THE ARTHRITIS RECOVERY PLAN:
WHY HEALING THE GUT MATTERS AND HOW TO DO IT

Susan S. Blum, MD, MPH
Founder and Director
Blum Center for Health
Rye Brook, NY
www.blumcenterforhealth.com
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• Founder and Director of Blum Center for Health, a Functional Medicine and Lifestyle Education Center
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• Co-Founder of Organic Pharmer, a healthy grab-and-go Juice and Food company.
  • No conflict for this presentation
Affiliations

- Assistant Clinical Professor, Department of Preventive Medicine, Icahn School of Medicine at Mount Sinai, NYC
- Integrative Medicine, Greenwich Hospital, CT.
- Medical Advisory Board, Dr Oz Show
- Senior Teaching Faculty, Center for Mind Body Medicine, Washington
- Advisory Board, Institute for Integrative Nutrition
- Council of Directors, GLiMMER/True Health Coalition
- Certified Practitioner, Institute for Functional Medicine
- Board Certified in Preventive Medicine
Functional Medicine

• Work at the roots to find and treat the cause of disease
• Rule of tacks:
  • Find and remove triggers of illness
• Treatment with:
  • Food: Nutritional Medicine, Functional Nutrition, Nutrigenomics, Personalized Nutrition
  • Lifestyle Medicine and health behavior modification: sleep, stress, exercise, detox the environment
  • Supplements and nutra-ceuticals for targeted treatment
    • Genetics and deficiencies
    • Personalized medicine
My Story

- Hashimoto’s
- Worked through all the functional medicine testing and treatment programs to figure out how to cure it
- Within 1 year all my antibodies were gone
- Put together a program I’ve been using for over a decade with my patients
- Share with you today
4 Step Functional Medicine Program to Treat Autoimmune Disease:

1. Using Food As Medicine
2. Balancing Stress Hormones
3. Healing the Gut
4. Supporting the Liver
Arthritis Recovery Plan

• If studies show that Rheumatoid Arthritis (RA) and Spondylarthritis (SpA) are associated with altered gut flora and dysbiosis…
• And that dysbiosis and leaky gut can cause systemic inflammation…
• And that different probiotic species are active in immune modulation and improvement in arthritis…
• Can we create an approach to treating arthritis that is focused on Gut Repair using a Functional Medicine approach?
• Yes…and today I will show you the studies and then teach you how to do this
What we will discuss today...

• Rheumatoid Arthritis (RA) and Spondylarthritis (SpA)
  • Clinical features, conventional treatment, microbiome studies

• Gut-Arthritis Connection:
  • Gut Basics
  • Dysbiosis
  • Leaky gut syndrome

• Restoring gut health to treat arthritis:
  • Arthritis recovery plan
  • Case study
ARTHRITIS
RA, Spondylarthritis
Rheumatoid arthritis

• **Autoimmune disease**: chronic joint inflammation with severe pain and swelling, joint damage and disability
• 1% of the world population.
• 3:1 women to men

**Clinical**
- Polyarthritis: 5 or more joints
- Symptoms of malaise, fatigue, muscle soreness
- Monocyclic, polycyclic and progressive
- Ultimately joint destruction and loss of function
- Labs: diagnostic: Rheumatoid Factor, anti-CCP: anti-citrullinated peptide (CCP ab)
- Can be antibody + before disease, and sero-negative with clinical symptoms

• Kerstin Klein; Steffen Gay. *Epigenetics in Rheumatoid Arthritis.* Curr Opin Rheumatol. 2015;27(1):76-82
RA: Epigenetics

• Cause unknown
• Genetic component only explains 20% of RA
• Interaction between environmental trigger in genetically susceptible person
  • Smoking is #1
  • Infectious trigger?
  • Change in DNA methylation and histone acetylation
• Studies now underway to understand genetic methylation patterns

• Kerstin Klein; Steffen Gay. Epigenetics in Rheumatoid Arthritis. Curr Opin Rheumatol. 2015;27(1):76-82
RA: Immunology

- Synovial inflammation and hyperplasia
- Autoantibody production
- Cartilage and bone destruction
- Migration and accumulation of immune effector cells
  - Macrophages and osteoclasts,
  - Myeloid and plasmacytoid dendritic cells (DCs)
  - B cells and T cells.
- Increased Th17 subsets: inflammatory
  - Produce interleukin (IL)-17 and IL-21 (cytokines)
- Functional impairment in regulatory T cells (Tregs).

Sue Ellen Verbrugge; Rik J Scheper; Willem F Lems; Tanja D de Gruijl; Gerrit Jansen. Proteasome Inhibitors as Experimental Therapeutics of Autoimmune Diseases. Arthritis Res Ther. 2015;17(17)
Gut microbiome in RA

• Rheumatoid arthritis (RA) extensively studied with respect to dysbiosis and deranged microbiome architecture
• Missing link to explain pathophysiology of RA
• Manipulating the microbes by traditional dietary modifications, probiotics, and antibiotics and by currently employed disease-modifying agents seems to modulate the disease process and its progression

• SANDHYA, Debashish DANDA, Disha SHARMA and Vinod SCARIA. Does the buck stop with the bugs?: an overview of microbial dysbiosis in rheumatoid arthritis. International Journal of Rheumatic Diseases 2015
Does the buck stop with the bugs?: an overview of microbial dysbiosis in rheumatoid arthritis
Proposed mechanism of pathophysiology of RA modulated through microbial dysbiosis
Proposed Mechanism for RA

- Gut microbial dysbiosis:
  - Pro-inflammatory cytokine production
  - Increased intestinal permeability: bacterial cell wall components (BCWC) in the bloodstream.
  - BCWC of intestinal bacteria have been identified in joints
- Studies have shown destruction of joints in model systems challenged with BCWC
- RA patients: immune response against BCWC of the enterobacteria and intestinal Gram-positive bacteria.
  - Induce inflammation at various sites, including joints.

- SANDHYA, Debashish DANDA, Disha SHARMA and Vinod SCARIA. Does the buck stop with the bugs?: an overview of microbial dysbiosis in rheumatoid arthritis. International Journal of Rheumatic Diseases 2015
Microbiome and RA: Zhang Study

- Authors created an RA-associated gut microbiome pattern, to be used diagnostically
- Discovered a specific pattern of gut and oral microbial dysbiosis in RA patients
  - Associated with clinical symptoms
- RA subjects: consistently enriched with *Lactobacillus salivarius* and *bacteriodes*.
- Controls: enriched with *Hemophilus* spp.
- Low *Hemophilus* levels were correlated with serum anti-CCP, RF and CRP.

- Zhang, Xuan. *The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment*. Nature medicine VOLUME 21 | NUMBER 8 | AUGUST 2015
Microbiome and RA: Zhang Study

- DMARD treatment partially restored the gut microbiome
  - Most received MTX and/or glycosides of the traditional Chinese medicinal component *Tripterygium wilfordii* (thunder god vine).
  - Both had + effect, separately and together.
  - Suggest different outcomes for different meds.
- Change in microbiome toward healthy controls was correlated with clinical improvement
- Changes in microbiome predicted better outcomes

Study Conclusion: Zhang

**Conclusion:**

- RA represents a state of chronic inflammation that might be provoked or aggravated by the overgrowth of pathogenic bacteria or a lack of immune-modulating commensal bacteria.

- Authors suggest that *microbiome profiling* will some day be used for:
  - Patient stratification
  - Risk prediction
  - Supplement diagnosis
  - Early detection and prevention of disease

*Zhang, Xuan. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nature medicine VOLUME 21 | NUMBER 8 | AUGUST 2015.*
Preventella

- Specific bacterial genes have been implicated in the pathophysiology of disease
- Studies have suggested that a low load of *Prevotella*, can trigger new-onset RA
  - In a genetically susceptible person
- Individuals neg for genetics would need a significantly higher bacterial burden to have the same effect


<table>
<thead>
<tr>
<th>Bacterial species</th>
<th>Site</th>
<th>Arthritis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevotella intermedia</td>
<td>Oral</td>
<td>RA</td>
<td>[12–14]</td>
</tr>
<tr>
<td>Porphyromonas gingivalis</td>
<td>Oral</td>
<td>RA</td>
<td>[12–14]</td>
</tr>
<tr>
<td>Tannerella forsythia</td>
<td>Subgingivally</td>
<td>RA</td>
<td>[16*]</td>
</tr>
<tr>
<td>Streptococcus Anginosus</td>
<td>Supragingivally</td>
<td>RA</td>
<td>[16*]</td>
</tr>
<tr>
<td>Haemophilus</td>
<td>Lung</td>
<td>RA</td>
<td>[19*]</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>Lung</td>
<td>RA</td>
<td>[19*]</td>
</tr>
<tr>
<td>Prevotella copri</td>
<td>Fecal</td>
<td>RA</td>
<td>[20*]</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>Fecal</td>
<td>AS and uveitis</td>
<td>[23]</td>
</tr>
<tr>
<td>Flagellin</td>
<td>Serum</td>
<td>AS</td>
<td>[39*]</td>
</tr>
</tbody>
</table>

AS, ankylosing spondylitis; RA, rheumatoid arthritis.
Oral cavity

• Periodontal disease associated with RA
• Prevotella, bacteroideal and most commonly P. gingivalis have been observed in RA patients.
• Many gut and oral bacteria have enzymes called peptidyl-arginine-deiminase (PAD) and gingipains can cause citrullination of host-proteins, leading to an autoantibody response

Possible mechanism for disease activity

- In the oral cavity *Porphyromonas gingivalis*:
  - Peptidyl-arginine-deiminase (PAD) and gingipains cause protein citrullination.
  - Cigarette smoke could augment the process of citrullination.
- A genetically susceptible host mounts an immune response to citrullinated antigens
  - Causes T cell and B cell activation and subsequent production of anti-citrullinated peptide antibodies.

Oral cavity

• Oral bacteria DNA found in synovial fluid of RA and PsA patients compared to controls
• “While it is possible that oral bacterial DNA could translocate to joints, triggering synovial inflammation, it is more likely that inflamed joints could entrap these bacterial DNA, leading to augmentation of inflammation”.

• Moen K, Brun JG, Valen M et al. (2006) Synovial inflammation in active rheumatoid arthritis and psoriatic arthritis facilitates trapping of a variety of oral bacterial DNAs. Clin Exp Rheumatol 24, 656–63
Spondyloarthritis (SpA)

- Spondyloarthritis (SpA): family of immune-mediated inflammatory disorders
  - Includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), juvenile spondyloarthritis (JSpA), and acute anterior uveitis.
- Clinical overlap between SpA and inflammatory bowel disease
- Microbial dysbiosis of gut commensals implicated
- Epithelial permeability: cause or effect of gut inflammation
  - Implicated in loss of mucosal tolerance
- **Microbiome research has the potential to revolutionize research, diagnosis, and treatment of SpA**

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*Tejpal Gill; Mark Asquith; James T. Rosenbaum; Robert A. Colbert. The Intestinal Microbiome in Spndyloarthritis. Curr Opin Rheumatol. 2015;27(4)*
Psoriatic Arthritis (PsA)

- Systemic inflammatory condition that effects 20-30% of people with psoriasis.
  - Skin manifestations precede arthritis in >80%, decade or more
  - Potential involvement of diverse tissues, including peripheral and axial joints, enthesitis, dactylitis and skin and nail disease. Uveitis, iritis.
- Peak age 30-50, men and women equal, except axial disease favors men 3:1
- Clinical diagnosis. No markers. ESR and CRP often normal, RF/ACPA can be +

Psoriatic Arthritis (PsA)

- **Gastrointestinal involvement** with a resemblance to IBD is common
- Many patients with psoriasis or psoriatic arthritis have subclinical gut inflammation
- Lower commensals: Ruminococcus and Akkermansia in PsA compared to controls.
- Organisms play a role in producing SCFA’s that support gut homeostasis

# Bacteria Linked to Arthritis

<table>
<thead>
<tr>
<th>Bacteria/Bacterial product</th>
<th>Disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacteriodetes spp.</em></td>
<td>Arthritis</td>
<td>[10]</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>AS and Crohn's Disease (CD) CD</td>
<td>[11]</td>
</tr>
<tr>
<td>Flagellin</td>
<td>CD</td>
<td>[12]</td>
</tr>
<tr>
<td><em>Bacteriodes thetaiotamicron</em></td>
<td>Colitis</td>
<td>[13]</td>
</tr>
<tr>
<td><em>Bacteriodes vulgatus</em></td>
<td>Colitis</td>
<td>[14]</td>
</tr>
<tr>
<td><em>Mycobacteria</em></td>
<td>Psoriasis</td>
<td>[15]</td>
</tr>
<tr>
<td><em>Prevotella copri</em></td>
<td>Rheumatoid Arthritis (RA) RA</td>
<td>[16]</td>
</tr>
<tr>
<td><em>Prevotella spp.</em></td>
<td>RA</td>
<td>[17]</td>
</tr>
<tr>
<td><em>Chlamydia tracomatis</em></td>
<td>Reactive Arthritis (ReA) ReA</td>
<td>[18,19]</td>
</tr>
<tr>
<td><em>Salmonella Omp</em></td>
<td>ReA</td>
<td>[20]</td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td>ReA</td>
<td>[21,22]</td>
</tr>
<tr>
<td><em>Yersinia</em></td>
<td>ReA</td>
<td>[21,22]</td>
</tr>
</tbody>
</table>

*Tejpal Gill; Mark Asquith; James T. Rosenbaum; Robert A. Colbert. The Intestinal Microbiome in Spndyloarthritis. Curr Opin Rheumatol. 2015;27(4)*
Ankylosing spondylitis

- Multiple studies looking at microbiome:
  - There was an increase in the abundance of Lachnospiraceae, Ruminococcaceae, and Prevotellaceae in AS patients
  - Decreased abundance of Streptococcus and Actinomyces
  - Increase in sulphate reducing Bacteroides
  - Recolonization of the gut of germ-free animals with Bacteroides led to gut inflammation, whereas Lactobacillus and fusiform bacteria did not result in inflammatory lesions
- High Klebsiella IgA

Juvenile spondylarthritis

- Decreased abundance of *Clostridium leptum* similarly to AS patients.
- Another member of the *Clostridiales* family known as *Fecalibacterium prausnitzii* was also decreased in patients with juvenile SpA compared with healthy controls.
  - No difference in serum IgA/IgG levels to these org
- Study of the microbiota of juvenile SpA patients
  - Patients could be stratified into two distinct clusters, one dominated by *Bacteroides* genus members, the other by *Akkermansia muciniphila*.

References:
Conventional treatment: RA

- **DMARDS**: disease-modifying anti-rheumatic drugs
  - Methotrexate (MTX)
- Glucocorticoids (steroids)
- Biologics: antibodies to the pro-inflammatory cytokines: TNF alpha and IL-6
  - Rituximab, Abatacept
- Monotherapy with MTX: limited long term efficacy
- Combinations of conventional DMARDs, particularly methotrexate, with biological agents:
  - Clinical remission and prevention of radiological deterioration in approximately 50% of RA patients, but the remaining 50% of patients still experienced insufficient disease activity reduction or sustained active disease.

Psoriatic arthritis treatment

• Target for treatment: ‘minimal disease activity’
• NSAIDS and Corticosteroids
• DMARD:
  • Sulfasalazine: arthritis: 59% improvement with drug: 47% controls. No protection for joint damage
  • Leflunamide: 58.9% LEF/29.7% controls. Increases LFT’s.
• Cyclosporin and Tacrolimus: inhibit T cells. Renal toxicity and HTN. Close monitoring
• MTX: methotrexate: cornerstone of therapy although not good outcome studies for PsA.
  • Only + results with >15 mg/week.
  • Works best when combined with DMARD.
• Biologics: TNF inhibitors.
  • DoQuyen Huynh; Arthur Kavanaugh. Psoriatic Arthritis: Current Therapy and Future Approaches.
    Rheumatology. 2015;54(1):20-28
Conventional treatment: PI’s

- Newest in autoimmune treatment
- **Proteosome inhibitors**: inhibits NFkB, plasma cell apoptosis
- Refractory SLE and hemolytic anemia
- Side effects: peripheral neuropathy, thrombocytopenia, diarrhea and an increased risk of developing infectious complications
- Not for RA or SpA: other therapies are safer and more effective

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*Sue Ellen Verbrugge; Rik J Scheper; Willem F Lems; Tanja D de Gruijl; Gerrit Jansen. Proteasome Inhibitors as Experimental Therapeutics of Autoimmune Diseases. Arthritis Res Ther. 2015;17(17)*
Antibacterial action of RX

- Previously thought anti-inflammatory properties were mechanism for improvement
- Now, believe change in microbiome could be at least partly responsible
  - **Sulphasalazine**: inhibits non-sporing anaerobes, Clostridia and Enterobacteria.
  - **Tetracyclines** previously used in the 1960’s. Minocycline sometimes still used.
    - Tetracyclines inhibit matrix metalloproteinase and nitric oxide synthase, suppress adaptive immune cells and increase IL-10.
  - **Antimalarials**: Plaquenil: similar antimicrobial and anti-inflammatory properties

*Pulukool SANDHYA, Debashish DANDA, Disha SHARMA and Vinod SCARIA. Does the buck stop with the bugs?: an overview of microbial dysbiosis in rheumatoid arthritis. International Journal of Rheumatic Diseases 2015*
Conventional treatment and microbiome

- RA patients: high levels of Clostridium perfringens vs controls in 4 studies.
  - SSZ: decreased counts in 2 studies
  - NSAIDS: 1 study: increased counts
- Vegan diet changed flora and improved symptoms

- Pulukool SANDHYA, Debashish DANDA, Disha SHARMA and Vinod SCARIA. Does the buck stop with the bugs?: an overview of microbial dysbiosis in rheumatoid arthritis. International Journal of Rheumatic Diseases 2015
Need for better therapy

• Even when DMARDS and Biologics drive initial remission, long term is of concern
• Studies addressing dose reduction and withdrawal are currently under way.
• High remission in RA, better rates in PsA.
• Despite advances in therapy, there remain patients who fail to respond to classic DMARDs and TNF’s or who have loss of efficacy over time.
PROBIOTICS AND ARTHRITIS

Study review
Probiotics and RA: review

• 4 randomized double-blind placebo controlled trials of probiotics in RA
• Lactobacillus rhamnosus GG x 12 months.
  • Improved well being, but no change disease activity scores or inflammatory markers
• L. rhamnosus GR-1 and Lactobacillus reuteri RC-14: same results
• Bacillus coagulans x 1 month:
  • improvement in pain scores, patient global assessment scores and reduction in inflammatory markers
• L. Casei: 8 weeks.
  • Improved disease activity and reduced inflammatory markers and cytokine levels

Mechanism of action: probiotics

- Microorganisms effect systemic immunity by:
  - MAMP: microorganism-associated molecular patterns
    - interact with the pattern recognition receptors (PRPs) such as toll-like receptors (TLRs) on the dendritic cells (DCs)
    - gut lumen or gut-associated lymphoid tissue (GALT)
  - Strain-specific: stimulation or down-regulation of immune system function

- Effect on T regs
  - Increase potency: work better
  - Decrease apoptosis: increase numbers
  - Suppress bacterial adenosine triphosphate which prevents conversion to Th17 cells: decrease shift into inflammation pathway

- Mechanism: probiotics induce enzymes that make all-trans retinoic acid (ATRA).
  - ATRA induces naïve T cells to T regs.

RA and Lactobacillus Casei

• Study: The effect of *L. casei* in RA patients
• Significantly lower serum proinflammatory cytokines (TNF-[alpha], IL-6, and IL-12) in the probiotic-treated group
• Higher level regulatory cytokine (IL-10)
• Clinically, the disease activity score was significantly decreased with *L. casei* 01 supplementation
• Suppresses the type II collagen-reactive effector function of Th1-type cellular and humoral immune responses in arthritic inflammation

Effects of *Lactobacillus casei* supplementation on disease activity and inflammatory cytokines in rheumatoid arthritis patients: a randomized double-blind clinical trial

Effect of probiotic supplementation on cytokine percent changes in the two intervention groups; statistically significant diff
RA and Lactobacillus Casei

- *L. casei* 01 supplementation decreased serum hs-CRP levels, tender and swollen joint counts and GH scores
  - improved cytokines
  - improved DAS28
- Decreased number tender and swollen joints
- *L. casei* strains have been shown in several *in vitro* and animal studies to efficiently regulate immune system function
- Dose: 100 million CFU x 8 weeks. 1 capsule/day.
- Is more better? Not necessarily. Studies haven’t been done on dosing

RA and other Lactobacillus

• Lactobacillus reuteri and Lactobacillus casei, but not Lactobacillus plantarum, prime monocyte-derived DCs to drive the development of Treg cells

• Smits, Hermelijn H, et al. Selective probiotic bacteria induce IL-10-producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin. Journal of Allergy and Clinical Immunology (2005), 115(6), 1260-1267
RA and L rhamnosis/L reuteri

• 30 subjects, 15 in probiotic group. RA, 3 month double blind, placebo controlled.

• **L rhamnosis, L reuteri**

• Inclusion criteria: 4 swollen, 4 tender joints, stable meds, no steroids for at least 1 month prior to and during study

• ACR20 responses, serum cytokine levels, safety parameters and HAQ (health assessment questionnaire)

• **Improvement only in the HAQ. No change in other markers**

Sacharomyces Boulardi

- S. boulardii: influences several important facets of intestinal host-pathogen interaction
  - Neutralization of bacterial virulence factors
  - Enhancement of the mucosal immune response
  - Interference with bacterial adhesion
  - Strengthening of enterocyte tight junctions
  - Altering immune cell redistribution
  - Modulating inflammatory signaling pathways of the host

Innate immune recognition of the microbiota promotes host-microbial symbiosis

Hiutung Chu & Sarkis K Mazmanian

Pattern-recognition receptors (PRRs) are traditionally known to sense microbial molecules during infection to initiate inflammatory responses. However, ligands for PRRs are not exclusive to pathogens and are abundantly produced by the resident microbiota during normal colonization. Mechanism(s) that underlie this paradox have remained unclear. Recent studies reveal that gut bacterial ligands from the microbiota signal through PRRs to promote development of host tissue and the immune system, and protection from disease. Evidence from both invertebrate and vertebrate models reveals that innate immune receptors are required to promote long-term colonization by the microbiota. This emerging perspective challenges current models in immunology and suggests that PRRs may have evolved, in part, to mediate the bidirectional cross-talk between microbial symbionts and their hosts.

Conventional wisdom suggests that the immune system evolved to combat infection and that distinguishing between self and non-self molecules is a basic feature of innate immunity. As Charles Janeway proposed, the recognition of microbial molecules, termed pathogen-associated molecular patterns (PAMPs), is critical to selectively drive immune responses to infectious agents. Studies identifying and characterizing host receptors that recognize specific PAMPs, called ‘pattern-recognition receptors’ (PRRs), have provided evidence that PRR signaling is critical in coordinating immune responses and protection against pathogens. This view, however, has been challenged by the emerging appreciation that animals have a diverse and complex symbiotic microbiota, which normally does not trigger inflammation. PAMPs, by definition, are universally conserved, generally invariant and essential in all microorganisms. Thus, PAMPs are not limited to pathogens but are also common to the microbiota. As such, it has been proposed that these molecules be renamed microbe-associated molecular patterns (MAMPs). Furthermore, host PRRs are constantly exposed to MAMPs in the absence of infection. These MAMPs are largely provided by the commensal microbiota that colonize our skin and mucosal surfaces. Despite the continuous presence of many MAMPs, commensal microbes usually do not elicit inflammatory responses but rather may contribute to various aspects of host development and enhanced immune function. To our surprise, this beneficial influence is mediated, in part, by commensal stimulation of host PRRs.

How these molecules and receptors can achieve such divergent and opposing responses between pathogens and symbionts is a frontier in our understating of innate immunity. It has been proposed that the context in which the host receives MAMP stimulation dictates the quality of the immune response. During infection, MAMP signals are received in the presence of other cues, such as cell damage caused by infection and/or cytokytic detection of MAMPs, resulting in inflammation. During symbiosis, not only does the microbiota generally not harm host cells and MAMPs are sensed in the absence of exposed self antigens, but it appears that some MAMPs directly promote beneficial outcomes. In this Review, we will focus on how recognition of MAMPs by PRRs under steady-state conditions promotes immune development, protection from disease and maintains homeostasis. The concepts presented here collectively demonstrate that PRRs may have evolved in both the invertebrate and vertebrate immune systems to communicate with commensals and maintain beneficial, symbiotic coexistence with the microbiota.

Pattern recognition in Drosophila promotes homeostasis

Extensive work using D. melanogaster as a model system has highlighted the important functions of PRRs in host defense as well as in homeostasis. Toll, one of the first PRRs to be identified, was initially discovered in D. melanogaster. However, the realization that D. melanogaster Toll does not directly recognize MAMPs, unlike the PRRs in the mammalian Toll-like receptor (TLR) signaling pathway, left the open question of how bacterial ligands are recognized. D. melanogaster has 13 peptidoglycan recognition protein (PGRP) genes that are alternatively spliced into 19 different proteins, which is one of the largest repertoires of PGRPs currently known for any organism. The role of D. melanogaster PGRPs as PRRs was discovered during the identification of upstream receptors that activate the signal-transduction pathways, Toll and IMD (immune deficiency), which are highly similar to the mammalian interleukin 1 (IL-1)–TLR and tumor necrosis factor (TNF) pathways. However, Toll does not function as a PRR because it does not directly recognize MAMPs.

Probiotic Bifidobacterium Breve increases T regulatory cells and improves signaling in T regs to reduce inflammation. This is a local and systemic effect.

Chu, Hiutung and Mazmanian, Sarkis K.

Innate immune recognition of the microbiota promotes host-microbial symbiosis.

Nature Immunology 14, 668-675 (2013).
Summary and idea…

- Studies have shown that:
  - Gut microbiome is altered in RA and SpA
  - Probiotic treatment with specific strains results in clinical and laboratory improvement
- Can we apply the Functional Medicine 5 R Gut Repair program to:
  - Do an even better job at repairing both microbial balance and gut integrity
  - Use as a primary treatment approach?
- YES!
GUT BASICS

Dysbiosis and leaky gut
Gut Basics

- Terms: Gut = digestive system = gastrointestinal tract
- Mouth to anus
- Huge exposure to the environment
- Surface area of a tennis court
- Stomach is the sterilizer: pH 1.5
- Then immune system takes over:
  - Innate and Adaptive Immune System
Intestinal Flora

- Diverse community of microorganisms
- Human intestine harbors 100 trillion microbes, mainly over 500 species of bacteria
- Each species colonizes a specific niche
- Mutually beneficial relationship
- We provide nourishment
- Microbe by-products of digestion provide vitamins, nutrients and help with resistance to colonization by potential pathogens

**see slide 57 for multiple references**
Intestinal Flora: Immune function

- Antibacterial action against pathogens
- Modulate epithelial cells to increase sIgA
- Enhance intestinal barrier function
- Influence the maturation and phenotype of dendritic cells
- Directs functioning of antigen presenting cells with modulation of T cell responses
- Interact with enteric nervous system which effects immune system

**see slide 57 for multiple references**
Dysbiosis

- Imbalance in microbe population of the gut
- Can be overgrowth of harmful bacteria, yeast or parasites
- And/or too little good bacteria
- May or may not have gut symptoms

Caused by:
- Stress
- Antibiotics
- PPI’s and antacids
- Gut infections
- Diet

**Dysbiosis can lead to Leaky Gut**

**Leaky Gut is associated with RA and SpA**

**see slide 57 for multiple references**
Intestinal Microbiome references

• Denise Kelly et al. Commensal gut bacteria: mechanisms of immune modulation. TRENDS in Immunology. Vol.26 No.6 June 2005
• Hsin-Jung Wu and Eric Wu. The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes 3:1, 1–11; January/February 2012
• Pulukool SANDHYA, Debashish DANDA, Disha SHARMA and Vinod SCARIA. Does the buck stop with the bugs?: an overview of microbial dysbiosis in rheumatoid arthritis. International Journal of Rheumatic Diseases 2015
‘Dysbiosis contributes to compromised epithelial Integrity and disrupted Immune tolerance’

Microbial influences on epithelial integrity and immune function as a basis for inflammatory diseases

Summary: Certain autoimmune diseases as well as asthma have increased in recent decades, particularly in developed countries. The hygiene hypothesis has been the prevailing model to account for this increase; however, epidemiology studies also support the contribution of diet and obesity to inflammatory diseases. Diet affects the composition of the gut microbiota, and recent studies have identified various molecules and mechanisms that connect diet, the gut microbiota, and immune responses. Herein, we discuss the effects of microbial metabolites, such as short chain fatty acids, on epithelial integrity as well as immune cell function. We propose that dysbiosis contributes to compromised epithelial integrity and disrupted immune tolerance. In addition, dietary molecules affect the function of immune cells directly, particularly through lipid G-protein coupled receptors such as GPR43.

Keywords: microbiota, epithelium, GPR43, short-chain fatty acids

Introduction
A new direction in immunology research has emerged recently that considers the effects of diet on the gut microbiota and immune responses. Gastrointestinal microbes have co-evolved with vertebrates and provide benefits to the host, including maintenance of epithelial integrity and regulation of immune responses. However, the composition of the gut microbiota can differ considerably between individuals, and this difference appears to relate to diet (1–3). This may be particularly relevant to human inflammatory diseases, several of which associate with western lifestyle and obesity. While several studies and reviews (including by us) have highlighted the direct effects of dietary molecules on immune cells (4, 5), a new and possibly equally important element is the gut epithelium. The gut is lined by epithelial cells, which provide an important physical barrier and defense against pathogens. The integrity of the epithelial barrier is important to reduce...
SIBO: Small intestinal bacterial overgrowth

- Most people are very symptomatic, lots of gurgling, gas and bloating
  - But more than 20% of apparently healthy controls have been diagnosed with SIBO
- FODMAP-restricted diets reduce total bacterial count
  - Fermentable oligo-di-mono-saccharides and polyols
- Rifaximin: rate of success in SIBO eradication is at least 50% across different series
  - Bactericidal action against both aerobic and anaerobic bacteria
  - Best results have been achieved with doses of 1200–1600 mg daily
  - Recurrence is frequent. Must address underlying cause

the gut flora doesn’t develop properly because our environment is too clean, which in turn prevents immune system from functioning properly.

Rook, Graham A. W.

LEAKY GUT SYNDROME

Increased Intestinal Permeability
What is a leaky gut?

- **Intestinal Barrier:** the functioning separation of the gut lumen from the host.
  - Mechanical, humoral, immune, muscular and neurological elements

- **Intestinal Permeability:** normal functioning of the intestinal barrier
  - Normal: stable; found in healthy people

- **Impaired** Intestinal Permeability = **Leaky Gut**

- **Definition:**
  - “disturbed permeability being non-transiently changed compared to the normal permeability leading to a loss of intestinal homeostasis, functional impairments and disease”

What Causes Leaky Gut?

- Dysbiosis
- Medication: steroids, antacids, PPI’s, advil
- Alcohol
- Antibiotics
- STRESS
- Acute trauma: emotional or physical
- Toxins
- Infections

Leaky Gut and Immune Function

- Microbial peptides **trigger** ongoing immune reactions
- Increases T effector cell activity: lots of antibodies, and killer cells, inflammation
- T regulators aren’t doing their job to turn it off
- Fixing the leaky gut will **reduce the constant triggering** of the immune system
- In my opinion, until proven otherwise, everyone with arthritis has a leaky gut

*Pulukool SANDHYA, Debashish DANDA, Disha SHARMA and Vinod SCARIA. Does the buck stop with the bugs?: an overview of microbial dysbiosis in rheumatoid arthritis. International Journal of Rheumatic Diseases 2015*
Leaky Gut and Autoimmune Diseases
Alessio Fasano

Abstract Autoimmune diseases are characterized by tissue damage and loss of function due to an immune response that is directed against specific organs. This review is focused on the role of impaired intestinal barrier function on autoimmune pathogenesis. Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to non-self antigens. Zonulin is the only physiologic modulator of intercellular tight junctions described so far that is involved in trafficking of macromolecules and, therefore, in tolerance/immune response balance. When the zonulin pathway is deregulated in genetically susceptible individuals, autoimmune disorders can occur. This new paradigm subverts traditional theories underlying the development of these diseases and suggests that these processes can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing the zonulin-dependent intestinal barrier function. Both animal models and recent clinical evidence support this new paradigm and provide the rationale for innovative approaches to prevent and treat autoimmune diseases.

Keywords Antigens · Autoimmunity · Gut permeability · Immune response · Tight junctions · Zonulin

Introduction
The intestinal epithelium is the largest mucosal surface providing an interface between the external environment and the mammalian host. Its exquisite anatomical and functional arrangements and the finely-tuned coordination of digestive, absorptive, motility, neuroendocrine, and immunological functions are testimonial of the complexity of the gastrointestinal (GI) system. Also pivotal is the regulation of molecular trafficking between the intestinal lumen and the submucosa via the paracellular space. The dimensions of the paracellular space are estimated to be between 10 and 15 Å, suggesting that under physiological circumstances, solutes with a molecular radius exceeding 15 Å (~3.5 kDa) will be excluded from this uptake route. Macromolecule trafficking is dictated mainly by intestinal paracellular permeability, whose regulation depends on the modulation of intercellular tight junctions (TJ). A fast growing number of diseases, including autoimmune diseases, are recognized to involve alterations in intestinal permeability related to changes in TJ competency.

Classical Theories on the Pathogenesis of Autoimmune Diseases
Soon after autoimmune diseases were first recognized more than a century ago, it was believed that their development was associated with viral and bacterial infections. The connection between infection and autoimmune disease is often explained by a mechanism known as “molecular mimicry,” whereby microbial antigens are postulated to resemble self-antigens [1]. The induction of an immune response to the microbial antigens results in a cross-reaction with the self-antigens and the induction of autoimmunity.
Alessio Fasano. Zonulin, regulation of tight junctions, and autoimmune diseases. Leaky gut and RA.

Leaky Gut References

• Lerner, A. et al. *Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease.* Autoimmunity Reviews 14 (2015) 479–489


Intestinal permeability and SpA

- Epithelium
  - Physical and chemical barrier between host and microbes: promote tolerance
  - Provide mucus and metabolites to support colonization
- Many studies support increased intestinal permeability in SpA patients.
- Loss of integrity can be transient, or subclinical, or overt
- “Chicken and egg”:
  - Local inflammation drives damage to the epithelium itself, causing change in microbes
  - Dysbiotic changes or a disrupted epithelium promotes a breakdown of mucosal homeostasis with resulting inflammation

The importance of the intestinal barrier in regulating the innate and adaptive immune system

The intestinal epithelium is a single-layered tissue that constitutes the largest and most important barrier against the external environment. It acts as a selectively permeable barrier, permitting the absorption of nutrients, electrolytes, and water while maintaining an effective defense against intraluminal toxins, antigens, and enteric flora. The epithelium maintains its selective barrier function through the formation of complexes of protein-protein networks that mechanically link adjacent cells and seal the intercellular space. The protein networks connecting epithelial cells form 3 adhesive complexes: desmosomes, adherens junctions, and tight junctions. These complexes consist of transmembrane proteins that interact extracellularly with adjacent cells and intracellularly with adaptor proteins that link to the cytoskeleton. Over the past decade, there has been increasing recognition of an association between disrupted intestinal barrier function and the development of autoimmune and inflammatory diseases. In this review we summarize the evolving understanding of the molecular composition and regulation of intestinal barrier function. We discuss the interactions between innate and adaptive immunity and intestinal epithelial barrier function, as well as the effect of exogenous factors on intestinal barrier function. Finally, we summarize clinical and experimental evidence demonstrating intestinal epithelial barrier dysfunction as a major factor contributing to the predisposition to inflammatory diseases, including food allergy, inflammatory bowel diseases, and celiac disease.

(Allergy Clin Immunol 2009;124:3-20.)

Key word: Intestinal epithelium

The intestinal epithelium is a single layer of cells lining the gut lumen and has 2 critical functions. First, it acts as a barrier to prevent the passage of harmful intraluminal entities, including foreign antigens, microorganisms, and their toxins. Its second...
MICROBIOME TESTING AND TREATMENT
Testing: Assessing the Flora

- **Testing:**
  - Dysbiosis self-test: symptoms and triggers
  - Urine test looking for dysbiosis markers
    - Genova, Metametrix, Great Plains
  - Stool testing: Genova, Metametrix, Doctors Data, Diagnostechs, Great Plains
  - Some limitations in NY, but available.
  - If no access to testing, treat for dysbiosis anyway
  - Asymptomatic dysbiosis is common in autoimmune disease and arthritis. Therefore stool testing or treatment is mandatory
### Organix™ Comprehensive - Urine

Ranges are for ages 13 and over.

<table>
<thead>
<tr>
<th>Component</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoate</td>
<td>&lt;DL*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippurate</td>
<td>199</td>
<td></td>
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<td>Phenylacetate</td>
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<td>&lt;DL*</td>
<td></td>
<td></td>
<td></td>
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<td>Phenylpropionate</td>
<td>&lt;DL*</td>
<td></td>
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<td>p-Hydroxybenzoate</td>
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<tr>
<td>p-Hydroxyphenylacetate</td>
<td>11</td>
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<tr>
<td>Indican</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tricarboxylate</td>
<td>0.39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. acidophilus / general bacterial</td>
<td>&lt;DL*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-Lactate</td>
<td></td>
<td>2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridial species</td>
<td>&lt;DL*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,4-Dihydroxyphenylpropanoate</td>
<td>&lt;DL*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeast / Fungal</td>
<td>&lt;DL*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-Arabinintol</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Methodology:** LC/Tandem Mass Spectrometry Spectroscopy

*<DL* = less than detection limit*
Immune Health: Fix the Flora

• Treat dysbiosis and improve the microbiome balance is the first goal of treatment
• Giving probiotics isn’t enough for remission
• Functional Medicine 5 R GUT program
  • Remove: bad food and harmful microbes
  • Replace: digestive enzymes, bile, stomach acid
  • Reinoculate: the good bacteria
  • Regenerate: a healthy intestinal lining/barrier
  • Retain: long term health and resiliency
Step 1 Remove: Herbal Antibiotics

- Herbal treatment of dysbiosis
  - Recommend for 2 months initially; often repeating treatment 6 months later.
  - Combination formulas

- Berberine

- Artemesia
Herbal Antibiotics Cont’d

• Uva Ursi

• Black Walnut and Sea Buckthorn

• Grapefruit seed extract

• Oregano:
SIBO: Herbs vs Rifaximin Study

• The high prevalence rate for SIBO of 64% in a tertiary care referral gastroenterology practice.
• The response rate for normalizing breath hydrogen testing in patients with SIBO was 46% for herbal therapies vs 34% for Rifaximin.
• Study herbs: mixture of >20 herbs in 4 different supplements given at the same time.
• Herbal treatment as effective as Rifaximin
• Advantages: cost, does not promote yeast, well tolerated

Step 2: Replace

• Digestive enzymes:
  • Clinical evaluation: GERD, gas and bloating after meals
  • Laboratory: low nutrients on testing despite a good diet. Low levels on stool testing

• Options:
  • Plant based
  • Pancreatin from animals
  • Apple cider vinegar before meals

• Test for and treat hypochlorhydria

• Bile acids: especially if gall bladder has been removed or trouble digesting fat
  • Option to use a combination enzyme formulas that have ox bile in it

Step 3: Reinoculate with Probiotics

- Combination formulas: 100 billion for 6 months.
- Strains researched in Arthritis:
  - **Lactobacillus casei**
Probiotics for Arthritis cont’d

• Lactobacillus acidophilus
  • Amdekar, Sarika et al. Lactobacillus acidophilus Protected Organs in Experimental Arthritis by Regulating the Pro-inflammatory Cytokines. Ind J Clin Biochem (Oct-Dec 2014) 29 (4): 471-478

• Lactobacillus rhamnosus and reuteri

• Lactobacillus GG

• Lactobacillus salivarius
Probiotics for Arthritis cont’d

- **Bifidobacterium Bifidum**

- **S. Boulardi**
  - Beneficial to microbiome, but no direct studies showing helpful in arthritis patients.
  - Citation: Chen X, Yang G, Song J-H, Xu H, Li D, et al. (2013) Probiotic Yeast Inhibits VEGFR Signaling and Angiogenesis in Intestinal Inflammation
Improve the Flora with Food

- **Cultured foods**: non-dairy yogurt, kefir
  - With live active cultures of lactobacillus, bifidobacteria and sacharomyces boulardi
- **Fermented foods**: kimchi, sauerkraut, other vegetables
- **Prebiotics**: vegetables and fiber.
  - Fructo-oligo-sacharides (FOS), which are compounds found in onions, garlic, leeks, rye, chicory, blueberries, and bananas.
  - Inulins, which are found in chicory and artichokes.

*References on next slide*
References: food and microbiome


• Wlodarska M, Willing BP, Bravo DM, Finlay BB. Phytonutrient diet supplementation promotes beneficial Clostridia species and intestinal mucus secretion resulting in protection against enteric infection. Sci Rep. 2015 Mar 19;5


Step 4: Regenerate: Heal the lining

- Repair the lining with food: permanent
  - Ghee (butyrate)
  - Coconut oil and medium chain triglycerides
  - Glutamine: found in all animal protein, such as chicken, beef, and dairy, but also in beans, cabbage, beets, spinach, and parsley, so don’t focus only on animal sources.
  - Turmeric and cinnamon
- Supplementation: 1 year minimum
  - Glutamine: loose powder is best: 7-8 grams/day
  - Whey protein is also gut healing

Step 5: Retain

• **Long term treatment**: protocol used at our Clinic:
  • Repeat 30 day herbal treatment every 4-6 months until stool testing is normalized.
  • Rotate formulas
  • 1-2 years of high dose probiotics (100 billion) and glutamine (4-7 grams)
  • Prebiotics and enzymes: use supplements for 6 months, then taper off and use Food as Medicine
Terroir de Gut

• Recommendations based on experience
• For long term gut health, focus on the ‘soil’
• Nutrition: vegetable based diet rich in prebiotic fiber
• Identify and lessen all the damaging behavior:
  • Stress: direct effect on gut micro-environment
  • Ingested Toxins
  • Alcohol
  • Medication: PPI’s, antacids, steroids, NSAIDS
• Oral microbiome: bacteria seed the gut
Fecal Transplant: FMT

- **C Difficile**: FMT is the first conv treatment to alter the intestinal microbiome
  - Falls under US Food and Drug Admin: biologic product and a drug.
  - No double blind randomized control studies, so not approved yet. Investigational new drug status. unregulated

- **Study review**:
  - Whole stool preps. Working on encapsulated formulas
  - Donor eligibility
  - Delivery method: NG tube, colonoscopy, duodenal infusion, rectal catheter, enema
  - Long term safety? Few short term adverse effects
  - Transmission of infectious agents. (think Hep C from transfusions)
  - Goal: defined microbial consortia targeted to treat specific diseases.

Figure 1. Mechanisms underlying successful treatment of recurrent CDI with FMT. Improvement in symptoms after FMT has been associated with changes in microbial community structure, such as a decrease in Proteobacteria as well as restoration of microbial divers...


http://dx.doi.org/10.1053/j.gastro.2015.05.008
Case Study: Deb I.

- 51 year old woman, new dx of RA with RF of 32.
- Doesn’t want medication
- Pain in feet and toes. Fatigue
- Long history of gut issues:
  - antibiotics for strep
  - Travelers diarrhea multiple times beginning at age 13
  - 10 years of gas and bloating; constipation;
- Chronic vaginal yeast infections and gum inflammation
- Saw another FM doc before me: diet and detox helped energy but not joint pain.
Case Study: Deb I.

- I have seen her every 3-4 months for 3 years
- She is a good example of a patient who improves slowly because they need to do the program their way
- For the first 2 years she was able to follow maybe 50% of my recommendations.
  - Slowly improving but not resolving.
  - However in the past year she finally felt able to do the treatment I recommended and her arthritis finally resolved completely with normalizing of her RF.
- Reminder that the terrain of the gut/immune system takes time to shift and heal.
### Treatment history chart for patient Deb I.

<table>
<thead>
<tr>
<th>Visit every 3-4 months</th>
<th>RF</th>
<th>Arthritis sx</th>
<th>Gut sx</th>
<th>Stool test</th>
<th>Gut Treatment given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 2 (1st follow up with results)</td>
<td>32</td>
<td>8/10. Pain in feet</td>
<td>Gas and bloating</td>
<td>Yersinia Candida Bacterial dysbiosis</td>
<td>Cipro 5 d x 2 Undecylenic Acid x 1 mo Boulardi and diflucan (didn’t take) Culturelle</td>
</tr>
<tr>
<td>Visit 3</td>
<td>Not tested</td>
<td>Pain 8/10 no change</td>
<td>resolved</td>
<td></td>
<td>Boulardi and diflucan (didn’t take) Culturelle</td>
</tr>
<tr>
<td>Visit 4</td>
<td>16.8</td>
<td>Slightly Improved 7/10</td>
<td>Gas and bloating</td>
<td></td>
<td>Probiotic with boulardi. Glutamine.</td>
</tr>
<tr>
<td>Visit 5</td>
<td>16.4</td>
<td>Slightly Improved 5/10</td>
<td>improved</td>
<td></td>
<td>Probiotic with boulardi. Glutamine.</td>
</tr>
<tr>
<td>Visit 6</td>
<td>Not tested</td>
<td>Continues to improve slowly, 5/10</td>
<td>Resolved</td>
<td></td>
<td>Probiotic with boulardi. Glutamine.</td>
</tr>
<tr>
<td>Visit 7</td>
<td>Not tested</td>
<td>Improved but not resolved 3/10</td>
<td>Resolved</td>
<td>pending</td>
<td>Oregano, Berberine herbal blend (didn’t take)</td>
</tr>
<tr>
<td>Visit 8</td>
<td>RF: 14.6</td>
<td>Improved but not resolved 2/10</td>
<td>none</td>
<td>Candida Bacterial dysbiosis</td>
<td>Oregano, Berberine herbal blend (didn’t take) Probiotics + glutamine</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>--------------------------------</td>
<td>------</td>
<td>-----------------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td>Visit 9</td>
<td>RF: 14.8</td>
<td>2/10</td>
<td>none</td>
<td>Candida gone Bacterial dysbiosis improved but not resolved</td>
<td>Change to different Mild Berberine herbal blend. Change probiotic, stop boulardi.</td>
</tr>
<tr>
<td>Visit 10</td>
<td></td>
<td>STRESS; daughters bat mitzvah 2/10</td>
<td>Heartburn, noisy, gurgly</td>
<td>Send stool and SIBO</td>
<td>Digestive enzymes, probiotics, glutamine</td>
</tr>
<tr>
<td>Visit 11</td>
<td><strong>finally willing to do a full dose gut treatment regimen</strong></td>
<td>New psoriasis Still mild joint pain when stressed or sick</td>
<td>Gas and bloating</td>
<td>Candida Bacterial dysbiosis</td>
<td>Nystatin 1 m Rifaximin 1 m Glutamine and probiotics</td>
</tr>
<tr>
<td>Visit 12</td>
<td>RF: 12.8 ANA and CCP still neg</td>
<td>Arthritis is resolved Psoriasis gone</td>
<td>Resolved</td>
<td>SIBO negative Candida Bacterial dysbiosis</td>
<td>Stronger herbal blend x 3 weeks Oregano x 2 m Nystatin x 2m Glutamine and probiotics</td>
</tr>
<tr>
<td>Visit 13</td>
<td></td>
<td>Resolved</td>
<td>Resolved</td>
<td>Stool test is improved. No candida</td>
<td>Probiotics Glutamine</td>
</tr>
</tbody>
</table>
We can help…

• The Immune System Recovery Plan:
  • 4 Step Do-it-With-Us! Free Program:
  • http://blumcenterforhealth.com/online-programs/do-it-with-us/
    • Step 1: Using Food As Medicine, with recipes
    • Step 2: Balancing Your Stress Hormones
    • Step 3: Healing Your Gut
    • Step 4: Supporting Your Liver
If you do not change direction, you may end up where you are heading.”

--Lao Tzu