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Diagnosis and Integrative Treatment of Intracellular Bacterial Infections in Chronic Fatigue and Fibromyalgia Syndromes, Gulf War Illness, Rheumatoid Arthritis and other Chronic Illnesses

Garth L. Nicolson,* PhD, Marwan Y. Nasralla,*+ PhD, A. Robert Franco,‡ MD,
Nancy L. Nicolson,* PhD, Robert Erwin,* MD, Richard Ngwenya,† MD, and Paul A. Berns,* MD

*The Institute for Molecular Medicine, Huntington Beach, CA 92649 USA,
+International Molecular Diagnostics, Inc., Huntington Beach, CA 92649 USA
‡Arthritis Center of Riverside, Riverside, CA 92501 USA,
†James Mobb Immune Enhancement, Harare, Zimbabwe

Address correspondence to: Prof. Garth L. Nicolson, The Institute for Molecular Medicine, 16371 Gothard St. H, Huntington Beach, CA 92647. Tel: 714-596-6636; Fax: 714-596-3791; Website: www.immed.org; Email: gnicolson@immed.org.

ABSTRACT

Bacterial and viral infections are associated with many chronic illnesses as causative agents, cofactors or more likely as opportunistic infections in immune suppressed individuals. The prevalence of invasive pathogenic *Mycoplasma* species infections (and possibly other bacterial infections, such as *Chlamydia, Borrelia*, etc.) in patients with Chronic Fatigue Syndrome, Fibromyalgia Syndrome, Gulf War Illness, Rheumatoid Arthritis and other chronic illnesses was significantly higher than in healthy controls. When we examined chronic illness patients for multiple *Mycoplasma* species infections, we found that almost all patients had multiple intracellular infections, suggesting that multiple bacterial infections commonly occur in certain chronic illness patients. These patients generally respond to particular antibiotics if administered long-term, but an important part of their recovery involves nutritional supplementation with appropriate vitamins, minerals, immune enhancement and other supplements. Nutraceuticals appear to be necessary for recovery and maintenance of a strong immune system. In addition, patients should be removed from potentially immune-depressing drugs, such as some antidepressants, to allow recovery of their immune systems. Other chronic infections (viral), may also be involved in various chronic fatigue illnesses with or without mycoplasmal and other bacterial infections, and these multiple infections could be important in causing patient morbidity and resulting difficulties in treating these illnesses.

INTRODUCTION

Most if not all debilitating chronic illnesses are characterized by the presence of chronic fatigue (1), the most commonly reported medical complaint of all patients seeking medical care (2). The fatigue syndromes, such as Chronic Fatigue Syndrome (CFS or Myalgic Encephalomyelitis [ME]), Fibromyalgia Syndrome (FMS) and Gulf War Illnesses (GWI), share many complex, multi-organ signs and symptoms (3-6), including immune system abnormalities (7), but are distinguishable as separate syndromes that have muscle and overall fatigue as major signs. These syndromes usually have overlapping signs and symptoms, including muscle pain, chronic fatigue, headaches, memory loss, nausea, gastrointestinal problems, joint pain, vision problems, breathing problems, depression, low grade fevers, skin disorders, tissue swelling, chemical sensitivities, among others (5, 6, 8). Because of the complex nature of these illnesses, many patients are often diagnosed with multiple syndromes, and their potential to recover from their chronic illness is usually poor at best.

Chronic illness patients usually have cognitive problems, such as short-term memory loss, depression, difficulty concentrating and psychological problems that can result in practitioners diagnosing chronic illness patients with somatoform disorders rather than organic problems (6, 8). Thus due to the lack of definitive laboratory or clinical tests that could identify the cause(s) of chronic illnesses, such disorders are thought to be caused for the most part by psychological stressors. In fact, emotional stress is often an important factor in somatoform disorders, and stress itself can have many effects on the hormonal and immune systems that could be detrimental in virtually any chronic illness (9). But we feel strongly that stress alone is unlikely to cause most of the chronic illnesses discussed here, the most classic being GWI (6, 8), where battlefield stress was promoted as the cause of the illness (10). GWI patients are often diagnosed with Post Traumatic Stress Disorder (PTSD), but the evidence that stress or PTSD is the source of GWI is based on the assumption that veterans must have

suffered from stress by virtue of the stressful environment in which they found themselves during the Gulf War (10). The notion that stress is the major factor in GWI or indeed in other chronic illnesses, we feel, is not supported by most evidence that suggests that these illnesses were caused by toxic exposures (10, 11).

There is growing awareness that the chronic fatigue illnesses, such as CFS/ME, FMS, GWI and certain autoimmune illnesses, such as Rheumatoid Arthritis (RA), among others, can have an infectious nature that is either responsible (causative) for the illness, a cofactor for the illness (required but not the only causative factor) or more likely appears as an opportunistic infection(s) responsible for aggravating or causing patient morbidity (8, 11, 12). There are several reasons for this notion, including the nonrandom or clustered appearance of the illnesses, often in immediate family members, the course and signs/symptoms of the illnesses and their responses to therapies based on treatments directed at infectious agents and enhancement of immune responses. Most chronic fatigue illnesses are difficult to treat and do not have effective therapies, and these patients rarely recover from their illnesses (11), causing in some cases catastrophic economic problems. Here we will discuss methods for diagnosing chronic infections in patients with CFS/ME, FMS, GWI, RA and other chronic illnesses and offer some suggestions for appropriate treatments directed at some of the chronic infections that play important roles in these illnesses.

SIMILAR SIGNS AND SYMPTOMS OF CHRONIC ILLNESSES

Most chronic illnesses have complex but relatively nonspecific signs and symptoms that are not characteristic for a particular disease. However, other chronic illnesses, such as RA, are well established in their diagnostic profiles (13, 14). One difference between some of the most common chronic illnesses appears to be in the severity of particular signs and symptoms. For example, in CFS/ME essentially all patients complain of chronic fatigue and joint pain, stiffness and soreness, whereas in FMS essentially all patients complain of muscle and overall pain, soreness and weakness. But when secondary signs and symptoms of these chronic illnesses are compared, they look very similar (6, 8). For the most part, the signs/symptom profiles of CFS/ME, FMS, GWI illnesses *are* similar (Fig. 1). Thus the chronic illnesses under discussion here have overlapping signs and symptoms, suggesting that these illnesses may be related (8). In addition, CFS/ME, FMS and GWI patients often show increased sensitivities to various environmental irritants and chemicals and enhanced allergic responses, suggesting that their immune systems are, at least in part, dysfunctional. This is supported by laboratory studies on the natural immune and other immunological abnormalities in chronic illness patients (7).

The overlapping signs and symptoms of many chronic illness patients are easily documented. For example, the patient signs/symptoms data presented in Figure 1 were obtained using patient Illness Survey Forms to determine common signs and symptoms at the time when blood was drawn from patients for analysis. In this figure the intensity of approximately 120 patient signs and symptoms prior to and after onset of illness were recorded on a 10-point rank scale (0-10, extreme). The data were then arranged into 29 different signs and symptoms groups and were considered positive if the average value after onset of illness was two or more points higher than prior to the onset of illness. The CFS/ME and FMS patients had complex signs and symptoms that were similar to those reported for GWI, and the presence of rheumatic signs and symptoms in each of these disorders indicates that there are also some similarities to RA (13-15) (Fig. 1). Some differences were noted, however, when patients with chronic illnesses without evidence of intracellular bacterial infections were compared to the above groups (Fig. 1). The data suggest that patients with intracellular bacterial infections have more complex clinical signs/symptoms.

In our signs/symptom analyses it was not unusual to find immediate family members who displayed similar chronic signs and symptoms. For example, we found that the spouses and children of GWI patients often slowly developed chronic illnesses with signs and symptoms similar to GWI, but only some time after the return home of veterans who developed GWI (8, 10, 11). That these civilian patients contracted their illnesses from chronically ill family members with GWI was a likely explanation (8) that was supported by the finding of similar chronic infections in these families (8, 11).

CHRONIC INFECTIONS AND MORBIDITY IN CFS/ME, FMS AND GWI

Although chronic illnesses have been known in the medical literature for years, most patients with CFS/ME, FMS, GWI and in some cases RA have had few treatment options. This is probably due to the fact that the underlying causes of most chronic illnesses are unknown and treatments have been mainly palliative or supportive. Even if the causes or triggering events in chronic illnesses are not understood, these illnesses may show similarities in their progression; that is, they could have different initial causes or triggers but similar secondary events that result in progression (8, 11). We have proposed that the secondary event(s) could be opportunistic viral and/or bacterial infections that cause significant morbidity and illness progression (10-12). With time these secondary events may evolve or progress to be important or even dominant factor(s) in determining overall signs/symptoms and treatment

strategies.

Since indirect evidence suggests the infectious nature in at least certain subsets of chronic illness patients (8, 11, 12), we have been examining chronic illness patients for pathogens that could explain, at least in part, their complex signs and symptoms. One type of infection that could fulfill the criteria of association with a wide range of chronic illness signs and symptoms are certain microorganisms of the class Mollicutes (8, 11, 12). This is a class of small bacteria, lacking cell walls and genetics for lipid and other macromolecule synthesis pathways. It is primarily composed of *Mycoplasmas*, and although most species are nonpathogenic, some pathogenic *Mycoplasma* species are capable of invading several types of human cells and tissues and are associated with a wide variety of human diseases (11, 15-19).

Are pathogenic *Mycoplasma* species and other intracellular bacteria (*Chlamydia, Borrelia*, etc.) associated with chronic illnesses such as CFS/ME, FMS, GWI and RA? We (6, 8, 11, 15, 17-19, 24) and others (20-23) have examined chronic illness patients for the presence of mycoplasmal blood infections and have found a strong association with the presence of chronic illnesses. In our studies the clinical diagnosis of these disorders was obtained from referring physicians according to the patients' major signs and symptoms. Blood was collected, shipped over night at 4°C and processed immediately for Nucleoprotein Gene Tracking (NPGT) after isolation of blood leukocyte nuclei (17, 18) or Polymerase Chain Reaction (PCR) after purification of blood leukocyte DNA using a Chelex procedure (6, 8, 15, 19). These procedures are very sensitive and specific and can detect down to a few copies of intracellular bacteria in a blood sample. The sensitivity and specificity of the methods were determined by examining serial dilutions of purified DNA of *M. fermentans*, *M. pneumoniae, M. penetrans* and *M. hominis* in blood samples. Amounts as low as 1-10 fg of purified microorganism DNA were routinely detectable. Using PCR the amplification with the appropriate primers produced the expected fragment size in all tested species, which was confirmed by hybridization with an inner probe or DNA sequencing to confirm the sequence of the PCR product.

We used the NPGT and the PCR procedures to examine chronic illness patients for *Mycoplasma* species and *Chlamydia* species infections. For example, using NPGT to analyze the blood leukocytes of GWI patients we found that 91/200 (~45%) were positive for mycoplasmal infections. In contrast, in nondeployed, healthy adults the incidence of mycoplasmal infections was 4/62 (~6%) (17, 18). Similarly, others have more recently used PCR to examine GWI patients and found that 55% were positive for *Mycoplasma* species and 36% were found to have *M. fermentans* infections (23). The slight difference in percentage of positive patients is probably due to the differences in sensitivities of these two methods. Using PCR procedures 52-63% of CFS/ME and FMS patients (n~1,000) had mycoplasmal infections (6, 19-24), whereas only 6-15% of controls (n~450) tested positive.

An important observation was that patients with chronic illnesses that test positive for mycoplasmal infections usually have multiple infections. When we examined mycoplasma-positive CFS/ME and FMS patients (~60% of such patients are usually mycoplasma-positive) for the presence of *M. fermentans*, *M. pneumoniae, M. penetrans, M. hominis* infections, multiple infections were found in the majority of approximately 100 patients (19). CFS/ME/FMS patients had two (>30%) or three (>20%) species of mycoplasmal infections, but only when one of the species was *M. fermentans* or *M. pneumoniae* (19). We also found higher score values for increases in the severity of signs and symptoms after onset of illness in CFS/ME/FMS patients with multiple infections. Also, CFS/FMS patients with multiple mycoplasmal infections generally had a longer history of illness, suggesting that patients may have contracted additional infections during their illness (19). Most of these patients also show evidence of various viral and *Chlamydia* species infections. Thus it is likely that most CFS/ME and FMS patients have multiple bacterial and viral infections.

DIAGNOSIS OF CHRONIC INFECTIONS IN ARTHRITIS PATIENTS

The causes of rheumatic diseases are for the most part unknown, but RA and other autoimmune diseases could be triggered or more likely exacerbated by infectious agents (25). In some animal species infection by certain *Mycoplasma* species can result in remarkable clinical and pathological similarities to RA and other rheumatic diseases. Aerobic and anaerobic intestinal bacteria, viruses and mycoplasmas have all been proposed as possible agents in the etiology of RA (25-30), and there has been increasing evidence that mycoplasmas may play a role in the initiation or more likely progression of RA (13, 15, 30-32). Mycoplasmas have been proposed to interact nonspecifically with B-lymphocytes, resulting in modulation of immunity, autoimmune reactions and promotion of rheumatic diseases (31), and mycoplasmas have been found in the joint tissues of patients with rheumatic diseases, suggesting their pathogenic involvement in these and other chronic illnesses (29).

Using PCR *Mycoplasma* species are commonly found in RA patients' blood. For example, when Haier et al. (15) and Vojdani and Franco (23) examined RA patients' blood leukocytes for the presence of mycoplasmas, they found that approximately one-half were infected with various species of mycoplasmas. The most common species found was *M. fermentans*, followed by *M. hominis*, *M. pneumoniae* and finally *M. penetrans* (15, 23).

Similar to what we reported in CFS/FMS patients (19), there was a high percentage of multiple mycoplasmal infections in RA patients when one of the species was *M. fermentans* (15).

Mycoplasma species and other intracellular pathaogenic bacteria could be important factors or cofactors in the development of inflammatory responses in rheumatic diseases and for progression of RA. As an example of the possible role of *Mycoplasma* species in rheumatic diseases, *M. arthritidis* infections in animals can trigger and exacerbate autoimmune arthritis in animal models of RA (32, 33). *M. arthritidis* can also suppress immune cells and release substances that act on polymorphonuclear granulocytes, such as oxygen radicals, chemotactic factors and other substances (33). Mycoplasmal infections can increase pro-inflammatory cytokines, such as Interleukin-1, -2 and –6 (34), suggesting that they are involved in the development and possibly progression of rheumatic diseases such as RA. In addition, mycoplasmas have been detected in the synovial fluid of RA patients' joints (29).

A variety of microorganisms have been under investigation as cofactors or causative agents in rheumatic diseases (8, 15, 25, 26). The discovery of EB virus (27) and cytomegalovirus (28) in the cells of the synovial lining in RA patients suggested their involvement in RA, possibly as cofactors. There are a number of bacteria and viruses that are candidates in the induction or progression of RA (15, 25, 26). In support of a bacterial involvement in RA, antibiotics like minocycline can alleviate the clinical signs and symptoms of RA (Table 1) (35). This and similar drugs are likely suppressing infections of sensitive microorganisms like mycoplasmas, although certain antibiotics could also cause other effects in susceptible patients.

MYCOPLASMAL INFECTIONS IN OTHER CHRONIC ILLNESSES

Mycoplasmas have been associated with the progression of immunosuppressive diseases, such as HIV-AIDS (36). These infections have also been associated with certain lethal human diseases, such as an acute fatal illness found with *M. fermentans* infections in non-AIDS patients (37). Importantly, mycoplasmal infections are now thought to be a major source of morbidity in HIV-AIDS (38). Expanding further on this, Blanchard and Montagnier (38) have proposed that certain mycoplasmas like *M. fermentans* are important cofactors in the progression of HIV-AIDS, accelerating disease progression and accounting, in part, for the increased susceptibility of AIDS patients to increased viral replication and additional opportunistic infections. Since most studies on the incidence of mycoplasmal infections in HIV-AIDS patients have employed relatively insensitive tests, it is likely that the actual prevalence of mycoplasmal infections in HIV-AIDS patients is much greater than previously thought and may be associated with a rapid fatal course of the disease. For example, in HIV-AIDS mycoplasmas like *M. fermentans* can cause renal and CNS complications (39), and mycoplasmas have been found in various tissues, such as the respiratory epithelial cells of AIDS patients (40). Other species of mycoplasmas have been found in AIDS patients where they have also been associated with disease progression (41), and it is likely that several viral and bacterial infections are involved in the progression of this disease. In addition to immune suppression, some of this increased pathogenecity may be the result of mycoplasma-induced host cell membrane damage from toxic oxygenated products released from intracellular bacteria (42). Also, mycoplasmas may regulate HIV-1 virus replication. Interestingly, HIV-LTR-dependent gene expression can be regulated by the presence of certain pathogenic mycoplasmas (43).

There is some preliminary evidence that mycoplasmal and other infections are associated with various autoimmune diseases. For example, in some mycoplasma-positive GWI cases some of the signs and symptoms of Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), Lupus, Graves' Disease and other complex autoimmune diseases have been seen. Such usually rare autoimmune responses are consistent with certain chronic infections, such as mycoplasmal infections, that penetrate into nerve cells, synovial cells and other cell types and probably stimulate autoimmune responses by their own or host antigens. Thus the autoimmune signs and symptoms in these patients could be the result of intracellular pathogens, such as mycoplasmas, escaping from cellular compartments and incorporating into their own structures pieces of host cell membranes that contain important host antigens that can trigger autoimmune responses. Alternatively, mycoplasma surface components, sometimes called 'superantigens,' may directly stimulate autoimmune responses (44). Perhaps the most important event, the molecular mimicry of host antigens by mycoplasma surface components, may explain, in part, their ability to stimulate autoimmune responses (45).

Pulmonary infections are often seen in chronic illness patients. For example, asthma, airway inflammation, chronic pneumonia and other respiratory diseases are known to be associated with mycoplasmal infections (46). It has been noted that *M. pneumoniae* is a common cause of upper respiratory infections (47), and severe asthma is frequently associated with mycoplasmal and other infections (48). Chronic illness patients with respiratory signs and symptoms usually have bacterial infections.

An emerging area of interest is the possible involvement of chronic infections in a variety of coronary conditions. Cardiopathies can be caused

by chronic *Mycoplasma* species (49) and *Chlamydia* species (50) infections, resulting in myocarditis, endocarditis, pericarditis and other types of infections. These cardiac infections are often due to *Mycoplasma* species, *Chlamydia* species and possibly other intracellular bacteria and other infectious agents, and they are emerging agents in coronary diseases.

Mycoplasmal infections are also associated with a variety of miscellaneous illnesses, such as *M. hominis* infections in patients with hypogamma-globulinemia (30), and *M. genitalium* infections in nongonococcal urethritis patients (51). Mycoplasmas can exist in the oral cavity and gut as normal flora, but when they penetrate into the blood and tissues, they may be able to cause or promote a variety of acute or chronic illnesses. These cell-penetrating species, such as *M. penetrans*, *M. fermentans*, *M. hominis* and *M. pirum,* among others, can cause infections that result in complex systemic signs and symptoms. Mycoplasmal infections can also cause synergism with other infectious agents. Similar types of chronic infections caused by cell-invasive *Chlamydia, Brucella, Coxiella* or *Borriela* species may also be present either as single agents or as complex, multiple infections in many chronic illnesses (8, 11).

CONVENTIONAL TREATMENT OF CHRONIC BACTERIAL INFECTIONS

Once chronic intracellular bacterial infections, such as *Mycoplasma* species infections, have been identified in the blood of subsets of CFS/ME, FMS, GWI, RA and other chronic illness patients, they can be treated using conventional and alternative approaches. Appropriate treatment with antibiotics should result in patient improvement and even recovery, and this has been found in most but not all chronic illness patients (8, 11, 17, 18, 52-54) (Table 1). The recovery is usually slow and gradual after an initial period of Herxheimer and other adverse reactions that make patients temporarily more symptomatic. This period can last for several weeks. The recommended treatments for mycoplasmal blood infections are usually long-term antibiotic therapy, usually multiple 6-week cycles of doxycycline (200-300 mg/day), ciprofloxacin (1,500 mg/day), azithromycin (250-500 mg/day) or clarithromycin (750-1,000 mg/day), among others (53). Multiple 6-week cycles are required, because few patients recover after only a few cycles of antibiotics. This is probably due to the intracellular locations of mycoplasmas like *M. fermentans* and *M. penetrans* or other bacteria, such as *Chlamydia* species, the slow-growing nature of these infections, their inherent insensitivity to most antibiotics and the persistence of the infections in metabolically inactive forms. For most patients, treatment must be continuous for at least 6 months, followed by additional 6-week cycles of antibiotics, if necessary. Some treat these infections by administration of antibiotics every other day, and some recommend daily dosing. Due to poor gastrointestinal absorption in certain patients or the acuteness of signs and symptoms, intravenous therapy has been used for a few weeks, followed by oral antibiotics. Most patients cannot tolerate intravenous antibiotics for more than a few weeks or complications can then occur, so follow-on therapy with oral antibiotics is necessary.

Can antibiotic therapy be successful in treating intracellular bacterial infections often found in chronic illness patients? Yes, but antibiotics should not be used solely or exclusively to treat intracellular bacterial infections. They have proven successful for many if not most patients; however, many patients eventually fail on antibiotic therapy alone. For example, of 87 GWI patients that tested positive for mycoplasmal infections, all patients relapsed after the first 6-week cycle of antibiotic therapy, but after up to 6 cycles of therapy 69/87 previously mycoplasma-positive patients recovered and returned to active duty (17, 18). Since few patients recovered within 6 months of antibiotic therapy, as discussed above, this is now the minimal recommendation of antibiotic treatment (54). These were relatively young patients (most <25 years of age) that were healthy before their illness, and this could have played a role in their higher response rates compared to civilians with chronic illnesses which tend to be on the average older and not as healthy. The clinical responses that were seen in patients were not due to placebo effects, because administration of some antibiotics, such as penicillins, resulted in patients becoming more not less symptomatic, and they were not due to immunosuppressive effects that can occur with some of the recommended antibiotics. Interestingly, CFS/ME, FMS and GWI patients that slowly recovered after several cycles of antibiotics were generally less environmentally sensitive, suggesting that their immune systems were slowly returning to pre-illness states. If such patients had illnesses that were caused by psychological or psychiatric problems or solely by chemical or viral exposures, they should not have responded to the recommended antibiotics and slowly recovered. In addition, if such treatments were just reducing autoimmune responses, then patients should have immediately relapsed after the treatments were discontinued and they should not have responded to antibiotics that do not suppress immune systems.

Although the majority of GWI patients in these unblinded, initial studies responded to antibiotic therapy, the studies have been justifiably criticized for not being controlled, blinded clinical trials. In the case of GWI, large double-blinded, placebo-controlled studies have recently been initiated using doxycycline. In the case of RA, however, double-blinded, placebo-controlled antibiotic trials using minocycline have been successfully conducted. These trials show that the treatment of RA patients with minocycline is clinically effective and results in

recovery of approximately one-half of an unselected group (not tested for chronic infections) of patients (Table 1) (35, 55). The reason for the incomplete responses among RA patients was probably due to the fact that only a portion of the patients under study probably had intracellular bacterial pathogens as their main clinical problem. Viruses and other pathogens may also play an important role in these patients, and minocycline would not be expected to have any effect on this type of infection.

Another less conventional approach to the treatment of chronic illness patients with intracellular bacterial infections is oxygen therapy. Hyperbaric oxygen, intravenous ozone and hydrogen peroxide have been used to treat anaerobic infections similar to the infections discussed here. Most patients with anaerobic infections respond to such therapy with at least temporary alleviation of signs and symptoms, but additional evidence is needed before one can conclude that such therapy results in sustained suppression of anaerobic infections, such as those caused by *Mycoplasma* and *Chlamydia* species. Since these therapies are mainly cytostatic not cytotoxic, they must be sustained for some period of time. However, the use of long-term protocols that include oxygen therapy is likely to prove useful, and it is certainly beneficial in patients who cannot tolerate antibiotics due to chemical sensitivities or other reasons. In some patients, alternating antibiotic and oxygen therapies may be useful, but this has not been done in a controlled study.

NUTRITIONAL SUPPLEMENTS FOR CHRONIC ILLNESS PATIENTS

For the therapy of chronic illness patients to be successful we believe that a comprehensive approach involving conventional and alternative therapies must be undertaken with each patient. An important part of chronic illness treatment programs should be the use of certain dietary supplements, particularly to boost and maintain immune systems (Table 2). In addition to treatments like antibiotics and antivirals, oxygen therapy and removal of toxic agents from the patients' systems, nutritional supplementation should also be undertaken, especially in those patients with environmental toxic exposures (56). Although for the most part these alternative medical approaches have not been carefully evaluated in blinded trials, practitioners that have used them strongly support their usefulness.

Since chronic illness patients often have nutritional and other deficiencies, these should be corrected with the use of various supplements (Table 2) (53). For example, chronic illness patients are often depleted in vitamins B, C and E, among others, and certain minerals. Unfortunately, patients with chronic illnesses often have poor gastrointestinal absorption capacities. Therefore, relatively high doses of some vitamins must be used (vitamins C and E). Others, such as vitamin B complex, cannot be easily absorbed by the gastrointestinal systems of chronic illness patients, so sublingual or parentral *natural* B-complex vitamins (riboflavin, niacin, vitamin B-6, B-12 and pantothenic acid) should be substituted for oral preparations. General vitamins plus extra C, E, CoQ-10, beta-carotene, folic acid, bioflavoids and biotin are necessary. L- cysteine, L-tyrosine, L-glutamine, L-carnitine, malic acid and flaxseed or fish oils are reported by some to be useful. Certain minerals are also often depleted in these patients, such as zinc, magnesium, chromium and selenium, and these should be supplemented as well (Table 2) (56). One problem with providing supplements in a program that also uses antibiotics is that they cannot be taken at the same time of day as the antibiotics because they may inhibit antibiotic uptake or interfere with antibiotic transport. Another problem is the consumption of foods that can naturally suppress immune systems, such as processed sugar. We generally suggest that chronic illness patients undergoing therapy should make an effort to eliminate if possible sugar, alcohol, caffeine or other foods that may interfere with a patient's immune system.

There are also other important considerations in patients undergoing antibiotic or antiviral therapy (53). Antibiotics deplete normal gut bacteria, which can result in over-growth of less desirable bacteria. To supplement bacteria in the gastrointestinal system live cultures of *Lactobacillus acidophillus* in tablets, capsules or powder are recommended. One product is a mixture of *Lactobacillus acidophillus*, *Lactobacillus bifidus* and other bacteria with FOS (fructoologosaccharides) to promote growth in the gastrointestinal system. Various commercial formulations of probiotics are available to replenish gastrointestinal bacteria that have been killed or suppressed by antibiotic therapy.

A number of natural remedies that boost the immune system can be useful in the therapy of chronic illnesses. Among these are whole lemon/olive extract drink or an extract of olive leaves with antioxidants, plant extracts or purified plant products or milk proteins, such as whey. These products are useful during or after antibiotic therapy has been completed. Although these products appear to help some patients, their clinical effectiveness in various chronic illness patients for the most part has not been carefully evaluated. An exception is a Chinese herbal formulation (Calm Colon; Samra) that has been tested for benefit in Irritable Bowel Syndrome. In a randomized, double-blinded, placebo-controlled clinical trial this formulation was found to be effective in reducing the symptoms of Irritable Bowel Syndrome (57). In some cases natural products are known to stimulate immune systems, as shown in various in vitro assays (58). They should be used by patients during therapy to boost immune systems and especially after antibiotic therapy in a maintenance program to prevent relapse of illness (53).

Traditional herbal supplements have proven useful in the treatment of chronic illness patients (57, 58), especially in a maintenance program to prevent relapse of illness. African and Chinese natural immune enhancers and cleansers can help to restore natural immunity and aid absorption. This is an often overlooked but nonetheless important recommendation (Table 2). Unfortunately, it is difficult to recommend specific supplements as useful in all patients, but many patients that have undergone more traditional antibiotic and/or antiviral therapies often relapse after the therapy is completed without continued support with dietary supplements. Some of the recommended products in Table 2 have mild natural antibiotic, antiviral and antifungal properties, so they can be useful in certain patients. Although these natural products are known to help many chronic illness patients, their clinical effectiveness in GWI/CFS/FMS/RA patients has not been carefully evaluated.

Another consideration is the elimination of drugs that might suppress immunity. We have recommended that patients be taken off antidepressants and other potentially immune-suppressing drugs. Some of these drugs are used to help alleviate certain signs and symptoms, but in our opinion they can interfere with therapy, and they should be gradually reduced or eliminated.

CONCLUSIONS

We have proposed that chronic infections, especially multiple chronic bacterial and viral infections, are an appropriate explanation for much of the morbidity seen in rather large subsets of CFS/ME, FMS, GWI and RA patients, and in a variety of other chronic illnesses. Not every patient, however, will have this as a diagnostic explanation or have the same types of chronic infections. These infections need not be the triggering factor or cause of chronic illnesses and are probably more important in causing progression of disease. Nonetheless, chronic infections may cause most of the morbidity seen in these patients, and selective therapy of chronic infections supports this view. Additional research will be necessary to clarify the role of multiple infections in chronic diseases, but these patients should benefit from appropriate antibiotic, antiviral and nutraceutical therapies that alleviate morbidity. Additional controlled studies should be performed to determine the clinical effectiveness of alternative therapies and nutritional supplements in treating chronic illnesses.

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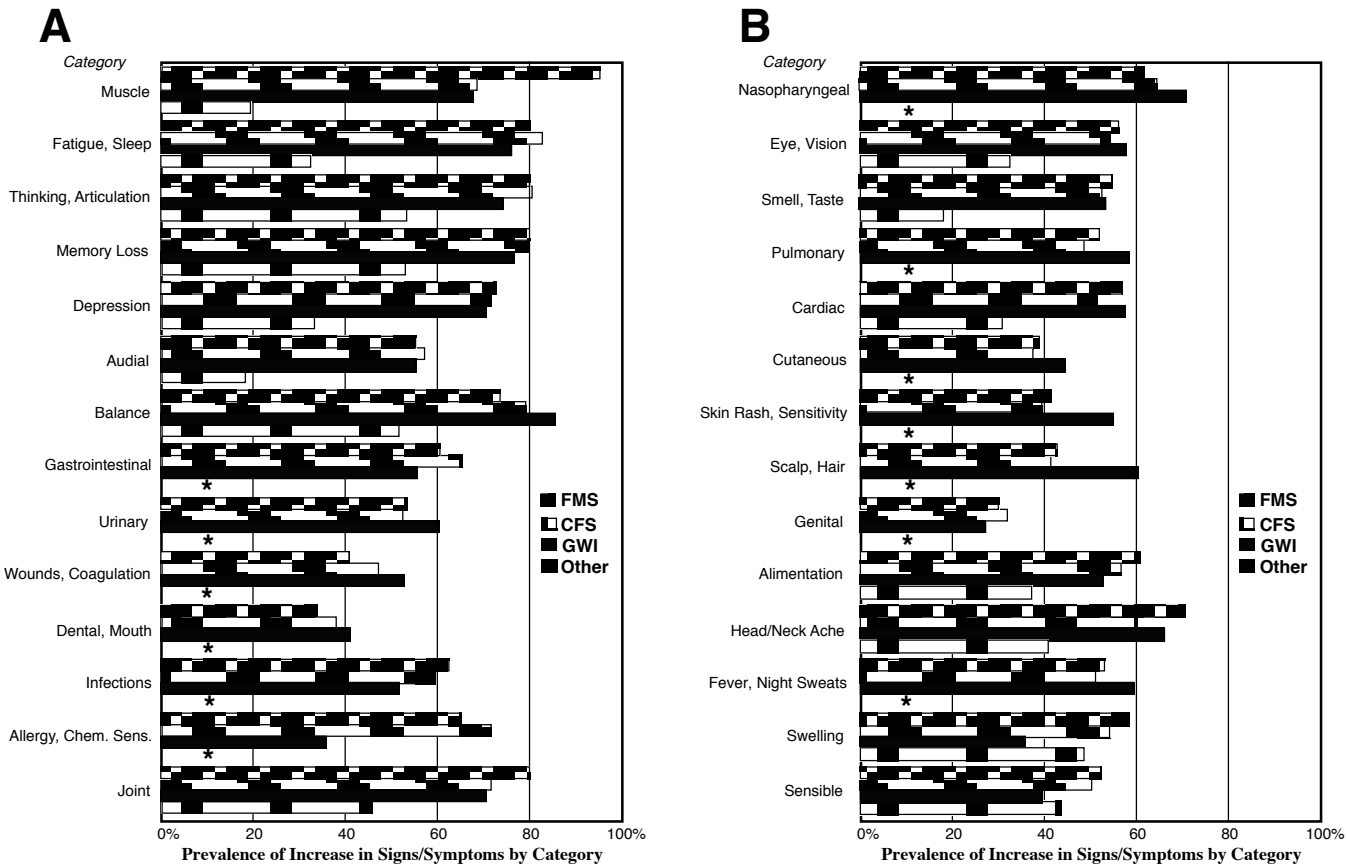
FIGURE LEGENDS

Figure 1A and 1B. Incidence of increase in severity of signs and symptoms in 300 chronic illness patients. Severity of illness was scored using 118 signs and symptoms on a 10-point scale (0, none; 10 extreme) prior to and after the onset of illness. Scores were placed into 29 categories containing 3-9 signs/symptoms and were recorded as the sum of differences between values before and after onset of illness divided by the number of questions in the category. Changes in score values of 2 or more points were considered relevant. Patient groups were: CFS, FMS, GWI or chronic illness patients without evidence of bacterial infection. Asterisk (*) indicates score = 0.


A
Category
Muscle
Fatigue, Sleep
Thinking, Articulation
Memory Loss
Depression
Audial
Balance
Gastrointestinal
Urinary
Wounds, Coagulation
Dental, Mouth
Infections
Allergy, Chem. Sens.
Joint
FMS
CFS
GWI
Other
0%
20
40
60
80
100%
Prevalence of Increase in Signs/Symptoms by Category
B
Category
Nasopharyngeal
Eye, Vision
Smell, Taste
Pulmonary
Cardiac
Cutaneous
Skin Rash, Sensitivity
Scalp, Hair
Genital
Alimentation
Head/Neck Ache
Fever, Night Sweats
Swelling
Sensible
FMS
CFS
GWI
Other
0%
20
40
60
80
100%
Prevalence of Increase in Signs/Symptoms by Category