

TAKEAWAYS FROM THE 2017 INTEGRATIVE SIBO CONFERENCE

Takeaways from the 2017 Integrative SIBO Conference Practice
update from the speakers By Natural Medicine Journal

Printer Friendly Page The 2017 Integrative SIBO Conference
took place March 25–26 at the National University of the
Health Sciences in Lombard, Illinois. Take-home messages
have been summarized by fellow presenters (and one attendee)
and are provided here for the benefit of both those who
attended the conference and those who missed it. Small
intestine bacterial overgrowth (SIBO) is a syndrome in which
excessive bacteria exist in the small intestine. The symptoms
of SIBO may include diarrhea, constipation, flatulence,
abdominal pain, bloating, and bloating. This conference
focused on the mechanisms underlying the condition and its
diagnosis, treatment, prognosis, and associations with other
conditions. SIBO Overview: Causes, Effects, Diagnosis, and
Treatment Presenter: Allison Siebecker, ND, MSOM, LAc
Reviewer: Carmello Scarpignato, MD, DSc, PharmD, MPH,
FRCP (Lond), FACP, FCP, FACG, AGAF SIBO Overview •
Common condition; thought to cause the majority (~60%) of
irritable bowel syndrome (IBS) cases • Represents an

accumulation ($\geq 10^5$ CFU/mL) of bacteria in the small intestine

- Symptom severity varies and covers the full range of digestive complaints, along with systemic symptoms
- Most common underlying cause: absent or impaired migrating motor complex (MMC)
- Common causes/risk factors of SIBO: food poisoning, proton pump inhibitors (PPIs), and adhesions

Primary pathophysiology: carbohydrate (CHO) malabsorption via bacterial fermentation

- The large number of conditions that can cause IBS symptoms makes testing for and properly diagnosing SIBO very important
- Standard lab test: hydrogen and methane breath test using glucose or lactulose

Treatment Considerations

- Chronic/relapsing in two-thirds of cases, requiring ongoing management
- Treatment algorithm: retest if not 90% better within 2 weeks of initial treatment; multiple treatment rounds are often needed
- Treatment options: diet, antibiotics, herbal antimicrobials, elemental diet, and prokinetics
- Antibiotics, herbal antimicrobials, and an elemental diet are equally effective
- Rifaximin alone is used in diarrhea-predominant cases; rifaximin with either neomycin or metronidazole (double therapy) is used in constipation-predominant cases
- Rifaximin is not a typical antibiotic; rifampin
- is not systemically absorbed ($<1\%$)
- works best in the small intestine (bile soluble)
- increases Bifidobacteria and Lactobaccilli (eubiotic effects)
- has anti-inflammatory activity via stimulation of human nuclear receptor pregnane-X receptor (PXR)
- does not cause C. difficile or yeast overgrowth
- has very low side effect profile ($\leq$ placebo)
- prevents antibiotic

resistance of neomycin by inhibiting plasmids • does not lead to antibiotic resistance, and continues to work after 6 rounds of treatment • The 2 most common herbal antibiotic strategies: single herbs used together (usually 2–3 at a time) or big combination formulas • Berberine, oregano, and neem are used in diarrhea–predominant cases; stabilized allicin is added to these herbs for constipation predominant cases • Elemental diet (ED) can decrease severe gas levels in one 2–week course • Many diets that can be used for SIBO; all target and reduce fermentable carbohydrates • Overarching diet tips for active SIBO: • Avoid raw food, salad, and beans • Be careful with whole grains, nuts/seeds, winter squash • Choose low–FODMAP fruit and vegetables (see Monash University Low–FODMAP app) • Starch may be tolerated: white rice, white potato, white flour (if gluten is tolerated); often one starch is tolerated but not another • Lactose–free dairy, sugar, clover honey, and cocoa are often tolerated • Quantity matters–small amounts of individual foods may be tolerated when larger amounts aren’t • Experimentation and customization is necessary for best success • Prokinetics are used between treatment rounds and after eradication to prevent relapse by stimulating the MMC • Common prokinetics: low–dose erythromycin, low–dose prucalopride, low–dose naltrexone, Iberogast, MotilPro, ginger • Other preventions of relapse: diet, meal spacing (4–5 hours apart and 12–hour overnight fast to allow MMC to be active), decrease stress, visceral manipulation/body work • Key treatment points for success

include: • Test (breath test: hydrogen and methane) • Successive treatment rounds needed • Methane and/or constipation cases are harder to treat • Different treatment needed for methane and/or constipation • Die-off is common • Vary treatment method as needed (antibiotics, HAbx, elemental diet; often 1 or 2 don't work) • Retest to assess results • Both prokinetic and diet for prevention • Customize diet to the individual SIBO, Food Intolerances, and the Bi-phasic Diet Protocol

Presenter: Nirala Jacobi, BSc, ND
Reviewer: Leonard B. Weinstock, MD, FACG
Comment: Jacobi has a natural approach to healing the gut in the setting of SIBO. Her professional background leads her to pursue a pure diet and herbal approach. She has acquired an amazing knowledge of herbs, spices, and plans and applies them widely in her practice. Her overall goal is to starve the bacteria prior to starting herbal antimicrobial therapy. She addressed food intolerances and SIBO.

Bi-Phasic Diet in SIBO • Phase 1: Reduce and Repair (4–6 weeks) • Reduce: fermentable starches and fibers and therefore bacterial fermentation • Repair: intestinal damage • This phase starts out with very restricted food plan and then moves into “semi-restricted” as soon as symptoms improve • Phase 2: Remove and Restore (4–6 weeks) • Remove bacteria (and fungi) with herbal antimicrobials • Start broader low-FODMAP/SIBO Specific Food Guide diet than phase 1 • Take Rx to increase small bowel motility • Mucosal repair is important for both phases • Tight junction repair • Vitamin D helps mucosal barrier

homeostasis and decreases inflammation • Vitamin A • Quercetin • Epithelial cell repair • Zinc carnosine • L-glutamine • Increases production of human growth hormone • Major fuel source for enterocytes/epithelial cells • Supports tight junctions • Reduces interleukin (IL)–6 and IL–8, increases IL–10 Comment: Prebiotics are mentioned during entry to Phase 2 but I am not a fan of this if it possibly could increase SIBO counts. The diets for the 2 phases and what to avoid completely were presented in 4 key slides. Food intolerances in SIBO: common and likely due to increased intestinal permeability Comment: Jacobi stated that she sees many patients with reactions to histamine, salicylates, and oxalates.

- Histamine can be elevated in SIBO due to 2 main causes: • Food-sourced histamine (exogenous histamine absorption) • Mast cell infiltration (endogenous histamine release) Comment: Jacobi had 11 slides on histamine, an excellent summary of review of literature and of Charles Lewis (Enteroimmunology, Psy Press 2013). The most interesting slide was how to tame the mast cells naturally. • Histamine clearance • DAO supplement with food • B6, Magnesium, Copper • Pantothenic acid 1,000–2,000 mg • B12, folic acid — she stated that this needed to be started slowly • B1 100–200 mg • Mast cell stabilization • Vitamin C to bowel tolerance • Quercetin • Albizia • Perrilla Comment: Jacobi had 11 slides on salicylates and stated that interaction with patients who have SIBO and dysbiosis is common. • Salicylates • Natural plant substances, which help the plant defend itself against bacteria, fungi, and

other pests. Salicylates are toxic to everyone in very high doses, but with a salicylate sensitivity the threshold is much lower before a reaction occurs. • Salicylates are chemically very similar to the manmade chemical acetylsalicylic acid, a key ingredient in aspirin and other pain medications. • Sources include: • Herbal products (most will contain salicylates) • Curcumin (especially high) • Medications: most NSAIDs • Cosmetics, fragrances, shampoo • Cleaning products • Air fresheners • Breath mints, lozenges, gum • Support for phase 2 clearance of toxins • Glycine conjugation: Glycine 1,000–1,500 mg daily • Glucuronidation: calcium d-glucarate 1,500 mg daily • Support for kidney clearance • Alkalizing minerals • Trace minerals

Comment: Jacobi discussed commercial combination products for toxin clearance but could not use trade names in the talk; product “BA”—calcium, potassium, magnesium, sodium, zinc, selenium, chromium, stevia small amount of maltodextrin—and product “BE”—potassium, magnesium, zinc, and calcium, excipient-free. SIBO and Skin Diseases Presenters: Michael Traub, ND, DHANP, FABNO with Leonard Weinstock, MD, FACP Reviewer: Ryan Bradley, ND, MPH

Comment: Traub and Weinstock presented an integrative naturopathic and gastroenterological perspective on the state of the science regarding known interactions between the gut microbiome and skin health, including associations with acne, atopic dermatitis, psoriasis, urticaria, systemic sclerosis, skin cancer, and rosacea. Notable highlights from this dynamic and highly integrative presentation included the following: • A

conceptual model of the mechanistic connections between the gut and acne, mediated through psychological stress (slowed intestinal transit times, reduced blood flow to the gut, and increased bacterial overgrowth) and diet (modified sebum composition), affecting sebum volume and final composition, encouraging *Propionibacterium acnes* growth on the skin. • Additional support for this relationship was provided by cited evidence on the connection between hypochlorhydria, or inadequate stomach acid production (either functionally or induced pharmacologically by proton pump inhibitors), and preliminary clinical trials suggesting potential benefits of probiotics to reduce lesion count in acne and impact some known mechanisms of acne, including insulin-like growth factor-1 expression. • Findings suggest people with psoriasis have increased malabsorption and a relatively common prevalence of positive lactulose–breath test (LBT) results suggestive of SIBO. • Notable increases in both *H. pylori* and SIBO infections in people with chronic spontaneous urticaria; treatment of *H. pylori* appeared to reduce number and frequency of urticarial lesions, while treatment of SIBO did not seem to change lesion frequency or severity despite the detected associations. • Findings may have been due to differences in lesion severity in the SIBO group and/or inadequate treatment type and duration. • Systemic sclerosis (SSc) has also been associated with SIBO, estimated to be present in 30% to 63% of patients with SSc who also have gut symptoms. SIBO eradication resulted in clinical improvements

in 52% of patients. • Patients with more severe gut-based symptoms of SSc and SIBO tended to have greater elevations in fecal calprotectin, indicating frank gut-based inflammation.

- Case series evidence was presented supporting the use of low-dose naltrexone for treatment of pruritus and pain in SSc.

- Evidence supporting a connection between SIBO and skin cancers is primarily mechanistic and hypothetical; however Traub presented several candidate mechanisms, primarily the potential for unwanted pathogenic microflora to affect production of Th17 cells, impacting regulation of immunological surveillance and tolerance, alterations that can induce chronic inflammatory and carcinogenic signaling pathways. •

Weinstock outlined evidence connecting GI disease with rosacea, including observational research and isolated case reports of positive patient response to rifaximin. • Evidence from Europe suggests SIBO may be present in ~50% of rosacea patients. Randomized trial results suggest rifaximin led to marked improvement in ~93% of patients (30 of 32), with greater response in those testing positive for SIBO based on lactulose breath testing (LBT). • These findings are supported by additional findings in a small trial of 63 patients with rosacea where rifaximin led to moderate or greater improvement in rosacea symptoms, including lesion count and severity. • Isolated case report examples also support a potential role for SIBO-targeted antimicrobial treatment in ocular rosacea, with an expected response rate of 33%.

Comment: The presentation by Traub and Weinstock outlined

theoretical and established connections between the gut and skin health and submitted a convincing hypothesis about the clinical relevance of these connections in the context of numerous high-morbidity dermatologic conditions. Additional case series and controlled experiments with natural and pharmaceutical agents targeting the gut are desperately needed in larger samples of patients to further validate these observations and provide clinicians with effective therapeutic options. The Microbiome-Brain Connection: SIBO, the Liver, Cognition, Depression and Anxiety Presenter: Steven Sandberg-Lewis, ND, DHANP Reviewer: Heidi Turner, MS, RDN, CD • Microbiota and enteric nervous system development • Gut flora is needed for proper maturation of enteric neurons in the area of density and activity. • Microbes in the intestines use gut peptides to communicate with the digestive system and the brain. • Gut health and mental health • Gut infections or SIBO, gut-derived inflammatory molecules, or oxidative stress can lead to mental health issues. • Gut bacteria strongly affect both the peripheral nervous system and central nervous system (CNS) by production of functionally active neurotransmitters, including serotonin, dopamine, gamma aminobutyric acid, acetylcholine, and epinephrine. • Bacterial production of higher levels of methane and hydrogen can lead to a wide range of symptoms ranging from functional disorders of the bowel to low-level depression. • Bacterial wall lipopolysaccharides (LPS) • A healthy mucous membrane keeps all but a tiny amount of LPS (endotoxin) from entering

the bloodstream. • There are 1 million copies of LPS in each gram-negative microbe, which are continuously shed by both live and dead bacteria. • The adult human gut is thought to contain at least 1 gram of LPS. • Enterobacter-derived LPS can be 1,000 times more potent than LPS derived from other gram negative bacteria. • LPS is one of the metabolites that trigger the zonulin pathway. • LPS and systemic effects • A healthy liver can remove tiny amounts of LPS in the blood via deacetylation and excretion through the bile. • If detoxification is not sufficient, the LPS re-enters circulation, binds to transport proteins, and returns to the liver for reprocessing. • When LPS is absorbed at slightly higher levels, it triggers NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway, impaired excretion of toxins, and resulting emotional and cognitive effects. • LPS impact on CNS • LPS and inflammatory cytokines can induce transcription of IL-6, IL-1 β and tumor necrosis factor (TNF)- α in discrete areas of the brain. • Increased systemic inflammation can trigger CNS inflammation that may cause depression. • LPS and tryptophan • Inflammation triggered by LPS can alter tryptophan metabolism and convert to kynurenine, which can trigger depression, anxiety, and insomnia. • The composition of the microbiota largely determines the levels of tryptophan in the systemic circulation and, indirectly, the levels of serotonin in the brain. • LPS and obesity • Obese humans may have 2- to 3-fold increase in LPS levels compared to lean humans • LPS and secretory IgA (sIgA) • sIgA inactivates LPS, which

prevents NF–KB pathway, interferon (IFN), IL–6, TNF–alpha • Stress and its impact on microbiome • Stressed mice exhibit immediate changes in cecal flora: a reduction in Bacteriodes and increase in Clostridium • Stressed mice show an increase in circulating cytokines that are reduced when mice were treated with antibiotic prior to stress onset • Microbiome and post–traumatic stress disorder (PTSD) • Imbalanced gut microbiota early in life may make individuals more susceptible to developing PTSD after trauma. • May be possible to target abnormalities in this system by manipulation of certain gut bacteria communities via diet, supplementation, or other approach. • Enteric nervous system and short chain fatty acids (SCFAs) • SCFAs derived from bacterial fermentation of soluble fiber mediate microbial/mitochondrial/host cross–talk. • SCFAs are systemically absorbed and cross the BBB that modulates CNS inflammation. • SCFAs and secondary bile metabolites react with receptors on entero–endocrine cells leading to altered serotonin levels and resulting anxiety, sleep, and pain sensitivity alterations. • SIBO, insulin, and the brain • A high–carbohydrate diet can lead to both insulin resistance and SIBO. • Blood sugar surges after high–carbohydrate meals can lead to depletion of neurotransmitters, B vitamins, and magnesium. • These deficiencies lead to stress on the liver and nervous system, and insulin resistance. • Resulting glycation leads to neurodegeneration and depression. • Anxiety and depression in GI disorders • State anxiety was related to food allergies and SIBO. • Trait anxiety was related to IBS, food

allergies, and SIBO. • Current depression was related to IBS, celiac disease, and SIBO. • State and trait anxiety was directly correlated with a number of GI diseases. • Women showed higher levels of anxiety and depression than men. Methylation, Genomics, and SIBO Presenter: Paul Anderson, NMD Reviewer: Miranda LaBant, ND • Methylation's effects on physiology and health • Neurotransmitter function: Most neurotransmitters have a methylation step in synthesis or degradation. • Detoxification: Many phase 2 pathways up-regulate with faster methylation. • GI repair and maintenance, cell replication • Without methylation, DNA repair and replication is very slow or absent. • Genomic-GI connection • There is no portion of the GI system that is not affected by genomic influences. • Assessing and treating nutri-genomic areas in patients can improve outcomes. • SNPs and epigenetics • Single nucleotide polymorphisms (SNPs): genetic variations in a DNA sequence that occur when a single nucleotide in a genome is altered • Presence of SNP does not mean it is activated/expressing • Epigenetics: factors that affect gene expression, phenotypic outcome and other interactions that can minimize or exaggerate expression of potentially pathogenic SNPs or other phenotypic determinants • The more epigenetic stressors, more likely a SNP will be active and expressing • Many epigenetically activated SNPs can be inactivated by proper treatment. • Quick methylation points • The whole cycle must be considered and addressed (not just methylene tetrahydrofolate reductase [MTHFR]). • In order to normalize

any methylation imbalances with a nutrigenomic strategy all parts of the methyl cycle must be treated. • Where in biochemistry do the methyl cycles exist? • Histamine partial reduction • Ornithine–arginine cycling/removal of CO₂ and NH₄ • Catecholamine reduction • Sulfite reduction • Phase 2 priming • Immune system genomics • More IgE SNPs = more type 1 and histamine reactions • More IgA SNPs = more mucosal issues • More IgG SNPs = more immune memory issues • Immunoglobulin stimulation (IgA) • Colostrum, *Saccharomyces boulardii*, mushrooms, thymus • Immunoglobulin stimulation (IgG) • Methylation and marrow support, mitochondrial support, immune balancing • FUT2 gene polymorphism • FUT2 polymorphism is associated with secretor status. • Nonsecretors have an altered intestinal microbiota and have a propensity for intestinal aberrations. • Acetaldehyde exposure • Inefficient conversion of ethanol: damaging to the liver, pancreas, GI tract, brain • Increased carbohydrate intake allows opportunistic yeast (*Candida albicans*) to produce acetaldehyde in the GI tract by sugar fermentation • Pollution: burning of tobacco, petroleum fuels, natural gas, wood, and trash—aldehydes are present in the air we breathe • Acetaldehyde produced in the gut can eventually reach more parts of the body, flooding the system and increasing the risk for damage • Acetaldehyde and nutrient deficiencies • In addition to its toxic effects, acetaldehyde induces deficiencies of nutrients used for its detoxification. • Thiamine is depleted through alcohol and acetaldehyde

detoxification. • Molybdenum is involved with acetaldehyde metabolism: converts irritating sulfites into harmless sulfates. • Alcohol and acetaldehyde breakdown • Alcohol dehydrogenases (ADH): group of enzymes that serve to break down alcohols that are otherwise toxic • Alcohol-ADH-acetaldehyde-ALDH-acetate • In yeasts, plants, and many bacteria some ADH enzymes catalyze the opposite reaction as part of fermentation to ensure a constant supply of NAD+ • Cytochrome P (CYP) phase 1 in the GI tract ◦ Preliminary evidence proposes that CYP metabolizing enzymes responsible for the majority of phase I drug metabolism reactions are in the small intestinal mucosa rather than liver (specifically CYP3A). • Mitochondria • Involved in the pathology of most chronic (slow resolution) cases • Slow to repair, but as it does the major symptoms lessen or are eliminated • Restore energy: poly-MVA, B-vitamins, iron (ferritin over 30-40 minimum), thyroid • Repair: phospholipids, alpha lipoic acid, carnitine, taurine • ReDox: omega 3, tocopherols, ascorbate, glutathione • Biofilms • Have the ability to make tests falsely negative, and cause “recurrent” cases • Bismuth-thiol complex: is the strongest phase 2 agent available • Bismuth-thiol is a nontoxic compound: dithiol is bound to the bismuth, thus toxicity of bismuth and chelating ability are negated • Immune response with use of bismuth-thiol is a positive finding: this means the biofilm is “opening” and the immune system is activated • Anecdotally, more aggravations with oral biofilm therapy vs intravenous (IV) therapies • Oral biofilm Rx: ◦ DMPS 25

mg/ALA 100 mg/bismuth subnitrate 200 mg per capsule ◦
Ideally no substitutions ◦ DMSA 100 mg can sub for DMPS ◦
Bismuth subcitrate can sub for subnitrate (will make product weaker) ◦ Dose: ▪ 1 cap QD away from food, 3x/wk for 1 week at test dose ▪ 1–4 cap QD — BID away from food 3–5x/week •
Normal trial period is 60–120 days during other antimicrobial therapy • Important to support adrenals and occasionally thyroid • 3–12 months may be needed to break through biofilms • Nutrigenomics in SIBO • Many SIBO cases are cleared without knowledge of nutrigenomics, but nutrigenomic interventions improve outcomes • A genetic slow-down or absence of an enzyme system will cause slower production of the enzyme, slower elimination, imbalances, excessive consumption of collateral pathway cofactors •
Treatment order: outside-in ◦ Diet: colorful vegetables/flavonoids, avoid sensitivities and sugar ◦
Inflammation and phase 2 support ◦ Trace minerals + Mg + multivitamin if tolerated ◦ Methylation support as indicated
Addressing SIBO Biofilms and Advanced Methods for Treating Methane Presenter: Michael Ruscio, DC Reviewer: Paul Anderson, ND • Biofilms: ◦ are real, pathologically active entities ◦ can exist in the small intestine ◦ are associated with 65% of all infections ◦ are key creators of antibiotic resistance ◦ form and exist in a spectrum of complexity leading to a need for multiple treatment options • Methanogenic bacteria do form biofilms with other biota • Treatment options are broad and exist in a spectrum of strengths from preventive to

therapeutic. ◦ Enzymes, aromatic herbs and anti-infective agents can be effective especially in less complex biofilms. ◦ Probiotics are likely preventive and therapeutic in many biofilms. ◦ Bismuth-thiol complex molecules can be effective in more advanced biofilms. ◦ Early data from presenter's clinic (N=12) using combination of anti-infective and biofilm agents outperform anti-infectives alone in H₂ and mixed-gas SIBO, but not CH₄.

SIBO and Rheumatology: Does Bacterial Overgrowth Impact Autoimmunity? Presenter: Heidi Turner, MS, RDN, CD Reviewer: Lisa Shaver, ND, Lac Dysbiosis and autoimmunity

- Dysbiosis leads to increased intestinal permeability, loss of immune tolerance, immune response, activating immune cells to joints and specific microbiome shifts.
- Anti-CdtB antibodies (cytolethal distending toxin B) • Cross-react with vinculin in the interstitial cells of Cajal (ICC) of small intestine lining leading to abnormal motility and autoimmune state
- SIBO is common in rheumatoid arthritis (RA).
- SIBO frequency increased in RA (1993 study); digestive symptoms need not be present.
- Causes of SIBO in rheumatology include post-infectious inflammatory bowel syndrome (IBS), adhesions/structural abnormalities, PPI use, opioid use dysmotility, systemic sclerosis, Ehlers-Danlos syndrome, Hashimoto's thyroiditis.
- Histamine impacts SIBO

◦ Stress leads to mast cell activation via binding of corticotropin releasing hormone (CRH) to mast cell CRH receptor sites which increases VEGF production, associated with RA and psoriasis.

◦ Mast cells present in GI tract secrete histamine and

other cytokines, leading to digestive and systemic inflammation.

- RA + SIBO + histamine intolerance is very common combination.
 - Intestinal inflammation leads to DAO enzyme deficit, increasing histamine circulation with symptoms of diarrhea, joint swelling, neuralgia.
 - Histamines impact via H1–H4 receptors. RA and H4 receptors with increased H4R in synovial fluid cells.
 - Reducing histamine
 - *L. rhamnosis*, *B. infantis* and *L. plantarum* decrease histamines. Note: *L. casei* and *L. bulgaris* increase histamine production.
 - Histamine symptoms include constant allergic reactions, symptoms worse from stress/seasonal change, urticaria, tachycardia/hypotension, anxiety, insomnia, headache/migraine, neuropathy, joint pain/swelling, diarrhea/gas/bloating, increase in perimenopausal symptoms.
 - Elimination of dietary histamines often leads to significant symptom amelioration in RA and SIBO.
 - Consider low–histamine diet when symptoms do not resolve with SIBO treatment and diet.
 - Dietary modification
 - Modify the diet to the individual with SIBO
 - Encourage plants/organic/anti–inflammatory foods, enlist a nutritionist
 - Beware of history of eating disorders
- Restless Legs Syndrome: The Role of SIBO and Inflammation
Presenter: Leonard Weinstock, MD, FACP
Reviewer: Nirala Jacobi, ND
- Restless leg syndrome (RLS) classification
- Idiopathic
 - Familial (known genomic markers)
- Secondary RLS Pathophysiology of RLS — several mechanisms
- CNS iron deficiency
 - Low CNS iron found in primary and secondary RLS
 - Increase in hepcidin, a protein made in the

liver ◦ Hepcidin reduces iron transport and absorption from small intestine ◦ Low iron in the choroid plexus/CNS=RLS via decreases in dopamine 2 receptor function and numbers in substantia nigra ◦ Treatment: IV iron—complete symptom resolution in 68% of those with iron deficiency • Altered dopaminergic system ◦ Down-regulation of D2 dopamine receptors ◦ Up-regulation of tyrosine hydroxylase (rate limiting step for dopamine synthesis) ◦ Down-regulation of D2 receptors implies increased dopamine in RLS patients, but many RLS patients respond to dopaminergic treatment • Peripheral neuropathy • SIBO ◦ Higher levels of TNF- α lead to increased gut permeability and LPS translocation and IL-6 increase. Both LPS and IL-6 increase hepcidin. ▪ Low iron in the choroid plexus/CNS=RLS • Inflammation and endorphin deficiency ◦ Less endorphin binding=greater severity of RLS. ◦ SIBO and inflammation may explain significant portion of idiopathic RLS and 2o RLS. ◦ Endorphin deficiency exacerbates CNS iron deficiency-induced dopamine dysfunction. ◦ Some types of RLS are associated with increased cRP, IL-6, ferritin, natriuretic peptide, 8-OHdG (8-hydroxy-2'-deoxyguanosine), and low transferrin saturation. • Rifaximin and low-dose naltrexone (LDN) studies ◦ Several studies demonstrate improvement of RLS symptoms with rifaximin. ◦ Sequential rifaximin and LDN studies: marked-mod responders=65%–78% ◦ SIBO-negative patients—marked-mod responders with LDN = 57% • Potential mechanism of action of LDN for RLS ◦ Increases endorphin levels in brain tissue ◦ Increases motility

and migrating motor complex ◦ Decreases systemic inflammation ◦ Blocks toll-like receptors in the brain to reduce pain • Conclusion from rifaximin studies ◦ SIBO is common in idiopathic RLS. ◦ GI symptoms are common in RLS. ◦ 10 days of rifaximin reduces RLS severity (may not be long enough). ◦ The connection between SIBO and hepcidin should be investigated in both 1o and 2o RLS.

Herbal Considerations to Effectively Treat SIBO and SIFO Presenter: Nirala Jacobi, ND, LAc Reviewer: Michael Traub, ND, DHANP, FABNO • Berberine ◦ Multiple mechanisms that overcome bacterial resistance ◦ Inhibits biofilm formation ◦ Reduces H₂-producing bacteria ◦ Dosage: 2–3 g/d • Garlic ◦ Reduces CH₄-producing bacteria • Syzygium aromaticum (clove) ◦ Antibacterial, antifungal ◦ Stimulates gastric mucous production ◦ Cholinergic: stimulates motility in IBS-C ◦ May increase bleeding time • Punica granatum (pomegranate) ◦ Antibacterial, anticandidal, antiparasitic ◦ Significantly enhances growth of *Lactobacillus* spp, *Bifidobacterium breve*, *Bifidobacterium infantis* ◦ Inhibits growth of pathogenic *Clostridia* and *Staphylococcus aureus* ◦ Dosage: 10 mL daily of 1:2 tincture • Small intestinal fungal overgrowth (SIFO) ◦ SIFO comorbid with SIBO in 20% ◦ SIFO found in 26% of patients with “unexplained GI symptoms” ◦ Issues with *Candida* spp: ▪ Often cause similar symptoms to SIBO ▪ Commonly forms biofilm ▪ Overgrowth easily evades detection ◦ Classic antifungal herbs: Pau D’Arco, Uva Ursi, berberine-containing herbs ◦ Essential oils of clove, oregano, and thyme ◦ Oregano ▪ Effective against *Candida* spp, *S.*

aureus, *Pseudomonas a.*, *Blastocystis hominis* ▪ Effective for SIFO and methanogens ▪ Effective against candida biofilm ▪ Dose: oil of oregano (50–100 mg 2x daily) • *Pseudowintera colorata* (horopito) ◦ Strong antifungal activity against *Escherichia coli* and *Salmonella*, *C. albicans*, *C. utilis*, *C. krusei*, *Cryptococcus neoformans*, *S. cerevisiae*, *T. mentagrophytes*, *T. rubrum* and *Penicillium marneffe* ◦ Moderate antibacterial activity against both gram–positive bacteria (including *Bacillus subtilis* and *Staphylococcus aureus*) and gram–negative bacteria • Liquid antimicrobial formulas ◦ SIBO formula–7.5 mL 2x daily: ▪ Oregon grape (or coptis/goldenseal) ▪ Pomegranate ▪ *Artemisia* ▪ Burr marigold ◦ SIBO/SIFO formula–7.5 mL 2x daily: ▪ Pomegranate ▪ *Usnea* ▪ Horopito ▪ Oregon grape (or coptis/goldenseal) • Herbal prokinetics ◦ Dr. J's Herbal Bitters formula: ▪ Oregon grape/Gentian/Baical Skullcap/Dandelion root: 2–3 whole droppers in water 15 min before meal ◦ "Iberogast"—*Iberis amara*, *Angelica archangelica* *carumcarvi*, *Silybum marianum*, *Melissa officinalis*, *Chelidonium majus*, *Mentha piperitae*, *Glycyrrhiza* ▪ Dose: 20 drops 3x daily before meals and before bed, or 60 drops at bed time ◦ "Motil Pro": Ginger, 5HTP, acetyl L carnitine, P5P ▪ Dose: 3 caps morning and night • Carminatives—gas removal from GI tract ◦ Caraway seed — very effective carminative and spasmolytic ◦ Fennel ◦ Carminative tea (crush 1 tsp of each and steep for 20 minutes in 1 cup of water. Drink after each meal.): ▪ Caraway seeds ▪ Fennel seeds ▪ Anise seeds Comment: Parting thought: use herbs before microbiome–disrupting antibiotics. Manipulation

of Gut Microbiota and GI Motility for Treatment and Prevention of SIBO Presenter: Carmello Scarpignato, MD, DSc, PharmD, MPH, FRCP (Lond), FACP, FCP, FACG, AGAF Reviewer: Allison Siebecker, ND, LAc • Dysbiosis definition=bad coexistence of host and microflora ◦ Consequences: damage to epithelium with increased cell turnover, toxin and/or gas production, immune weakening/reaction ◦ PPIs, H2 blockers and antisecretory drugs can profoundly influence microbiota even more than antibiotics. • SIBO definition: increase in number and/or change in type of bacteria (oropharyngeal or colonic) ◦ Increased intestinal permeability occurs in SIBO with colonic type but not salivary bacterial overgrowth and is reversed when SIBO is eradicated • SIBO presentation ◦ Common: gas-related symptoms (bloating, abdominal pain, flatulence, diarrhea) ◦ Uncommon: malabsorption syndrome (B12 and iron anemia, Vitamin A/D/E deficiency, edema) ◦ Malabsorption can occur when SIBO has been present for a long time ◦ SIBO diagnosis is made with both presentation and breath test • Breath testing ◦ New North American Consensus Paper: established dose of substrates, criteria of 20 ppm hydrogen rise by 90 min, and that it should not be used as a test for oro-cecal transit time because lactulose increases motility, producing a false value ◦ Glucose is preferred since it matches culture testing ◦ Using fructose and sorbitol in addition to glucose increases the diagnostic and therapeutic response: It increases the number of SIBO patients identified (compared to just using glucose) and identifies who is likely to respond to antibiotics. ◦ Testing

for hydrogen sulfide gas significantly increases the sensitivity of the lactulose breath test by identifying hydrogen-negative but hydrogen sulfide-positive SIBO patients. • Causes/risk factors

- Generally: when homeostatic mechanisms that control small intestine bacteria are disrupted such as gastric acid lowering and motility abnormalities
- Risk factors are endless and can include: demographics (old age), structural abnormalities (strictures, diverticula), organ system dysfunction (cirrhosis, chronic pancreatitis), and medications (PPIs, opioids)
- “An absent or disordered migrating motor complex pattern is almost always invariably associated with SIBO.”
- PPIs are a cause of iatrogenic SIBO—25% of long-term PPI patients develop SIBO symptoms over time with a 2.3 increased risk of SIBO. The probiotic *L. paracasei* F19 can prevent this. •

Associated conditions

- SIBO and SIFO (small intestine fungal overgrowth) coexist in 34% of SIBO patients; many antibiotics (a prime treatment for SIBO) can increase fungal overgrowth.
- SIBO and IBS: There is 5x more prevalence of SIBO in IBS compared to healthy controls.

- Studies show a wide difference in SIBO and IBS prevalence statistics; this is due to:
- Geographic region of population studied
- IBS diagnostic criteria (Manning, Rome I–IV)
- SIBO test type (glucose vs lactulose)
- SIBO test diagnostic criteria (single or double peak)

- SIBO is an umbrella term encompassing functional, organic, and hepatic conditions, so if you target SIBO you will be able to target many GI diseases. •
- It is not always possible to correct the underlying cause. •
- Systemic antibiotics can be

very effective for SIBO but create antibiotic resistance, affect the whole body, and profoundly disturb the microbiota. •

Rifaximin ◦ Rifaximin is the best antibiotic for SIBO because it is effective against gut bacteria, acts in gut only, prevents antibiotic resistance, is nontoxic, is safe in

children/elderly/pregnant women, and has few side effects. ◦

Rifaximin is anti-inflammatory through NF- κ B and the PXR gene, a master gene critical for maintenance of intestinal integrity. ◦ Rifaximin has eubiotic effects; it increases

Bifidobacteria and Lactobacilli. ◦ A recent meta-analysis of rifaximin for SIBO showed an average eradication rate of 70% with significant (70%) improvement of symptoms. ◦ Two

factors increase rifaximin eradication rate: higher dose and cotherapy with prebiotics/fiber or mesalazine (which can modify intestinal microbiota). • Recurrence ◦ 45% recurrence

by 9 months, especially if underlying cause is not corrected, which is often the case ◦ Cyclic use of rifaximin (7–10 days

every 4 weeks), followed by probiotics (Lactobacilli–Bifido mix)

• Probiotics ◦ 47% eradication with *Bacillus clausii* spores •

Prokinetics prolong remission time ◦ “Maintaining well the

housekeeping activity of the intestine is a must” ◦ Prucalopride is a safe option because it is very selective for the 5HT₄

receptor • Treatment is multifactorial and often long-term