Complex Chronic Diseases
SIBO and Intestinal Barrier
A Clinical Prospect

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University of British Columbia, BSc in Cell Biology, Bastyr University 1991

Complex Chronic Disease Program at BC Women's Hospital and Health Center in Vancouver

- ME/CFS, FM, Chronic Lyme, Long COVID
- Referral
- We do direct clinical care and involved in the facilitation of research
- We also have an ongoing educational resource for patients
- I want to share this background since one of the contributing factors to my patients symptoms is GI health and more specifically SIBO
- I'll be sharing with you my clinical experience and some of the latest research.
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Complex Chronic Disease

(ME/CFS, FM, Chronic Lyme, Long Covid)

Symptoms reported in CCD patients:

- Fatigue
- Post Exertion Malaise (PEM)
- Cognitive Dysfunction (brain fog/memory)
- GI issues: bloating/gas, abdominal distention, and pain, GERD, constipation/diarrhea
- Sleep difficulties (unrefreshing)
- Feels like the flu at times
- Pain; hurts all over, can change from one area to the other

Diagnosis dependent on:

- Exclusion of disease
- Symptoms rather than signs
- Thus far difficult to get reproducible laboratory findings
- Gold standard is "expert opinion

Typical Case

at CCDP

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

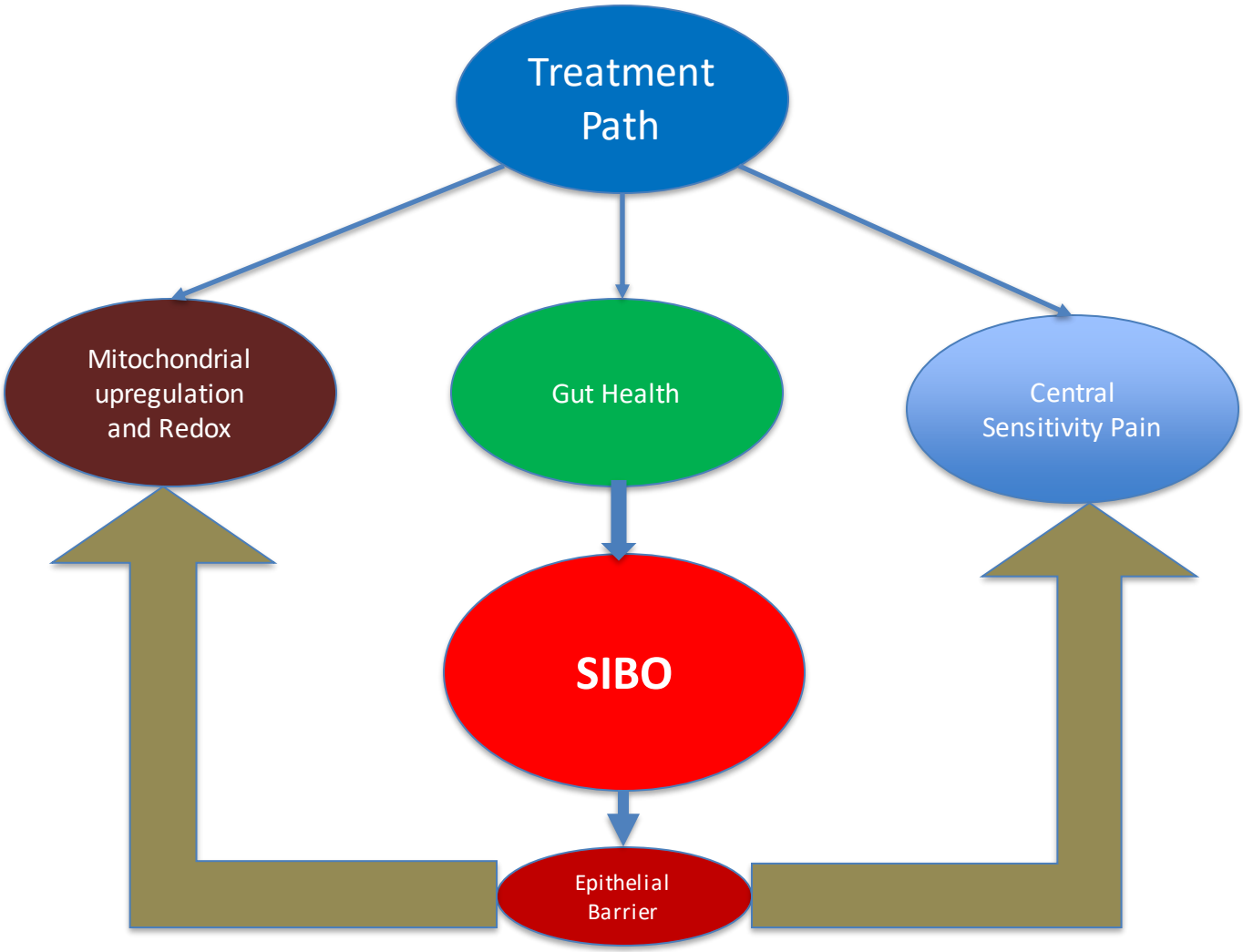
Top 5 symptoms:

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

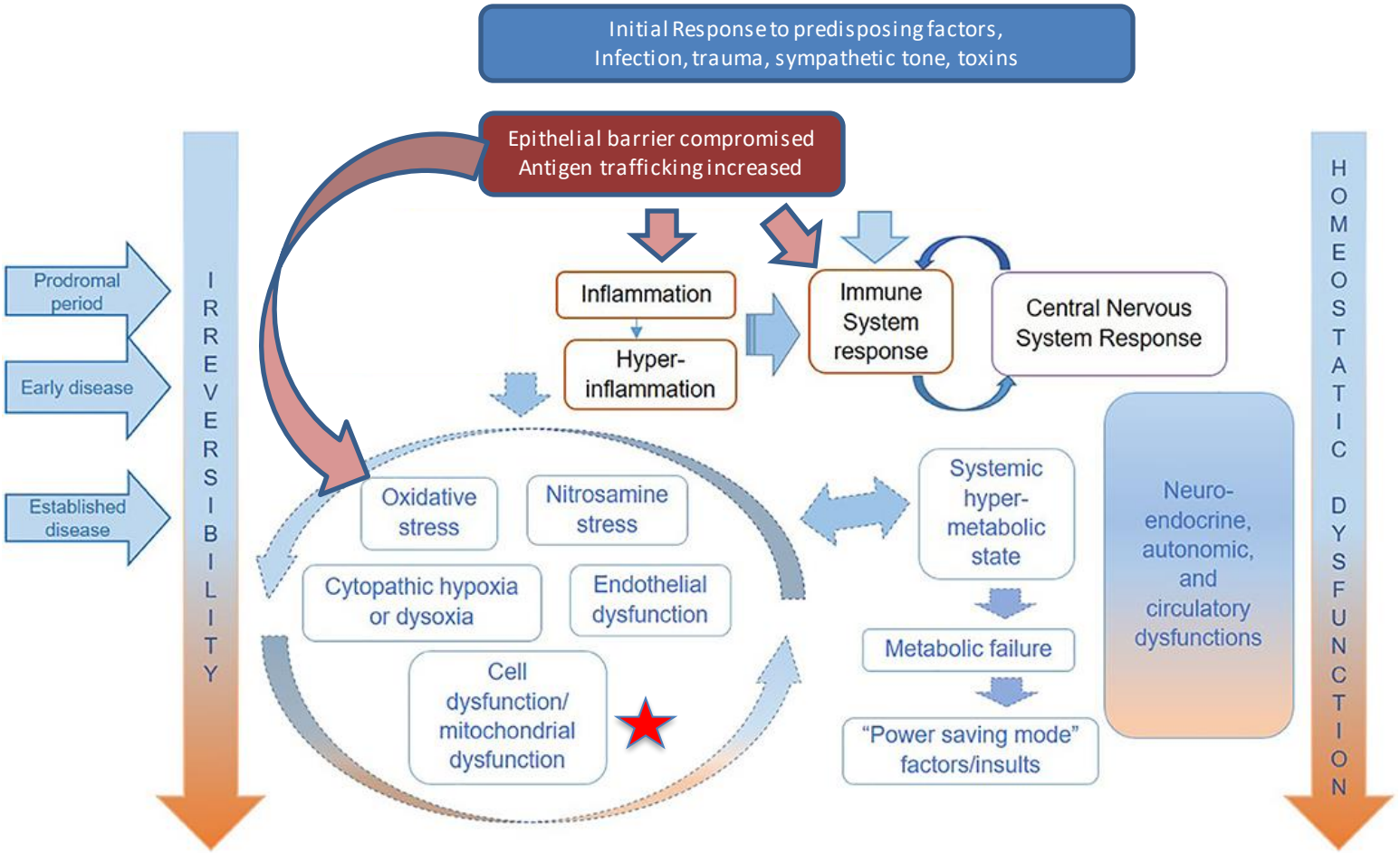
Currently on polypharmacy. Although they help somewhat with sleep, it remains unrefreshing. Pain is debilitating but medication just don't seem to work. Stress makes everything worst. Meditation helps.

Antibiotics during concomitant conditions have helped some symptoms. Improving SIBO helps alleviate symptoms.

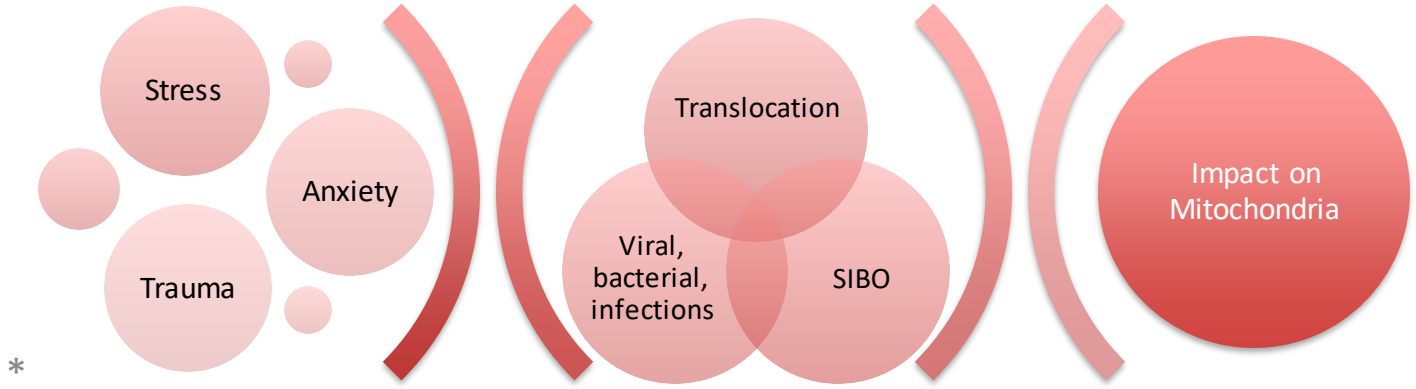
Treatment Paths
and SIBO Connection



PATHOPHYSIOLOGY



MITOCHONDRIAL FACTORS TO DYSFUNCTION



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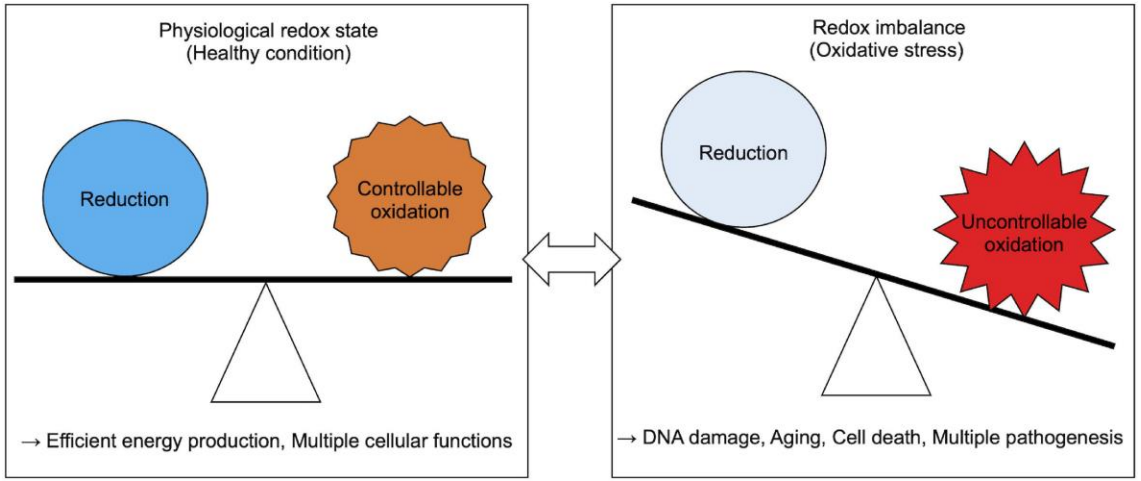
Sympathetic Response

GI Permeability, Infections

SIBO

System compromised dysfunction

Mitochondrial Redox Key Element

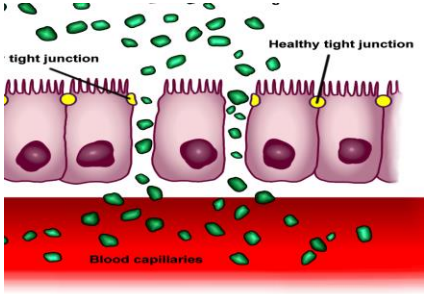


Presentation

i. Background
ii. Clinical Manifestations in Complex Chronic Diseases, a link to the microbiome
iii. Complex Chronic Diseases, paths and possible etiologies
iv. Interesting New Developments
v. Microbiome, An Overview
vi. Extrinsic and Intrinsic factors on Microbiome composition/distribution
vii. SIBO defined
viii. Pathophysiology
ix. Diagnosis and Testing
x. Management of SIBO
    i. Antibiotic Therapy
    ii. Herbal Therapies
    iii. Prokinetics and probiotics
    iv. Elemental diet
xi. Last Words

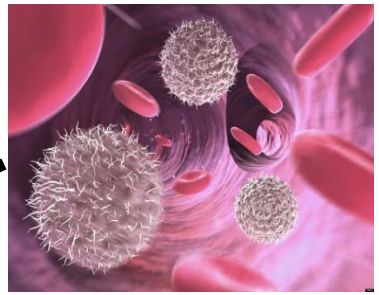
An Overview of Five Key Systems

Contributing to Symptomology

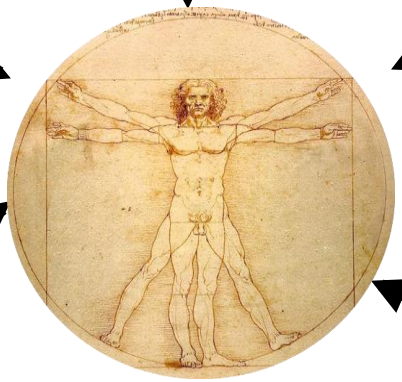


Increased Gut Permeability

Human Genome



Immune Response



Environmental Factors (Stress)

Clinic Outcome

Microbiome

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

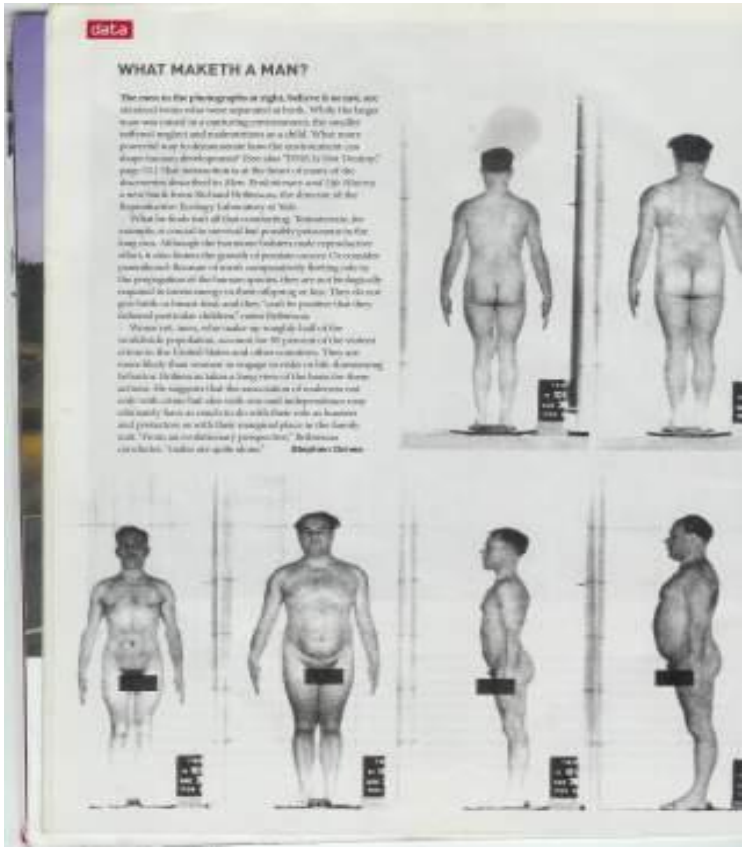
- Bacteria exceed the number of host somatic cells
  - Gut bacterial population ~100 trillion
  - 500-1000 different species of bacteria
  - 60% of fecal biomass is from bacteria
- Microflora exerts important effects on:
  - Structure, physiology, biochemistry, immunology, maturation of vasculature, 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**

Beneficial bacteria, what they do

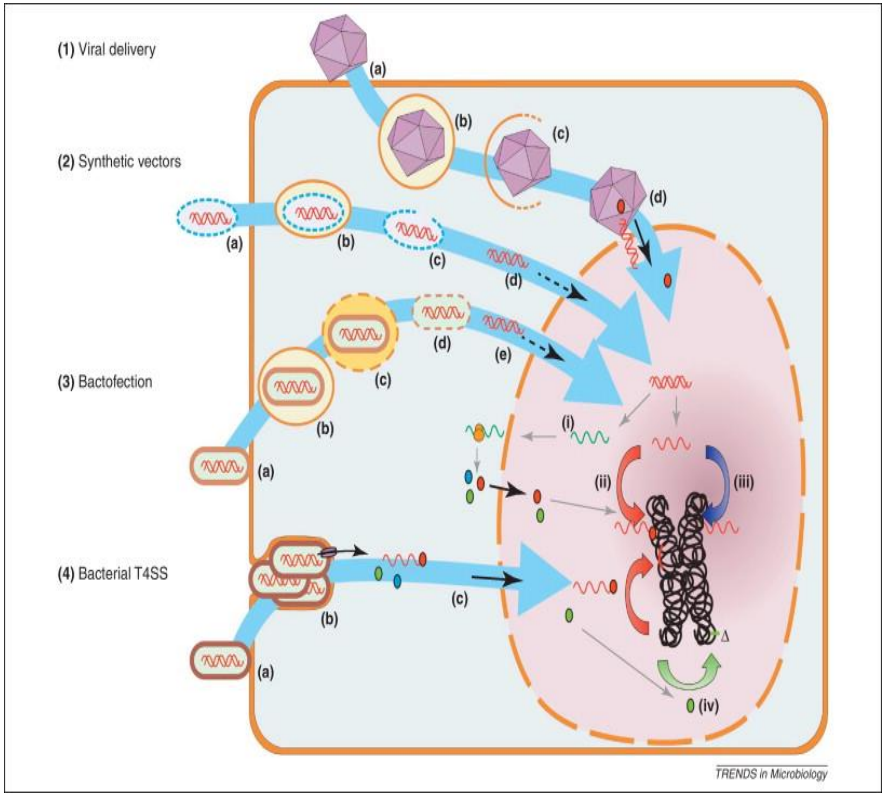
- ✓ Digestion-caloric extraction
- ✓ Detoxification
- ✓ Epigenomic expression e.g., butyrate and histone deacetylase inhibition (HDAC1, HDAC3)-associated with anti-inflammatory immune phenotype including decreasing pro-inflammatory cytokines (IL-6,8, TNF-alpha and NF-kappaB).
- ✓ Immunomodulatory cell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

Environmental Influence Impacts the Genome
Big player is GUT-Microbiome

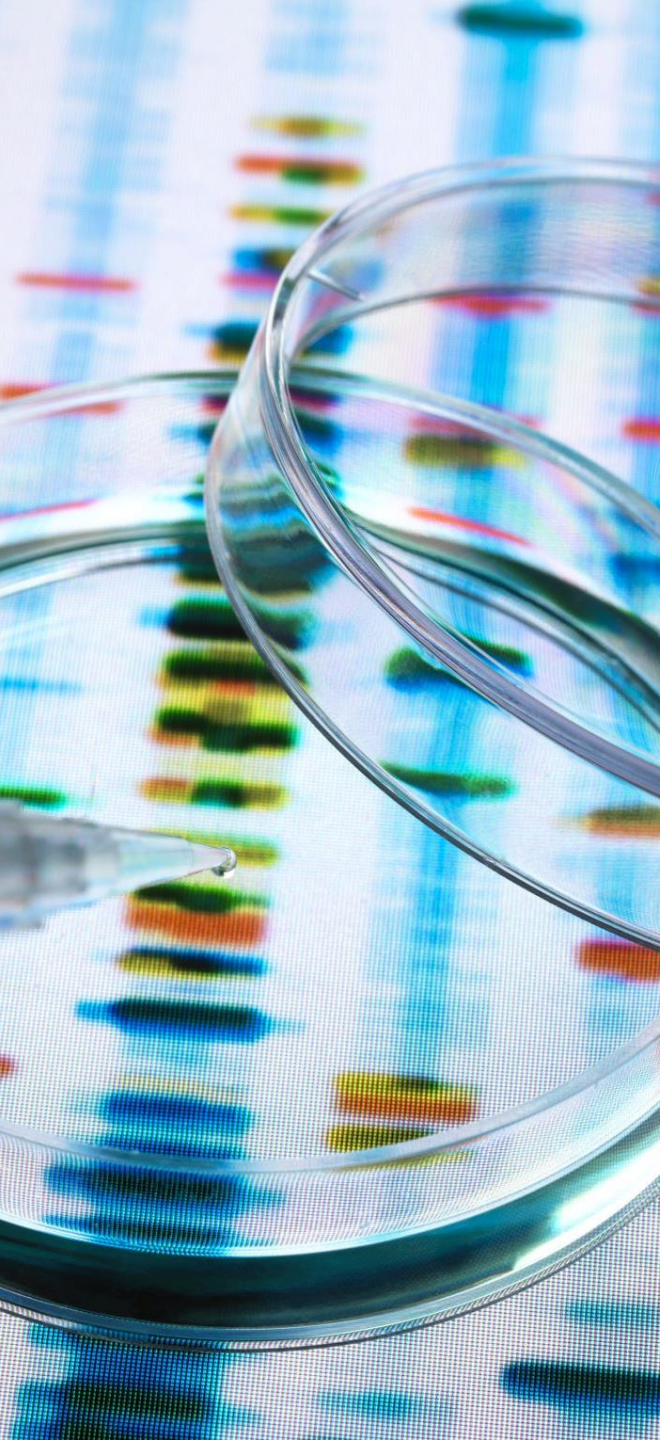
DNA is not a destiny



Interaction



100 trillion bacteria, 3.3 million genes



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)

Bacteria and Pain

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 Citations

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 connection with FM

Complexities

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?

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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.

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 impacted

Altered microbiome composition in individuals with fibromyalgia

Amir Minerbi [1], Emmanuel Gonzalez [2 3], Nicholas J B Brereton [4], Abraham Anjarkouchian [5], Ken Dewar [3 6], Mary-Ann Fitzcharles [1 7], Stéphanie Chevalier [5 8 9], Yoram Shir [1]

Affiliations + expand

PMID: 31219947 DOI: 10.1097/j.pain.0000000000001640

Abstract

Fibromyalgia (FM) is a prevalent syndrome, characterised by chronic widespread pain, fatigue, and impaired sleep, that is challenging to diagnose and difficult to treat. The microbiomes of 77 women with FM and that of 79 control participants were compared using 16S rRNA gene amplification and whole-genome sequencing. When comparing FM patients with unrelated controls using differential abundance analysis, significant differences were revealed in several bacterial taxa. Variance in the composition of the microbiomes was explained by FM-related variables more than by any other innate or environmental variable and correlated with clinical indices of FM. In line with observed alteration in butyrate-metabolising species, targeted serum metabolite analysis verified differences in the serum levels of butyrate and propionate in FM patients. Using machine-learning algorithms, the microbiome composition alone allowed for the classification of patients and controls (receiver operating characteristic area under the curve 87.8%). To the best of our knowledge, this is the first demonstration of gut microbiome alteration in nonvisceral pain. This observation paves the way for further studies, elucidating the pathophysiology of FM, developing diagnostic aids and possibly allowing for new treatment modalities to be explored.

Fecal Transplant

Fecal transplantation and butyrate improve neuropathic pain, modify immune cell profile, and gene expression in the PNS of obese mice

Raiza R. Bonomo[a], Tyler M. Cook[a], Chaitanya K. Gavini[a], Chelsea R. White[a], Jacob R. Jones[b], Elisa Bovo[a], Aleksey V. Zima[a], Isabelle A. Brown[a], Lara R. Dugas[c,d], Eleonora Zakharian[b], Gregory Aubert[a,e], Francis Alonzo III[f], Nigel A. Calcutt[g], and Virginie Mansuy-Aubert[a,1]

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Edited by Lawrence Steinman, Stanford University School of Medicine, Stanford, CA, and approved August 27, 2020 (received for review April 23, 2020)

Obesity affects over 2 billion people worldwide and is accompanied by peripheral neuropathy (PN) and an associated poorer quality of life. Despite high prevalence, the molecular mechanisms underlying the painful manifestations of PN are poorly understood, and therapies are restricted to use of painkillers or other drugs that do not address the underlying disease. Studies have demonstrated that the gut microbiome is linked to metabolic health and its alteration is associated with many diseases, including obesity. Pathologic changes to the gut microbiome have recently been linked to somatosensory pain, but any relationships

nociceptors (13). Many previous studies have focused on hyperglycemia as the initiating insult in the development of prediabetic and diabetic neuropathy, while a growing body of evidence has also implicated dyslipidemia as a distinct pathogenic event (14–17).

The relationship between the gut microbiota and neurological diseases, including pain, has received increasing attention in recent years. The gut microbiome and its lipid metabolites have been linked to peripheral immune regulation (18–25), visceral pain (26–29), chemotherapy-induced pain (30), and fibromyalgia (31). A recent case report described amelioration of painful

icrobiome transplantation (FMT)
atient (32). We have therefore be-
f the gut microbiome in obesity-
r data demonstrate that reshaping
neuropathic mice by transplanting
ed the pathophysiology of the dis-
in-associated behaviors and loss of
ncing and flow cytometry identified
ve system (PNS) calcium signaling

een accompanied by a rise in the
europathy. Because there is no
aradigm-shifting research on pain
abolic syndrome, and type 2 dia-

Fecal Microbiota Transplantation for Fibromyalgia: A Case Report and Review of the Literature

T. Thurm[1], J. N. Ablin[2], D. Buskila[3,4], N. Maharshak[1*]

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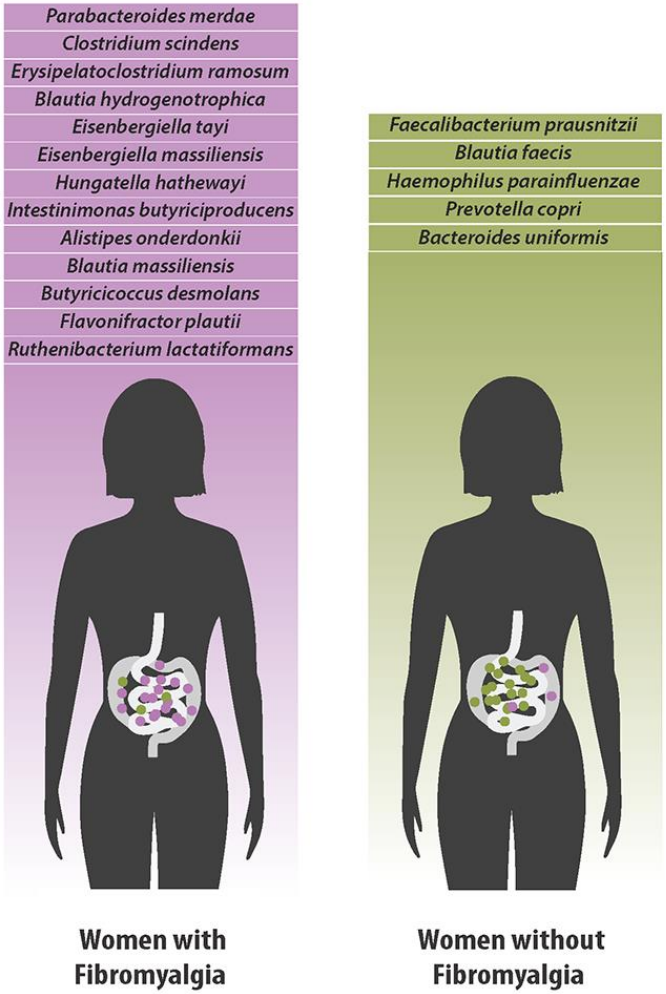
DOI: 10.4236/ojgas.2017.74015 **PDF** **HTML** **XML** **2,087** Downloads **10,870** Views Citations

Abstract

A 58-year-old patient diagnosed with fibromyalgia, irritable bowel syndrome (IBS) and chronic fatigue syndrome (CFS), non-responsive to variety of treatments over the years, suffered from significant social and occupational disabilities. The patient was interested in fecal microbiota transplantation (FMT), but given that FMT is not approved for these indications, he used an online protocol for FMT screening and preparation and self-instilled the filtrate using an enema 6 times. FMT resulted in a gradual improvement of symptoms and 9 months after the last treatment, the patient reported full recovery of symptoms, going back to work at full time employment. Improvement of symptoms was associated with major alterations of the enteric microbiota, according to next generation sequencing analysis performed before the first FMT and after the last FMT. Most prominent alterations at the genus level included a decrease in fecal Streptococcus proportion from 26.39% to 0.15% and an increase in Bifidobacterium from 0% to 5.23%. This case is added to several additional case reports that demonstrated the effectivity of FMT in these functional disorders that are lacking an otherwise good medical therapeutic intervention. We conclude that randomized controlled trials are required to ground FMT as a possible therapy for these difficult-to-treat conditions.



Gut bacteria associated with chronic widespread pain (Dr. Amir Minerbi) (McGill University Health Center)

Greater presence or absence of certain species of bacteria

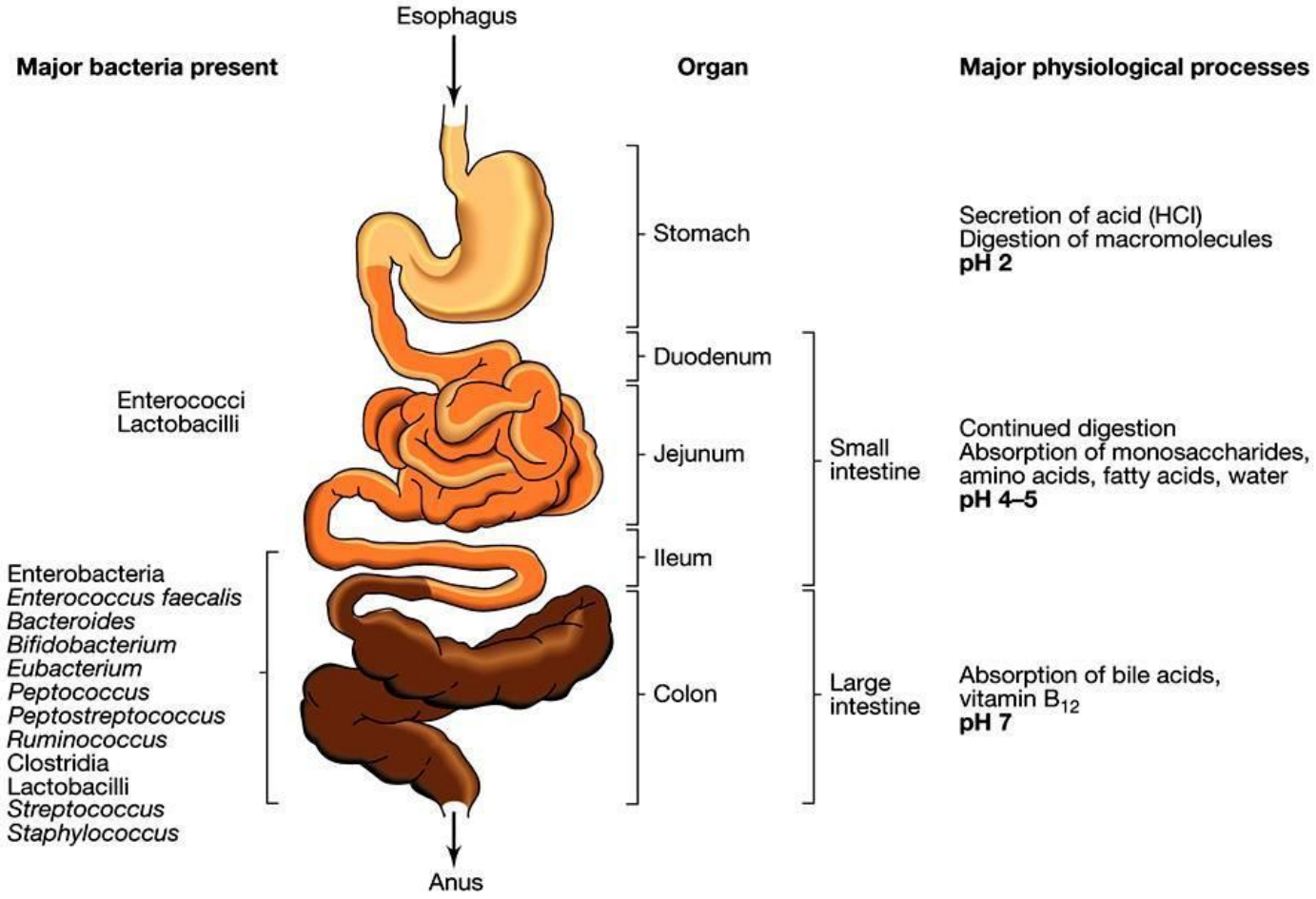
"Used a range of techniques, including Artificial Intelligence, to confirm that the changes seen in the microbiomes of fibromyalgia patients were not caused by factors such as diet, medication, physical activity, age, and so on, which are known to affect the microbiome.

Dr. Amir Minerbi

"We found that fibromyalgia and the symptoms of fibromyalgia – pain, fatigue and cognitive difficulties - contribute more than any of the other factors to the variations we see in the microbiomes of those with the disease. We also saw that the severity of a patient's symptoms was directly correlated with an increased presence or a more pronounced absence of certain bacteria – something which has never been reported before."

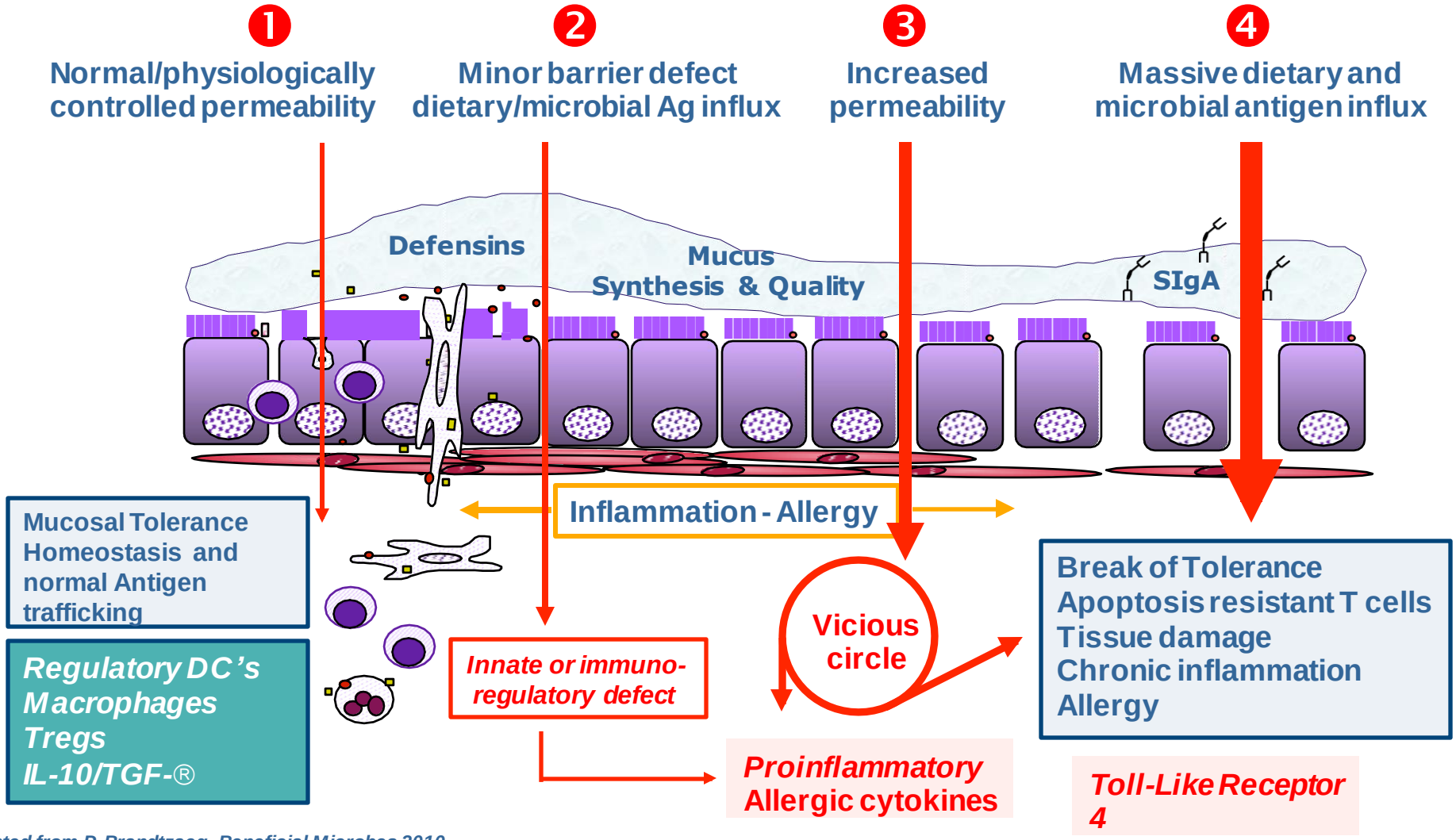
Distribution of Bacteria

Levels of pH



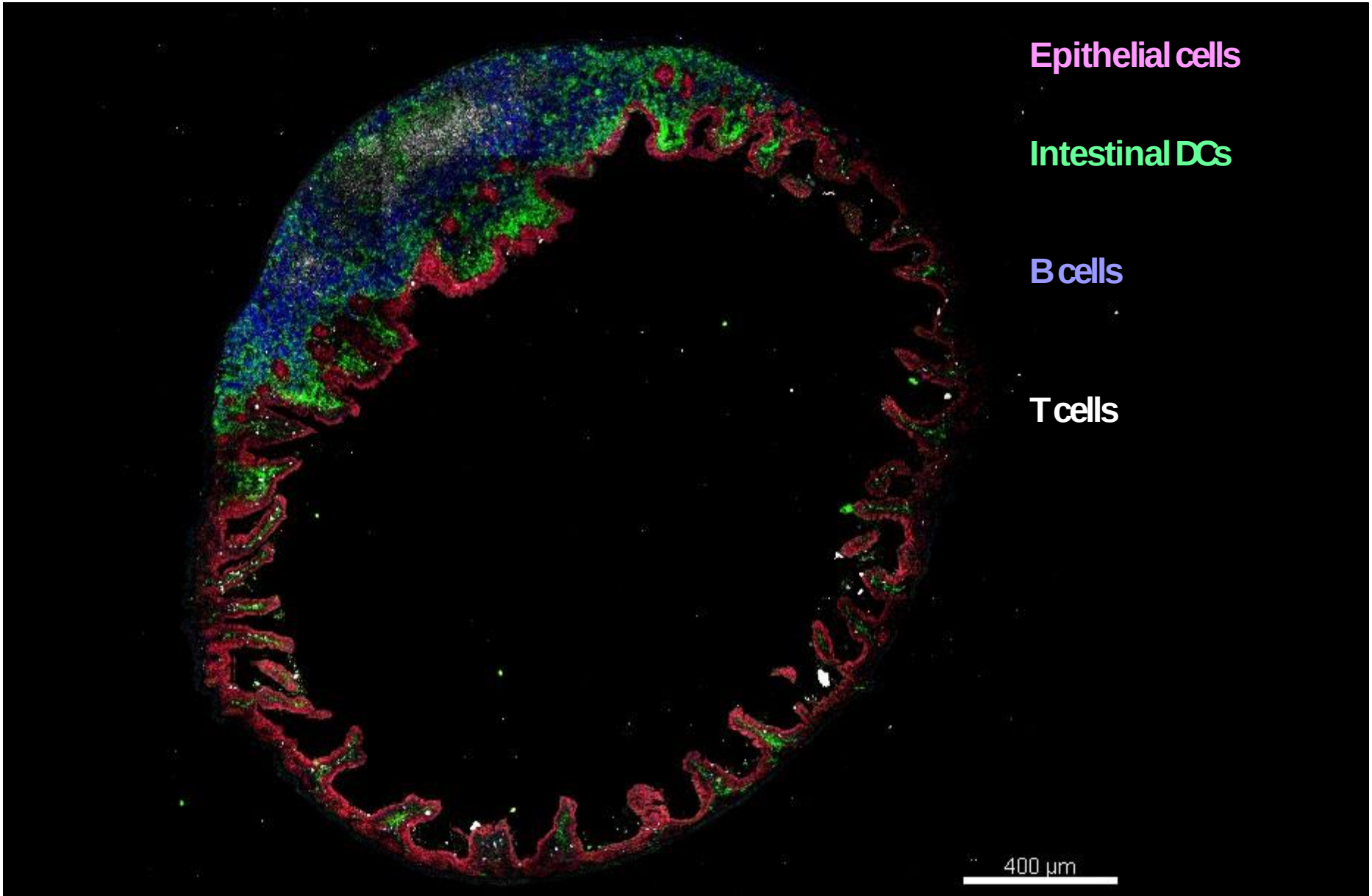
Loss of Mucosal Immune Homeostasis

Chronic Inflammation-Allergy



Adapted from P. Brandtzaeg, Beneficial Microbes 2010

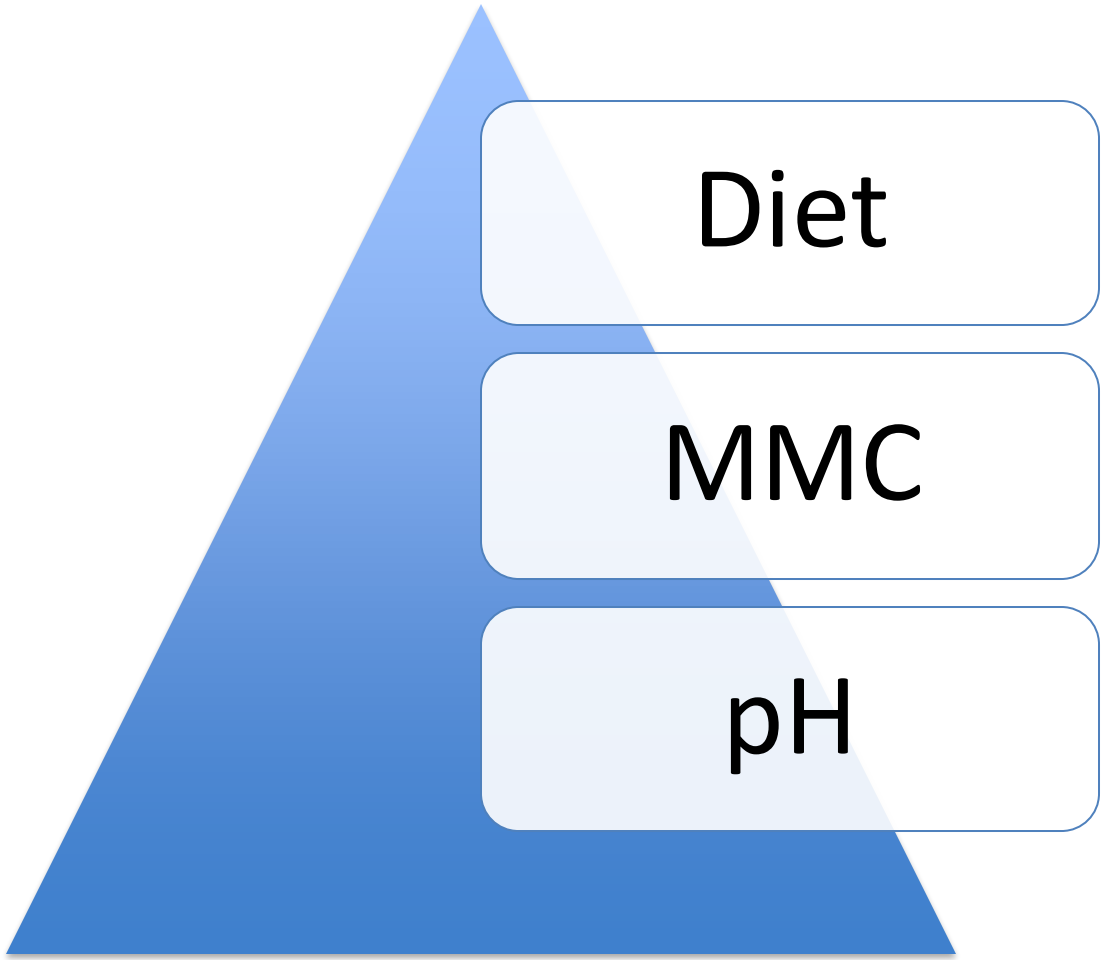
Several Cells Play a Role in Maintaining The Immune Homeostasis



The Problem?
Gut Is Not Vegas

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

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

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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.

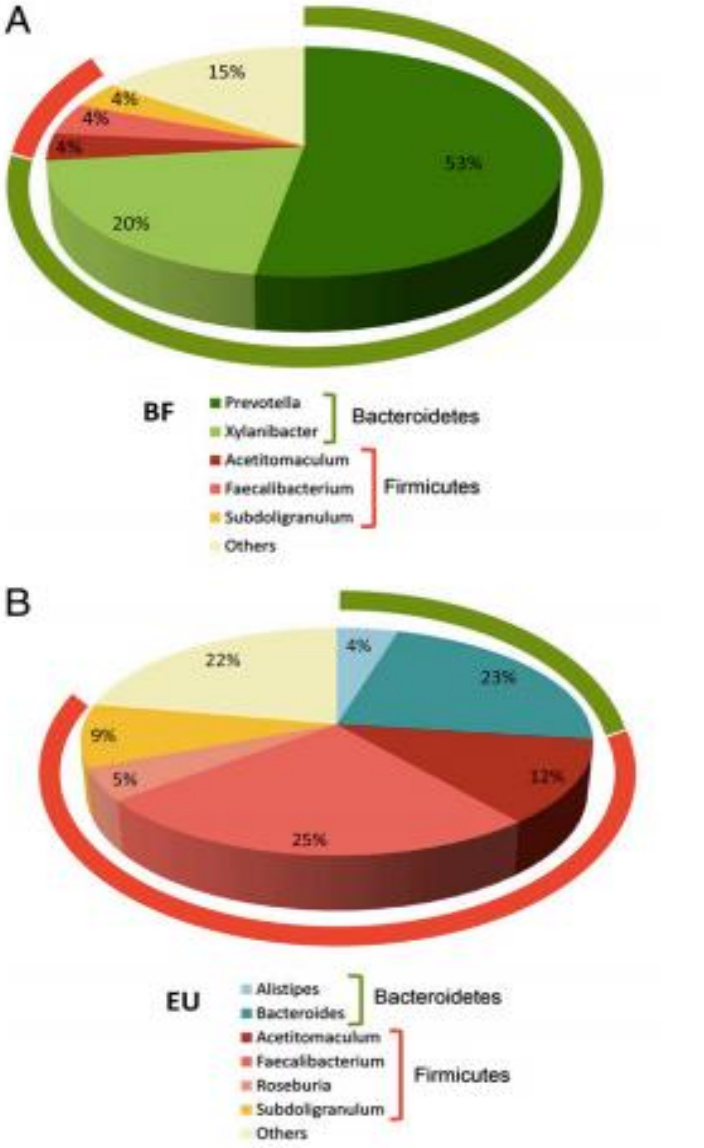
*This Direct Submission article had a prearranged editor.

Freely available online through the PNAS open access option.

Data deposition: Data were submitted to the Sequence Read Archive (SRA) using SA-tools (SAcreator and SAconverter, http://sato.sourceforge.net/index.html). The dataset is available at http://www.ebi.ac.uk/sra/sra-view/ERP000135.

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

This article contains supporting information online at www.pnas.org/cgi/content/supplemental/10.1073/pnas.1005963107/DCSupplemental.



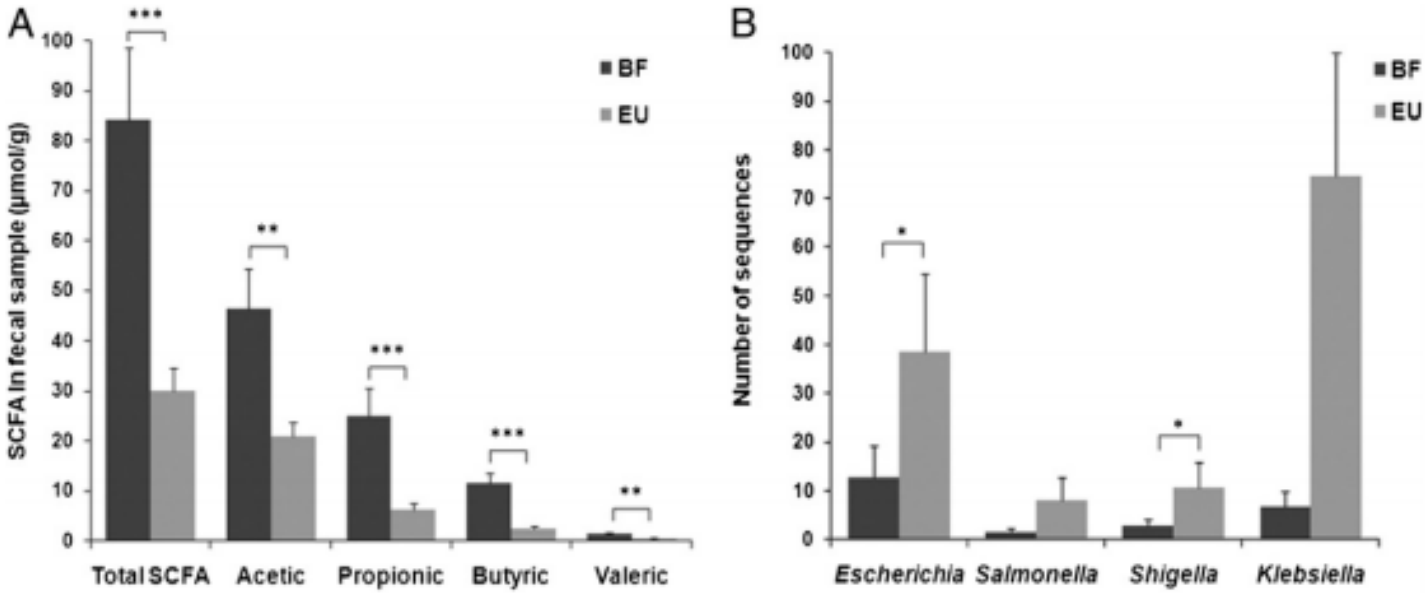
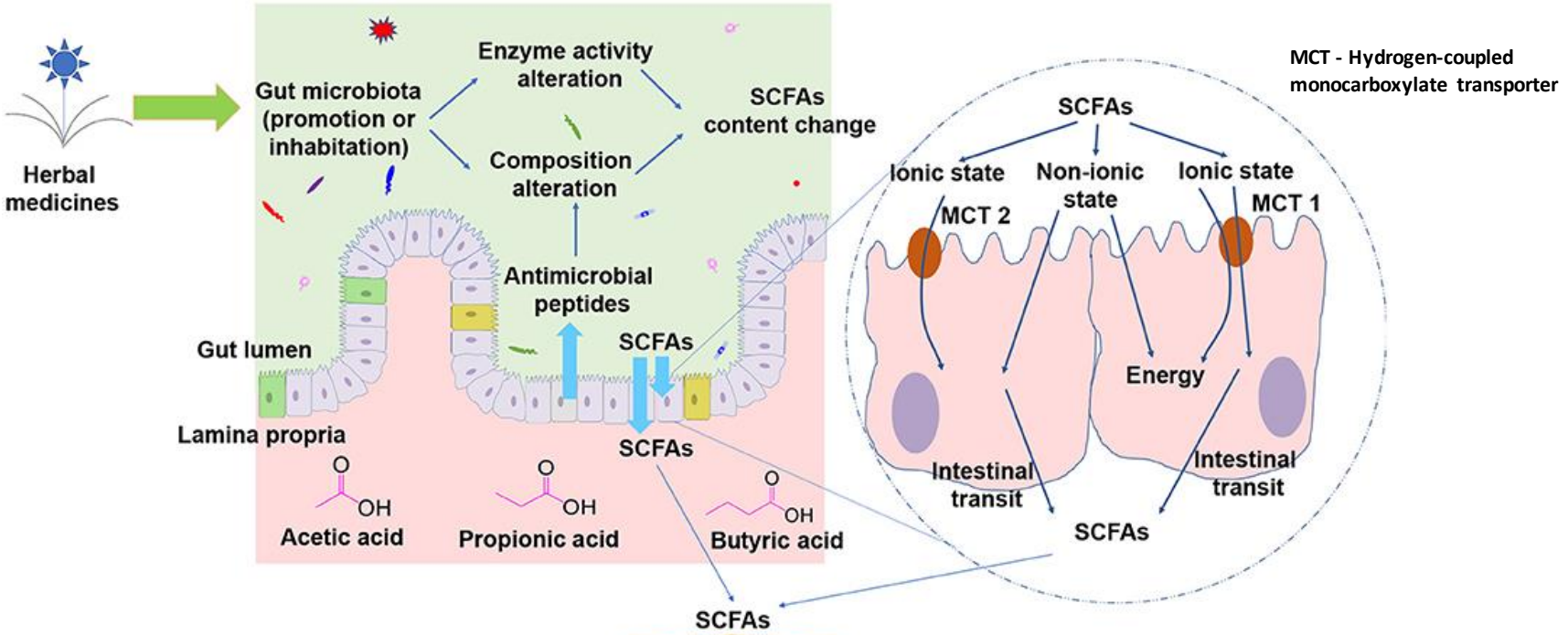


Fig. 3. SCFA-producing bacteria could help to prevent establishment of some potentially pathogenic intestinal bacteria. (*A*) Quantification of SCFAs in fecal samples from BF and EU populations by SPME-GC-MS. (*B*) Number of sequences relative to principal *Enterobacteriaceae* genera, in BF and EU children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

Burkina Faso and European children

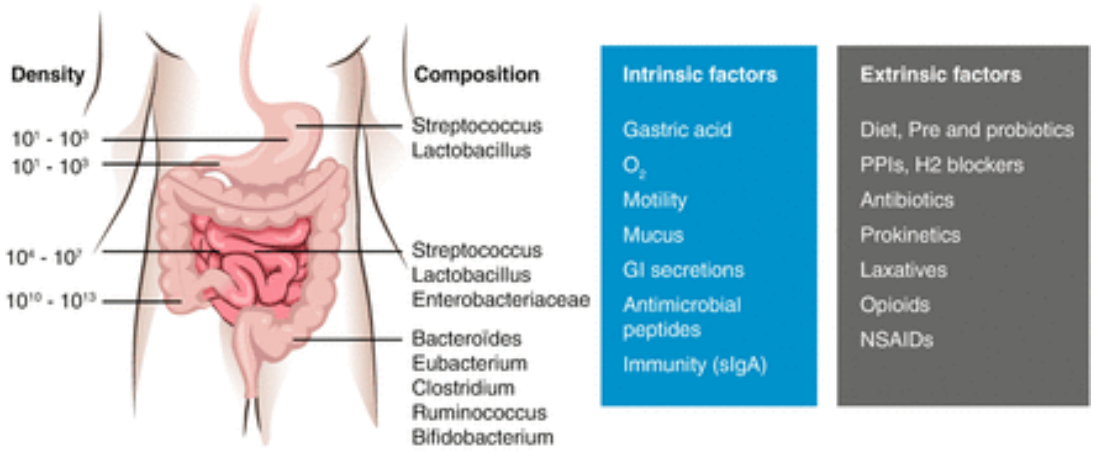
Short Chain Fatty Acids

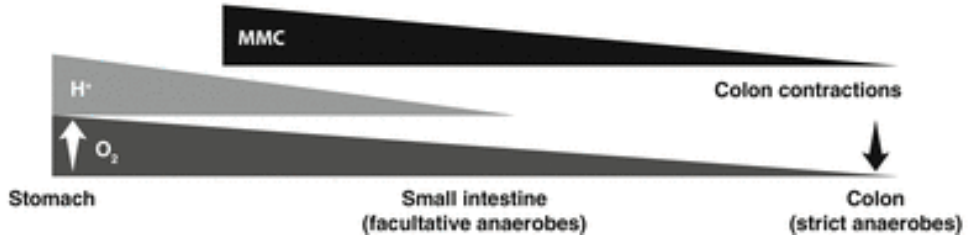


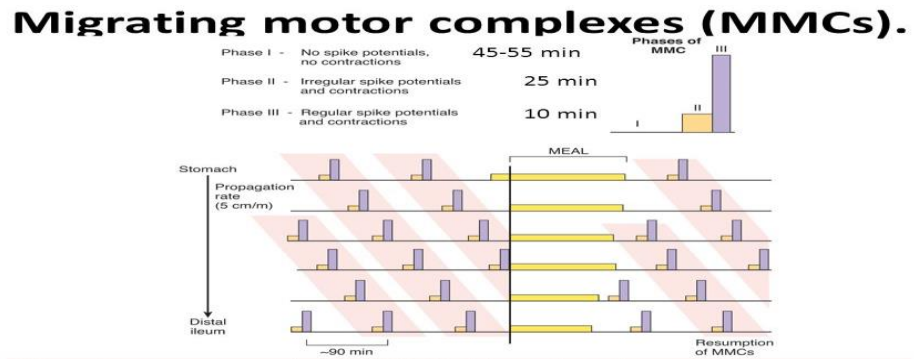
Maintenance of health	Targets and mediators	Treatment of disease
Energy source	Target organs	Diabetes
gut integrity	Liver, brain, muscle, gut, blood vessel, etc.	ulcerative colitis
appetite	Target cells	radiation proctitis
glucose and lipid metabolism	Adipocytes, macrophages, neutrophils, Treg cells, etc.	Crohn's disease
gut hormone production	Target molecules	colorectal cancer
immune regulation	FFAR2, FFAR3, HDAC1, HDAC3, OLFR78, etc.	Parkinson's disease
blood pressure	Triggered mediators	asthma
.....	MCP-1, NO, IL-6, IL-8, TNF-α, IFN-γ, etc.	.....

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

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







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

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

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

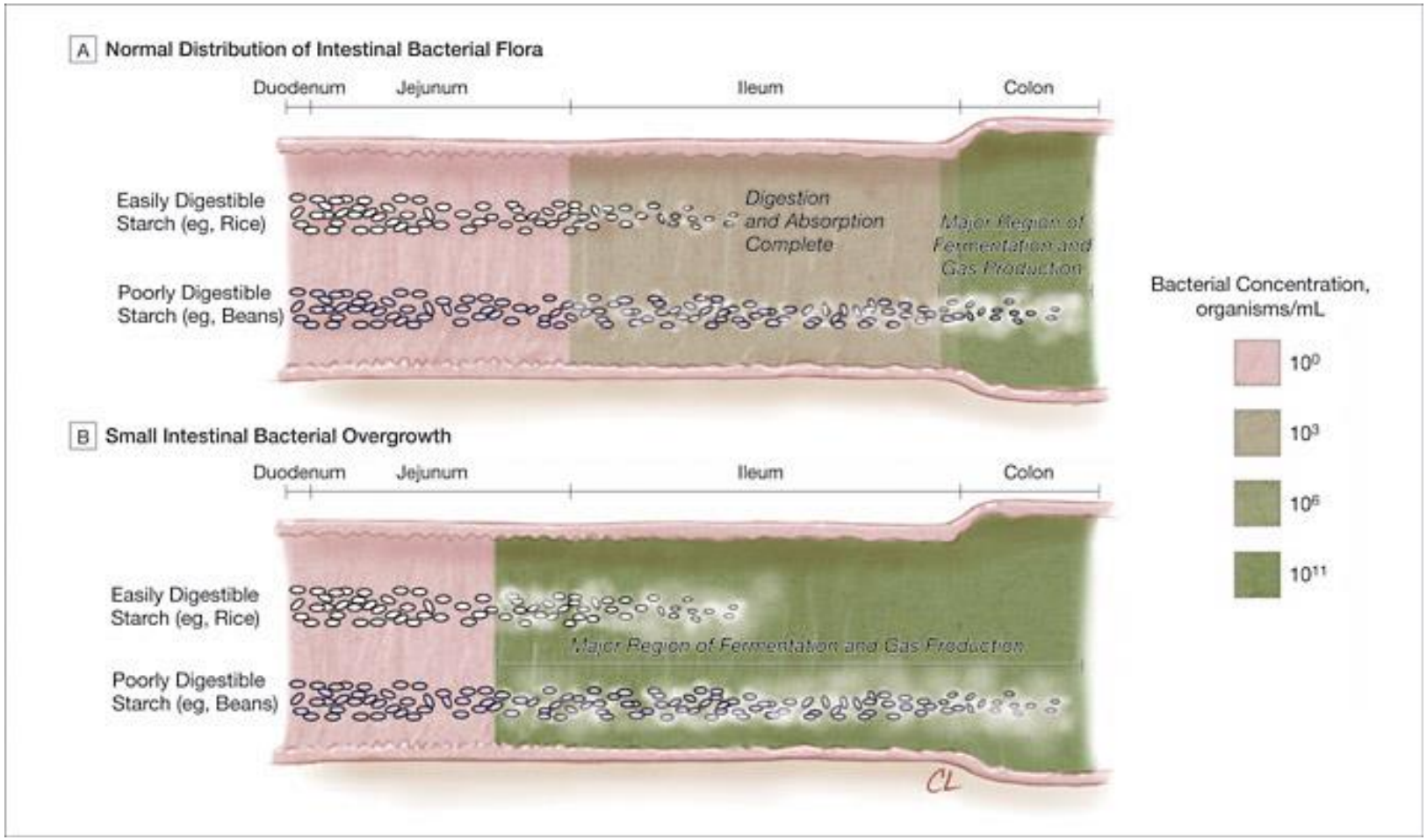
Small Intestinal Bacterial overgrowth

SIBO

SIBO
Small Intestinal Bacterial Overgrowth

SIBO: Review Clinical Presentation

SIBO defined



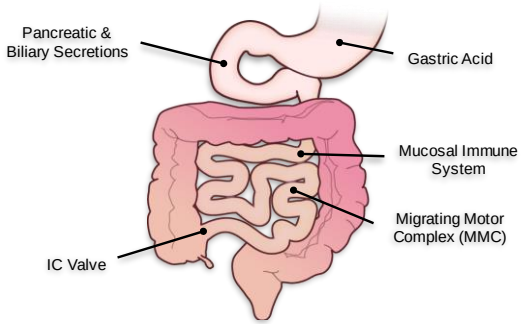
Background
What keeps things in check

HCL

Bile, Enzymes

MMC

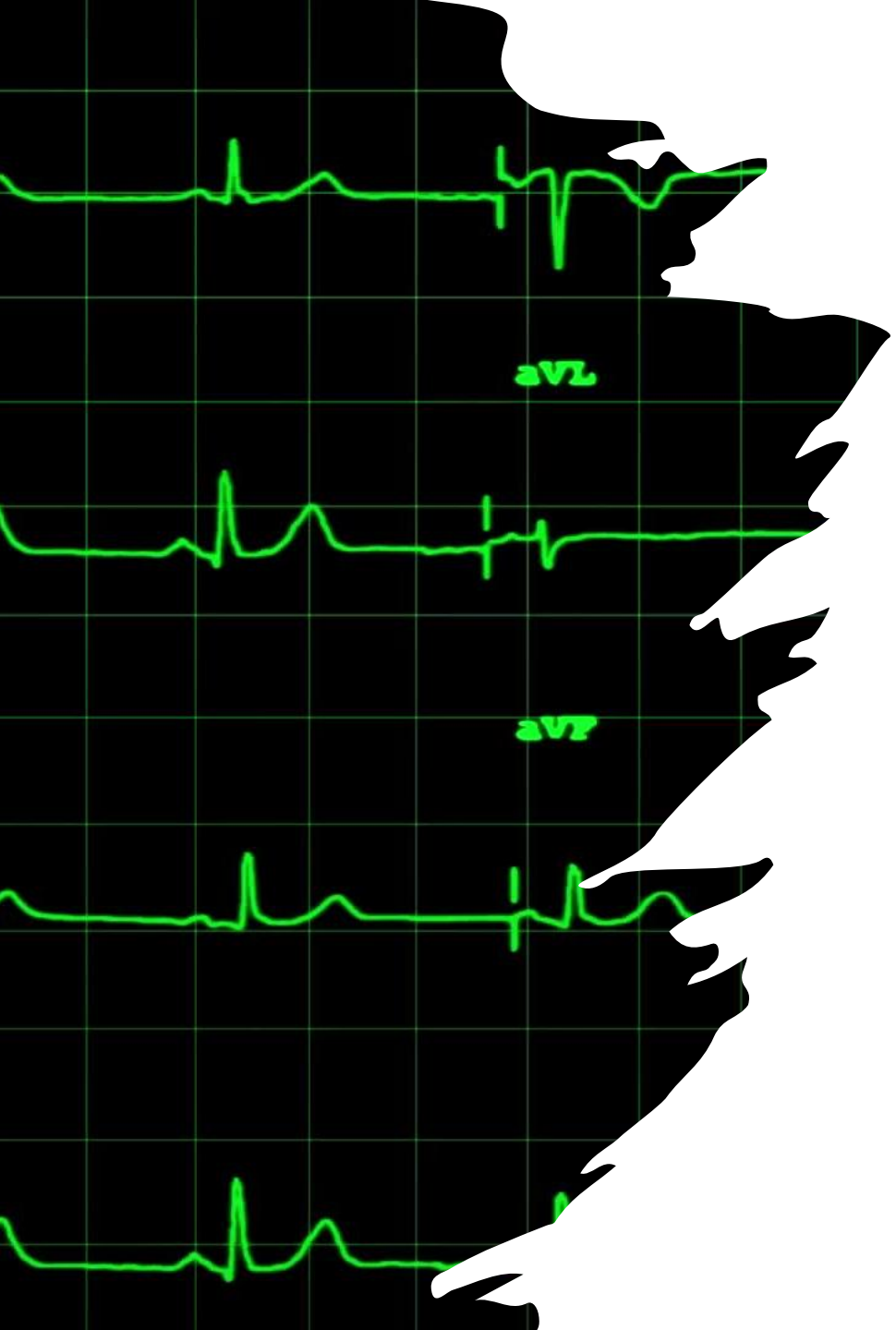
Ileocecal Valve



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

Summary: Causes of SIBO



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

Herbal Antibiotic Protocol

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

PPI and Prokinetics

JGH Open. 2018 Apr 2;2(2):47-53. doi: 10.1002/jgh3.12045. eCollection 2018 Apr.

Risk of small intestinal bacterial overgrowth in patients receiving proton pump inhibitors *versus* proton pump inhibitors plus prokinetics.

Revaiah PC[1], Kochhar R[2], Rana SV[2], Berry N[2], Ashat M[2], Dhaka N[2], Rami Reddy Y[2], Sinha SK[2].

Author information

Abstract

BACKGROUND AND AIM: Intestinal dysmotility is considered a risk factor for small intestinal bacterial overgrowth (SIBO). Prokinetics improve intestinal motility and are often prescribed with proton pump inhibitors (PPIs) in patients with gastroesophageal reflux disease (GERD) and/or functional dyspepsia. The present study aimed to evaluate the prevalence of SIBO and the orocecal transit time (OCTT) in patients taking PPI compared with those taking PPI plus prokinetics.

METHODS: The study is a single-center, cross-sectional study. Enrolled patients (with age > 12 years) were divided into two groups: patients taking PPIs for more than 3 months (Group A) and those taking PPIs with prokinetics for more than 3 months (Group B) for various indications. Lactulose breath test (LBT) for OCTT and glucose breath test (GBT) for SIBO were conducted for all patients.

RESULTS: Of the 147 enrolled patients, SIBO was documented in 13.2% patients in Group A *versus* 1.8% in Group B, $P = 0.018$. Median OCTT in Group A was 130 (105-160) min compared with 120 (92.5-147.5) min in Group B ($P = 0.010$). Median OCTT among SIBO-positive patients was 160 (140-172.5) min compared with SIBO-negative patients, where it was 120 (103.75-150) min ($P = 0.002$). The duration and type of PPI used were not associated with the occurrence of SIBO in our study.

CONCLUSION: The use of prokinetics in patients on PPI may reduce the risk of SIBO by enhancing intestinal motility and may reduce SIBO risk associated with long-term PPI use.

KEYWORDS: orocecal transit time; prokinetics; proton pump inhibitor; small intestinal bacterial overgrowth

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

Altern Med Rev. 2002 Oct;7(5):410-7.

The treatment of small intestinal bacterial overgrowth with enteric-coated peppermint oil: a case report.

Logan AC[1], Beaulne TM.

Author information

Abstract

Recent investigations have shown that bacterial overgrowth of the small intestine is associated with a number of functional somatic disorders, including irritable bowel syndrome (IBS), fibromyalgia, and chronic fatigue syndrome. A number of controlled studies have shown that enteric-coated peppermint oil (ECPO) is of benefit in the treatment of IBS. However, despite evidence of strong antimicrobial activity, ECPO has not been specifically investigated for an effect on small intestinal bacterial overgrowth (SIBO). A case report of a patient with SIBO who showed marked subjective improvement in IBS-like symptoms and significant reductions in hydrogen production after treatment with ECPO is presented. While further investigation is necessary, the results in this case suggest one of the mechanisms by which ECPO improves IBS symptoms is antimicrobial activity in the small intestine.

Comment in

Treatment with enteric-coated peppermint oil reduced small-intestinal bacterial overgrowth in a patient with irritable bowel syndrome. [Altern Med Rev. 2003]

ECPO

- May have other mechanisms of action not fully elucidated:

1. Relaxes intestinal smooth muscle
2. Antibacterial properties
3. Migrating motor complex activity

J Clin Gastroenterol. 2014 Jul;48(6):505-12. doi: 10.1097/MCG.0b013e3182a88357.

Peppermint oil for the treatment of irritable bowel syndrome: a systematic review and meta-analysis.

Khanna R[1], MacDonald JK, Levesque BG.

Author information

Abstract

GOALS: The aim of this study was to assess the efficacy and safety of enteric-coated peppermint oil capsules compared with placebo for the treatment of active irritable bowel syndrome (IBS).

BACKGROUND: IBS is a common disorder that is often encountered in clinical practice. Medical interventions are limited and the focus is on symptom control.

STUDY: Randomized placebo-controlled trials with a minimum treatment duration of 2 weeks were considered for inclusion. Cross-over studies that provided outcome data before the first cross-over were included. A literature search upto February 2013 identified all applicable randomized-controlled trials. Study quality was evaluated using the Cochrane risk of bias tool. Outcomes included global improvement of IBS symptoms, improvement in abdominal pain, and adverse events. Outcomes were analyzed using an intention-to-treat approach.

RESULTS: Nine studies that evaluated 726 patients were identified. The risk of bias was low for most of the factors assessed. Peppermint oil was found to be significantly superior to placebo for global improvement of IBS symptoms (5 studies, 392 patients, relative risk 2.23; 95% confidence interval, 1.78-2.81) and improvement in abdominal pain (5 studies, 357 patients, relative risk 2.14; 95% confidence interval, 1.64-2.79). Although peppermint oil patients were significantly more likely to experience an adverse event, such events were mild and transient in nature. The most commonly reported adverse event was heartburn.

CONCLUSIONS: Peppermint oil is a safe and effective short-term treatment for IBS. Future studies should assess the long-term efficacy and safety of peppermint oil and its efficacy relative to other IBS treatments including antidepressants and antispasmodic drugs.

PMID: 24100754 DOI: 10.1097/MCG.0b013e3182a88357

Gut Permeability PEA (palmitoylethanolamide)

Palmitoylethanolamide as a modulator of microglia and neuroinflammation.

(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.

PEA is an endogenous modulator

Produced on demand by macrophages, microglia, and dorsal root ganglions

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

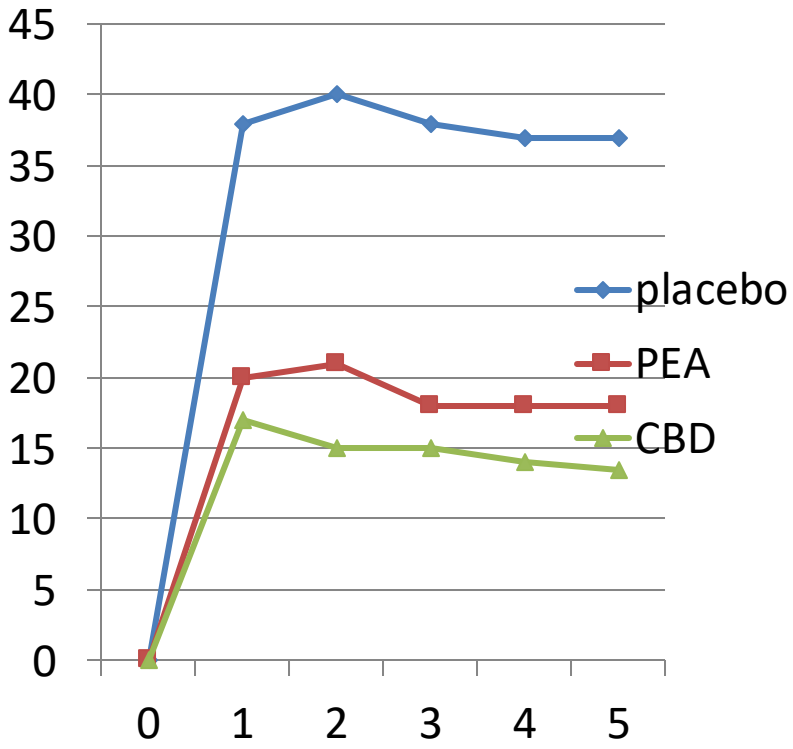


Figure 1 – The concentration ratios of urinary lactulose and mannitol over time in healthy participants treated with aspirin and either placebo, CBD or PEA, measured by LC MS. Results are expressed as mean ratios +/- SEM. Time points between groups were compared using two-way ANOVA using Dunnett's multiple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

Elemental Diet
(Overview)

Background

Elemental Diet

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, Iwabuchi 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: 0.16-0.98)] 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.

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)

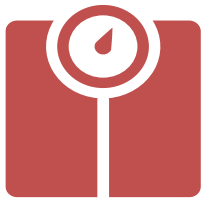
Good Follow up after ED:

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

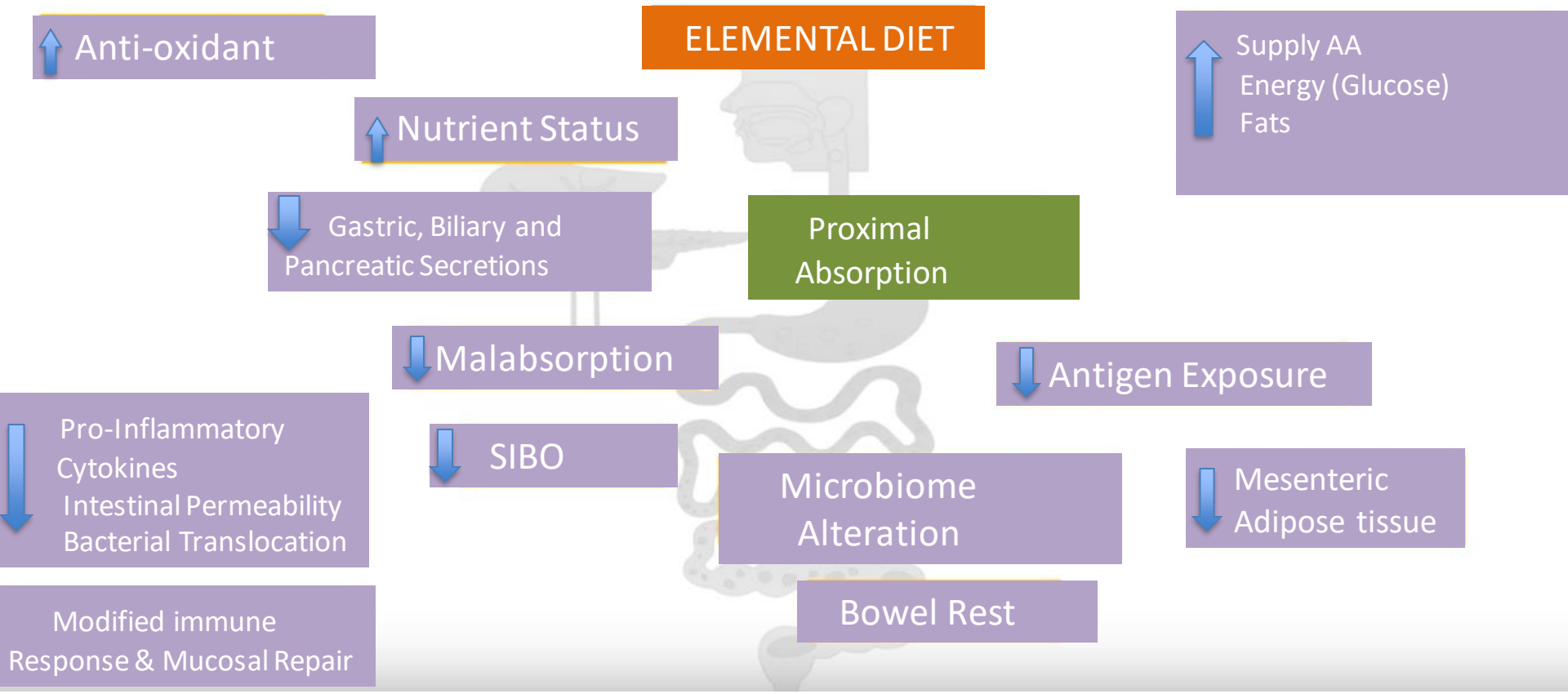
2. Transition Diet
    1. Day 1-2: No fiber, meats, eggs, lactose free dairy
    2. Day 2-3 : Add cooked pureed low FODMAP/fiber veggies (carrots, zucchini)
    3. Day 4 : Back to Whole Foods diet

Elemental Diet
Harris Benedict Equation



First Calculate BMR:

ELEMENTAL DIET MECHANISMS



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*

A hypothesized mechanism of action for the ED in cases of IBS with SIBO is that rapid absorption and assimilation of elemental nutrients leave minimal substrate for more distal bacteria. Pimentel and colleagues, however, propose 3 additional mechanisms of action to consider for SIBO:

1. An ED-induced increase in cholecystokinin leads to gallbladder emptying; this stimulates phase III of the migrating motor complex (MMC), resulting in a reduction of small intestinal bacteria.[18]
2. The ED stimulates jejunal secretion of immunoglobulins (eg, IgG, IgA) that helps clear overgrown organisms.[19]
3. The ED directly reduces coliforms, enterococci, and *Bacteroides*.[20] One study noted that the ED even eliminates duodenal (proximal) organisms,[21] confounding the proximal absorption theory and raising the question of direct bacterial-inhibiting effects.

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