Course Introduction: Updated December 14, 2017—this document is periodically revised so please refresh this document from its online location http://www.ichnfm.org/course-microbiome-dysbiosis to receive any updates—thank you.

- **Course overview:** This course provides core knowledge in the basic science and molecular biology of dysbiosis as well as the evidence-based clinical interventions used for effective health optimization and disease treatment. Students/attendees will gain a detailed understanding of the pathophysiology, clinical presentations, and therapeutic interventions. Consideration and contextualization includes the four components of evidence-based medicine/healthcare (clinical expertise, patient preference, research evidence, resource availability/socioeconomic context) to aid the data-analysis and treatment decision-making processes.

- **Topic overview:** New information on the “human microbiome” and “dysbiosis” is being published on a weekly basis, and healthcare providers and the general public alike are all becoming more aware of the role of microbes in human health and disease. Clinicians need a structured understanding of this material in order to take effective clinical action and in order to separate the helpful from the hype-ful with regard to clinical assessments and therapeutic interventions.

- **Clinician instructor overview:** Dr Vasquez (“DrV”) has been intensely studying this field since the mid-1990s when he first started studying functional medicine; what started out as a clinical and intellectual interest soon became a personal interest when DrV fell ill with a dysbiosis-induced disease. Later in clinical practice, DrV achieved impressive and sometimes amazing results by addressing the microbial component of persistent inflammatory disorders such as psoriasis, rheumatoid arthritis, and other forms of autoimmunity. DrV’s landmark paper “Nutritional and Botanical Treatments Against “Silent Infections” and Gastrointestinal Dysbiosis, Commonly Overlooked Causes of Neuromusculoskeletal Inflammation and Chronic Health Problems” (Nutr Perspectives 2006) is one of the most popular clinical papers detailing these topics, consistently ranked in the top 1% of papers on academia.edu with more than 6,000 downloads. DrV previously taught this information for the Institute for Functional Medicine, where he was faculty for more than 10 years.

**Instructor:** Alex Vasquez DC ND DO FACN

- **Biographical sketch:** Dr Alex Vasquez holds three doctoral degrees as a graduate of University of Western States (Doctor of Chiropractic, 1996), Bastyr University (Doctor of Naturopathic Medicine, 1999), and University of North Texas Health Science Center, Texas College of Osteopathic Medicine (Doctor of Osteopathic Medicine, 2010). Dr Vasquez is the author of many textbooks, including Integrative Orthopedics (2004, 2012), Integrative Rheumatology (2006, 2014), Musculoskeletal Pain: Expanded Clinical Strategies (published by the Institute for Functional Medicine, 2008), Chiropractic and Naturopathic Mastery of Common Clinical Disorders (2009), Integrative Medicine and Functional Medicine for Chronic Hypertension (2011), Migraine Headaches, Hypothyroidism, and Fibromyalgia (2012), and Mitochondrial Nutrition and Endoplasmic Reticulum Stress in Primary Care (2014). "DrV" has also written more than 100 letters and articles for professional magazines and medical journals such as British Medical Journal (BMJ), TheLancet.com, Annals
of Pharmacotherapy, Journal of Clinical Endocrinology and Metabolism, Journal of the American Medical Association (JAMA), Alternative Therapies in Health and Medicine, Journal of the American Osteopathic Association (JAOA), Nutritional Perspectives, Journal of Manipulative and Physiological Therapeutics (JMPT), Current Allergy and Asthma Reports, Integrative Medicine, Nature Reviews Rheumatology, and Arthritis & Rheumatism, the Official Journal of the American College of Rheumatology. Dr Vasquez lectures worldwide to healthcare professionals and provides expert consultations to physicians and patients internationally. The former Editor of Naturopathy Digest and a reviewer for Journal of Naturopathic Medicine and Autoimmune Diseases and PLOS One and Alternative Therapies in Health and Medicine, Dr Vasquez is currently the Editor of International Journal of Human Nutrition and Functional Medicine®. All of DrV's books and several articles are available at amazon.com/author/alexvasquez and ichnfm.academia.edu/AlexVasquez and Pubmed respectively.

Course Content and Criteria for Successful Completion/Passing—Outline and Checklist: The material in this program is provided in written/text formats as well as audio-video presentations. Participation in any forums or live discussions is optional/ancillary and not included in the core CE/CME program.

1. **Pretest—sampling of material**: CE/CME standards encourage the use of a pretest to assess the preexisting “learning gap” and to allow before and after comparison to assess the post-instruction attainment of knowledge. The pretest also allows students/attendees to become familiar with the software interface, test system compatibility on multiple devices, and the terminology, concepts, level of detail, and clinical applications of the information. No minimum passing score is required; students/attendees are encouraged to take the test without studying, preferably prior to reading the clinical monograph.

2. **Monograph**: The text portion of the clinical monograph contains 144 pages with 635 footnotes/citations, providing 70,500 words not including diagrams, footnotes, textboxes and exercises. Rounding to 71,000 words to include diagrams and textboxes, and using 12,000 words per hour as the standard per Distance Education Accrediting Commission: 71,000 words of text / 12,000 words per hour = 5.9 hours = 6 hours awarded for the reading of this textbook, including diagrams, textboxes, and some of the footnotes. The entire text of the clinical monograph is available within the ICHNFM learning interface at NutritionAndFunctionalMedicine.org; because of the simplicity of the interface and also for ease of reading and speed of access on mobile devices, the online text has a simple format without color, graphics, and footnotes. (For chiropractic credits, all hours need to be clocked within the online learning interface.) For those who want to purchase the complete monograph in book format, several options are available per preference of speed of shipping, grayscale printing vs full-color printing, and—new in 2016—digital ebook formats within the larger textbooks:

- **Full-color**: https://www.createspace.com/5518130 with discount code: Q4QKVJBX
- **Black/white printing**: https://www.createspace.com/5520172 with discount code: 9BZJ32PJ
- **Full retail with immediate shipping**: http://www.amazon.com/dp/0990620417/
- **Textbooks & digital ebooks**: The monograph is also included in Chapter 4 of Inflammation Mastery 4th Edition and in the 2-volume set of the same work published as Textbook of Clinical Nutrition and Functional Medicine, Volume 1; both of these books are available discounted from ICHNFM.ORG and in ebook/digital format from major online bookstores such as Amazon.com (via the free Kindle software for phone, iPad, and computer) and Barnes&Noble.

After the course is completely developed and deployed, the several hundred updated presentation slides will be available for discounted purchase as a printed bound book (presentation slides are not distributed electronically, because unethical persons will pirate the material); again, attendees will have access to low-cost discount pricing to cover printing/shipping costs.
Neuroinflammation in fibromyalgia and CRPS is multifactorial

Alex Vasquez

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.

Littlejohn1 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 Hallegra4 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 sensitization7.

Vitamin D deficiency is prevalent in chronic pain and fibromyalgia patients and promotes pain sensitization, myalgia and bone pain (osteomalacia)8. Human clinical trials have shown that vitamin D supplementation can alleviate inflammation, intestinal hyperpermeability, fibromyalgia pain and other neuromusculoskeletal pain. Vitamin D reduces experimental microglial activation9, a component of neuroinflammation and central sensitization.

Mitochondrial dysfunction, noted in fibromyalgia10 and CRPS11, may be triggered by gastrointestinal dysbiosis via LPS, D-lactate, hydrogen sulfide, and inflammation; mitochondrial dysfunction exacerbates and perpetuates microglial activation and glutamatergic neurotransmission12, thereby promoting pain sensitization centrally while also contributing to muscle pain peripherally12. Treatment of mitochondrial dysfunctions with ubiquinone alleviates many biochemical and clinical manifestations of fibromyalgia13. Thus, neuroinflammation in fibromyalgia and CRPS has biological contributions including gastrointestinal dysbiosis, vitamin D deficiency, and mitochondrial dysfunction. These independent contributions commonly coexist, and each of these is additive/synergistic with the others in the promotion of peripheral and central hyperalgesia. The consistent pain-alleviating benefits of treatments for intestinal dysbiosis (antibiotics), vitamin D deficiency (supplementation) and mitochondrial dysfunction (ubiquinone) establish that these painful conditions are multifactorial and maintained by ongoing physiologic insults, each of which is treatable.

Alex Vasquez is at the International College of Human Nutrition and Functional Medicine, Calle Balmes 184, 08028 Barcelona, Spain. E-mail: avasquez@ichnfm.org

3. Videos: Professionally produced and edited presentations are delivered via the learning management system (LMS) online interface. Passing this section and receiving CE/CME credit requires achieving a minimum score of 70%. Students/attendees are allowed to take the test up to five times; the highest score is used for evaluation.

4. Certifying examination: Students/attendees print or download the Certificate of Achievement and documentation/certification of CE/CME hours after completing parts 1, 2, 3 described above plus the exam:
   - Exam for Certificate of Completion (required): Approximately 50 questions (approximately 2 questions per hour of instruction) demonstrating familiarity and competence
   - Exam for Certificate of Excellence (optional): Approximately 50 questions (approximately 2 questions per hour of instruction) demonstrating deeper knowledge and greater mastery of the material

---

<table>
<thead>
<tr>
<th>Items</th>
<th>Topics, Objectives, Clinical Applications</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pretest</td>
<td>Online pretest: allows new students/attendees to interact with the information, concepts, and vocabulary and also to appreciate the level of knowledge acquisition that is expected, so that the appropriate amount of time and effort will be spent with the reading and lecture materials.</td>
<td>1</td>
</tr>
</tbody>
</table>
| 2. Clinical monograph | Text materials are available online and in printed formats: The entire text of the clinical monograph—Human Microbiome and Dysbiosis in Clinical Disease—is available within the ICHNFM learning interface: because of the simplicity of the interface and also for ease of reading and speed of access on mobile devices, the online text has a simple format without color, graphics, and footnotes. (For chiropractic credits, all hours need to be clocked within the online learning interface.) For the complete printed monograph, several options are available per preference of speed of shipping, grayscale printing, or full-color printing:  

1. Full-color, slower shipping: [https://www.createspace.com/5518130](https://www.createspace.com/5518130); discount code: Q4QKVJBX
2. Black/white (cheaper) printing, slower shipping: [https://www.createspace.com/5520172](https://www.createspace.com/5520172); discount code: 9BJ32PJ
4. The monograph is also included in Chapter 4 of Inflammation Mastery 4th Edition and in the 2-volume set of the same work published as Textbook of Clinical Nutrition and Functional Medicine, Volume 1; both of these books are available discounted from ICHNFM.ORG and in ebook/digital format from major online bookstores such as Amazon.com (via the free Kindle software for phone, iPad, and computer) and Barnes and Noble.  

Global Objectives and Clinical Importance:
- Discuss the role of microbial molecules and metabolites in the generation of disease and how to assess and intervene for prevention and treatment of microbe-induced disease
- Identify the pathologic mechanisms/effects/consequences of microbial colonization and know how to assess and intervene for prevention and treatment of dysbiosis-induced disease
- Describe the pathophysiology and treatment of dysbiosis-mediated disease
- Describe the importance, assessment, consequences, and provisional treatment of microbial colonizations
- List the 4 main components of evidence-based medicine:
  1. Published research, including review articles and case reports/series
  2. Physician experience and training
  3. Patient preference
  4. Socioeconomic context, available resources
| 3. Videos | Video #1: Course Introduction & Clinical Impact of Microbial Molecules: Introduction to the human microbiome and dysbiosis; terms and definitions, clinical relevance and contextualization | 2 |

Objectives and Clinical Importance:
- Be able to define and explain the clinical significance of: Dysbiosis, eubiosis, and the associated terminology in immunology, microbiology, and pathophysiology
- Define and explain the clinical significance of: Dysbiosis, Eubiosis, total microbial load (TML), total inflammatory load (TIL), probiotics, prebiotics, synbiotics, increased intestinal permeability (AKA: intestinal hyperpermeability, leaky gut)
- Explain: The role of multifocal polydysbiosis in metabolic and inflammatory diseases
- Analyze/Interpret: Laboratory results for significance and/or lack thereof, demonstrating judicious analysis
- Demonstrate: Knowledge of the means by which microbial molecules and metabolites such as LPS, H2S, and D-lactate lead to various clinical presentations directly or by contributing to complex diseases

Clinical narrative: The information in this presentation is critically important to begin the process of deciphering the enigma of “dysbiosis” into its component and manageable parts. Consistent with the “molecular basis of disease”, our understanding of dysbiosis-induced disease is founded on the appreciation of the effects of microbial metabolites and molecules and the varied pathophysiologic responses/consequences (reviewed in the next video) per patient. By understanding the major molecules involved, we as clinicians can...
translate the vague concept of “dysbiosis” into a concrete understanding of cause-and-effect that can be acted upon clinically.

Video #2: Physiologic and Pathologic Mechanisms of Dysbiosis

Objectives and Clinical Importance:

- Be able to define and explain the clinical significance of: Dysbiosis, eubiosis, and the associated terminology in immunology, microbiology, and pathophysiology
- Explain: Major pathways activated (e.g., LTR, NFkB) by microbial molecules and the clinical consequences (e.g., nonspecific inflammation, impaired CYP450)
  - TLR4—activated by LPS from Gram-negative bacteria
    - Mastery-level: What nutrients/drugs block this pathway?
  - TLR2—activated by exotoxin and cell wall debris from Gram-positive bacteria
    - Mastery-level: What nutrients/drugs block this pathway?
  - NFkB—activated by a wide range of microbial and ROS signals
    - Mastery-level: What nutrients/drugs block this pathway?
  - NLRP3 inflammasome—activated by a wide range of DAMP and PAMP
    - Mastery-level: What nutrients/drugs block this pathway?
  - DAMP—damage/danger-associated molecular patterns, such as result from metabolic and mitochondrial dysfunction
  - PAMP—pathogen-associated molecular patterns, arising from a wide range of microbial exposures such as bacteria and viruses

- Identify: Actionable alterations in microbial patterns, phenotypes of dysbiosis-induced disease
- Demonstrate: Understanding of the pathophysiologic pathways that are activated in dysbiotic conditions
- Implement: Treatment interventions directed at the microbial molecules and their associated pathophysiologic signaling/transducing pathways

Clinical narrative: The information in this presentation helps “bridge the gap” between the vague concept of “microbiome” first to molecules and then to pathophysiologic pathways and responses that lead to the clinical manifestations, which are described in their prototype form in the next video.

Video #3: Prototypic Clinical Patterns of Dysbiosis-Induced Disease

Objectives and Clinical Importance:

- Explain and demonstrate appropriate clinical management of the dysbiotic component of the listed prototypic conditions:
  - Dysbiotic encephalopathies:
    - Hepatic encephalopathy
    - D-lactic acidosis
    - Autobrewery syndrome—one of the irrefutable prototypes of dysbiosis wherein an intestinal overgrowth of yeast ferments dietary carbohydrate into ethanol, allowing persons to become inebriated “drunk” with alcohol despite no intentional/direct/oral intake of alcoholic beverages.
    - Fibromyalgia—this pain syndrome is well-known to be caused by SIBO, which results in mitochondrial dysfunction and activation of the NLRP3 inflammasome, resulting in neuroinflammation and central sensitization to pain
    - Atopic dermatitis / eczema—well-known to be proximally triggered by bacterial inflammogens and an IgE-mediated response to skin bacteria, especially Staphylococcus aureus
    - Insulin resistance and type-2 diabetes—causatively linked with an inflammatory dysbiosis as well as possible dermal overgrowth of Staphylococcus aureus
    - Psoriasis—well-known, thanks largely to the work of Dr Patricia Noah and colleagues, to be triggered by multifocal polydysbiosis
    - Bowel-associated dermatitis arthritis syndrome, short-bowel syndrome—a very elegant model of the effects of SIBO, resulting in multicomponent pathophysiology including generalized inflammation, immune-complex pathophysiology resulting in arthritis/dermatitis/vasculitis, and also cell-mediated bacterial allergy

- Analyze/Interpret: Laboratory results for significance and/or lack thereof; judicious analysis
- Identify: Actionable alterations in microbial patterns, phenotypes of dysbiosis-induced disease
- Implement: Treatment plans consistent with the 4 main components of evidence-based medicine
- Must be able to name and clinically apply a 3-pronged treatment plan addressing each of the 3 main components of dysbiosis

Clinical narrative: The information in this presentation completes the next step in our translation of molecules via pathophysiologic responses to various “patterns of inflammation” that distill into various clinical prototypes; by appreciating these prototypes, clinicians can see the clinical presentation of various patterns of dysbiosis-induced disease

Video #4: Clinical Approach: Testing Microbes vs Treating Dysbiosis and How the Clinical Approach to Dysbiosis Differs from the Approach Used to Treat Infectious Disease

1.25
### Objectives and Clinical Importance:

- **Explain:** Major concepts in dysbiosis-induced disease and specifically explain the relative importance of laboratory testing and microbial identification in the treatment of dysbiosis-induced disease
  - What are the strengths and limitations of laboratory assessment for patients who may have dysbiosis but who do not have evidence of clinical infection?
  - What is the overall clinical value, and what are the adverse effects of excessive laboratory testing?
  - What are the financial and ethical implications of overuse of laboratory testing, as well as the judicious use of laboratory testing which turns out to be inaccurate due to faulty methodology and false advertising?

- **Identify:** Microbe-disease associations from the perspective of dysbiosis rather than from the perspective of classic Microbiology or Infectious Disease

### Clinical narrative:
The information in this presentation provides opportunity and contextualization to enable a broader perspective on the assessment and treatment of microbe-induced disease; most physicians inexperienced with dysbiosis-induced disease will assume that microbe-induced disease requires microbiologic testing and microbe-specific antibiotics—this is not generally and not always true, and the appropriate approach depends on the clinical disease and the suspected microbes, ie, requires knowledge and judgement rather than the reflexive “shoot from the hip approach” of antibiotic prescribing.

---

### Video #5: Dysbiosis by Location—The Mouth

**Objectives and Clinical Importance:** This is the first video in the series on “dysbiosis by location” which is Dr Vasquez’ unique approach to understanding and addressing multifocal polydysbiosis—dysbiosis that occurs in multiple locations via multiple microbes.

- **Be able to define and explain the clinical significance of:**
  - Halitosis—minor problem or major clinical indicator?
  - Systemic diseases associated with orodental dysbiosis and gingivitis
  - Specific microbial association with rheumatoid arthritis and the exact molecular mechanism
  - Clinical means for optimizing orodental health
  - Bacterial translocation from the gingival mucosa

- **Know the strengths and limitations per the research for the following treatments:**
  - Nutritional therapy, especially with folate, ubiquinone, vitamin D
  - Scaling and planing
  - Flossing
  - “Oil pulling”
  - Antiseptic mouthwashes

**Clinical narrative:** The information in this presentation fills some very important gaps in medical education specifically and the education of most clinicians generally; the mouth is one of the most commonly excluded locations from clinical education, having been resigned to the specialty of the dental profession. We now appreciate that orodental health is an indicator and influencer of systemic health, with powerful implications for the pathogenesis of rheumatoid arthritis. Students/attendees should be able to name the exact microbe and molecule connecting orodental dysbiosis with rheumatoid arthritis.

---

### Video #6: Dysbiosis by Location—The Sinuses and Respiratory Tract

**Objectives and Clinical Importance:**

- **Be able to define and explain the clinical significance of:**
  - Dysbiosis of the nares is linked with the following diseases/disorders:
    - ANCA vasculitis, formerly Wegener’s granulomatosis—what is the microbe and what is the exact molecule that lead to vasculitis?
    - Chronic rhinosinusitis—notice the current understanding of this condition, specifically that it is a perfect fit with Dr Vasquez’s description of dybiosis, namely that “persons with dysbiosis-induced disease commonly present with a pathologic inflammatory response to nonpathogenic microbes”
    - Atopic dermatitis—what microbe is the main trigger, how do we rid it from the nares? What other steps need to be taken? What are the instructions and cautions with the following treatments:
      - Clinical interventions—know the implementation and cautions of the following
        - Antibiotic therapy, such as with cephalaxin, trimethoprim/Bactrim
        - Antimicrobial therapy with dilute hypochlorite
        - Antimicrobial therapy with 5% iodine or mupirocin
        - Saline lavage of the sinuses—what is the main caution, what is the name of the most worrisome pathogen, and what are the means to prevent this infection?

**Clinical narrative:** The information in this presentation brings the nose/nares/sinuses into clinical perspective with regard to systemic/dermal/vasculitic diseases; clinicians will learn several different evidence-based approaches to treating dysbiosis-induced disease that originates from the nares and sinuses.
Video #7: Dysbiosis by Location—Genitourinary Tract

Objectives and Clinical Importance:
- Be able to define and explain the clinical significance of: Dysbiosis, eubiosis, and the associated terminology in immunology, microbiology, and pathophysiology
- Explain: The role of multifocal polydysbiosis in metabolic and inflammatory diseases
- Analyze/Interpret: Laboratory results for significance and/or lack thereof; judicious analysis
- Identify: Actionable alterations in microbial patterns, phenotypes of dysbiosis-induced disease
- Demonstrate: Familiarity with the published research, especially the work of Noah and colleagues as well as Rashid and Ebringer
- Implement: Treatment plans consistent with the 4 main components of evidence-based medicine

Clinical narrative: The genitourinary tract is known to be a common location of infection-induced systemic inflammation as appreciated with classic Reiter’s syndrome, which is now termed reactive arthritis. Likewise, available evidence points to the genitourinary tract as a source of microbe-induced immunostimulation in persistent arthritis, such as rheumatoid arthritis.

Video #8: Dysbiosis by Location—Blood, Tissue, Parenchymal Dysbioses

Objectives and Clinical Importance:
- Bacterial translocation to the blood from the gastrointestinal tract
- Bacterial translocation to the blood from the gingival mucosa
- Laboratory findings directly or indirectly consistent with bacterial translocation
- L-form bacteria
- Bonus: Discuss the role of tissue dysbiosis in the genesis and pharmacologic antimicrobial management of chronic low-back pain

Clinical narrative: The information in this presentation provides an eye-opening experience for clinicians by showing the presence of live bacteria in the blood and tissues of patients with common and chronic conditions such as diabetes type-2 (bacterial translocation from the gastrointestinal tract) and low-back pain (bacterial intervertebral disc infection, responsive to drug antimicrobial treatment).

Video #9: Dysbiosis by Location—Skin and Environmental Dysbiosis

Be able to define and explain the clinical significance of:
- Exposure to air-borne microbial immunogens
- IgE-mediated “allergic”-type responses to dermal bacteria in atopic dermatitis

Clinical narrative: The information in this presentation shows how microbes outside of the body—in the nearby environment and on the skin—can contribute to systemic and/or dermal inflammatory disease; students/attendees should demonstrate skill in the use of various treatments and assessments related to the material in this section (written and video).

Video #10: Dysbiosis by Location—Prototypes of Gastrointestinal Dysbiosis

Objectives and Clinical Importance:
- Be able to define and explain the clinical significance of the following microbes along with strategies (as needed) for treatment:
  - Gamma strep, Enterococcus; Group A streptococci,
  - Staphylococcus aureus
  - Segmented filamentous bacteria (SFB)
  - Aeromonas hydrophila
  - Citrobacter rodentium, freundii
  - Hafnia alvei
  - Helicobacter pylori
  - Klebsiella pneumoniae
  - Pseudomonas aeruginosa
  - Proteus mirabilis
  - Blastocystis hominis
  - Dientamoeba fragilis
  - Endolimax nana
  - Entamoeba histolytica
  - Giardia lamblia
  - Candida, yeasts

- Explain: All clinical aspects of the following major prototypes and patterns of gastrointestinal dysbiosis:
  - Insufficiency dysbiosis
  - Bacterial overgrowth, small intestinal bacterial/microbial overgrowth (SIBO/SIMO)
  - Immunosuppressive dysbiosis—eg, mucosal immunosuppression due to gliotoxin
  - Hypersensitivity/allergic dysbiosis—bacterial allergy and IgE-mediated allergic responses to bacteria
  - Inflammatory dysbiosis—classically exemplified by reactive arthritis
### Human Microbiome and Dysbiosis in Clinical Disease

- Amoebas, cysts, protozoas, and other parasites
- Metabolic/dysmetabolic dysbiosis—classically exemplified by diabesity as well as by fibromyalgia
- Neurotoxic dysbiosis—classically exemplified by D-lactate acidosis
- Neuroinflammatory dysbiosis—eg, Bickerstaff brainstem encephalitis resulting from gastroenteritis

**Clinical narrative:** The information in this presentation again helps bring specificity and discernment to huge topic; in this case “gastrointestinal dysbiosis” which exists in discrete patterns, which can overlap; by appreciating each different prototype of gastrointestinal dysbiosis, clinicians will be better able to identify these patterns among patients in clinical practice and will—with study and experience—be able to appreciate when these patterns co-exist and overlap concomitantly.

### Video #11: Dybiosis by Location—Gastrointestinal Dysbiosis Solutions

<table>
<thead>
<tr>
<th>Objectives and Clinical Importance:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analyze/Interpret:</strong> Laboratory results for significance and/or lack thereof; judicious analysis</td>
</tr>
<tr>
<td><strong>Identify:</strong> Actionable alterations in microbial patterns, phenotypes of dysbiosis-induced disease</td>
</tr>
<tr>
<td><strong>Demonstrate:</strong> Skill in clinical reasoning with the clinical use of the following antimicrobial/eubiotic agents and antidybiotic interventions specific to the gastrointestinal tract:</td>
</tr>
<tr>
<td>Dietary modification, including fiber and phytochemical diversity and carbohydrate specificity</td>
</tr>
<tr>
<td>Nutritional supplementation—for example, what is the role of glutamine (and zinc) in the pathophysiology of 1) intestinal hyperpermeability, 2) inflammatory responses mediated by TLR4 and NFkB, and 3) immunodefensive responses. Also, what nutrients have specific modifying effects on the gastrointestinal microbiome?</td>
</tr>
<tr>
<td>Oregano</td>
</tr>
<tr>
<td>Undecylenic acid</td>
</tr>
<tr>
<td>Berberine</td>
</tr>
<tr>
<td>Rifaxamin</td>
</tr>
<tr>
<td>Nystatin</td>
</tr>
<tr>
<td>Diflucan/fluconazole</td>
</tr>
<tr>
<td>Augmentin</td>
</tr>
<tr>
<td>Azithromycin</td>
</tr>
<tr>
<td>Metronidazole/tinidazole</td>
</tr>
<tr>
<td>Oral Vancomycin</td>
</tr>
<tr>
<td>Doxycycline</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Combination botanical medicines—research base and clinical implementation, specifically the relative effectiveness when compared with “standard antimicrobial drug treatment” with rifaxamin, per the recent clinical trial.</td>
</tr>
<tr>
<td>Name the specific dietary protocol that provides the “best case scenario” for the eradication of dysbiosis and the maintenance of eubiosis</td>
</tr>
</tbody>
</table>

**Clinical narrative:** The information in this presentation empowers clinicians to address gastrointestinal dysbiosis from the “worst case scenario” to the “best possible treatment”, while also facilitating 1) early treatment, starting on day #1, 2) reduced reliance on drug antibiotics, and 3) enhanced skill in prescribing.

### Video #12: Gut-Brain Connection

<table>
<thead>
<tr>
<th>Objectives and Clinical Importance:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Be able to define and explain the specific molecular, metabolic, neurologic, and inflammatory pathways involved in the gut-brain axis:</strong></td>
</tr>
<tr>
<td>Microbial metabolites and debris</td>
</tr>
<tr>
<td>Inflammatory pathways activated that alter neurotransmitter synthesis and neurotransmitter reception</td>
</tr>
<tr>
<td>Mitochondrial consequences</td>
</tr>
<tr>
<td>Various mechanisms of neurocortical excitation</td>
</tr>
<tr>
<td>Efferent and afferent signaling via cranial nerve 10</td>
</tr>
<tr>
<td>Laboratory assessments</td>
</tr>
<tr>
<td>Concrete clinical examples of pathophysiology and clinical intervention</td>
</tr>
</tbody>
</table>

**Clinical narrative:** The information in this presentation deciphers the complexity of the “gut-brain axis” into comprehensible and actionable components.

### Video #13: Review, Summary of Major Concepts, Preparation for Certifying Exam

<table>
<thead>
<tr>
<th>Objectives and Clinical Importance:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demonstrate competence in the subject matter by achieving a score of 70% or higher on the final examination</strong></td>
</tr>
<tr>
<td><strong>Illustrate the ability to make proper clinical decisions based on the cases and information provided</strong></td>
</tr>
</tbody>
</table>

---

Syllabus and course design copyright © 2016 International College of Human Nutrition and Functional Medicine® ICHNFM.ORG Page 8
• Interpret laboratory tests and clinical presentations to arrive at the proper assessment/diagnosis and the corresponding treatment of the condition
• Identify important indicators of dysbiotic disease
• Employ/Use laboratory assessments and therapeutic interventions appropriate for the assessment, monitoring, and treatment of microbiome imbalances and dysbiosis-induced disease
• Determine proper clinical actions, doses of drugs and other therapeutics.
• Identify mechanisms by which microbes contribute to persistent disease in the absence of overt infection.
• Advise and educate patients about the role of microbes in their illness in order to enhance patient understanding and treatment compliance.

**Exam**

| Multiple Choice Certifying Exam followed by printing of Certificate of Completion: A second, optional, and more difficult exam is available for attendees who wish to achieve the Certificate of Excellence in this course. | 0.5 |

**Total hours** 30

**Course Delivery:** The intellectual content of this course is delivered primarily via two media—printed monograph and online videos. Students/attendees have 120 days (4 months) from the time of entry (following population of all course materials) in order to complete the course. Additional time can be requested.

**Accreditations for continuing education / continuing medical education (CE/CME):**

- **CME (medical, pharmacy, and nursing):** Accreditation statements:
  - **AMA PRA Category 1 Statement:** This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Foundation for Care Management (FCM) and International College of Human Nutrition and Functional Medicine (ICHNFM). FCM is accredited by the ACCME to provide continuing medical education for physicians. Physicians may only claim those hours in actual attendance. FCM designates this educational activity for a maximum of 30 AMA PRA Category 1 credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity
  - **Nursing Statement:** The Foundation for Care Management is an approved provider of continuing nursing education by the Washington State Nurses Association WSNA A-CNE, an accredited Approver of Continuing Nursing Education.
  - **Pharmacy Statement:** The Foundation for Care Management is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. Objectives appropriate for pharmacists. This activity is 30 Contact Hours Pharmacy Credit. *This CME is Knowledge Based (K).

- **Planning committee and disclosures:** Fair and balanced discussion of any proprietary products/services has been provided. Dr Alex Vasquez has served as a consultant researcher and lecturer for Biotics Research Corporation; he has no financial relationships with laboratory services mentioned. Jeanette Dunn, RN, MSN, EdD, CNS has no financial relationships with products or services mentioned. Lisa Chamberlain, PharmD has no financial relationships with products or services mentioned.

- **Commitments to change—the purpose of continuing medical education (CME):** The general purpose of accredited CME activities is to “bridge the gap” between new information and previous practice routines; new information must be presented to bridge or fill the “knowledge/learning gap” with an emphasis on changing behavior(s) in clinical practice. Attendees/students in this course should generally commit to the following:
  1. Gaining and using a more nuanced and detailed appreciation of the role of the microbiome—in its various main locations as detailed in this course—in various disease states and taking appropriate action with regard to laboratory assessment and clinical intervention.
  2. Appreciating the strength of research supporting the use of nonpharmacologic interventions in the favorable elimination of pathogens and/or promotion of eubiosis; reducing dependency on antibiotic drugs; avoiding the promotion of antibiotic resistance via overuse of antibiotic drugs.
  3. Know the precise interventions for the nonpharmacologic management of dysbiosis per the following: 1) orodental dysbiosis, 2) nares dysbiosis, 3) berberine, 4) oregano oil, 5) hypochlorite, 6) 5% topical iodine, 7) scaling and planing, 8) dietary intervention.

**Course Access, Required Resources, Contact:**

- **Course textbook**—Described above with various methods of delivery and discounts; students purchase their preferred format of book (either full-color or black-and-white printing) and delivery speed/method; the simple text of the book is included in the online educational interface but reading real books is generally considered essential to the learning
process and also provides access to case reports and hundreds of citations to provide vicarious experience and also the confidence needed to implement these protocols in clinical practice.

- Videos, assessments, printing/downloading of certificate—High-speed internet access with standard and current software, specifically including an interface-compatible internet browser; students/attendees enter the course at www.NutritionAndFunctionalMedicine.org. Certificate of completion can be downloaded in PDF format and/or printed via student/attendee’s printer.
- Instructor contact: avasquez @ ichnfm.org

Required and Recommended Resources:

- Required technology: High-speed internet and compatible computer system(s) and software program(s)
- Required textbook: Human Microbiome and Dysbiosis in Clinical Disease; in 2016 this monograph was incorporated verbatim into Inflammation Mastery 4th Ed and Textbook of Clinical Nutrition and Functional Medicine, Volume 1.
  1. The plain text of the book—without footnotes and diagrams—is available within the course
  4. Retail with overnight delivery option: http://www.amazon.com/dp/0990620417/
  5. The monograph is also included in Chapter 4 of Inflammation Mastery 4th Edition and in the 2-volume set of the same work published as Textbook of Clinical Nutrition and Functional Medicine, Volume 1; both of these books are available discounted from ICHNFM.ORG and in ebook/digital format from major online bookstores such as Amazon.com (via the free Kindle software for phone, iPad, and computer) and Barnes and Noble.
- Recommended drug reference: http://epocrates.com/ free online drug/prescribing/interaction reference
- Recommended medical references: Such as Merck Manual https://www.merckmanuals.com/Professional;
  - Microbiology: http://textbookofbacteriology.net/.

You will find this to be a very convenient and effective learning approach: 1) pre-test for familiarity and baseline assessment, 2) reading text, studying diagrams, taking notes, 3) watching expert content delivery, and learning the "conversational style" of the material, and 4) finishing with a final assessment. Self-paced multi-modal learning all from the convenience of your home, office, or favorite cafe or local gym: multi-modal learning allows you to access the material in various ways and various environments to help the material "sink in" via various learning styles, allowing you to make impressive gains in knowledge acquisition and clinical skill-building.

Behavioral Expectations and Terms of Use:

- ICHNFM is committed to creating and maintaining a work environment conducive of optimal teaching and learning, and free from drama and unpleasantness. Among members/students/instructors/attendees, professional-level communication and behavior is expected per common courtesy and standards of etiquette/netiquette. Use of any ICHNFM websites/forums/courses/programs implies agreement with ICHNFM Terms of Use: http://www.ichnfm.org/about. Inappropriate behavior or misuse of ICHNFM materials, as judged by ICHNFM administration, will be judged as forfeiture of access/participation and will result in expulsion/exclusion without refund.
Orientation to ICHNFM learning: www.NutritionAndFunctionalMedicine.ORG

Introduction: Welcome to International College of Human Nutrition and Functional Medicine (ICHNFM) and the available free sample course, which provides you an opportunity to see the layout, content samples, and technical delivery.

Learning and Teaching Styles: Among the many considerations that shape the process of knowledge transfer, five of which shape ICHNFM content delivery are the following:

- **Different people have different learning styles, but everyone benefits from a mix of different approaches:** ICHNFM content delivery meets 4 of the 4 main learning styles:
  1. **Visual learning:** Via graphs, charts, illustrations, and text
  2. **Physical / kinesthetic learning:** Printed books allow highlighting, note-taking, drawing, and hand-written exercises and sample exams to provide a physical-tactile component to learning. People get to actually “touch” the information, draw on it, follow the diagrams physically and mentally. Additionally, with mobile learning, attendees/students can review the videos while exercising or while somehow active but not seated in front of a computer.
  3. **Auditory-digital learning:** Learning by hearing words, concepts, and conversations.
  4. **Auditory-tonal learning:** Learning by hearing tones, emphasis, repetition, rhymes, acronyms, voices, emotions.

- **People learn at their own pace, in their own style:** ICHNFM provides flexibility in timing and methods of access.

- **People need time to review and repeat the information:** Our delivery systems allow for review and rumination, to allow the information to "sink in"; note that this contrasts with the one-time exposure of conferences, which typically only provide superficial exposure to new material. For detailed information that requires practical application in clinical practice, one-time "conference exposures" are among the worst ways to transmit new material.

- **People learn via interaction and conversation:** ICHNFM provides opportunities via forums and conversations for students/attendees to learn the material and to gain additional perspectives.

- **People learn by accountability, feedback, and correction:** One of the greatest adages in modern medical education is that "Assessment drives learning." (Leinster S. Assessment in medical training. Lancet. 2003 Nov) Without assessments, students can delude themselves into thinking they understand the material simply because they learn some vocabulary and some new concepts; we all need to be held to high standards so that we can learn material not simply superficially but to some level of practicality and applicability en route to mastery. Great teachers provide this perspective, challenge, and opportunity.

Assessment of clinical competence

Val Wass, Cees Van der Vleuten, John Shatzer, Roger Jones

Tests of clinical competence, which allow decisions to be made about medical qualification and fitness to practise, must be designed with respect to key issues including blueprinting, validity, reliability, and standard setting, as well as clarity about their formative or summative function. **Multiple choice questions, essays, and oral examinations could be used to test factual recall and applied knowledge**, but more sophisticated methods are needed to assess clinical performance, including directly observed long and short cases, objective structured clinical examinations, and the use of standardised patients. The goal of assessment in medical education remains the development of reliable measurements of student performance which, as well as having predictive value for subsequent clinical competence, also have a formative, educational role.

**Assessment drives learning.** Many people argue that this statement is incorrect and that the curriculum is the key in any clinical course. In reality, students feel overloaded by work and respond by studying only for the parts of the course that are assessed. **To promote learning, assessment should be educational and formative—students should learn from tests and receive feedback on which to build their knowledge and skills.** Pragmatically, assessment is the most appropriate engine on which to harness the curriculum.

THE LANCET • Vol 357 • March 24, 2001
Sample questions:

1. A young child is brought to your office for treatment of eczema. Atopic dermatitis is commonly known as eczema and is generally treated with anti-inflammatory agents (e.g., "steroid cream"), antihistamines, immunosuppressants, immunomodulators, and moisturizers. Patients with atopic dermatitis show increased production of IgE and histamine following exposure to which of the following microbes, and eradication of this microbe via the use of antimicrobials (e.g., cephalexin, diluted hypochlorite baths) results in clinical alleviation:
   A. Candida albicans
   B. Saccharomyces boulardii
   C. Streptococcus pyogenes
   D. Pseudomonas aeruginosa
   E. Staphylococcus aureus
   F. Klebsiella pneumoniae
   G. Escherichia coli

2. Your patient developed an autoimmune disorder following an infection. Amino acid homology produces molecular mimicry, which is necessary for the resultant immune cross-reactivity. Cross-reactivity between sequences in *Acinetobacter* and *Pseudomonas aeruginosa* is most relevant for patients with:
   A. Chronic fatigue syndrome / systemic exertion intolerance
   B. Fibromyalgia
   C. Ankylosing spondylitis
   D. Neuritis
   E. Atopic dermatitis
   F. Psoriasis
   G. Antiphospholipid antibody syndrome

3. Your patient presents with persistent nasal congestion and crusting and had a recent event of hemoptosis. ANCA-associated vasculitis (formerly Wegener’s granulomatosis, also called "granulomatosis with polyangiitis") is a life-threatening autoimmune/vasculitic disease which is most commonly associated with colonization/dysbiosis of which of the following microbes, which produces an antigenic acid phosphatase enzyme which haptenizes to vascular endothelial cells to create an immunogenic neoantigen:
   A. Candida albicans
   B. Saccharomyces boulardii
   C. Streptococcus pyogenes
   D. Pseudomonas aeruginosa
   E. Staphylococcus aureus
   F. Klebsiella pneumoniae
   G. Escherichia coli

4. A radiologist asks you about the mechanism of action and clinical benefits of probiotics. Probiotic foods and prebiotic nutritional supplements have gained wide popular and professional use and acceptance over the past several years. Which of the following are expected to be increased by administration of probiotic bacteria:
   A. Superantigens and LPS and IL-10
   B. BactDNA and H2S and p-cresol
   C. Butyrate and p-cresol and tyramine
   D. Superantigens and p-cresol
   E. Butyrate and IL-10 and Treg
   F. Th17 and IL6

5. Your patient has suffered from a debilitating illness for many years. Which of the following conditions is most noteworthy for being characterized by SIBO, mitochondrial impairment, neuroinflammation ("brain inflammation") and deficiency/insufficiency of L-tryptophan and co-enzyme Q10 (ubiquinone):
   A. Chronic fatigue syndrome / systemic exertion intolerance
   B. Fibromyalgia
   C. Ankylosing spondylitis
   D. Neuritis
   E. Atopic dermatitis
   F. Psoriasis
   G. Antiphospholipid antibody syndrome
6. Your patient has a persistent inflammatory/metabolic disease. The microbial stool analysis did not show evidence of inflammation or dysbiotic colonization, and you suspect the presence of a nonculturable microbe. Segmented filamentous bacteria have been found in the gastrointestinal tract of humans and are specifically and most importantly noted to increase which of the following:
   A. Superantigens
   B. BactDNA
   C. Butyrate
   D. P-cresol
   E. Treg cells
   F. Th17 cells
   G. B cells

7. Your patient wants to be informed of options to hypoglycemic drugs for the treatment of diabetes. The antidiabetic effect of metformin is most similar (clinical effectiveness, impact on microbiome) to which of the following treatments:
   A. Artemesinin
   B. Oregano
   C. Berberine
   D. Rifaxamin
   E. Vitamin D

8. Microbe-induced disorders can be treated with a variety of strategies, including antimicrobial therapy. Eradication of *Staphylococcus aureus* in the nares is most affordably, safely, and effectively accomplished by which of the following:
   A. Trimethoprim-cotrimoxazole
   B. Cephalexin
   C. Povidone iodine
   D. Mupirocin
   E. Vancomycin
   F. Metronidazole

9. The ability to achieve sustained remission in rheumatoid arthritis is impressively low with the use of current immunosuppressive and antiinflammatory drugs (Prince et al. Sustained rheumatoid arthritis remission is uncommon in clinical practice. *Arthritis Research & Therapy* 201214:R68 doi:10.1186/ar3785). In the treatment of the orodental dysbiotic component of rheumatoid arthritis, the most important initial component of the treatment plan, for reducing pain and inflammation, is scaling and planing. Improving orodental health has been shown to reduce pain and inflammation in patients with rheumatoid arthritis. While some of the benefit is via nonspecific reductions in gingival permeability and bacterial inflammogen load/absorption, the specific goal is to reduce/eradicate Porphyromonas gingivalis because of its production of which of the following?
   A. Peptydil-arginine deiminase
   B. Transglutaminase
   C. Acid phosphatase
   D. Peptidase
   E. Protease
   F. Beta-glucuronidase

10. Microbial molecules are capable of inducing a wide range of human physiologic disruption. Which of the following microbial molecules is noteworthy for its abilities to 1) promote systemic inflammation, 2) increase intestinal permeability, 3) impair cytochrome p450 "detoxification" enzymes, 4) impair mitochondrial function and ATP production, and 5) promote pain sensitization via peripheral and central mechanisms:
    A. Lipoteichoic acid
    B. Lipopolysaccharide
    C. Acetate
    D. Peptidoglycan
    E. Bacterial capsule