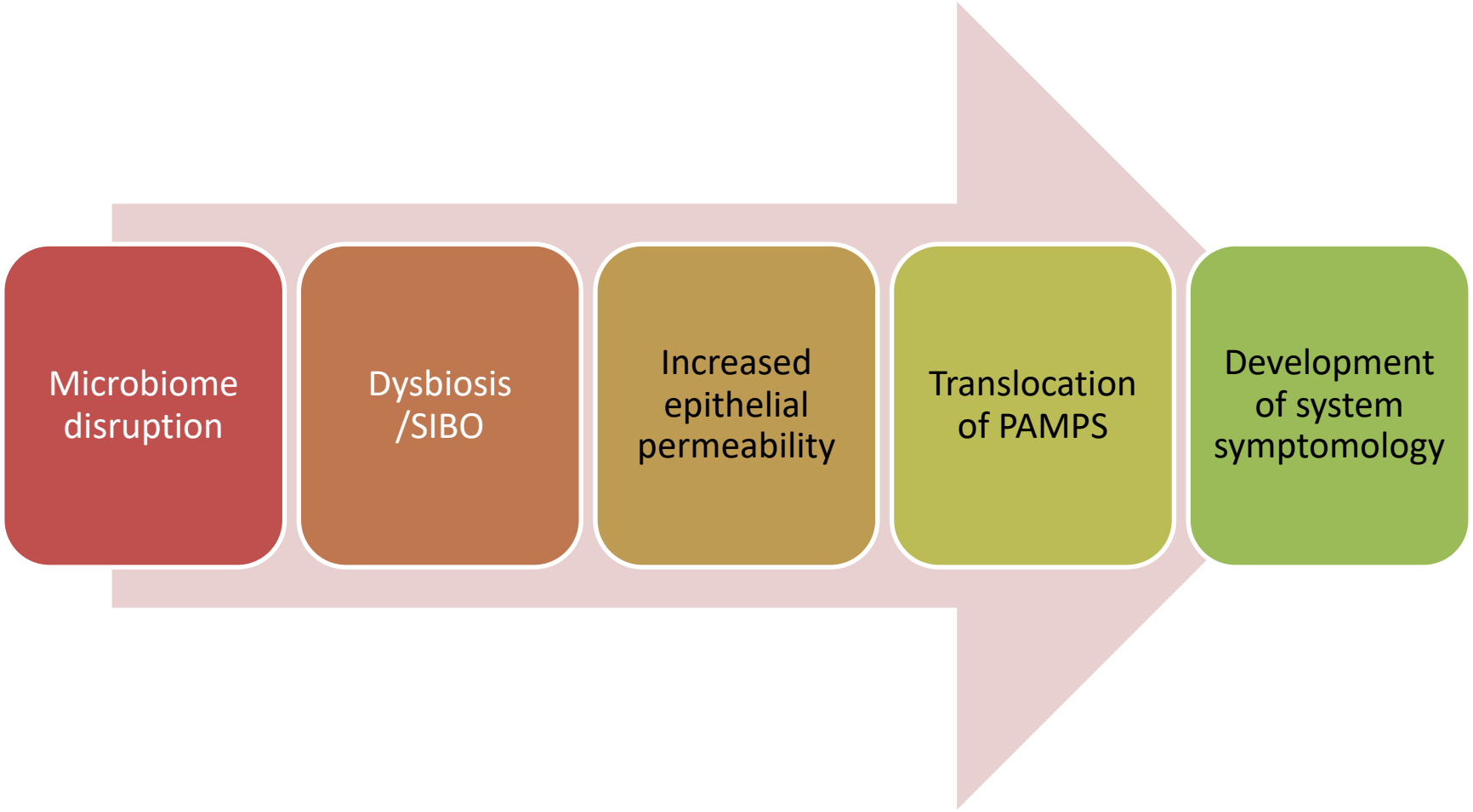


Adapted from P. Brandtzaeg, Beneficial Microbes 2010

Several Cells Play a Role in Maintaining The Immune Homeostasis



The Gut connection

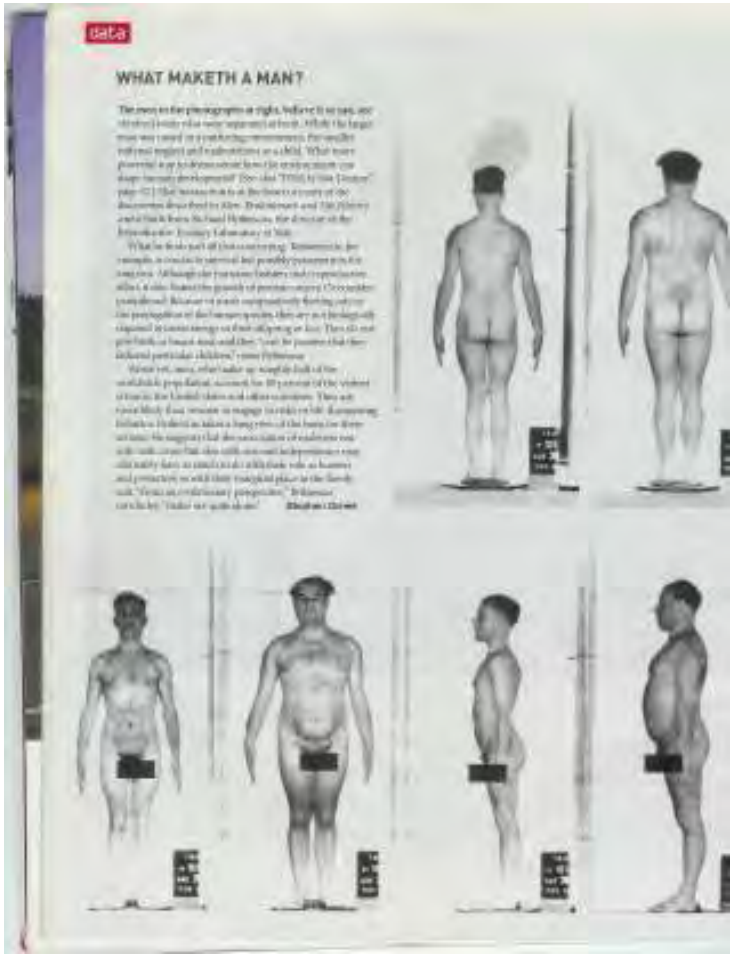


The Problem?
Gut Is Not Vegas

What happens in the gut, absolutely does NOT stay in the gut!

We Are Not Born With The Destiny to Develop Chronic Inflammatory Diseases

Environmental Influence Impacts the Genome
Largest exposure is GUT



Human genome-microbiome interaction: metagenomics frontiers for the aetiopathology of autoimmune diseases

Abstract:
A short while ago, the human genome and microbiome were analyzed simultaneously for the first time as a multi-omic approach. The analyses of heterogeneous population cohorts showed that **microbiome components were associated with human genome variations**. In-depth analysis of these results reveals that the majority of those relationships are between immune pathways and autoimmune disease-associated microbiome components. Thus, it can be hypothesized that autoimmunity may be associated with homeostatic disequilibrium of the human-microbiome interactome. Further analysis of human genome–human microbiome relationships in disease contexts with tailored systems biology approaches may yield insights into disease pathogenesis and prognosis.

Microbiome Genome 2017 April 26:3(4)

The Gut Microflora in Health and GI Disease "we are not alone"

- Bacteria exceed the number of host somatic cells
  - Gut bacterial population ~100 trillion
  - 500-1000 different species of bacteria
  - 60% of fecal biomass is from bacteria
- Microflora exerts important effects on:
  - Structure, physiology, biochemistry, immunology, maturation of vasculature, and gene expression
  - Human genome is in a sense static, microbiome is not (23,000 genes vs. 3.3 million genes)
  - Role in IBD, SIBO, IBS, diverticular disease?
  - Symbiotic relationship and keep less desirable bacteria at bay
  - **CANT LIVE WITHOUT THEM**

Typical Case
CCDP program BC Women's Hospital

A 40 yr old female diagnosed with ME/CFS, on polypharmacy circa 8 years, reports 5 key symptoms:

1. Fatigue with post exertion malaise
2. Cognitive dysfunction: brain fog, memory
3. Sleep dysfunction
4. GI issue: bloating/gas, constipation/diarrhea

She reports abdominal bloating and discomfort after eating various foods, abdominal cramping, feels better when she avoids foods.

Elevation in stress levels intensifies her symptoms.

Typical Case
CCDP program BC Women's Hospital

A 60 year old woman comes in with a diagnosis of ME/CFS, FM, MCS. She has suffered with symptoms since her twenties. Claims symptoms started after a bout with mononucleosis. Further investigation demonstrate gut dysfunction after trip to third world country .

Top 5 symptoms:

1. Fatigue with post exertion malaise
2. Pain
3. GI issues: bloating/gas, abdominal pain, constipation/diarrhea
4. Cognitive dysfunction
5. Sleep issues

Currently on polypharmacy. Although they help somewhat with sleep, it remains unrefreshing. Pain is debilitating but medication just don't seem to work. Stress makes everything worst. Meditation helps.

Antibiotics during concomitant conditions have helped some symptoms.

Microbiome

Distribution and composition

Microbiome at the beginning

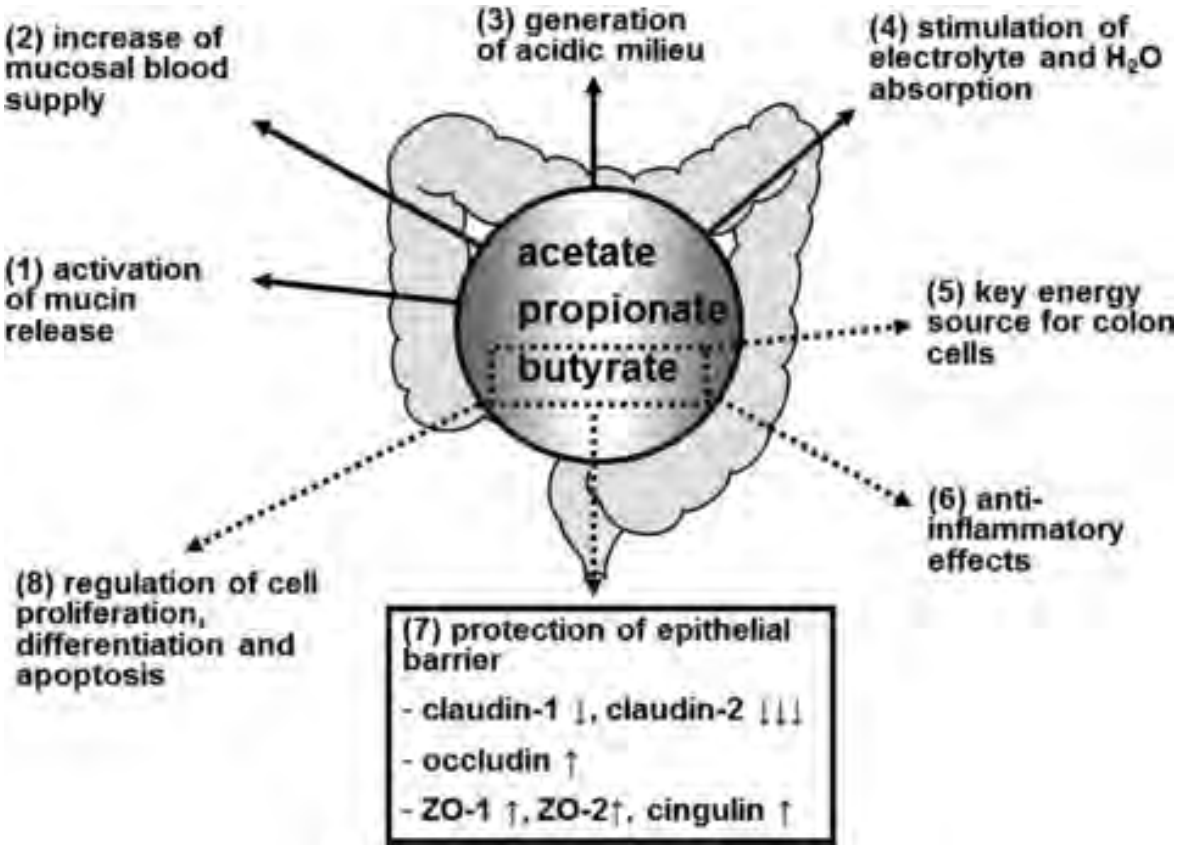
- We inherit our gut flora from the mother at birth
- Birth canal exit allows baby to swallow first mouthfuls of bacteria which begin to inhabit baby sterile gut
- Breast feeding continues the process
- It takes approximately 2 years for baby's immune system to fully develop

It is interesting that both microbiome and mitochondria are maternally inherited.

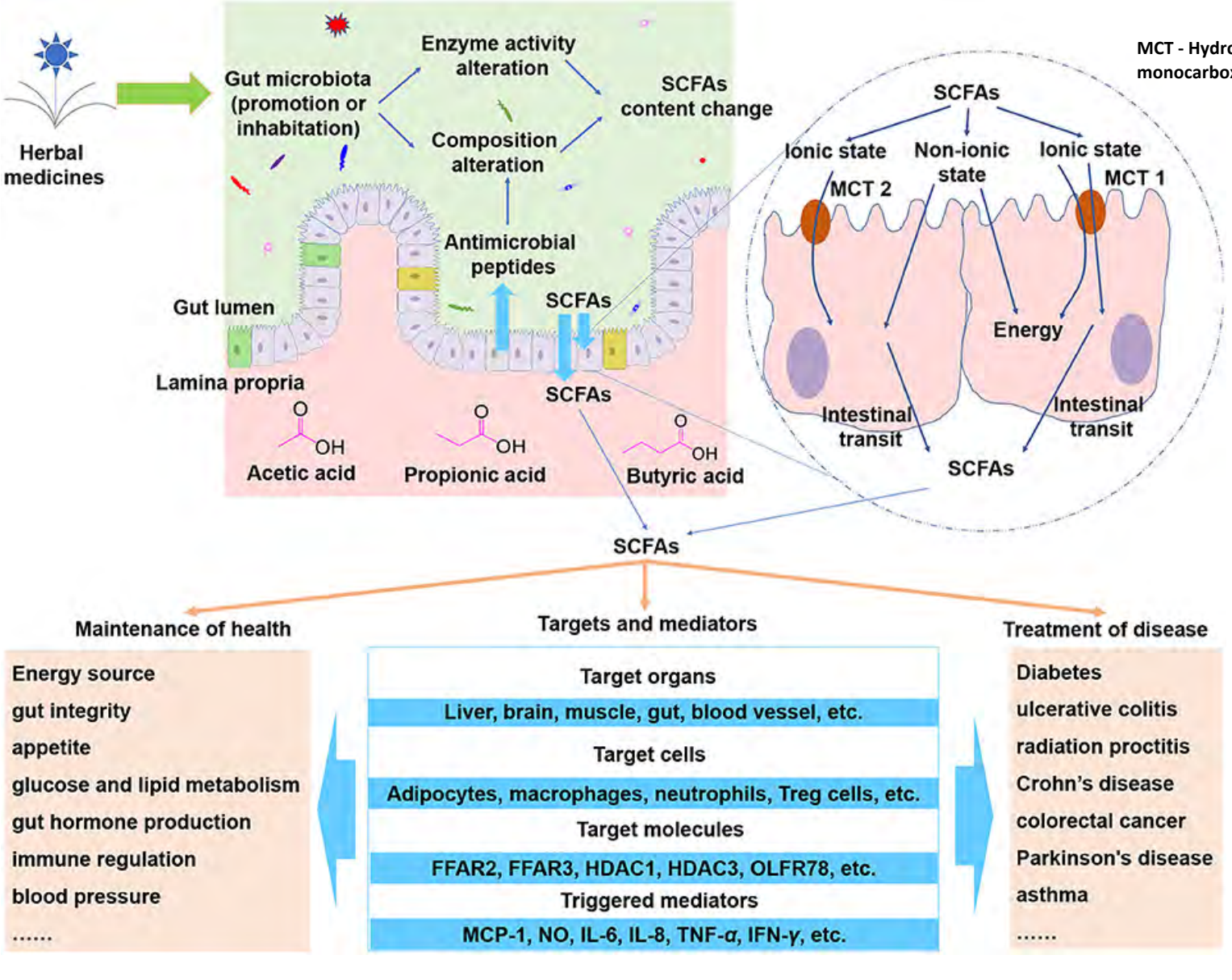
Beneficial bacteria, what they do

- ✓ Digestion-caloric extraction
- ✓ Detoxification
- ✓ Epigenomic expression e.g., butyrate and histone deacetylase inhibition (HDAC1, HDAC3)-associated with anti-inflammatory immune phenotype including decreasing pro-inflammatory cytokines (IL-6,8, TNF-alpha and NF-kappaB).
- ✓ Immunomodulatory cell signaling
- ✓ Cytokine modulation – insulin/leptin, interleukin 10
- ✓ Vitamin modification
- ✓ Neurotransmitters
- ✓ SCFAs and gut hormones/permeability
- ✓ Talk to the vagus nerve

Butyrate and Proprionate



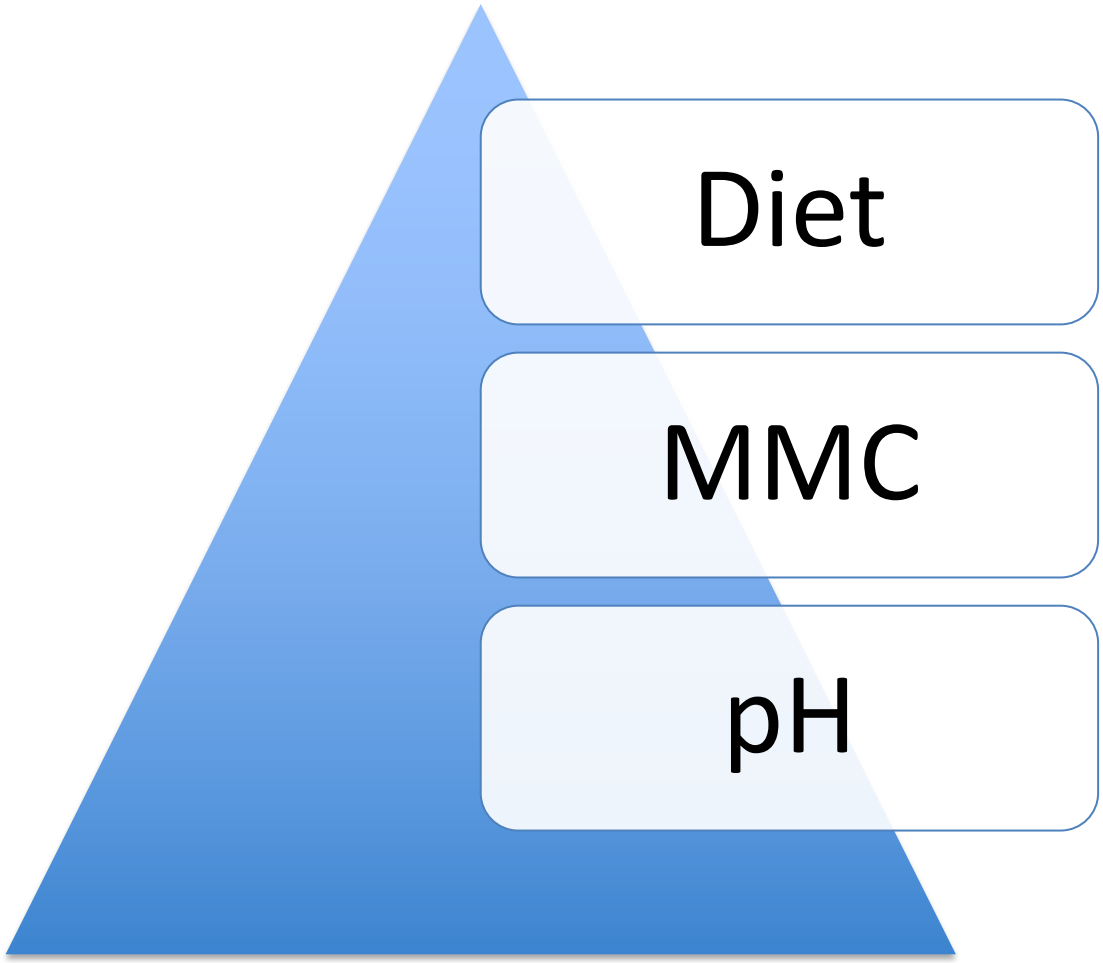
Short Chain Fatty Acids



MCT - Hydrogen-coupled monocarboxylate transporter

FFAR-free fatty acid receptor, HDAC-nuclear class histone deacytylase, OLFR-olfactory receptor, MCP-1-macrophage chemoattractant protein

Factors influencing composition and distribution of Microbiome



Food and the microbiome
(Burkina Faso)

- 75% of food in Western diet is of limited or no benefit to the microbiome of the lower gut.

- Refined CHO's absorbed proximally

- What reaches the large intestine has limitations; small amounts of the minerals, vitamins and other nutrients necessary for the maintenance of the microbiota.

Nutrients 2013. 5, 162-207; doi: 10.3390/nu5010162

Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Carlotta De Filippo[a], Duccio Cavalieri[a], Monica Di Paola[b], Matteo Ramazzotti[c], Jean Baptiste Poullet[d], Sebastien Massart[d], Silvia Collini[b], Giuseppe Pieraccini[e], and Paolo Lionetti[b,1]

[a]Department of Preclinical and Clinical Pharmacology, University of Florence, 50139 Firenze, Italy; [b]Department of Pediatrics, Meyer Children Hospital, University of Florence, 50139 Firenze, Italy; [c]Department of Biochemical Sciences, University of Florence, 50134 Firenze, Italy; [d]DNA Vision Agrifood S.A., B-4000 Liège, Belgium; and [e]Centro Interdipartimentale di Spettrometria di Massa, University of Florence, 50139 Firenze, Italy

Edited* by Daniel L. Hartl, Harvard University, Cambridge, MA, and approved June 30, 2010 (received for review April 29, 2010)

Gut microbial composition depends on different dietary habits just as health depends on microbial metabolism, but the association of microbiota with different diets in human populations has not yet been shown. In this work, we compared the fecal microbiota of European children (EU) and that of children from a rural African village of Burkina Faso (BF), where the diet, high in fiber content, is similar to that of early human settlements at the time of the birth of agriculture. By using high-throughput 16S rDNA sequencing and biochemical analyses, we found significant differences in gut microbiota between the two groups. BF children showed a significant enrichment in Bacteroidetes and depletion in Firmicutes ($P < 0.001$), with a unique abundance of bacteria from the genus *Prevotella* and *Xylanibacter*, known to contain a set of bacterial genes for cellulose and xylan hydrolysis, completely lacking in the EU children. In addition, we found significantly more short-chain fatty acids ($P < 0.001$) in BF than in EU children. Also, *Enterobacteriaceae* (*Shigella* and *Escherichia*) were significantly underrepresented in BF than in EU children ($P < 0.05$). We hypothesize that gut microbiota coevolved with the polysaccharide-rich diet of BF individuals, allowing them to maximize energy intake from fibers while also protecting them from inflammations and noninfectious colonic diseases. This study investigates and compares human intestinal microbiota from children characterized by a modern western diet and a rural diet, indicating the importance of preserving this treasure of microbial diversity from ancient rural communities worldwide.

metagenomics | nutrigenomics | biodiversity | 454-pyrosequencing | short-chain fatty acids

The human gut "metagenome" is a complex consortium of trillions of microbes, whose collective genomes contain at least 100 times as many genes as our own eukaryote genome (1). This essential "organ," the microbiome, provides the host with enhanced metabolic capabilities, protection against pathogens, education of the immune system, and modulation of gastrointestinal (GI) development (2).

We do not yet completely understand how the different environments and wide range of diets that modern humans around the world experience has affected the microbial ecology of the human gut.

Contemporary human beings are genetically adapted to the environment in which their ancestors survived and which conditioned their genetic makeup. In mammals, both diet and phylogeny influence the increase in bacterial diversity from carnivore to omnivore to herbivore (3). Dietary habits are considered one of the main factors contributing to the diversity of human gut microbiota (2). Profound changes in diet and lifestyle conditions began with the so-called "Neolithic revolution" with the introduction of agriculture and animal husbandry ≈10,000 y ago (4). After that time, food resources became more abundant and constant, the concentration of large populations in limited areas created selective pressure that favored pathogens specialized in colonizing human hosts and probably produced the first wave of emerging human diseases (5). It has been hypothesized that bacteria specialized in human-associated niches, including our gut commensal flora, underwent intense transformation during the social and demographic changes that took place with the first Neolithic settlements (6).

Western developed countries successfully controlled infectious diseases during the second half of the last century, by improving sanitation and using antibiotics and vaccines. At the same time, a rise in new diseases such as allergic, autoimmune disorders, and inflammatory bowel disease (IBD) both in adults and in children has been observed (5), and it is hypothesized that improvements in hygiene together with decreased microbial exposure in childhood are considered responsible for this increase (7). The GI microflora plays a crucial role in the pathogenesis of IBD (8), and recent studies demonstrate that obesity is associated with imbalance in the normal gut microbiota (9, 10).

The aim of this study was to compare the gut microbiota of children aged 1–6 y living in a village of rural Africa in an environment that still resembles that of Neolithic subsistence farmers with the gut microbiota of western European children of the same age, eating the diet and living in an environment typical of the developed world. These two childhood populations provided an attractive model for assessing the impact of many environmental variables on the gut microbiota.

In our study, we address three general questions regarding the geography and evolution of the human microbiota: (*i*) how is bacterial diversity partitioned within and between the two populations studied; (*ii*) is there a possible correlation between bacterial diversity and diet; and (*iii*) what is the distribution of well-known bacterial pathogens in the two populations, given the different hygienic and geographic conditions?

Results and Discussion

Characterization of Dietary Habits of Children from the Boulpon Rural Village and from Florence, Italy. In this study, we characterized the fecal microbiota of 14 healthy children from the Mossi ethnic

Author contributions: C.D.F., D.C., and P.L. designed research; C.D.F., M.D.P., S.M., and S.C. performed research; G.P. contributed new reagents/analytic tools; M.R. and J.B.P. analyzed data; and C.D.F., D.C., M.D.P., and P.L. wrote the paper.

The authors declare no conflict of interest.

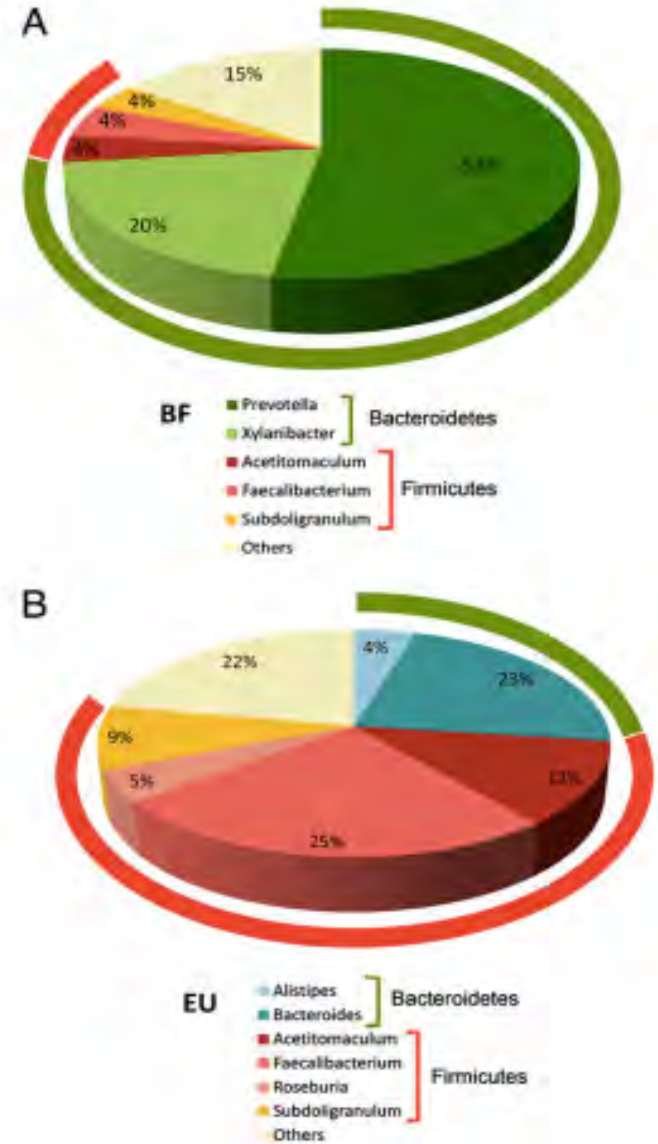
*This Direct Submission article had a prearranged editor.

Freely available online through the PNAS open access option.

Data deposition: Data were submitted to the Sequence Read Archive (SRA) using ISA tools (ISAcreator and ISAconverter, [illegible]). The dataset is available at [illegible].

[1]To whom correspondence should be addressed. E-mail: paolo.lionetti@unifi.it.

This article contains supporting information online at [illegible].



Burkina Faso and European children

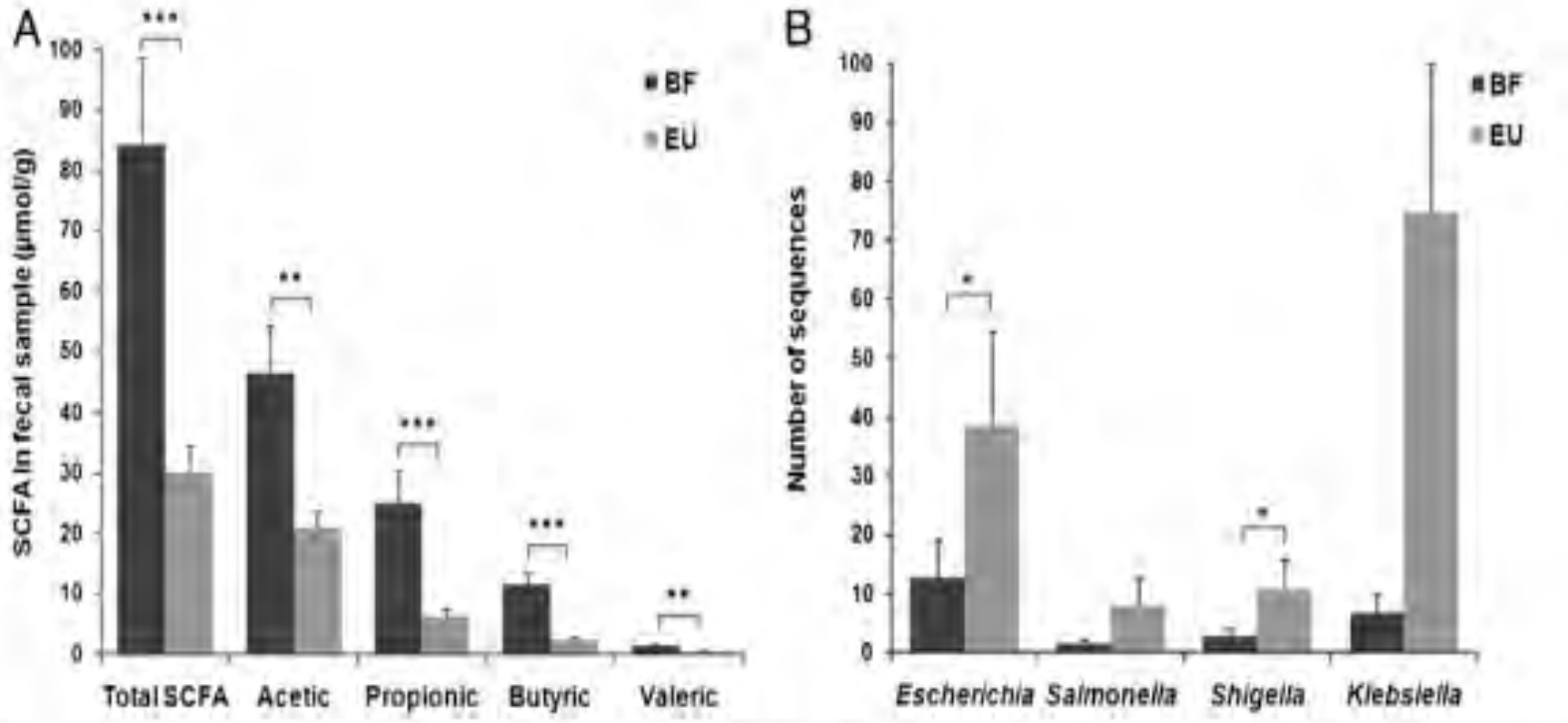
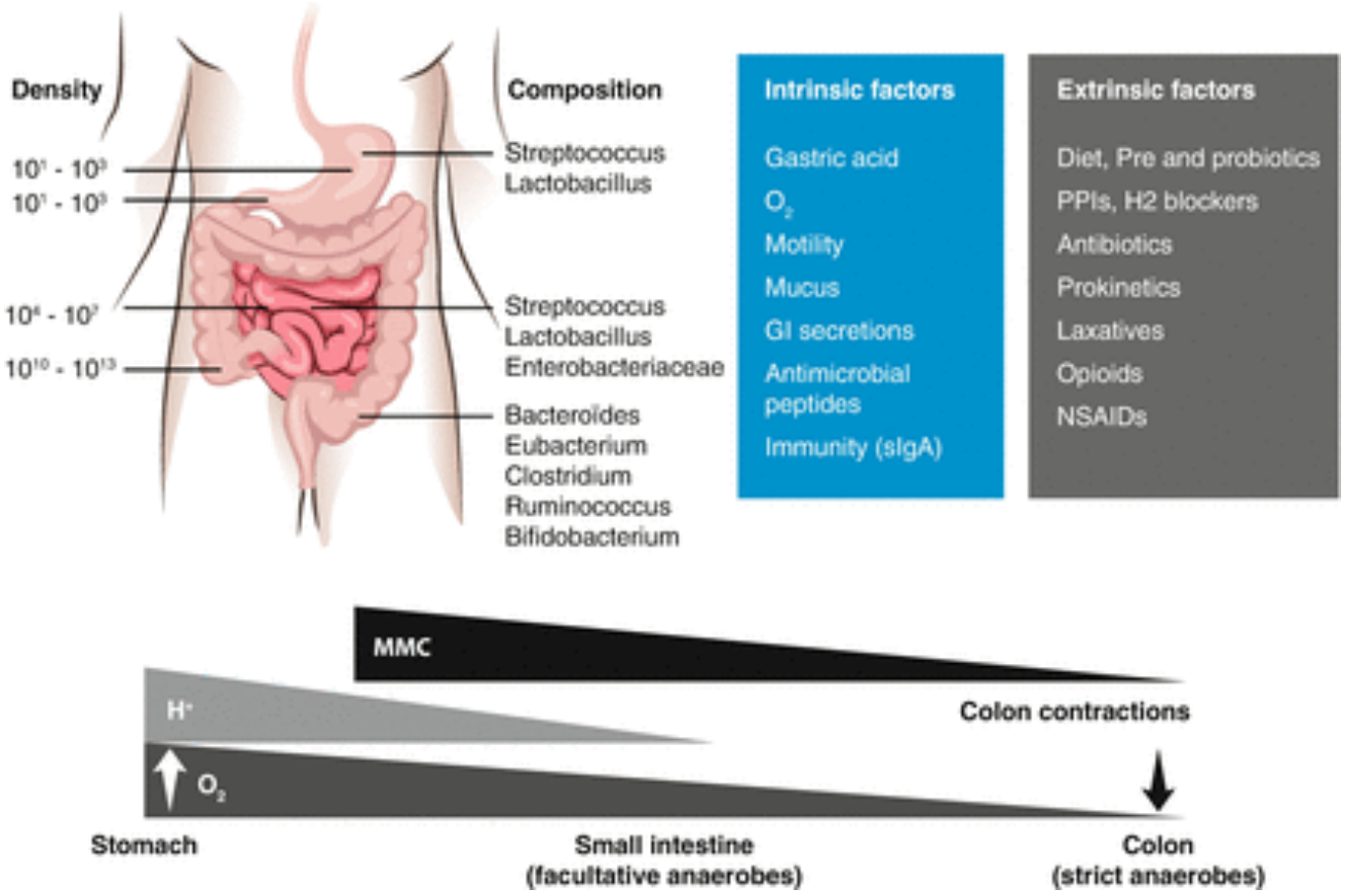


Fig. 3. SCFA-producing bacteria could help to prevent establishment of some potentially pathogenic intestinal bacteria. (*A*) Quantification of SCFAs in fecal samples from BF and EU populations by SPME-GC-MS. (*B*) Number of sequences relative to principal *Enterobacteriaceae* genera, in BF and EU children microbiota. Mean values (±SEM) are plotted. Asterisks indicate significant differences (one-tailed Student *t* test of all data points: $*P < 0.05$; $**P \leq 0.01$; $***P \leq 0.001$).

Extrinsic and Intrinsic factors Affecting the distribution and composition of the microbiome

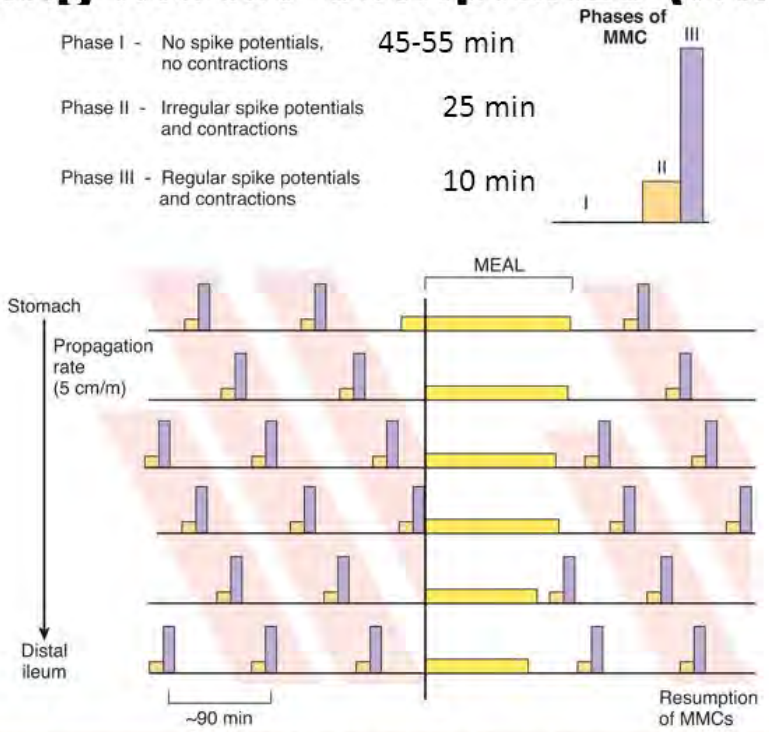


Migrating Motor Complex

- Begins 90 minutes after eating
- Cleansing Wave: Waves from stomach through small intestine
- During night: 3-4 waves so have clean SI when waking
- Turned OFF during eating: DO NOT GRAZE
- Eat three meals at least 4-5 hours apart
- Do a fast from dinner to breakfast

MMC

Migrating motor complexes (MMCs).



Migrating motor complexes (MMCs). Note that the complexes move down the gastrointestinal tract at a regular rate during fasting, that they are completely inhibited by a meal, and that they resume 90–120 minutes after the meal

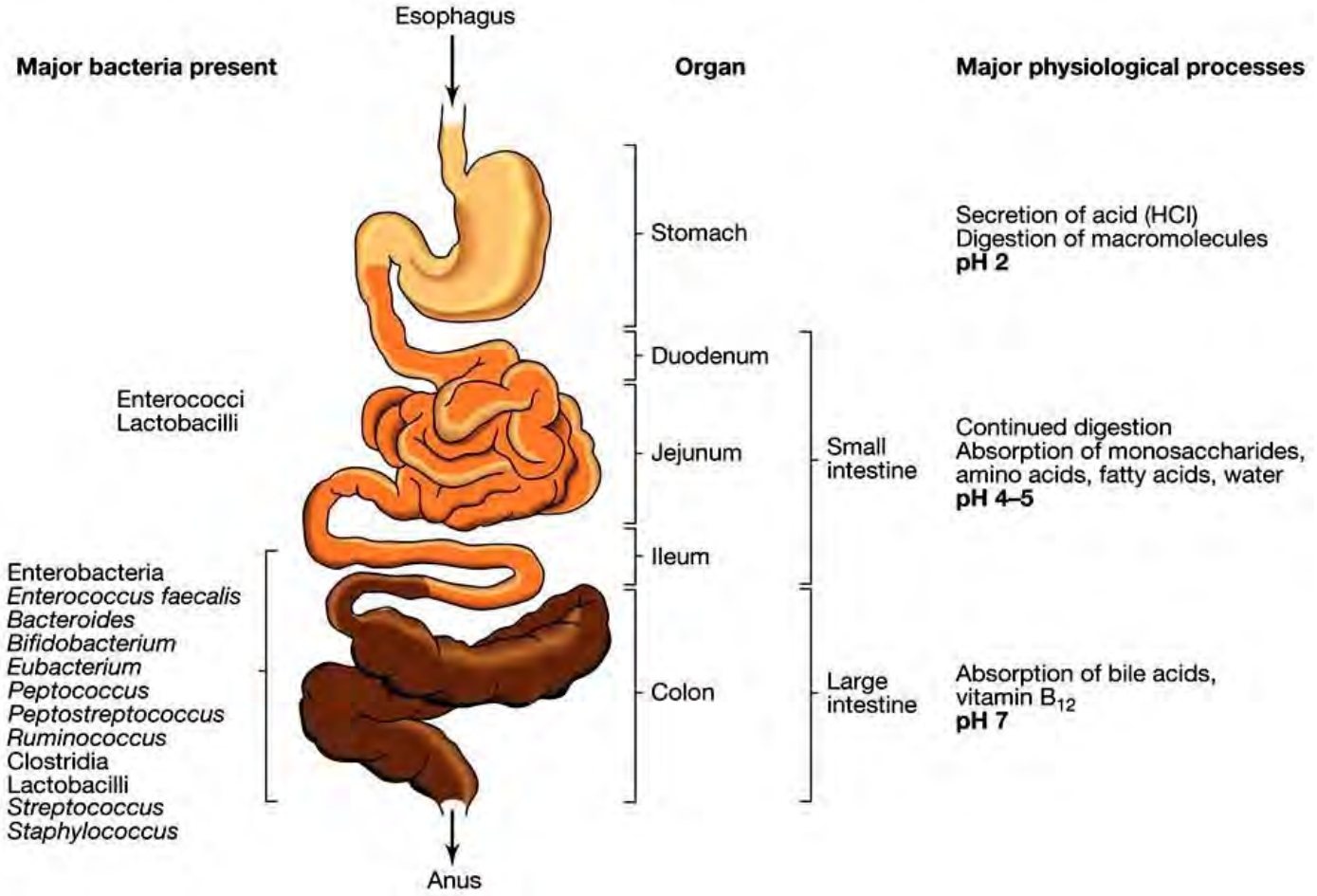
MMC

Causes leading to dysfunction

- Slowing of Migrating Motor Complex
  - DDX
    - Morphine/opiates
    - Mixed meal
    - Stress
    - Eating
    - Diabetic neuropathy
    - Ehlers-Danlos Syndrome
    - Adhesions
    - Small gut diverticula
    - Blind loops (gastric bypass patients)
    - Narcotic use
    - Tumors of bowel
    - Extra loops of small bowel
    - Small gut obstruction

Distribution of Bacteria

Levels of pH



Noteworthy contributions to alterations of the human microbiome

- Dietary changes e.g. refined, processed simple starches and sugars “carbohydrate-dense” foods
- Marked decreases in fermentable fiber
- Antibiotic use in prescriptions and in industrialized foods
- Glyphosate as an anti-microbial
- Hygiene hypothesis
- Prior GI infections; H. pylori; systemic infections Medications e.g. PPIs, steroids, chemotherapy

Small Intestinal Bacterial overgrowth

SIBO

SIBO
Small Intestinal Bacterial Overgrowth

- Definition:
  - Disruption of the normal small bowel bacterial population (usually number); may result in gas, bloating, flatulence, altered bowel function, malabsorption, pain, diarrhea/constipation
  - Accepted definition is when jejunal aspirate is $>10^5$ CFU/ml

- Wide array of effects
  - Direct injury, changes in function/sensation, gut immunology, permeability, and loss of brush border enzymes
- This imbalance can not only cause difficult to deal with GI issues but also lead to systemic complications.
  - Leaky gut, central sensitivity pain, skin , cognitive dysfunction (brain fog, memory), arthritis , fatigue, anxiety, depression, GERD

SIBO: Review Clinical Presentation

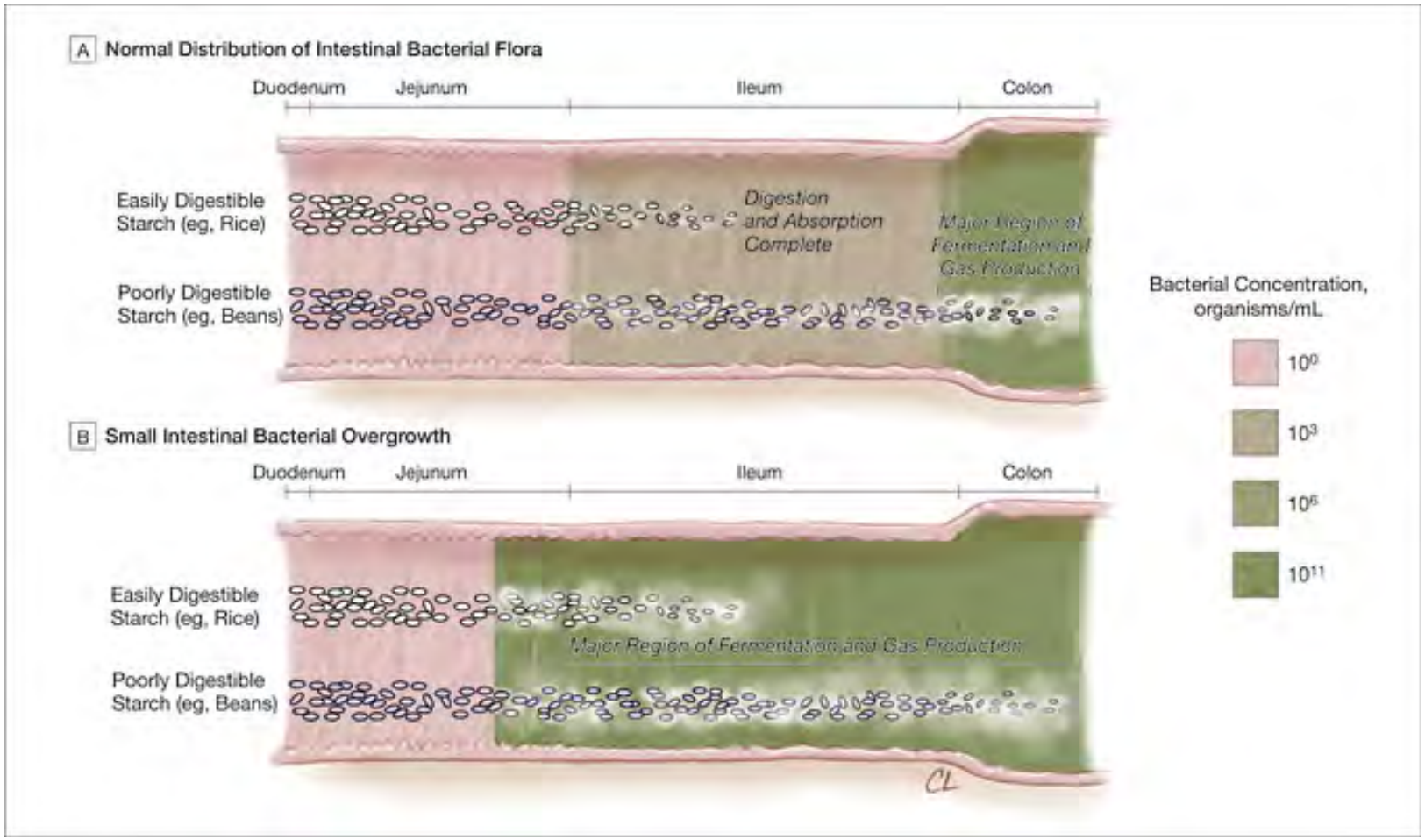
Symptoms (gas related)

- Abdominal Pain
- Bloating/Flatulence
- Diarrhea

Other Symptoms

- Malabsorption syndrome
- Increased GUT permeability
- IBS

SIBO defined



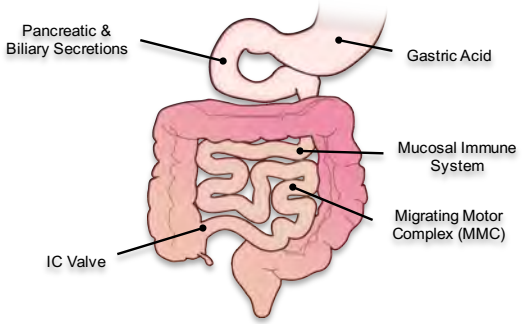
Background
What keeps things in check

HCL

Bile, Enzymes

MMC

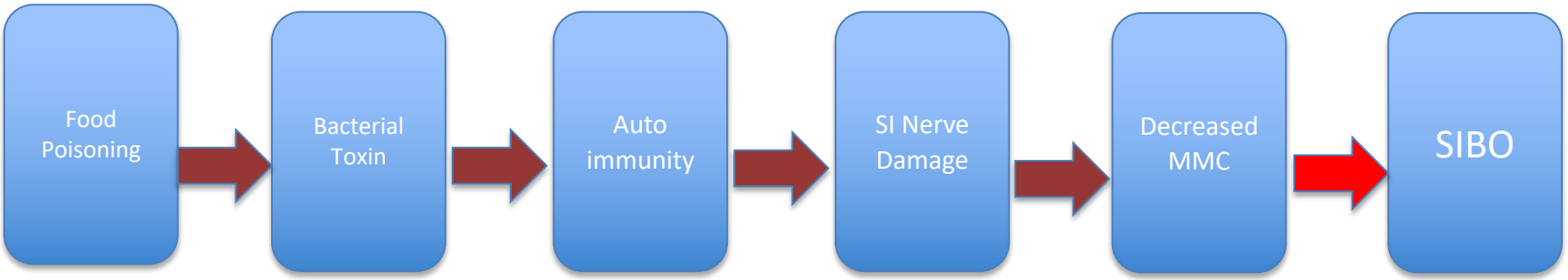
Ileocecal Valve



Immune System

Failure of these systems can contribute to the formation of SIBO; this is what is actually wrong with the body that creates the problem

Pathophysiology
How Food Poisoning leads to SIBO



C. Jejuni
E. Coli
Shigela
Salmonella
C. diff

Cytolethal Distending Toxin

Cdt B

Anti-Vincullin Antibodies

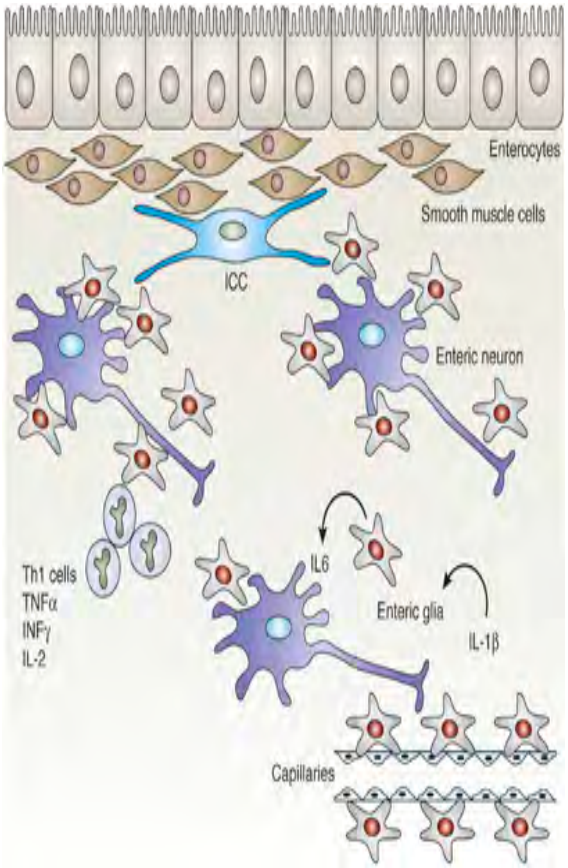
Impacts ICC (interstitial Cells of Cajal)

MMC Dysfunction

Bacterial Overgrowth

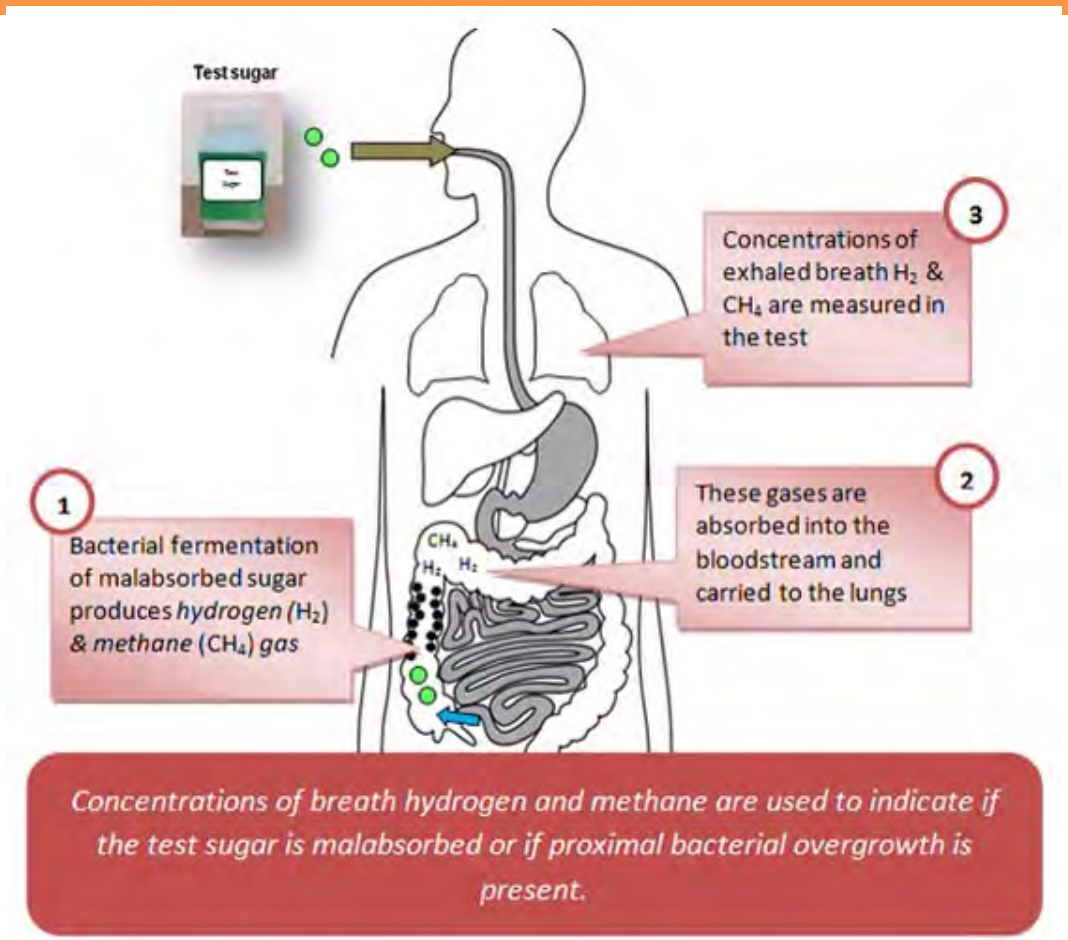
Interstitial Cells of Cajal (cahal)

- Intestinal cell—pacemaker which creates stimulus slow wave causing contraction of smooth muscle in gut.
- Form networks in submucosa, intra-mucosa and inter-muscular layers of gut
- Drives spontaneous rhythmic motility
- ICC Pacemaker
  - 3 per minute in stomach
  - 12 per minute in duodenum
  - 10 per minute in ileum
  - 3 per minute in colon
- CDTb induced loss of ICC→interrupt normal neural control of GI contractions



Testing for SIBO

Lactulose-10g
Glucose-75g (or 1 g/kg)



Breath Testing assesses bacterial fermentation over 90-100 minutes after ingestion of a substrate usually Lactulose or Glucose or both.

Measures methane and hydrogen gases (these are not produced by humans)

SIBO Testing

Currently 2 main useful tests: .

1. Breath: Lactulose or Glucose or both
2. Blood: Cdt B and Vinculin Antibodies

Breath:
Interpretation:
Note: Lactulose and Glucose have different parameters for testing positive

a. Hydrogen: Positive with a rise of 20 ppm over the lowest preceding level (90-100 minutes) for lactulose.
b. Hydrogen: Positive with a rise of 12 ppm over the lowest preceding level (90-100 minutes) for glucose
c. Methane: Positive with a rise of 12 ppm over the lowest preceding level (90-100 minutes) for both glucose or lactulose.

SIBO Testing

IBS check is a blood test developed by Mark Pimentel, MD at Cedars-Sinai Medical Centre for IBS

Dr. Pimentel and his team conducted a 2500 patient clinical trial which showed anti-vinculin and anti-CdtB (Cytolethal distending toxin)as effective markers for the diagnosis of diarrhea-predominant or mixed symptoms IBS (3 ml blood drawn)

SIBO Associations

1. Sibo and Anemia:

Many patients with IBS and SIBO will often have low to abnormally low Ferritin levels
Well established that bacterial overgrowth can deplete Fe and B12 stores.

Flo TH, Smith KD, Sato S, Rodriguez DJ, Holmes MA, et al. (2004) Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. Nature 432: 917–921.

Treatment

- Sympathetic response downregulation
- Anti-Microbial Therapy
- Prokinetic Support
- Gut Repair
- Dietary Considerations
- Elemental Diet

Treatment with Antibiotics

Consists of two parts:

1. Antibiotic for 14 days
    1. Rifaxamin 550 mg tid
    2. * Add Neomycin 500 mg bid (for methane/constipation)
2. Followed by Prokinetic
    1. Erythromycin 50 mg at night for 3 months

Herbal Antibiotic Protocol

Hydrogen Only

- Berberine (500mg): 3 capsules t.i.d.
- Oregano(180 mg): 2 softgels b.i.d

Methane (constipation)

- Berberine (500mg): 3 capsules t.i.d.
- Garlic (allicin) (500 mg): 3 softgels b.i.d.

Hydrogen and Methane

- Berberine (500mg): 3 capsules t.i.d.
- Garlic (allicin)(500mg): 3 softgels b.i.d.
- Oregano (180mg): 2 softgels b.i.d.

Prokinetics

Prokinetics induce activity of the MMC and help prolong remission.
Used to help prevent relapse of SIBO
Should be started immediately after finishing treatment
Pharmaceutical:

1. Erythromycin (50 mg): 1 tablet nightly for 90 days.
2. LDN (low dose naltrexone); 2.5 mg

Botanical Approach

1. Ginger: 1000 mg per day
2. 5HTP: 50 mg at night
3. ECPO: 3 softgels at night

Enteric Coated Peppermint oil

- Remains one of the most under rated and under utilized natural “gut” products
- Measureable outcomes for gas/bloating on first dose.
- Key is delivery of product to S.I. through enteric coating
- pH of stomach important determining factor on efficacy
- Test with 1 softgel
- Proper dosing: 3-4 capsules at one time

Gut Permeability
PEA (palmitoylethanolamide)

Palmitoylethanolamide (PEA), an endogenous fatty acid amide, has been demonstrated to bind to a receptor in the cell nucleus – the peroxisome proliferator–activated receptor – and performs a great variety of biological functions related to chronic and neuropathic pain and inflammation, as has been demonstrated in clinical trials.

These include peripheral neuropathies such as diabetic neuropathy, chemotherapy-induced peripheral neuropathy, carpal tunnel syndrome, sciatic pain, osteoarthritis, low-back pain, failed back surgery syndrome, dental pains, neuropathic pain in stroke and multiple sclerosis, chronic pelvic pain, postherpetic neuralgia, and vaginal pains.

PEA is an endogenous modulator

Latest research shows PEA has an impact in reducing gut permeability

A RANDOMISED DOUBLE BLIND CONTROLLED TRIAL EXAMINING THE EFFECT OF PEA AND CBD ON THE PERMEABILITY OF THE HUMAN GUT IN VIVO

DG Couch, C Ortori, D Barrett, JN Lund and SE O'Sullivan
School of Medicine, Faculty of Science, University of Nottingham

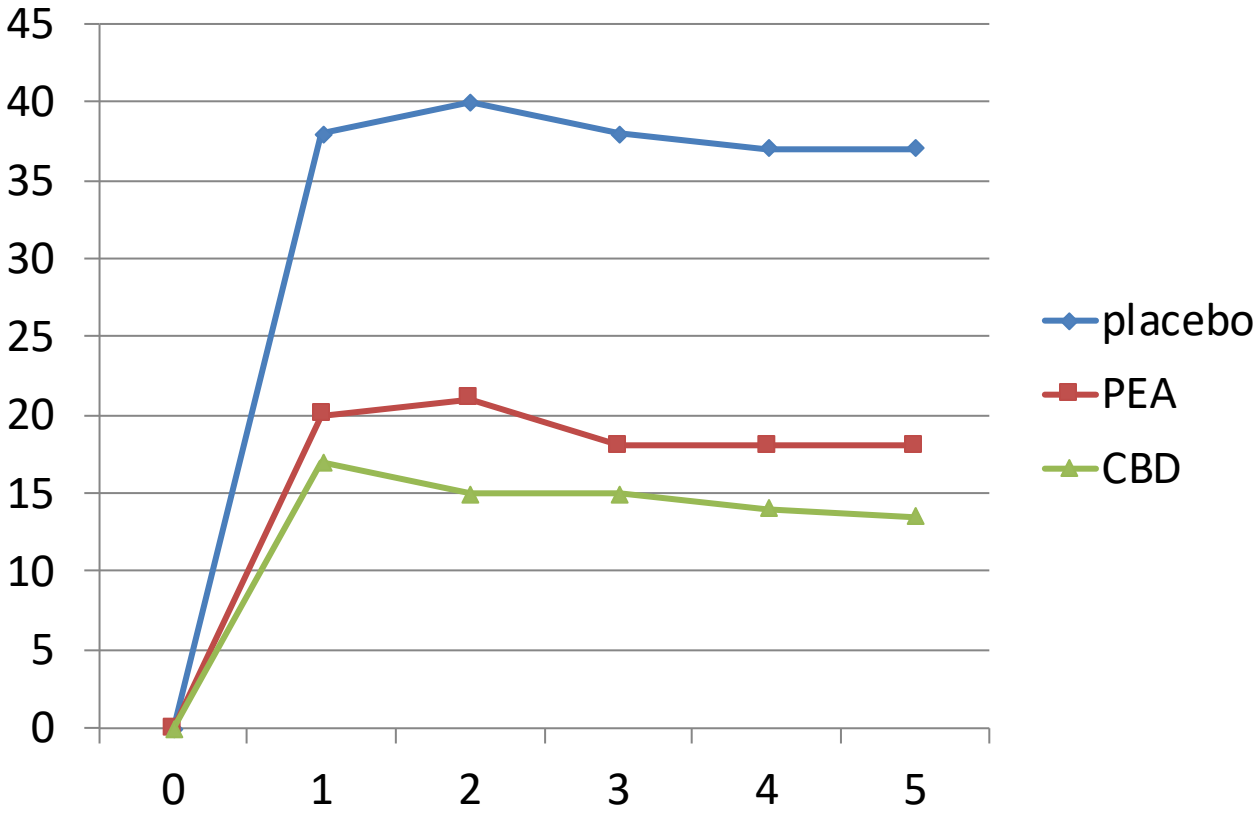


Figure 1 – The concentration ratios of urinary lactulose and mannitol over time in healthy participants treated with aspirin and either placebo, CBD or PEA, measured by LC MS. Results are expressed as mean ratios +/- SEM. Time points between groups were compared using two-way ANOVA using Dunnett's multiple comparisons test comparing to placebo at the same time point (*p

Supportive Nutrients

1. NAC : Acts as a biofilm disruptor. NAC has been shown to breakdown biofilms. Although the use of Berberine can disrupt biofilms this could be an add on.

   Dosage: 1200 mg per day

2. Melatonin: 2-5 mg at bedtime can improve motility and help with sleep.
3. Probiotic: 5 billion cfu BB536: 1 capsule at night (Antibody effect)
4. Vitamin B12 (1000 mcg): Take one sublingual tablet daily. SIBO patients have low Vitamin B12 due to issues with intrinsic factor.
5. Iron Factors: 1 tablet daily.
6. PharmaGABA (100 mg): Helps up regulate parasympathetic response. Start at 100 mg 2x per day, move to 200 mg 2x per day.

Elemental Diet
(Overview)

A. Background

1. Medical Food Beverage
2. Predigested, proximally absorbed
3. Thus used to support GI disorders (helps with malabsorption and gut rest)
4. Literature shows use to treat IBD (Crohn's, UC), Celiac, SIBO, Pancreatitis, Eosnophilic Esophagitis, GI damage (Radiation enteritis)
5. We use it in hospital for nutritional support:
   I. Enteral Nutrition: feeding tube or oral
   II. Paraenteral Nutrition: IV feeding

B. Composition:

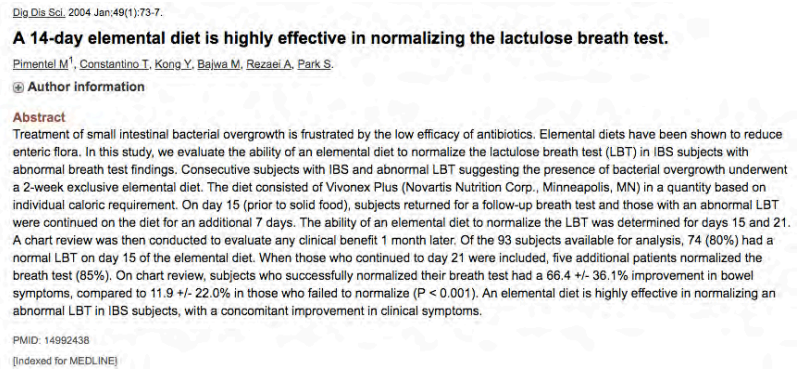
1. Macronutrients:
   1. Proteins – single form amino acids
   2. CHO's- simple sugars
   3. Fats- MCT's, safflower, olive
   4. Micronutrients: Vitamins, Minerals and electrolytes

C. Absent:

1. Whole Protein
2. Fiber, Gums
3. Food items supplying micronutrients

D. Elemental Diet for SIBO (key points)

1. Used as an alternative to Abx/Habx
2. Pimental (2004), demonstrated as effective as Abx
3. Starves bacteria bit feeds patient
4. Consumed in place of all other foods for 2-3 weeks
5. Significantly reduces gas after 2-3 weeks (over 130 ppm) and impacts both hydrogen and methane (Abx reduces up to 30 ppm).
6. No Abx/Habx concurrently, stop all non essential medicines
7. Caution with diabetics



Dig Dis Sci. 2004 Jan;49(1):73-7.

A 14-day elemental diet is highly effective in normalizing the lactulose breath test.

Pimentel M[1], Constantino T, Kong Y, Bajwa M, Rezaei A, Park S.

Author information

Abstract

Treatment of small intestinal bacterial overgrowth is frustrated by the low efficacy of antibiotics. Elemental diets have been shown to reduce enteric flora. In this study, we evaluate the ability of an elemental diet to normalize the lactulose breath test (LBT) in IBS subjects with abnormal breath test findings. Consecutive subjects with IBS and abnormal LBT suggesting the presence of bacterial overgrowth underwent a 2-week exclusive elemental diet. The diet consisted of Vivonex Plus (Novartis Nutrition Corp., Minneapolis, MN) in a quantity based on individual caloric requirement. On day 15 (prior to solid food), subjects returned for a follow-up breath test and those with an abnormal LBT were continued on the diet for an additional 7 days. The ability of an elemental diet to normalize the LBT was determined for days 15 and 21. A chart review was then conducted to evaluate any clinical benefit 1 month later. Of the 93 subjects available for analysis, 74 (80%) had a normal LBT on day 15 of the elemental diet. When those who continued to day 21 were included, five additional patients normalized the breath test (85%). On chart review, subjects who successfully normalized their breath test had a 66.4 +/- 36.1% improvement in bowel symptoms, compared to 11.9 +/- 22.0% in those who failed to normalize ($P < 0.001$). An elemental diet is highly effective in normalizing an abnormal LBT in IBS subjects, with a concomitant improvement in clinical symptoms.

PMID: 14992438

[Indexed for MEDLINE]

Aliment Pharmacol Ther. 2006 Nov 1;24(9):1333-40.

Effectiveness of an 'half elemental diet' as maintenance therapy for Crohn's disease: A randomized-controlled trial.

Takagi S[1], Utsunomiya K, Kuriyama S, Yokoyama H, Takahashi S, Iwaguchi M, Takahashi H, Takahashi S, Kinouchi Y, Hiwatashi N, Funayama Y, Sasaki I, Tsuji I, Shimosegawa T.

⊕ Author information

Abstract

BACKGROUND: Although thiopurines have a proven role in maintenance therapy for Crohn's disease, an alternative therapy is needed for patients intolerant or resistant to thiopurines.

AIM: To evaluate the effectiveness of home enteral nutrition as a maintenance therapy regimen in which half of the daily calorie requirement is provided by an elemental diet and the remaining half by a free diet. We refer to this home enteral nutrition therapy as 'half elemental diet'.

METHODS: Between 2002 and 2005, 51 patients in remission from two hospitals were randomly assigned to a half elemental diet group (n = 26) or a free diet group (n = 25). The primary outcome measure of this study was the occurrence of relapse over the 2-year period.

RESULTS: The relapse rate in the half elemental diet group was significantly lower [34.6% vs. 64.0%; multivariate hazard ratio 0.40 (95% CI: 0.16-0.96)] than that in the free diet group after a mean follow-up of 11.9 months. Compliance was similar in the two groups. No adverse event occurred in any of the patients throughout the study.

CONCLUSION: This randomized-controlled trial shows the effectiveness of an half elemental diet, which is a promising maintenance therapy for Crohn's disease patients.

Elemental Diet

Surg Today. 2017 Dec;47(12):1519-1525. doi: 10.1007/s00595-017-1543-5. Epub 2017 May 22.

Adherence to an elemental diet for preventing postoperative recurrence of Crohn's disease.

Ohara N[1], Mizushima T[2,3], Iijima H[4], Takahashi H[1], Hiyama S[5,4], Haraguchi N[1], Inoue T[4], Nishimura J[1], Shinzaki S[4], Hata T[1], Matsuda C[1], Yamamoto H[1,6], Doki Y[1], Mori M[1].

⊕ Author information

Abstract

PURPOSE: An elemental diet (ED) can suppress inflammation in patients with Crohn's disease (CD); however, adherence to this diet is difficult. We examined the correlation between ED adherence and the postoperative recurrence of CD.

METHODS: The subjects of this study were 38 patients who underwent intestinal resection with anastomosis. We defined ED adherence as consuming the average daily ED dose (≥900 kcal/day) for 2 years after surgery. Patients who did not adhere to the ED were allocated to the non-ED group. We diagnosed symptomatic recurrence using the CD activity index and endoscopic recurrence using the Rutgeerts' score.

RESULTS: The ED and non-ED groups comprised 21 and 17 patients, respectively, with ED adherence of 55.3% (21/38). At the initial endoscopy, symptomatic and endoscopic recurrence rates were 4.8 and 14.3%, respectively, in the ED group, and 23.5 and 41.2%, respectively, in the non-ED group (P = 0.152 and P = 0.078, respectively). The overall symptomatic recurrence-free duration was significantly longer than the endoscopic recurrence-free duration (P = 0.022). Symptomatic and endoscopic recurrence-free durations were longer in the ED group than in the non-ED group (P = 0.003 and P = 0.021, respectively), and ED adherence was a prognostic factor for endoscopic recurrence (HR = 2.777, 95% CI = 1.036-8.767, P = 0.042).

CONCLUSION: Maintaining ED adherence for 2 years after surgery improved the symptomatic and endoscopic recurrence-free durations.

KEYWORDS: Adherence; Crohn's disease; Elemental diet; Postoperative recurrence

PMID: 28534264 DOI: 10.1007/s00595-017-1543-5

[Indexed for MEDLINE]

Background:

- Most studied strategy in dietary management
- Has been shown to be effective in reducing relapses in Crohn Disease patients

Elemental Diet Protocols

Full Elemental Diet

Full Elemental Diet: Patient consumes 100% of caloric requirements using ED. Sole source of nutrition for the designated time period 14-21 days (as evidenced by clinical trials).

Test on Day 15, if (+) result, diet can be extended for another week. If (-) begin follow up protocol

Application: Crohn's Disease, SIBO, normalizes LBT (lactose breath test) in IBS patients.

Dosage: The dosage is approximately 1800-2000 calories.

Calculate using BMR and Harris-Benedict equation (see below.

Take approximately 200-300 calorie servings every 2 to 3 hours over a 30 minute period till the caloric requirements are met (helps with blood sugar regulation).

Duration: Two weeks has been clinically validated, however, if more time is needed the physician can make that determination based on LBT outcomes.

Half Elemental Diet

Half Elemental Diet: Patient consumes 50% of daily caloric needs from ED and the other 50% from whole foods. Maintain remission from Crohn's Disease.

Used when compliance becomes difficult for patients on Full ED's for SIBO and IBS. Half ED's can also be used as starting and exiting conduits to Full ED's easing the patient experience and possibly improving compliance.

Application: Maintaining remission of Crohn's after completion of Full ED, used as conduits to Full ED's and in place of ED's for difficult compliant patients. Again this will be at the discretion of physician.

Dosage: The dosage is approximately 900-100.

Calculate using BMR and Harris-Benedict equation (see below) to calculate total caloric requirement (divide this by half to give you the calories needed from the Half ED).

Duration: There are no published reports regarding the duration of a Half ED, however, 4-6 weeks can be a good starting point. The duration would be calculated at the discretion of the physician taking into account various patient symptomology and other markers deemed important.

No food or beverage during ED, however in specific cases there can be continued observable therapeutics effect with the addition:
Chicken or steak (no fat), herbal or Black tea, coffee

Elemental Diet
(Follow up after completion)

Good Follow up after ED:

To prevent bloating and help with motility

1. Prokinetics with meals
    I. Ginger; 500 mg with each meal
    II. Eberogast: 1 ml (20 drops) three times per day with meals
    III. Prescription medication at night
2. Transition Diet
    1. Day 1-2: No fiber, meats, eggs, lactose free dairy
    2. Day 2-3 : Add cooked pureed low FODMAP/fiber veggies (carrots, zucchini)
    3. Day 4 : Back to Whole Foods diet

Elemental Diet
Harris Benedict Equation

First Calculate BMR:

- Women: **BMR** = 655 + (4.35 x weight in pounds) + (4.7 x height in inches)- (4.7 x age in years)
- Men: **BMR** = 66 + (6.23 x weight in pounds) + (12.7 x height in inches) - (6.8 x age in years)

Final Calculation with Harris Benedict Equation: This formula uses the calculated BMR and then applies an activity factor to determine your actual total daily energy expenditure in calories. Obviously, the more active you are the more calories you will use. Harris Benedict Factors are the following:

- Little to no exercise: BMR x 1.2 = Total Daily Calories
- Light exercise/sports 1-3 days/week: BMR x 1.375 = Total Daily Calories
- Moderate (moderate exercise/sports 3-5 days/week): BMR x 1.55 = Total Daily Calories
- Very Active (hard exercise/sports 6-7 days/week): BMR x 1.725=Total Daily Calories
- Extra Active (very hard exercise/sports): BMR x 1.9 = Total Daily Calories

Elemental Diet
Mechanisms of Action

The ED has numerous mechanisms of action imparting the benefits attained. The following factors have been proposed as possible mechanisms of action.

1. *proximal absorption* (early assimilation of pre-digested nutrients)
2. *nutritional effects* (correction of malnutrition)
3. *low residue* (resulting from proximal absorption of near monomers and the absence of fiber)
4. *bowel rest* (another potential mechanism for the ED's ability to induce remission in IBD)
5. *decreased antigenicity* (due to the absence of antigenic whole proteins, small peptides, and particles)
6. *decreased malabsorption* (possibly resulting from the ED's ability to eradicate SIBO, which can be produced by IBD)
7. *alteration of the microbiota* (possibly a central mechanism of action[16])
8. *decreased intestinal permeability*
9. *decreased proinflammatory cytokine response, may be increasing levels of interleukin 10 and Nfkappa B inhibitor*

ED Studies

- Tan X, Mao J, Tang H, Wang Y. Mechanisms underlying clinical efficacy of enteral nutrition in inflammatory bowel disease. *Int J Clin Exp Med*. 2017;10(2):2026-2035.
- Wędrychowicz A, Zając A, Tomasik P. Advances in nutritional therapy in inflammatory bowel diseases. *World J Gastroenterol*. 2016;22(3):1045-1066.
- Triantafillidis JK, Vagianos C, Papalois AE. The role of enteral nutrition in patients with inflammatory bowel disease: current aspects. *Biomed Res Int*. 2015;2015:197167.
- Kajiura T, Takeda T, Sakata S, et al. Change of intestinal microbiota with elemental diet and its impact on therapeutic effects in a murine model of chronic colitis. *Dig Dis Sci*. 2009;54(9):1892-1900.
- Pimentel M, Constantino T, Kong Y, et al. A 14-day elemental diet is highly effective in normalizing the lactulose breath test. *Dig Dis Sci*. 2004;49(1):73-77.
- Hopman WP, de Jong AJ, Rosenbusch G, et al. Elemental diet stimulates gallbladder contraction and secretion of cholecystokinin and pancreatic polypeptide in man. *Dig Dis Sci*. 1987;32(1):45-49.
- Colombel JF, Vaerman JP, Hällgren R, et al. Effect of intrajejunal elemental diet perfusion on jejunal secretion of immunoglobulins, albumin and hyaluronan in man. *Gut*. 1992;33(1):44-47.

Questions