A letter to the ME/CFS research community (+ doctors, + patients)

October 18th, 2017 by Amy Proal

Dear ME/CFS research community,

My name is Amy Proal. I am a microbiologist who also suffers from ME/CFS. I first became ill with ME/CFS in 2004, while studying medicine at Georgetown University. Almost immediately I began to research the disease from bed and wrote my undergraduate thesis on ME/CFS. Several years later, I obtained a fellowship from Murdoch University (Australia) that allowed me to study the human microbiome. I was awarded a PhD in microbiology in 2011. I've published many peer-reviewed papers/book chapters that discuss how microbiome imbalance can drive inflammatory disease processes (commissioned by the J. Craig Venter Institute, the NIH, and the European Autoimmunity Network among other groups).

When I fell ill with ME/CFS in 2004, few, if any, research teams were seriously studying the disease. Now I am thrilled that an increasing number of researchers across the globe are better analyzing the ME/CFS microbiome, metabolome, immune response and more. The results of these analyses have sparked new, exciting dialogue in the the ME/CFS community. By writing this letter I hope to add several of my own hypotheses/observations to the conversation.

Ample evidence suggests ME/CFS is driven by chronic infection

Most studies on ME/CFS, and the general history of the illness, suggest that infectious agent(s)/environmental exposures plays at least some role in driving the disease process. These include (but are not limited to!) early associations with EBV/HHV6, “autoantibodies”/antibodies detected in patients with the disease, and even the nature of early ME/CFS “outbreaks.” In fact, a significant number of ME/CFS patients I know have fallen ill with the disease after travel to a foreign country, or after a severe viral infection (suggesting a lack of immunity against acquired pathogens/toxins?).

Most of the latest findings on ME/CFS also make sense when viewed through the lens of chronic infection. Reports of cytokine activation in patients with ME/CFS clarify that the disease is characterized by a sustained inflammatory response. Montoya found this cytokine activation increased with disease severity, suggesting patients may struggle with a growing infectious burden over time. Two research teams have shown that the ME/CFS cerebrospinal proteome differs substantially from that of healthy controls. Since the vast majority of metabolites in the human superorganism are microbial in origin, the findings imply that
components of the ME/CFS microbiome may exist in a state of imbalance. Mark Davis and Lab at Stanford recently demonstrated massive clonal T cell expansion in patients with ME/CFS. It's likely these T cells are activated against an infectious threat. Indeed, patients with Lyme disease (known to be driven by infection) demonstrated a T cell response similar to that of the ME/CFS subjects. Another study analyzing the ME/CFS metabolome demonstrated a sustained hypo-metabolic response in patients with the disease. This dour-like state is “triggered by exposure to adverse environmental conditions”, as would be expected if the ME/CFS immune system is overwhelmed by a chronic infectious burden.

Other ME/CFS research teams have detected various forms of mitochondrial dysfunction in patients with the disease. While a number of mechanisms could account for these findings, intracellular pathogens are very capable of dysregulating human metabolic pathways. Also, an increasing number of studies have detected infectious agents in the brains of patients with Alzheimers, epilepsy and other conditions characterized by inflammation/immunosuppression. It's possible that similar pathogens in central nervous system (CNS) tissue could contribute to brain abnormalities reported in patients with ME/CFS. The recent discovery of the human CNS lymphatic system strengthens the likelihood that microbes easily traffic in/out of brain tissue.
The human microbiome persists in tissue and blood

With the above in mind, many research teams have searched for single pathogens in patients with ME/CFS. However, the discovery/characterization of the human microbiome challenges the validity of studying single infectious agents in isolation. Microbes in the human body are now understood to persist in complex communities, where they continually interact with neighboring species. Further, human microbiome ecosystems have now been shown to persist in every human body site/niche (blood, tissue, placenta, amniotic fluid etc). Indeed, just this past month, Stephen Quake and team at Stanford demonstrated the presence of thousands of previously undiscovered bacteria/viruses/fungi in human blood and tissue. These “new” microbes, along with those detected by similar analyses, allow us to study the role of infectious agents in ME/CFS with ample new data.

In addition, a growing number of inflammatory disease states are now tied to dysbiosis or imbalance of human microbiome populations. This dysbiosis is characterized by massive community-wide shifts in microbial population structure, often resulting in decreased species diversity.

Conditions associated with microbiome dysbiosis include type 1 and 2 diabetes, Crohn's disease, ulcerative colitis, psoriatic arthritis, among many others. Dramatic, continual alterations in the microbiome were reported during the development of tumors in a murine model of inflammation-driven colon cancer. These changes were directly responsible for tumor development. Urbaniak and team identified different bacterial profiles in breast tissue between healthy women and those with breast cancer. It follows that further studies of the ME/CFS microbiome (particularly in blood and tissue) may identify similar community-wide imbalances in patients with the disease.

We must study microbiome ACTIVITY

While species-based microbiome analyses (like those described above) are extremely informative, they are unlikely to paint a full picture of the ME/CFS disease process. For one thing, the species composition of any
Microbes often persist in complex biolm communitites. These include geographic location, food consumption, and even time of day (this is particularly true of gut microbiome studies). Many research teams studying inflammatory conditions related to ME/CFS have subsequently been unable to isolate disease-induced microbiome dysbiosis in the face of this “noise.”

To avoid this pitfall, the ME/CFS research community must also study what the microbes in any human ecosystem are doing to drive inflammatory processes. We must examine microbe activity, microbe gene expression, and the myriad ways in which microbes interact with the host immune system, the host genome, and each other.

**Microbes persist in complex communities**

As mentioned previously, microbes in the human body continually interact, both directly and indirectly (the proteins and metabolites they create are also in constant interplay). Microbial communities exhibit synergistic interactions for enhanced protection from host defenses, nutrient acquisition, and persistence in an inflammatory environment. These include biofilm formation and cooperative signaling via quorum sensing peptides.

Even viruses seldom act as single entities. Virgin and team found that enteric virus activity is regulated by “transkingdom interactions” — processes critical to their infectivity, disease induction, and control. For example, the virus MMTV binds lipopolysaccharide (LPS) on the surface of Gram-negative bacteria. This initiates innate immune responses that culminate in host tolerance, transmission, and viral replication.

**Microbes alter their collective gene expression to cause disease**

These interacting microbes often subvert the human immune response by collectively altering their gene expression. Analysis of these gene expression patterns (studies of the metatranscriptome) should be a priority for the ME/CFS research community. Time/money can be saved by studying the methods other research communities have developed to analyze these patterns. For example, Yost and team recently
performed an excellent gene ontology (GO) enrichment analysis of the oral microbiome during periodontal progression.

Gene expression of stable sites did not change over the two-month study period. In contrast, active sites that progressed to periodontitis were easily characterized by several functional genomic signatures. At the breakdown point these active sites expressed genes associated with ferrous iron transport and response to oxidative stress. At baseline, GO terms associated with potassium ion transport and isoprenoid biosynthesis (among others) were highly enriched.

Progression was also correlated with increased expression of putative virulence factors. In addition, ciliary and flagellar motility, as well as chemotaxis genes that direct bacterial movement, were all active at initial stages of periodontitis disease progression. Viral activity was also detected in all samples, with phage and herpesvirus activity higher in progressing sites as compared to baseline samples.

The team concluded that the entire oral microbial community, and not just a few select pathogens, drives the increase in virulence that leads to periodontitis progression. In effect, under conditions of increasing imbalance and inflammation, the whole community appeared to act together as a pathogen. This was supported by the fact that, in active sites, groups of microbes not usually considered pathogens upregulated a large number of putative virulence factors. S. mitis and S. intermedius, usually associated with dental health, were especially active.

### Intracellular “keystone” pathogens may drive microbiome dysbiosis

When it comes to dysbiosis, microbe quantity may be less important than microbe “quality” (what a microbe is capable of DOING). Community-wide shifts in microbiome virulence are often driven by “keystone pathogens.” Keystone pathogens can provoke inflammation even when present as quantitatively minor components of the microbiome. **For example**, P. gingivalis often comprises just .01% of periodontal biofilms,
yet impairs innate immune activity so profoundly that it becomes a central player in biofilm growth and development.

Most characterized keystone pathogens have evolved to persist inside the cells of the immune system. By surviving in this fashion, they can directly interfere with human transcription, translation, and DNA repair processes. Their persistence in the cell cytoplasm further dysregulates the epigenetic environment. If the accumulation of errors resulting from this interference exceeds the capacity of cellular repair mechanisms, serious dysfunction/illness can result.

The millions of proteins and metabolites expressed by intracellular pathogens additionally interact with the host genome, further altering human gene expression in a manner that can promote disease. Even bacterial quorum sensing molecules can dysregulate human pathways. Wynendaele and team found that, in vitro, quorum sensing peptides created by gram-negative bacteria altered human gene expression in a manner that promotes angiogenesis, tumor growth, and neovascularization in colon cancer.

The above is complicated by the fact that microbial proteins and metabolites are often identical or similar in structure to those created by their human hosts. For example, the human body and E. coli generate the same intermediate byproducts when metabolizing glucose. The “molecular mimicry” or sequence homology between these molecules makes it increasingly difficult for the host to recognize “foreign” from “self.”

Dozens of recent studies have better characterized mechanisms by which pathogens colonize and survive inside human cells. These include reorganization of the actin cytoskeleton, remodeling of vacuole proteolytic composition, development of “zipper and trigger” mechanisms, among many others.

**Different pathogens employ common survival strategies**

Identification and characterization of previously undetected keystone pathogens in patients with ME/CFS marks a promising area of research. However, it is likely, and expected, that different keystone pathogens may
be detected in different patients with the disease. This is because many keystone pathogens, or intracellular pathogens, employ common survival mechanisms to persist in host cells/tissue/blood. The metabolic dysfunction driven by these different microbes can subsequently result in similar clusters of human inflammatory symptoms.

The ability of different pathogens to dysregulate activity of the Vitamin D Nuclear Receptor (VDR) is an excellent example of how different microbes can drive similar disease processes. The VDR regulates expression of hundreds of genes, many of which regulate inflammatory/malignant processes (eg. metastasis suppressor protein 1). The receptor also expresses several families of antimicrobial peptides. Microbes capable of slowing VDR activity subsequently facilitate their survival by slowing the innate immune response. Many pathogens frequently linked to inflammatory disease have evolved to survive in this fashion. When lymphoblastoid cell lines are infected with Epstein Barr virus, activity of the VDR is downregulated as much as 15 times. The VDR expresses TACO, a protein critical to intracellular survival of \textit{M. tuberculosis}; not surprisingly then, \textit{M. tuberculosis} has also evolved to slow receptor activity. \textit{HIV}, \textit{Borrelia burgdorferi}, \textit{Cytomegalovirus}, and \textit{Mycobacterium leprae} also dysregulate VDR activity to varying degrees. The fungus \textit{Aspergillus fumigatus} secretes a gliotoxin which significantly downregulates VDR expression. Because disabling the innate immune system via the VDR pathway is such a logical survival mechanism, other uncharacterized microbes may have also evolved to dysregulate receptor activity.

It follows that ME/CFS patients with similar symptoms may not always test positive for the exact same pathogen(s). This trend is likely to continue as an increasing number of analyses examine components of the ME/CFS microbiome. Instead of worrying about these “inconsistencies,” the ME/CFS research community should strive to better characterize even more common mechanisms of pathogen survival.

\textbf{Microbes act differently depending on host infectious history and immune status}
Pathogens detected in patients with the ME/CFS are also regularly identified in healthy subjects. This is particularly true of studies that have searched for EBV, HHV6, cytomegalovirus and other easily characterized viruses in ME/CFS cohorts. While these “overlapping” results are often viewed as problematic, they make sense in light of research that clarifies how differently microbes can act depending on host immune status, neighboring species, and a wide range of other variables. For example, risk of HIV infection is now understood to vary based on the species composition and activity of other microbes in vaginal/penile microbiome communities.

Many microbes assumed to persist in a “commensal” state are also capable of virulent activity. Like their human counterparts, they evolve in the face of changing environmental conditions. For example, *S. aureus* can cause a range of illnesses, from skin infections to life-threatening diseases such as pneumonia, meningitis, and endocarditis. However, approximately 30% of the “healthy” human population harbors *S. aureus* as a member of the normal nasal microbiome. Krismer and team found that *S. aureus* virulence in these communities was determined by a number of factors, especially the signaling/competitive strategies employed by neighboring microbes.

The same is true of *Escherichia coli (E. coli)*, which also persists in numerous forms. One study found that “commensal” *E. coli* could evolve into virulent clones in less than 500 generations. For most microbes, this evolution towards pathogenicity occurs via the acquisition of new genes (a gain of function mechanism), or alteration of the current genome, including gene loss (a change-of-function mechanism). For example, in *Pseudomonas aeruginosa* the loss of mucA increases its ability to resist pulmonary clearance and evade phagocytosis.

**Unique infectious history shapes ME/CFS disease progression**

While keystone pathogens may be identified in ME/CFS, composition of the ME/CFS microbiome will likely differ between patients. Even in HIV/AIDS, where an easily detected virus dysregulates immunity, disease symptoms reflect a mix of those driven by HIV, and those driven by “co-infectious” agents able to take advantage of the immunocompromised host. No two patients with HIV/AIDS are expected to harbor the exact same mix of these other “co-infectious” agents.

This same pattern, in which unique infectious history drives symptom presentation may also occur in ME/CFS. A recent seminal study by Brodin and team demonstrates the profound impact infectious history on host immunity. The team performed a systems-level analysis of 210 healthy twins between the ages of 8 and 82. They measured 204 immune parameters, including cell population frequencies, cytokine responses, and serum proteins, and found that 77% of these are dominated, and 58% almost completely determined, by non-heritable environmental influences. Many of these parameters became more variable with age, emphasizing the cumulative influence of environmental exposure.

The team also calculated how acquisition of ONE chronic pathogen — cytomegalovirus (CMV) — conditions the immune response. Identical twins discordant for CMV infection showed greatly reduced correlations for many immune cell frequencies, cell signaling responses, and cytokine concentrations. In general, the
Influence of chronic CMV on the immune response (Brodin et al)

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Could “successive infection contribute to ME/CFS?”

The above suggests that ME/CFS may be driven by a process I have termed “successive infection.” During the successive infectious process, an “initial event” dysregulates the immune system. This makes it easier for certain microbes to subvert the immune response by acting as polymicrobial entities. Pathogens alter their gene expression in ways that promote community-wide virulence. Infected human cells fail to correctly express human metabolites in the presence of the proteins, enzymes, and metabolites generated by the accumulating pathogenic genomes. Dysfunction due to molecular mimicry accumulates. Intracellular pathogens slow the human immune response, causing the host to more easily acquire other infectious agents. This creates a snowball effect in which the microbiome becomes increasingly dysbiotic as the strength of the immune response decreases.

Eventually, the human host may present with clinically evident symptoms characteristic of ME/CFS or a related inflammatory diagnosis. The unique symptoms any one person develops vary depending on the location, species, and virulence of the pathogens driving dysbiosis, along with the semi-infinite number of ways in which the proteins and metabolites created by these microbes cause dysfunction by interacting with those of the host.

In some cases a specific “trigger” may jump start the successive infection process. For example, between the ages of 3-5 I was repeatedly hospitalized for no less than five severe infectious diseases: viral meningitis, double pneumonia, scarlet fever, measles and German measles (despite receiving the MMR vaccine). My twin sister suffered none of these illnesses and is still healthy today. While I can’t be sure, it’s possible that the pathogens driving these diseases states either persisted in my system, or dysregulated my immune response in ways that made me increasingly susceptible to microbiome dysbiosis over time. For example, the
Successive infection is driven by a patient’s unique infectious history

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Reports of several ME/CFS “outbreaks” over the past decades, in which dozens of people have developed the illness at relatively the same time, may well represent this phenomenon at work. For example, in 2004, many cases of chronic fatigue were reported to occur simultaneously after a water reservoir in Bergen, Norway, was contaminated with Giardia lamblia. Nonetheless, of the approximately 48,000 people who were exposed to the contaminated water, only 5% of the people went on to develop symptoms characteristic of ME/CFS.

The successive infectious process may even begin in the womb. Infants are seeded in the womb, during birth, and after birth by extensive microbiome populations in the placenta, breast milk, and the vaginal canal, among others. Depending on the health of the parents, these communities may already be dysbiotic. The breast milk microbiome of obese mothers has been shown to harbor a different and less diverse bacterial community than that of healthy subjects (Cabrera-Rubio et al., 2012). The amniotic fluid microbiome can predict perinatal complications prior to infant delivery.

Many aspects of “modern” living can additionally drive successive infection. Antibiotic use greatly disrupts the ecology of the human microbiome. For example, C. difficile better exploits other microbes in its community following antibiotic treatment. Antibiotic resistance genes are also regularly transferred from farm animals and produce into the human food supply. The immunosuppressive medications, steroids, and supplements often (paradoxically) prescribed for inflammatory disease further allow pathogens in the microbiome to proliferate. High levels of stress depress the immune response. Electromagnetic radiation from mobile phones and cellphone towers (among other sources) has been shown to lower immunity.

ME/CFS patients should not always be grouped into subgroups

Immunosuppressive effects of measles have now been shown to deplete host B and T lymphocytes for up to three years after “recovery.” As the study’s authors state, this profound immunosuppression “resets previously acquired immunity” and “renders the host more susceptible to other pathogens.”

In other cases, a toxic environmental exposure or the difficulty of enduring a traumatic event may push the immune system to a critical mass such that previously subclinical infections become obvious.

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ME/CFS is a spectrum disorder: patients are required to present with four out of eight required symptoms. If successive infection contributes to ME/CFS, this variability in symptom presentation is expected. Furthermore, factoring “unique infectious history” into the disease process helps explain why patients with ME/CFS often suffer from a multitude of symptoms not included in the official diagnostic criteria.

Because patients with CFS/ME suffer from such diverse symptoms, it has been argued that they should be grouped into separately studied “subgroups.” In some cases this makes sense. For example, studies that distinguish early-stage/late-stage patients may further elucidate how the ME/CFS immune response changes over time. However, if successive infection contributes to ME/CFS, future research should also focus on better understanding the common pathogenesis shared by all subjects.

“Autoantibodies” in ME/CFS are likely created in response to microbes

A number of autoantibodies have been detected in patients with ME/CFS. These include antiphospholipid antibodies, or antibodies directed against neurotransmitters such as serotonin, adrenals, adrenocorticotropic hormone. This has led some research teams to postulate that ME/CFS may be an “autoimmune” disorder.

However, autoantibodies are notoriously polyspecific. The autoantibodies detected in ME/CFS may actually be created in response to pathogens and possess a high degree of molecular mimicry. In effect, when the immune system generates antibodies in an effort to target pathogens, a proportion that are polyspecific may collaterally target human proteins. For example, Lekakh and team found that autoantibodies with polyspecific activity in the serum of healthy donors were able to cross-react with DNA and lipopolysaccharides (LPS) of widespread species of bacteria including Shigella boydii, E. coli, Salmonella, and Pseudomonas aeruginosa. Another analysis found that B cells infected with Epstein Bar Virus secrete antibodies capable of reacting with dozens of self and non-self antigens including albumin, renin, and thyroglobulin.
If the above is true, there is no need to “lump” ME/CFS into a category of “autoimmune disorders.” This is especially true in light of the fact that the “theory of autoimmunity” is being called into question by an increasing number of research teams.

**What about the human genome?**

The discovery of the human microbiome has forced science to redefine the human condition. Our bodies harbor more microbial cells than human cells, and the millions of genes expressed by the microbiome dwarf the approximately 20,500 genes expressed by our human genomes. Humans are subsequently best described as superorganisms, in which the human and microbial genomes continually interact to regulate metabolism. For example, the gene PTPN22 has been connected to rheumatoid arthritis, lupus, and diabetes mellitus. However, PTPN22 expression is also altered by the bacterial metagenome — it is upregulated as part of the innate immune response to mycobacteria.

Under normal conditions, components of the gut microbiome and its corresponding metabolites oscillate in a fashion that exposes them to different gut regions across the course of a day. The host interprets the microbial signals resulting from these interactions and alters its gene expression in a manner that promotes rhythmic homeostasis.

The above suggests that studies of the human genome in isolation are unlikely to paint a full picture of the ME/CFS disease process.

**The ME/CFS metabolome/proteome**

Studies of ME/CFS proteome/metabolome may further clarify metabolic dysfunction in ME/CFS. However, data from these analyses must be interpreted to account for the “molecular mimicry” between byproducts of
Summary of the dynamic relationship between circadian rhythms, intestinal microbiota, and immune response (Rosellat et al)

interactions between the genomes of *E. coli*, *Salmonella*, *Yersinia* and the human genome.

This means proteome/metabolome studies must continually ask: “What are we actually measuring?”: aka do samples contain human byproducts, microbial byproducts, or a mix of both?

The same is true of studies that characterize DNA in human tissue and blood. Sample analysis MUST account for microbial DNA and RNA that the human microbiome exudes from infected cells. For example, Stephen Quake and team recently discovered thousands of new microbes in human blood. They derived their results by correctly separating the microbe DNA in their samples from the human DNA in their samples.

**ME/CFS research must be supplemented by findings from related research communities**

The ME/CFS research community struggles with funding. However, the impact of current grants can be maximized if researchers follow the work of related research communities. Most inflammatory disease states are now connected to microbiome/metabolome dysbiosis. This suggests that common underlying processes may contribute to “separate” disease states.

The high levels of comorbidity and symptom overlap between patients with different inflammatory diagnoses strengthens this assumption. For example, composition of the lung microbiome can predict the onset of rheumatoid arthritis. The figure below demonstrates the profound overlap in disease presentation among patients with a broad range of inflammatory conditions.
It follows that “big picture” studies of the immune system, nervous system, and microbiome can directly inform ME/CFS research. For example, Davis and team reported massive T cell expansion in patients with ME/CFS. However this same trend was observed in cancer and multiple sclerosis. We can follow how the cancer/MS research communities build on these findings and extrapolate parts of this research towards ME/CFS.

Many research teams are also studying how “acute” pathogens can cause chronic symptoms by persisting in latent forms. These include groups studying Zika, influenza, and other well-characterized viruses. For example, tens of thousands of Ebola survivors have developed chronic symptoms months or years after initial infection, including joint pain, eye problems, extreme fatigue, severe pain, and a host of neurological problems. Ebola virus has even been detected in men's semen years after “recovery.” A better understanding of these “chronic sequelae” may also benefit the ME/CFS community.

**Treatment of infection often temporarily increases disease symptoms**

Immunosuppressive therapies represent the standard of care for most inflammatory conditions tied to autoantibody production. Corticosteroids, TNF-alpha antagonists, and rituximab are among the many treatments routinely used to slow immune activity. These treatments often provide short-term symptom palliation but allow pathogens in the microbiome to spread with greater ease.

This pattern is recognized in the context of acute infection. For example, Earn and team recently concluded that using antipyretic medications to suppress fever (and subsequently the immune response) in patients with influenza allowed viral particles to spread more easily between people. Thus, while subjects taking the antipyretic medications felt fewer symptoms, they were actually more contagious.

In contrast, treatments that SUPPORT or activate the immune system may allow patients to better target pathogens over time. Development of such therapies should be a priority for the ME/CFS research community.
However, most “immunostimulative” treatments are characterized by immunopathology—a cascade of reactions including inflammation, cytokine release, and endotoxin release that occur as part of the immune response to microbial death. The death of intracellular microbes is particularly hard for the host to manage, as the body must deal with debris generated from apoptosis and phagocytosis as well as the remains of the dying microbes that once inhabited the cells. The adaptive immune system may also respond to the presence of this pathogenic and cellular debris, generating antibodies in the process.

Immunopathology resulting from microbicidal treatment has been documented for over a century, with symptom presentation varying depending on the nature of the pathogen targeted. First referred to as the Jarisch–Herxheimer reaction, it was originally observed during therapy of secondary syphilis using mercury. Researchers have subsequently noted this reaction in a broad spectrum of chronic diseases such as relapsing fever, Leptospirosis, Brucellosis, and tuberculosis among others. Short-term immunopathology is also part of common acute infectious illness. When a patient develops the flu, symptoms are generated primarily as the immune system releases a host of cytokines and chemokines in response to the presence of the infectious agent.

More recently, an inflammatory syndrome similar to immunopathology has been documented in HIV/AIDS patients undergoing Immune Reconstitution Inflammatory Syndrome (IRIS) following treatment with Highly Active Antiretroviral Therapy (HAART). This condition occurs as HAART enables the once compromised host to target pathogens acquired during periods of severe immunosuppression. A number of prominent and easy-to-culture pathogens have been linked to IRIS: the herpes viruses, cytomegalovirus, hepatitis B and C, *Mycobacterium avium* complex, *M. tuberculosis*, and *Cryptococcus neoformans*. The presence of IRIS in culture-negative patients is common, suggesting many pathogens that cannot be detected without metagenomic tools might also be involved.

Luckily, immunopathology as a result of HAART or related treatments is temporary in nature. In most cases, immunopathology gradually subsides as an increasing number of infectious agents are eradicated. Eventually, patients often “turn a corner”, where they feel better as the body recovers.
While some ME/CFS physicians may feel uneasy about the temporary suffering induced by immunopathology, other research communities have become accustomed to treatments that cause discomfort. For example, the cancer community has developed a number of treatments that activate patient T cells. The “cytokine storm” resulting from these therapies leads to massive (temporary) symptom increases, and has even resulted in death (are infectious agents being killed!?). However, this risk is considered acceptable, as patients who survive the reaction often enter a state of remission.

PS: Hornig and team have reported distinct alterations in plasma immune signatures (including prominent activation of both pro-and anti-inflammatory cytokines) early in the course of ME/CFS. However these alterations were not observed in subjects with a longer duration of illness.

It’s possible that in early-stage ME/CFS, the immune system actively attempts to “battle” an increasing chronic infectious burden. Over time however, pathogens in the microbiome may disable the immune response to a point where “immune exhaustion” occurs. Immunopathology and cytokine production would subsequently drop. The resulting disease state could be compared to a garden, in which healthy plants become progressively stifled by kudzu vine over time.

This pattern suggests that treatments for ME/CFS should be employed as early as possible. Or, as Hornig writes, “alterations in opportunities for intervention may be transient.” This is because any treatment aimed at targeting infectious agents in ME/CFS will be most successful before the immune system becomes overly compromised.

It often takes patients with ME/CFS years to receive a diagnosis. This delay wastes much of the valuable period during which the ME/CFS immune system may be most responsive to treatment. Physicians must subsequently be educated to better recognize early-stage ME/CFS. Also, the ME/CFS research community should prioritize the development of predictive/preventative treatment options.
Fantastic Amy! You’ve given me a useful lens to look at new research through and broadened my understanding of disease. Hopefully other researchers and funders will see this.

Thank you Leela! I’m so glad you found the post to be informative:

So impressed by your ‘letter’ Amy. I have always felt this is an individual war, similarities in human body response but not actual subsets that can be found or identified. We are all ideosyncratic, our exposure has been to different infections, viral, bacterial, fungal, chemical toxins. Having had ME and immune breakdown
to the point of systemic candidiasis, Herxheimer's response was all too real. The sometimes adverse role of some medications subduing the immune response and enabling proliferation and symbiosis among persistent residual pathogens should make us all think. I hope your 'letter' is widely read, and research carried on in wider medical fields is found to be relevant and cost saving. Thank you. (It really exercised my brain, I hope I understood!)

Hi Audrey!

Thanks for such a kind comment. I know I didn't simplify the language of the piece: considering that you seem to follow what I said very well!

I've also dealt with herxheimer in response to fungal therapies. Brutal!

Take care and thanks again for writing,

Amy

A really thought-provoking piece, although it pretty clearly puts the idea of a quick-fix cure in perspective, and makes me think that those of us with ME need to continue to tend to promoting our overall health, including using diet to support the microbiome.

Best of luck with your work. 😊
Hi Janet,

Thanks for your feedback! Yes. A quick fix seems unlikely for those of us that have been sick for years. But like I said at the end of the piece, if we can diagnose very early stages of ME/CFS, treatments will be more effective. These include preventative approaches that attempt to keep the immune system/microbiome from becoming imbalanced in the first place.

Take care!
Amy

Hi Amy,

I read your letter with great interest as it resonates deeply with my own experience. I'd like to share an anecdote with you that I hope you will find interesting.

I am suffering from severe but also highly atypical CFS/ME with objective, idiopathic abnormalities. My disease history implies that the microbiome could play a causal role in those abnormalities and my condition generally.

Five years ago, during the prodromal phase of my ME, an alternative healthcare practitioner gave me a herbal antimicrobial to “kill candida” (which I did not have). Unfortunately, the antimicrobial caused me to crash from prodromal ME into serious illness. One bizarre side effect of the antimicrobial was extremely foamy urine. When I stopped it the foamy urine declined but never went away. As you will know, foamy urine is typically evidence of excess protein in urine, which is a symptom of kidney dysfunction. However, multiple tests over a number of years has never found this to be the case with me.

I believe the origin of the foamy urine may be a microbial metabolite. I have found some anecdotal reports online of others experiencing the same problem. Some have ME whilst others have non-specific symptoms
(painful joints, fatigue, etc). The common denominator is non-proteinuria foamy urine that was triggered by either herbal antimicrobials or prescription antibiotics (e.g. Azithromycin).

I have been attempting to investigate this hypothesis for quite some time. One course of action I have taken is to monitor my gut microbiome with testing from various different labs (American Gut Project, uBuome and Aperiomics). Again and again I am seeing an overgrowth in the same bacteria, paraprevotella. Very little is known about paraprevotella as it is usually a marginal presence in the gut. However, in my case it can account for 20% or more of my microbiome.

This in itself is not necessarily interesting. However, I persuaded one person I am in touch with who also has this strange symptom to also pursue microbiome testing with the American Gut Project. His result came back recently, and he too has a massive overgrowth of paraprevotella, except in his case it accounts for 50% of all the bacteria in his gut!

I am not a statistician, but this seems unlikely to me to be a coincidence that we both have this odd symptom and this unusual overgrowth. Nevertheless, even if there is a relationship, the direction of causality is a complete mystery. I am, however, pursuing treatment of the gut microbiome vigorously in an attempt to alter its composition, but it is proving very stubborn.

Anyway, I don't know if any of this resonated with you, but your letter certainly resonated with me, so I thought I would share my story.

Best wishes
Alex

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**Amy Proal**  Post author

October 27, 2017 at 6:12 pm

Hi Alex,

Thanks for sharing your experience. It's very common IMO, that treatments aimed at targeting Candida actually “stir up” other infectious agents. It's probably a good thing in theory that the immune system becomes more aware of these other pathogens, but the resulting symptoms can be hard to tolerate (as you know!).
That's very interesting about the parapretolla. I'm not even sure what to make of the fact that it accounted for 50% of your friend's microbial gut profile! That's definitely indicative of imbalance.

That being said, I don't know any special "tricks" to improve gut microbiome composition. I hope that the treatments you are currently trying improve with time? If anything helps, please post about it here so that others can benefit.

Good luck!
Amy

PS I'm interested in the Marshall Protocol and LDN as treatment options for ME/CFS, but I am somewhat uncomfortable officially recommending them, as both can be difficult to tolerate, and results vary greatly from person to person.

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Alex
October 28, 2017 at 6:05 pm

Hi Amy,

Thanks for getting back to me.

I do actually take LDN. It has helped me improve from being completely incapable of anything – unable to feed myself or speak to more than a few minutes at a time – to being able to use my laptop, listen to audiobooks, etc. The Marshall Protocol is not something I have seriously considered, as I am concerned that vitamin D deficiency could have deleterious longterm impacts, particularly given that in my current state I am at risk of osteoporosis.

I have tried many of the conventional routes to addressing my dysbiosis, which, at its worst, was so significant that only two genera occupied 70% of my microbiome. However, none of those worked. Most recently I have inoculated with Necator Americanus in recognition of the significant impact that the macrobiome can have on the microbiome and also on the likely role that immune dysregulation plays in ME. Depending on the outcome of that, I aim to have an FMT as I live in the UK and therefore theoretically have access to a clinic (supposing I am well enough to get there).

I have only recently embarked on this treatment direction, so cannot comment as to its efficacy yet. However, I will try to remember to update this post in, perhaps, 6 months or so. If I don't, feel free to send me an email.
to prompt me (I believe you have my email address as it is necessary in order to post here).

Best wishes
Alex

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**Amy Proal**  
*Post author*

November 2, 2017 at 6:55 pm

Alex hey!

Very interesting that LDN has significantly helped you! I'm really glad to hear that. Please do update more about your LDN experience etc in 6 months.

I'm also very interested in your experience if you are able to do the FMT.

Last, I worked with the Marshall Protocol in the early days. I think the vitamin D component of the treatment is not well understood. The following links have some more info on vitamin D:

http://microbeminded.com/2015/12/03/industry-ties-deeply-influence-guidelines-for-calciumvitamin-d-intake/

http://microbeminded.com/the-concept-of-vitamin-d-deficiency-is-flawed/

However, I wouldn't get too caught up with the vitamin D “debate.” Choose the treatments you really think are best for YOU!

Best,
Amy

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**Marcia**

October 27, 2017 at 2:48 pm
Dear Amy,

I'm curious if you still recommend the Marshall Protocol to treat ME/CFS?

Thank you.

Hi Marcia!

Thanks for writing. I still think the Marshall Protocol makes complete sense from a science perspective: aka trying to activate the immune system to better target infectious agents can address the “root cause” of the disease.

However, the Marshall Protocol is a very hard treatment. Patients deal with a huge amount of immunopathology. There are few medications to help “deal” with the reaction. Also, ME/CFS patients (as expected in my opinion b/c the disease is so serious!) often deal with the strongest and most debilitating immunopathology.

In order to manage this immunopathology, patients need a strong support system. By that I mean, I wouldn't attempt the treatment if you don't have someone who can help you on bad days etc. Also someone who really believes you and understands the treatment themselves.

Also, Trevor Marshall (who I still talk to regularly) is now studying the effects of cell phone and related radiation (EMF) on the immune system. He’s found that patients who lower the radiation level of their homes seem to do better on the Protocol. I’m not involved in this research, but it adds an extra layer of “difficulty” to the treatment (you would be encouraged to adapt your house to lower EMF levels).

If all that seems like something you are willing to take on, then I do think the Marshall Protocol is an intelligent treatment option:

Hope this helps and take care,

Amy
Hi Amy,

This was a fascinating read. You've tied so much together!

So, how do we get fixed, then? I've been fixing microbiome, replenishing nutrients, taking LDN and antivirals, doing IV antibiotics and IVIG, and doing hyperbaric oxygen therapy.

All seem to be helping, but wondering if it'll produce a cure. And your description of how these infections are do embedded is a little frightening...

It'd be nice if there were a magic pill, but as there's not, what's the answer?

Thank you!

Sharon hi!

If I had a definitive answer for how to treat ME/CFS I would relentlessly contact every member of the medical community about it;) Unfortunately I don't have definitive treatment advice at the moment. In fact, the main reason I wrote this letter to the ME/CFS is to encourage research that could lead to more information!

That being said, the treatments you are currently trying all make sense to me. In fact, I'm going to try starting LDN in a few weeks myself.
Also, when I first got sick, I did a treatment called the Marshall Protocol. It didn’t cure me, but allowed me to go from totally bedridden to partly functional. However, it’s a very difficult, long, treatment that involves a lot of immunopathology. But you might want to google it to be aware of what it entails.

Take care, and if any of the treatments you are trying help you…please post about them here!

Thanks,
Amy

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**ME/CFS patient**

October 29, 2017 at 12:23 am

Thanks, Amy.

I'd looked at the Marshall protocol previously and it didn't seem like a good fit. I have severe osteopenia due to MCAS, low TSH, low estrogen, and taking hydrocortisone. I have VDR SNPs, too, does that matter? My mother lost 6" of height due to severe osteoporosis from low vitamin D levels – her leg bones actually curve! And I've had cancer. Keeping vitamin D levels high is the advice I've gotten from my doctors and it takes 10,000 IUs daily to keep it at a reasonable level, if I back off, it drops to deficient rapidly.

Thrn, olmesartan contains lactose, not a good fit with my food allergies. I'm on telmisartan to try to help POTS, but contacted the Marshall people and was told only olmrsartan would do and last I checked it can't be compounded.

I'm not sure what you mean by stimulating the immune system. Will IVIG do it? I seem to have significant side effects each time.

Before I started it, I never really felt sick and temperature was low, though I had swollen lymph nodes and evidence of multiple infections.

What else would stimulate the immune system as you've mentioned?

Amy Proal
Hi ME/CFS patient,

By stimulate the immune system, I mean attempt to “support” it, so that pathogens are more likely to be killed. There are very few current mainstream treatments that attempt to do this. Most treatments go the other direction – they slow the immune response in an attempt to palliate symptoms. One of the reasons I wrote this last blog on ME/CFS is to encourage the research community to develop more treatments that could “support” the immune system...

Some alternative therapies and herbs attempt to support the immune system – but I am by no means an expert in that area! Also I don’t know much about IVIG.

As far as the Marshall Protocol goes, I worked with Trevor Marshall in the early days of the treatment. I think the vitamin D component of the treatment is misunderstood. The latest studies do not even support vitamin D supplementation for bone health etc. One of the reasons this is not understood is because the Vitamin D industry does not release that information. This blog post discusses that problem:

http://microbeminded.com/2015/12/03/industry-ties-deeply-influence-guidelines-for-calciumvitamin-d-intake/

Also, I wrote several short blogs about vitamin D “deficiency” etc that you can read here (based off the last book chapter I wrote on the topic for the European Autoimmunity Network):

http://microbeminded.com/basic-concepts/

That being said, I wouldn't get too caught up in this vitamin D debate:) I encourage you to do whatever treatment makes most sense to YOU from the literature you read...

Take care,
Amy
Hi,

very interesting! I think you are so right! Dumping somebody’s immune system is not good. Have you heard about Morley Robbins and his root case protocol? Unbound ferrosan feeds bacteria.

Hi Minna,

Thanks for writing, your English is good! I haven't heard of the root case protocol. But it's interesting that yet another Protocol for treating inflammatory disease has a focus on infection. I do know that microbes use iron for energy production.

If you’re on the Protocol I hope it's helping!

Amy

I mean: unbound iron feeds microbes. I am sorry about my bad english.