The Marshall Protocol for Lyme Disease and Other Chronic Inflammatory Conditions

Part Two: Scientific Background, Data, and Case Histories

by J.C. Waterhouse, PhD

Introduction

Part One of this article focused on how to apply the Marshall Protocol (MP) to chronic Lyme disease (a.k.a. post-treatment Lyme disease syndrome) and a variety of other chronic conditions.[1-5] Part Two will discuss the scientific background in more detail after first presenting data and case histories illustrating the effectiveness of the MP in treating a wide range of inflammatory diseases, including diseases associated with aging.

All the conditions responding to the MP appear to have a similar causation by treatment-resistant cell wall deficient bacteria (CWDB) (see Sidebar). The protocol involves immune modulation, which consists of vitamin D reduction and higher than usual dosages of the angiotensin II receptor blocker, olmesartan (Benicar). These two components of the protocol enable the immune system to kill the CWDB weakened by the third component of the MP, namely, very low dosages of certain antibiotics.[1,3]

Role of CWDB and Other Treatment Resistant Bacteria: Evidence

1. Decades of research on difficult-to-cultivate bacteria using different names: cell wall deficient bacteria, L-forms, cysts, filterable forms of bacteria, mollicutes, Russell bodies.[6]
2. Photographic evidence of CWDB and bacterial life cycles in Lyme disease, rheumatoid arthritis, uveitis, sarcoidosis, Alzheimer's disease, Parkinson's disease, etc…[7-9]
3. More recently, treatment-resistant bacterial forms termed nanobacteria, persisters, dormant forms, and biofilms are being studied.[10,11]
4. Failure of past antibiotic regimens to eradicate these bacteria leads to doubts of their importance.[7] This failure appears to be remedied by the Marshall Protocol.[1-5]

Early Results from Ongoing Phase Two Trial

Data

Preliminary results for chronic Lyme disease patients show that of the 51 patients who have been followed on the protocol study site for six to 22 months, 29 are reporting tangible improvement (Reenie Gentile, written communication, July 25, 2006).[3] Marshall[4] also finds significant improvement rates in various other chronic diseases (Table 1). These results probably underestimate the ultimate efficacy of the treatment, because many patients were still in fairly early stages of treatment and were still undergoing strong immunopathology responses to bacterial killing (a.k.a. Jarisch Herxheimer Reactions[1,3]).

Brief Case Histories

The following are brief case histories. (For additional information, please visit http://autoimmunityresearch.org/transcripts/recovery_lax2006.pdf; also see Table 1 for patient improvement rates in other chronic diseases.)

Patient 1 is a 14-year-old boy who has been ill with chronic Lyme disease (with Rickettsial and Chlamydial coinfections) since June 2004. He suffered from chronic severe headaches, debilitating fatigue, a Tourette-like tic occurring every few minutes, blurred/double vision, photophobia, nausea, vertigo, insomnia, and visual tracking problems that prevented him from reading or writing. After 16 months on the MP, all his symptoms have greatly improved, and his tic and visual problems have completely disappeared. He is now able to resume most of his previous activities and continues to improve on the protocol.

Patient 2 is a 58-year-old woman who was diagnosed with Lyme disease in 1999. She had been treated with oral doxycycline in 1999 and 2001. She relapsed after beginning extra vitamin D supplements and increasing sun exposure. Many symptoms have greatly improved in the 29 months since she began the MP, including muscle pain, stiffness and weakness, fatigue, headaches, panic attacks, colitis attacks, nausea, bloating, indigestion, and insomnia. She reports that on the MP, her low back pain has gone from a level 8 to a level 1 on a ten-point scale (attributed to bulging discs at L4 and L5 on MRI), despite decreasing her use of pain medication.

Patient 3 is a 55-year-old female who was diagnosed with rheumatoid arthritis ten years ago. She had previously been on high dose antibiotics (mostly oral, with some IV and IM) for six years prior to the MP and had minimal improvement. Her condition worsened while taking vitamin D prior to the MP (800 to 2400 IU daily over a two-year period). After 29 months on the MP, she reports reduced pain medication use, significantly greater strength and less pain in her hands and upper body, and less fatigue. Recently, her anti-nuclear antibody (ANA) tested negative, after having all 17 prior tests showing elevated levels (usually 1:640 or more).

Patient 4 is a 42-year-old man diagnosed with chronic fatigue syndrome and fibromyalgia. His illness began after he became ill with infectious mononucleosis at the age of 22. Prior to beginning the MP, he could only work two or three days per week and had adverse consequences for days following exercise. He began the MP in March of 2005, and since then, he has had 90-100% resolution of his headaches, light sensitivity, tinnitus, sinus congestion, sore throat, unrefreshing sleep, swelling of fingers and feet, fibromyalgia, and heart palpitations. He has had 70-75% resolution of brain fog, fatigue, and lymph node swelling. He still requires injections of IgG due to a deficiency of IgG3, but the injection interval has increased from an average of 14 days to more than 24 days since commencing the MP. After 22 months on the protocol, he reports feeling markedly better than anytime in the last 20 years and is able to work full time and perform strenuous physical activity.

Patient 5 is a 43-year-old man who had psoriasis since the age of seven, chronic insomnia beginning at the age of 26, and sarcoidosis, diagnosed at the age of 36. His wife had been diagnosed with sarcoidosis several years before. This is in accord with the familial tendency that has been observed among Th1 diseases due to spread of the bacteria among family members. Prior to the MP, numerous treatments had failed to help his psoriasis (e.g., PUVA, steroids, fish liver oil). In contrast, while on the MP, the psoriasis went from 70% coverage of his skin to one percent. The insomnia resolved completely soon after the Benicar was begun. The patient had also suffered from chronic kidney stones, which ceased when he began the protocol. Treatment with the MP has resulted in more than 95% resolution of his symptoms of sarcoidosis (coughing, fatigue, sinusitis, memory problems, muscle aches, etc.), and his chest X-ray is now normal as he continues his fourth year of the MP.

Patient 6 is a 48-year-old woman who was diagnosed with sarcoidosis in 1991. In 1998, she developed seasonal affective disorder (SAD) and began taking anti-depressants every winter to treat the depression. After beginning the MP in October of 2006, she found she was not depressed and did not need her anti-depressant. The combination of taking 40 mg Benicar every six hours and avoiding vitamin D was sufficient to relieve her SAD (she wears a zinc oxide that contains sunscreen to help minimize vitamin D production and NoIR sunglasses). She has only been on the MP for a few months, but finds her fatigue has significantly lessened.

Patient 7 is a 61-year-old woman with presumed sarcoidosis (based on CT scan), with unilateral tibial ➤

Table 1: Improvement Rates in Other Chronic Diseases

	Number of Patients/Numbers Reporting Improvement
Rheumatoid Arthritis	8 / 7
Hashimoto's Thyroiditis	25 / 20
Osteoarthritis	5 / 4
Chronic Fatigue Syndrome CFS/ME	77 / 40
Cardiac Arrhythmia	15 / 9
Sarcoidosis	92 / 57
Type 2 Diabetes	5 / 3
Uveitis	18 / 12
Fibromyalgia	34 / 20
Irritable Bowel Syndrome	10 / 8

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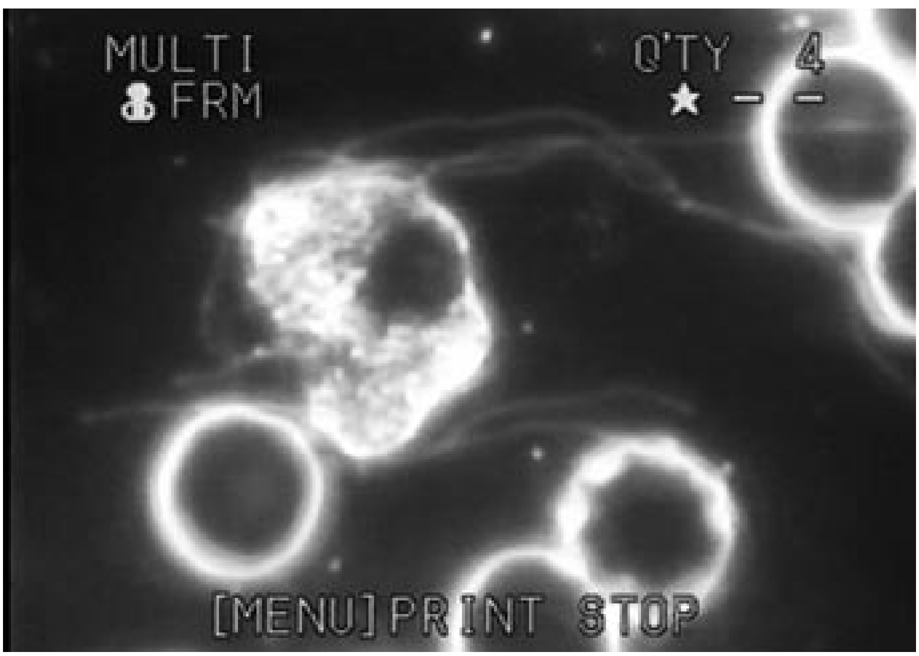
neuropathy presenting with altered sensation, severe foot atrophy, and calf muscle cramps. So far on the MP, she has regained 95% of her muscle tone, strength, and mobility in her foot and leg. Her fatigue, depression, and cutaneous lesions also resolved. Two other examples of severe neurosarcoidosis showing marked improvement on the MP are described elsewhere.[3]

Patient 8 is a 67-year-old man who has had sarcoidosis of multiple organs, including the heart and lungs, for over 20 years. He had a pacemaker implanted in 1995 and has undergone two quadruple bypasses. He had been in atrial fibrillation over 90% of the time in the two years prior to the MP. After three months of treatment with the MP, with no other changes in medication, his atrial fibrillation disappeared and has not returned in the following 20 months. His chest X-rays have improved significantly, and his shortness of breath and fatigue have also improved as he continues on the MP.

Patient 9 is a 51-year-old woman who has been diagnosed with numerous conditions over many years of being ill. Since beginning the Marshall Protocol, her symptoms of Lyme disease (muscle/joint pain, fatigue, cognitive problems) and her Sjogren's syndrome and Raynaud's symptoms have significantly improved. Her myasthenia gravis, diabetes insipidus, gastroesophageal reflux disease, Barrett's esophagus, interstitial cystitis, allergies, multiple chemical sensitivity, and migraines have greatly improved, and her chronic yeast infections (vaginal and esophageal) have completely resolved. She can now read, use the computer, drive a car, and walk without a cane, things she could not do before the MP.



This photograph shows a dying white blood cell from which cell wall deficient bacteria (CWDB), in the form of fine biofilm filaments, appear to be escaping. Biofilm filaments are composed of CWDB and a protective protein sheath. The other cells in this photo are red blood cells.

CWDB (a.k.a., L-forms or cysts) take on many different forms that often allow them to escape destruction by the immune system and/or antibiotics. However, the Marshall Protocol is able to circumvent their resistance mechanisms and successfully treat chronic inflammatory diseases, including Lyme disease, through a specific type of immune modulation combined with very low doses of carefully chosen pulsed antibiotics.

Early photography of CWDB originated nearly a century ago and was continued by the Wirostko, et al., Cantwell, Mattman, and others (3, 5, 6 and http://autoimmunityresearch.org/borrelia-survivalunderadverseconditions.pdf). The extensive photographic record reveals bacteria inside the cytoplasm of cells, as well as in various forms outside of the cells. (Photograph courtesy, Andrew Wright, MD, UK).

Scientific Background of the Marshall Protocol

Th1 Disease: Interferon-Gamma and Vitamin D Metabolites

Before going into more depth on the scientific background of each component of the MP, a brief discussion of Th1 inflammation is needed. In Part One,[1] an overview of vitamin D metabolites in relation to the Marshall Protocol was given. Sarcoidosis was presented as the prototype Th1 illness, in which infected macrophages convert the precursor form of vitamin D (25D) to the active, hormonal form (1,25D) at a high rate.

The T-helper Type 1 (Th1) immune response is usually defined as one that generates significant quantities of the proinflammatory cytokine, Interferon-gamma.[12] Many chronic diseases are associated with Th1 inflammation.[12] A high level of generation of Interferon-gamma (IFN-gamma) can result in an increase in conversion of 25D to 1,25D by activated macrophages by as much as 30-fold[13] and a failure of mechanisms that help regulate 1,25D.[14,15] Since 25D and 1,25-D circulate in the serum and IFN-gamma does not, these vitamin D metabolites can provide a more useful indicator of Th1 inflammation than serum IFN-gamma.[2,5,13,14]

The relationship between IFN-gamma and vitamin D metabolites means low 25D, high 1,25D, and/or a high D-ratio (1,25D/25D) can often be useful in diagnosing Th1 disease.[1,3] However, serum vitamin D tests are not a perfect indicator of Th1 inflammation. For instance, serum levels of 1,25D may not reach high levels, because the IFN-gamma levels may not be as high in some patients, thus allowing regulatory mechanisms to have an effect (e.g., by increasing breakdown of 1,25D by the kidneys). Another possibility is that, in some diseases, the inflamed tissues may receive less circulation. In these less vascularized areas, like the joints, 1,25D may reach high levels locally, but not appear very elevated in the serum.[15-17] In many cases, low 25D may be a good indicator of Th1 disease, because it becomes depleted by rapid conversion by macrophages to 1,25D.[1,2,14,15] However, in other cases, low 25D is less diagnostic, due to higher supplemental/dietary vitamin D ingestion and/or sun exposure raising its level.

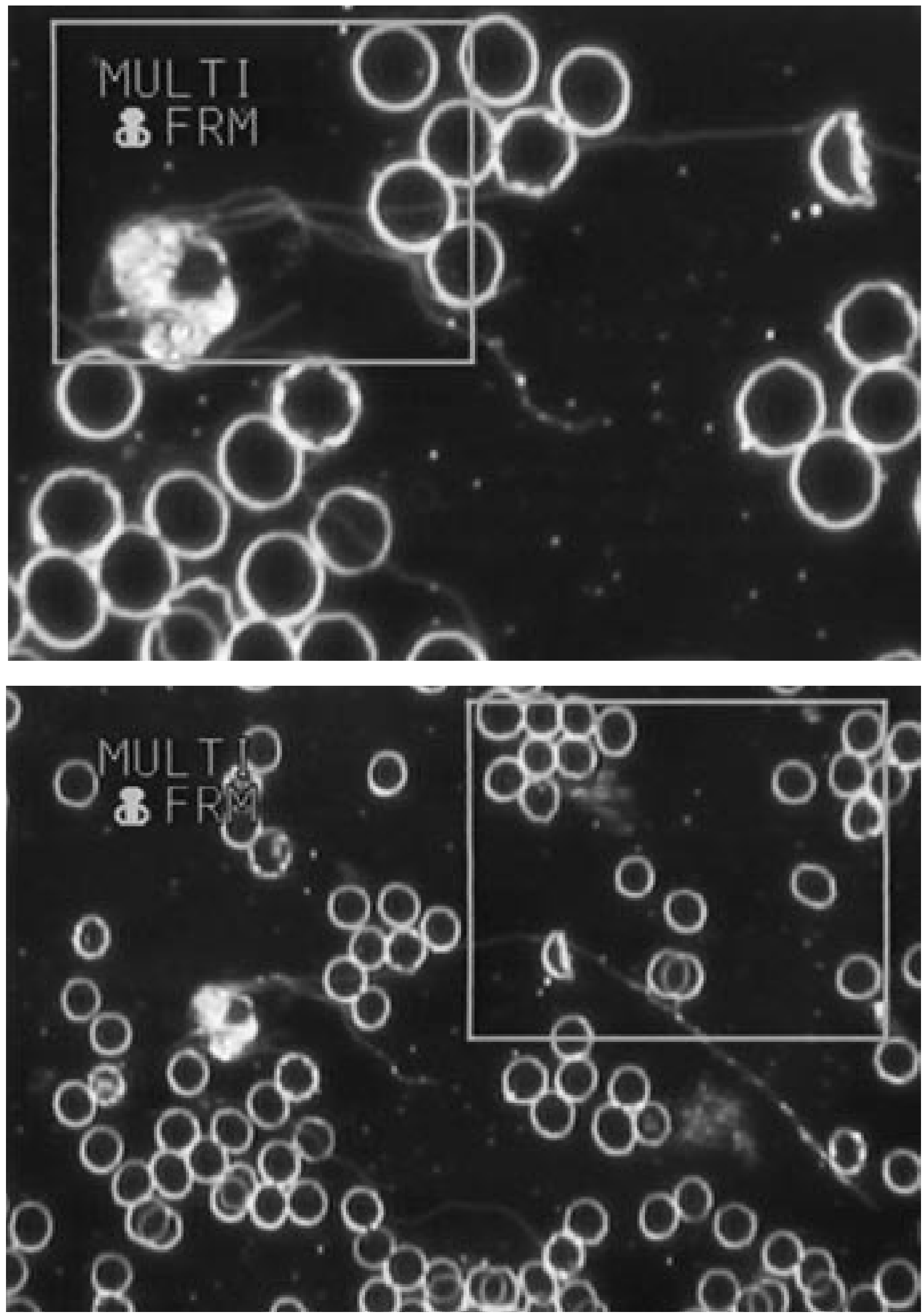
The levels of 25D, 1,25D, and the D-ratio, along with patient responses to therapeutic probes with the MP, support the view that many chronic inflammatory diseases, including chronic Lyme disease, are Th1 diseases caused by treatment-resistant forms of bacteria.[2-4,14,15] Even diseases that had been thought to be Th2 diseases, such as CFS and systemic lupus erythematosis, appear to be Th1 diseases.[3,5,14,15] The connection between low average levels of 25D and various chronic diseases can often be explained by the dysregulated vitamin D metabolism due to infection, rather than a vitamin D deficiency.[14,15]

Vitamin D and Its Role as a Steroidal Immunosuppressant

A number of chronic diseases have appeared to improve in the short term when large dosages of vitamin D are given.[1,17] If the active hormonal form, 1,25D, is tightly regulated, one might wonder how raising its inactive 25D precursor to high levels could have any effect? Molecular modeling results may provide an answer to this question.

Highly sophisticated computer models of the various vitamin D metabolites and the vitamin D receptor (VDR) show that only the 1,25D form is able to activate the VDR.[4,5,12,19,20] The affinity constants calculated show that other forms of vitamin D, including 25D, can bind to the VDR but do not activate it. These results indicate that above a certain level (approximately 20-25 ng/ml), 25D binds to the VDR and blocks receptor activation.

Blocking of the VDR has important consequences for innate immunity, the branch of the immune system that eliminates intracellular organisms. The VDR plays an important role in controlling certain toll-like receptors (TLR2 and TLR4), defensins, and other components of immune function used to detect and kill pathogens.[5] Thus, blocking the VDR with high doses of 25D suppresses the killing of CWDB and other intracellular pathogens. ➤



These photographs are lower magnifications of the photograph on page 87 and illustrate the length of the biofilm filaments and show how strong and cohesive they are.

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The various forms of vitamin D are all secosteroids, closely related to steroids, and the molecular modeling results show that they have a high affinity for various steroidal nuclear receptors.[12,19] In fact, at high enough levels, all the major vitamin D metabolites, including 1,25D, can also bind to the glucocorticoid receptor, alpha 2 thyroid receptor, and sex hormone receptors.[19,20] This can account for the hormonal and neurological changes that often occur when vitamin D metabolites become too high or when they are suddenly reduced by the MP.[1,3] It can also account for the well-known ability of 1,25D to suppress the adaptive immune system.[1,15-17] By binding to the glucocorticoid receptor, high 1,25D levels appear to be able to act in a manner similar to immunosuppressive drugs, such as prednisone.

To summarize, recent evidence indicates that high 25D suppresses innate immunity and high 1,25D suppresses adaptive immunity. It follows that high doses of vitamin D may sometimes produce short term anti-inflammatory effects but cause long-term pathogen increases. Conversely, lowering elevated levels of vitamin D as part of the MP is thought to be crucial to the elimination of persistent pathogens causing Th1 disease.[1-5]

Vitamin D and the Marshall Protocol: Osteoporosis, Inflammation, Cancer Risk

During the MP, vitamin D levels are modulated through restriction of ingested vitamin D and sun exposure.[2,3] Levels are kept in the range that generally maintains bone health, if one consumes adequate calcium. By reducing an elevated 1,25D hormone level, one is better able to maintain bone density, especially near areas of inflammation, where bone loss is more likely.[14,15] Too high a level of 1,25D has been shown to have negative effects on bone density in rheumatoid arthritis and inflammatory bowel disease,[14,15] and a high 25D (>33 ng/ml) has even been found to be a risk factor for prostate cancer.[15,18]

The new view of the role of vitamin D in chronic disease discussed above has required a new interpretation of previous studies on its role in osteoporosis and its relation to secondary hyperparathyroidism, as well as on what is a desirable level of serum 25D.[5,14,15] According to this new interpretation, certain recent assumptions regarding the optimal level of vitamin D have been erroneous.[14] The levels of inflammation and several other hormones, in addition to 1,25D, are seen as key factors in determining bone density.[5,21]

Benicar: An Angiotensin Receptor Blocker

One of the most important immune system effects of angiotensin receptor blockers (ARBs) is their ability to reduce excessive levels of nuclear factor kappa beta through blocking the angiotensin II receptor, thus reducing inflammation and oxidative stress associated with elevated IFN-gamma and TNF alpha.[22,23] Molecular modeling results[5,12,19] show that ARBs are also capable of activating the VDR and thus can produce all the various immune-enhancing effects that the VDR stimulates (see above). When 25D is too high and is blocking the VDR, Benicar is thought to be able to displace it to some extent and thus activate innate immunity.[3]

Benicar also binds to PPARgamma, which affects the function of phagocytic cells and CCR2b, which recruits monocytes to the site of inflammatory immune challenge.[12] Other ARBs bind to these receptors as well, but in some cases, they bind to certain receptors with too high an affinity.[3,19] Experience with the MP has shown that of all the ARBs, Benicar is the most effective for the purposes of the MP.[1,3]

Benicar was generally well-tolerated in safety evaluations, and has few contraindications.[1] Examples of some of the documented protective effects of ARBs include the ability to do the following: 1. prevent migraines,[24] 2. inhibit liver fibrosis and aid liver healing,[25] 3. protect the kidneys in diabetic nephropathy,[26] 4. reduce insulin resistance,[27] 5. protect the heart from damage from inflammation in myocarditis,[28] and 6. protect the mitochondria from age-associated damage from oxidation.[29] In addition, it has been proposed that angiotensin receptor blockers may also have a direct antibacterial effect in addition to their immunomodulatory role.[30]

The MP Antibiotics – Mechanisms of Action

It has been found that patients with Th1 diseases have a wide variety of bacteria contributing to their illness.[3] Used in particular combinations, the MP antibiotics were chosen to work together to target a very wide spectrum of bacteria while minimizing the risk of human toxicity. These antibiotics block protein synthesis, preventing the bacteria from reproducing and reducing their defenses against immune system attack.[3]

Minocycline is used due to its superior lipid solubility, central nervous system and cellular penetration, and broad spectrum ability.[3,5] Minocycline acts primarily by inhibiting bacterial protein synthesis by binding to the 30S ribosomal sub-unit.[3,5] Azithromycin is synergistic with minocycline in that it binds two molecules in the 50S subunit of the ribosome. An important characteristic of this unique antibiotic is its superior tissue penetration[32] and the long period of time in which it remains in the tissues. A different region of the 50S ribosome is blocked by clindamycin. Bactrim (trimethoprim/sulfamethoxazole) acts by inhibiting the enzyme dihydrofolatereductase. Experience has shown that these antibiotics are far more effective when used with the immune modulation of the MP (40 mg of Benicar every six or eight hours and vitamin D reduction) than when used apart from it (see **Caution** below).[1,3]

Future Developments – FDA Designation and Phase 3 Trials

The Autoimmunity Research Foundation has obtained Office of Orphan Product Development, Food and Drug Administration (OOPD FDA) designation for minocycline and clindamycin for treating sarcoidosis, paving the way for phase three clinical trials.[3] Application for OOPD status for post-treatment Lyme disease syndrome (PTLDS) is still pending.

In the future, this new protocol may be applied to many more common diseases. For example,

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Caution Regarding Implementation: The power of these antibiotics is so greatly enhanced by the immune modulation of the MP that patients may have serious or even life-threatening reactions if they do not start at low enough dosages and do not proceed according to the guidelines.[1,3] Starting dosages are usually 25 mg minocycline every other day, 1/16 to 1/8 of a 250 mg tablet once every ten days for azithromycin, 1/8 to 1/4 of a 150 mg capsule every other day for clindamycin, and 1/8 of a Double Strength (DS) or Single Strength (SS) Tablet every other day for Bactrim. One must proceed very slowly and cautiously according to the MP guidelines, starting with minocycline, which is added after acclimation to Benicar.[1,3] The patient must start at these very low antibiotic dosages, even if he or she has previously tolerated much higher dosages prior to the MP.

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the reversal of many age-related, inflammation-associated conditions in patients on the MP may have implications for the future treatment of many diseases of aging, including cardiovascular disease, diabetes, and osteoarthritis.[33]

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Health Care providers are responsible for the use of this information. Neither the ARF, nor the author, assume responsibility for the use or misuse of this protocol.

Note: Neither the author, Dr. Marshall nor the Autoimmunity Research Foundation have any financial connection with any product or lab mentioned with regard to the Marshall Protocol, and the information needed to do the Marshall Protocol is available free of charge on the Internet study site.

Notes

(For links to Dr. Marshall's papers and presentations: marshallprotocol.com/forum2/2274.html)

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Professor Trevor G Marshall, PhD, has research publications ranging through Cryptorchidism, male and female infertility, insulin infusion, Internet technologies, computer design, and molecular biology. Most recently, he has deduced and published a bacterial pathogenesis for the Th1 immune diseases, including sarcoidosis, rheumatoid arthritis, and chronic Lyme disease. From the pathogenesis, a treatment called the 'Marshall Protocol' has been derived and is being implemented by physicians worldwide. Dr Marshall is a director of the Autoimmunity Research Foundation, patron of the Australian Autoimmunity Foundation, and an Adjunct Professor with the School of Biological Sciences and Biotechnology, Murdoch University, in Western Australia.