Marshall Protocol

This document is a one-article summary of key issues related to the Marshall Protocol, especially those relevant to physicians. Many of the topics covered here are reviewed in greater depth throughout the Knowledge Base.

Resources for physicians

We strongly urge physicians and patients to take advantage of the following websites:

MPKB.org – The Marshall Protocol Knowledge Base contains links to the latest peer-reviewed research from ARF as well as articles about hundreds of topics and written for a variety of audiences.

CureMyTh1.org – Short for "Cure My Th1 Disease," CureMyTh1.org is open to all. At CureMyTh1.org, patients can ask questions about the MP, find a doctor, and share symptom reports. CureMyTh1.org is moderated by patient advocates.

MarshallProtocol.com – This site helps patients and physicians better understand the Marshall Protocol. MarshallProtocol.com is currently open to new patients by invitation and contains patients' symptoms reports and science-related discussions. Healthcare providers are encouraged to join the Private Section for Health Professionals forum on the MarshallProtocol.com study site, which is open by email request. MarshallProtocol.com is moderated by Professor Trevor Marshall, members of the research team, and patient advocates.

AutoimmunityResearch.org – At this site one can learn more about the Foundation that supports the Marshall Protocol and explore the full implications of a metagenomic pathogenesis of chronic disease.

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Bacteriality.com - Amy Proal's interviews with MP patients, together with articles about the science underlying the protocol.

While the physician is responsible for patient care, patients can do at least some of the footwork, retrieving information so that the physician can make fully informed decisions. Indeed, without active participation of patients at MarshallProtocol.com or CureMyTh1.org, Autoimmunity Research Foundation does not support or license the public use of this therapy.

Background and scientific rationale for the therapy

The Marshall Protocol (MP) is the name given to a therapy devised by Professor Trevor Marshall. Based on the pathogenesis Marshall has proposed for chronic inflammatory disease, the MP is aimed at targeting bacteria, fungi, viruses, and other microbes that appear to interact to cause chronic inflammatory diseases.

Marshall (and colleagues) have hypothesized that chronic inflammatory diseases, including many autoimmune diseases, are caused by dysbiosis of a metagenomic microbiota: communities of microbial pathogens, many of which persist intracellularly. A recent peer-reviewed paper describes this Pathogenesis in more detail.[1]

Supported by Autoimmunity Research Foundation, the MP has been available since 2002 and has been used in a wide range of chronic inflammatory illnesses.

A significant number of patients diagnosed with sarcoidosis, post-treatment chronic Lyme syndrome, chronic fatigue syndrome, uveitis, Hashimoto’s thyroiditis, rheumatoid arthritis, fibromyalgia, diabetes type II, psoriasis, lupus (SLE), multiple sclerosis, and a number of other diagnoses are showing a promising response from being treated with the Protocol.

In determining whether a patient can be successfully treated with the MP, a specific chronic disease diagnosis is not as important as the clinical assessment by a knowledgeable health care provider, the results of a therapeutic probe, and outcome of the vitamin D

metabolites blood test.[2]

According to the Marshall Pathogenesis, chronic inflammatory disease is characterized by dysregulation of the nuclear receptor pathways which control the innate immune response. For example, the Vitamin D nuclear receptor (VDR) expresses many of the body's antimicrobial peptides (along with TLR2). In addition to down-regulation of expression of the VDR itself by many common bacteria and viruses, antagonistic microbial metabolites incrementally block ligands from activating it. Ingested vitamin D slows activity of the receptor in this same manner, preventing the body from killing the pathogens at the heart of the disease state. That is why avoidance of ingested vitamin D (in food and supplements) is essential for the innate immune system to function correctly while patients are on the MP.[3] [4]

The MP uses multiple daily dosing of olmesartan medoxomil (Benicar, Olmecip, Olmetec) to re-activate the Vitamin D Nuclear Receptor, dislodging bacterial ligands in the process. This drug was developed as an Angiotensin II Receptor Blocker (ARB) but it has multiple actions in the human body when dosed as defined by Marshall. In addition to immunostimulation via the VDR, Olmesartan also reduces inflammatory cytokine production by inhibiting the NF kappa-B transcription pathway. This inhibits, among other things, the release of TNF-alpha, helping to protect the organs from effects of excessive inflammation.

Additionally, several pulsed, low-dose, bacteriostatic oral antibiotics may ***optionally*** be used. Five bacteriostatic antibiotics: minocycline, azithromycin (Zithromax), clindamycin, sulfamethoxazole-trimethoprim (Bactrim DS), and demeclocycline (Declomycin) have been found useful. Minocycline directly acts in an immunosuppressive manner on the PXR nuclear receptor, and this biochemical action may be useful in pulsing immunopathology to (for example) a 48 hour cycle.

N.B. azithromycin is no longer recommended for use while on the MP.

Seriously ill patients may develop photosensitivity during the healing process, so avoidance of direct and indirect sunlight may be necessary. Patients may need to protect their eyes from bright lights to prevent further retinal damage and reduce neurological symptoms

due to *inter alia*, the effect of ocular 1,25-D production on the brain.

Patients may also develop sensitivity to skin exposure to sunlight, and/or find that they need to avoid skin exposure to sunlight in order to maintain the low blood levels of vitamin D required by the Protocol. However, some patients do not experience significant photosensitivity during recovery, and those who do often find it more manageable several years into the therapy.

Immunopathology

When patients on the MP kill bacterial pathogens they experience a reaction called immunopathology. Immunopathology is an increase in one's present symptoms of Th1 inflammation, or a return of previous Th1 inflammatory symptoms, that is caused largely by cytokines generated by the immune response and endotoxins released from dying bacteria. Occasionally, immunopathology will result in a new symptom or abnormal laboratory value (e.g., elevated creatinine, elevated liver enzymes, low white blood count, etc.). The occurrence of subclinical bacterial inflammation is due to olmesartan's activation of the immune system. Immunopathology appears to be a necessary part of recovery. The amount of immunopathology a patient experiences on the Marshall Protocol (MP) tends to correlate with disease severity and bacterial load. Patients who are less sick will have comparatively less-strong immunopathology.

Immunopathology is sometimes used synonymously with the "Jarisch-Herxheimer reaction" or "herx."

Many MP patients who have experienced prolonged periods of immunopathology have reached stages of significant improvement or remission. This supports the conclusion that immunopathology is a necessary result of chronic bacterial death, and a precursor to disease reversal. The MP is not unique in this regard. A number of other diseases and/or therapies generate immunopathological or immunopathological-like reactions.[5] [6] [7]

Lab work and patient reports can be used to track clinical signs of immunopathology.

Patient eligibility and prerequisites

The Marshall Protocol has been used in a variety of chronic inflammatory diseases. The gold standard for evaluating whether the MP is warranted is the therapeutic probe, a brief trial of the Marshall Protocol to see if olmesartan medoxomil and pulsed low-dose minocycline will generate an immunopathological response. The results from a vitamin D metabolites test, while less definitive, may also suggest the presence of treatable condition. For an automated interpretation of the vitamin D metabolites, consult the Vitamin D Metabolite Calculator.

Other patient groups:

Pregnant/lactating women – Both olmesartan and minocycline, the two mainstay medications of the MP, are contraindicated during pregnancy and while breastfeeding. Women of childbearing age on the MP should take adequate contraceptive precautions.

Children – Children with certain diseases and conditions have been treated with the MP. There are more than a dozen in the study cohort who are doing well. The FDA recently approved the use of olmesartan for hypertensive children ages 6-16.

Before commencing therapy, physicians and patients should familiarize themselves with the pre-MP checklist, which reviews the medications, eye protection, and possible lifestyle modifications necessary for treatment success and safety.

Safety considerations

Some patients' immunopathology may be difficult to control - While most patients can adjust their antibiotics or levels of olmesartan in order to successfully tolerate immunopathology on a day-to-day basis, immunopathology in patients with severe forms of disease may be difficult to control. Physicians should help their patients learn the strategies for managing immunopathology.

Knowing how to manage the MP independently on a day-to-da basis will serve patients well should an urgent situation occur. Patients should be urged to seek support from the Foundation's websites.

- Patients on the MP should not take nimesulide (Aulin / Mesulid / Nimed). It could cause bleeding. One death has been reported during its use.

- ***Azithromycin*** is no longer regarded as safe, even in the small quantities formerly recommended for optional use while on MP

- **For sicker patients, immunopathology can be physically and mentally challenging** – Support from a knowledgeable doctor and family/friends becomes of paramount importance. Unless the patient has a good insight into IP and other inconveniences of the treatment, the patient should not start treatment.

Non-MP treatments

While there are notable exceptions, the Marshall Protocol (MP) should not be combined with any other protocols, treatments or supplements, especially those which are immunosuppressive or immunomodulatory. Using other treatments while on the MP can impede progress on the MP – or be dangerous to MP patients.

For intolerable symptoms, certain palliative medications such as sleep medication, pain medication, and antidepressants are acceptable. It is generally recommend that MP patients use the lowest dose of medication that is effective.

The following is a summary of common medications that have the potential to interfere with the MP. A more complete list of medications is available in the Non-MP treatments article.

- **Antibacterials** – Sulfusalazene, Plaquenil and Methotrexate are antimetabolite antibiotics with actions similar to Bactrim and may produce unwanted or uncontrolled immunopathology. They *must* be discontinued before starting the MP.

Antibiotics for acute infections – Olmesartan greatly potentiates the action of many antibiotics. Consequently, a severe or life-threatening immunopathological reaction may result if non-MP antibiotics are prescribed for an acute infection. Olmesartan should not be withdrawn during these periods as it protects vital organs from damage by cytokines. If a non-MP antibiotic is temporarily needed for an acute infection, please follow the instructions in the Notice for emergency medical personnel.

Anticoagulants – Olmesartan may profoundly affect the anticoagulant dosing requirement. It is absolutely essential to closely monitor any patient on anticoagulant therapy.

Antifungal agents – Medicines such as Diflucan and Lamisil are known to interfere with vitamin D metabolism and are generally contraindicated.

Antiviral agents – Antivirals may have profound effects on the immune system as well as a number of serious adverse effects. Routine use is generally contraindicated for MP patients.

Bisphosphonates – May cause calcium deposition into the soft tissues, reduced organ function and possible osteonecrosis of the jaw.

Calcium supplements – Should be avoided in the presence of hypercalciuria or hypercalcemia. Those without these conditions should generally consume 1000-1500 mg calcium daily, preferably from whole foods, but if this is not possible, calcium supplements without vitamin D are acceptable.

Corticosteroids – Therapy will not be effective while corticosteroids are suppressing the immune system. Begin or continue the gradual weaning process with the assistance of palliation from olmesartan. ACTH and cortisol production may be monitored to assess adrenal function.

Diuretics – Some diuretics including the thiazides are contraindicated for MP patients. If a diuretic is necessary, Lasix is preferred.

Folic acid (prescription or over the counter) – Folic acid makes it easier for occult bacteria to replicate and create new DNA. Consuming a balanced diet low in supplemental folic acid should provide adequate folic acid.

Hormonal Replacement Therapy (e.g. progesterone, estrogen and testosterone) – Because hormonal supplementation can interfere with the activity of many of the nuclear receptors, hormonal supplementation is contraindicated. However, under certain circumstances, patients may continue hormone replacement therapy, until they are able to wean from it. See article on hormonal replacement therapy.

Interferon therapy – Interferon therapy is immunosuppressive, reducing in number both cytokines and immune cells.

Intravenous Immunoglobulin (IVIG) – IVIG is derived from the blood of a pool of more than a hundred individuals, who could together harbor a large number of pathogens. There is a significant likelihood that pathogens from the blood of these people might spread to the recipient.

Nimesulide (Aulin / Mesulid / Nimed) may cause internal bleeding.

Statins – Statins have a range of documented negative side effects and have been shown to exacerbate certain kinds of chronic disease. Some compete for the VDR binding pocket. They are contraindicated.

Thyroid supplements – Need for these supplements may decline within a day or two of being on olmesartan alone. Monitor thyroid function closely and adjust the level of thyroid supplementation downward as needed.

TNF-alpha blockers – Tumor necrosis factor-alpha or TNF-alpha is a cytokine critical for effective immune surveillance. Anti-TNF drugs, also known as TNF-alpha blockers, are drugs which interfere with the body's production of TNF-alpha. While

olmesartan also reduces levels of TNF-alpha, it does so to a lesser extent and in a manner less detrimental to immune function. Olmesartan blocks the initial generation of the substance rather than disabling free-floating TNF-alpha after the cytokine has been produced.

Food and drink

Patients on the MP must avoid all food and drink that contains supplemental vitamin D or high levels of naturally-occurring vitamin D. MP patients must avoid foods and drinks high in chlorogenic acid – particularly coffee, concentrated juices, and supplements and multivitamins containing added folic acid. A low-carbohydrate, insulin-resistant diet is recommended for MP patients but is not required. Specific nutritional imbalances should in some cases be corrected, but this requires proper understanding of both the MP and the nutritional needs of the body by a health professional.

Photosensitivity

Abnormal sensitivity to sunlight and bright lights is known as photosensitivity and sometimes referred to as “sun flare” or photophobia. In the context of the MP, the ultimate cause of photosensitivity is the Th1 inflammatory disease process – not the treatment itself. Exposure to natural or bright artificial light in a photosensitive person can lead to flares of internal disease activity, including exacerbation of any inflammatory disease symptoms.

Photosensitivity can occur either when the skin is exposed to bright natural light or the eyes are exposed to either natural or artificial light. Photosensitivity symptoms can occur immediately after exposure or begin 1 to 3 days later, sometimes persisting 5 days or more.

Individuals who are photosensitive prior to the MP will likely become more photosensitive on the MP. Individuals who have no signs of photosensitivity may or may not become photosensitive on the MP. Individuals with limited inflammatory symptoms (suggesting early disease) are the most likely to be able to tolerate more light exposure

while on the MP. There is no certain way to tell in advance precisely how photosensitive an individual will be while on the MP. Only after an individual has begun treatment can photosensitivity be assessed.

Patients on the MP often benefit from wearing glasses that block a broader spectrum of light and in many cases must cover their skin when in the sun. Further guidelines are available at the Knowledge Base articles on Eye protection and Skin protection.

Laboratory tests

Most patients on the MP experience temporary but well-defined increases in various markers of disease state and inflammation, consistent with an immunopathological response. It is helpful, but not necessary, to measure % lymphocytes, C-Reactive Protein, alkaline phosphatase, triglycerides, relevant "autoantibodies", and serum ACE, to track systemic inflammation. Doctors may want to assess kidney function by testing creatinine or BUN and measure other indicators specific to each patient for a baseline and retest as appropriate. Some lab work – commonly HGB, HCT, eGFR, creatinine and BUN – may become temporarily abnormal, due to immunopathology reactions, until the inflammation resolves.

For example, a higher than usual BUN and creatinine is not an indication that olmesartan should be discontinued but a sign that immunopathology may be occurring in the kidneys or other nearby organs. In most cases where physicians have allowed such levels to remain temporarily out of range, BUN and creatinine have returned to range as microbial die-off in the kidneys subsides. We are not aware of any reports of MP patients needing dialysis, provided they remained on olmesartan.

If these markers indicate dysfunction sustained for more than several months, we advising using one or more methods to lower immunopathology levels.

Vitamin D metabolites

There are two main vitamin D metabolites:

1,25-dihydroxyvitamin D (1,25-D) – The presence of high levels of this active vitamin D hormone in patients suggests an ongoing chronic inflammatory disease process.[9] However, the absence of elevated levels does not mean a patient cannot benefit from treatment particularly since non-MP therapies such as TNF-alpha blockers and other unknown drugs and interventions can alter 1,25-D levels. Whenever possible, use the lab Quest Diagnostics. Quest has recently ceased to routinely freeze the 1,25-D samples, as we find necessary. However, the 1,25-D sample will not be frozen unless the patient specifically asks.

25-hydroxyvitamin D (25-D) – Unlike 1,25-D, serum samples of 25-D need not be frozen. 25-D is a secosteroid with possible immunosuppressive effects.[10] Thus, patients on the MP restrict consumption of vitamin D in order to reduce their 25-D at or below 12 ng/ml. Levels of 25-D should be tested every 6-12 months. *Be aware that as 25-D levels fall, immunopathology may increase, sometimes dramatically.*

If the vitamin D metabolite tests do not indicate Th1 inflammation but clinical observation suggests otherwise, a short course of the MP (1 to 2 months) should be used as a therapeutic probe. A longer time period may be needed if 25-D levels remain high, as a therapeutic probe is often not effective unless 25-D levels fall below 25 ng/ml.

Measures of blood pressure

The primary indication for olmesartan (Benicar) is as a mild hypotensive drug. As one can see from the FDA label for Benicar (right), the dose response curve for Benicar is asymptotic, with higher dosages of the drug having incrementally smaller decreases in blood pressure. For example, the difference between 40mg and 80mg of olmesartan results in a decrease of no more than 1mm Hg.

A decline in systolic pressure greater than 15mm Hg of mercury cannot solely be due to olmesartan's hypotensive action. Instead, the drop is also likely due to the disease processes itself.

For example, the widespread destruction of bacteria and human cells infected by bacteria can lower blood pressure. Although this isn't true of all bacterial forms, when some forms of bacteria are destroyed, they release endotoxins,[11] the bioavailability of which can lead to a steep decline in blood pressure.[12]

If a patient suffers low blood pressure before the MP, low blood pressure will return as a symptom of immunopathology while on the MP. In most cases, we find as bacterial die-off subsides, blood pressure levels begin to return to a normal range even as patients continue to take the same dose of olmesartan.

Thus, medications that raise blood pressure, such as fludrocortisone and dopamine, are contraindicated, both because they would do nothing to slow bacterial die-off and because they may have deleterious effects on immune function.

Olmesartan (Benicar)

For the purposes of the MP, olmesartan has two primary actions: it reduces inflammation by blocking the Nuclear Factor-kappaB cytokine pathway and it is an agonist of the Vitamin D Receptor (VDR). As a VDR agonist, olmesartan activates the innate immune response. Research supports the safety of the doses used by MP patients. Olmesartan has minimal interactions with other drugs and is one of the safest drugs on the market.

The half-life of olmesartan is reported to be 13 hours. This would imply that the drug would remain active during that period of time, however, we have found that in sick patients, olmesartan is most effective when administered every 4-6 hours, with a maximum of every 8 hours. This may be due to the fact that some intracellular infections (notably *Shigella*), upregulate activity of the caspases, which are proteases that cleave the VDR.[13] When the VDR is broken apart by the caspases, it is highly likely that any ligands bound to it (such as olmesartan) would stay bound to the fragments of the

protein. Therefore, a VDR agonist would be effective over shorter periods of time in patients with infected cells.

The U.S. Food and Drug Administration has set no safe limit for olmesartan medoxomil (Benicar), as no dose-related adverse events have been identified to this point. FDA post-marketing-experience has shown that Olmesartan has one of the safest profiles of any drug on the market. Note that this does not apply to the combination drugs, such as Benicar HCT, which contains a thiazide and *is* harmful, and should *never* be used with an MP dosing schedule.

The label for olmesartan medoxomil states that the drug is well-tolerated. Adverse events were similar to those experienced by the placebo group. Adverse events were generally "mild, transient and not related to dose." The frequency of adverse events also had no relationship to the dose of olmesartan.

A 2001 study published in the *Journal of of Pharmacology* found olmesartan to be safe and well tolerated at dosages of up to 160 mg/day.[14]

In placebo-controlled trials, the only side effect that occurred in more than 1 percent of olmesartan-treated patients vs. placebo-treated patients was dizziness (3 percent vs. 1 percent).[15]

The relevant Knowledge Base article reviews the safety profile of olmesartan/Benicar in greater detail.

Antibiotics

The Marshall Protocol has historically emphasized a role for antibiotics. However, as our understanding of the recovery process has progressed, this emphasis has been reduced. This change is gradually being reflected in the guidance available here. In the event of any uncertainty, patients or their physicians should seek guidance on the Protocol forums.

The Marshall Protocol **optionally** employs rotating combinations of subinhibitory bacteriostatic antibiotics on a pulsed dosing schedule. The antibiotics are dosed in this fashion to enhance the antibacterial

properties of these drugs while minimizing their immmunosuppressive effects.

The antibiotics are typically dosed at levels below the minimum inhibitory concentration (MIC) so as to reduce the likelihood of bacterial resistance. While the MIC may be relevant for acute infections, such dosing can suppress the immune response towards chronic pathogens and aid their growth. For instance, some antibiotics, when administered at levels above the MIC inhibit phagocyte function.[16] These effects seem to be independent of their antibacterial effect.[17]

Thus, dosing at levels below the MIC improves the Marshall Protocol's effectiveness against chronic pathogens and further reduces the likelihood of bacterial resistance. At the same time, pulsed dosing modulates microbial transcription[18] and greatly reduces the incidence of biofilm persister cells.

Starting a patient on the Marshall Protocol

1. **Test vitamin D metabolites** – Follow the vitamin D metabolites testing instructions. Remind the drawing lab that the 1,25-D sample must be clotted no more than 30 minutes before centrifuge and the resulting serum must be frozen for shipment. Consult the Vitamin D Metabolite Calculator for suggestions on interpreting this lab data.

2. **Restrict dietary vitamin D intake** – Patient must restrict all supplements and foods high in Vitamin D. It is recommended that, over the course of treatment, the patient reduce 25-D to the therapeutic target of approximately less than 12 ng/ml. Retest 25-D periodically to make sure 25-D is dropping toward the lower end of the therapeutic range. Many MP patients have kept their 25-D below 5 ng/ml for many years, without any adverse effect.

3. **For patients taking corticosteroids, begin olmesartan** – Corticosteroids are contraindicated for MP patients. Before weaning them, patients should first begin olmesartan (see

below), which can greatly relieve withdrawal symptoms and help ensure weaning success. It is recommended that olmesartan be started a week or two before beginning to wean. See the weaning guidelines for detailed instructions.
Withdraw or begin to wean contraindicated therapies

4. **If necessary, avoid light** – If necessary to avoid the symptoms of photosensitivity, patients should avoid outdoor light and bright indoor lights by staying indoors as much as possible, using heavy curtains or window shades, and covering up well whenever venturing outside during daylight hours. Patients may also need to protect their eyes from both outdoor and indoor light.

5. **Begin olmesartan** – Commence therapy by prescribing 40mg pure olmesartan medoxomil every six hours (e.g.: 6am, noon, 6pm, midnight) to interrupt the inflammatory cycle and reduce the severity of potential immunopathology. Our observations suggest that olmesartan medoxomil is the only angiotensin receptor blocker (ARB) that activates the patient's innate immune system. "No substitutions" should be written on the prescription. Avoid any combination formulation such as Benicar hydrochlorothiazide (Benicar HCT). Because patients often begin to feel worse when decreasing light and/or vitamin D, olmesartan should be prescribed concurrently with the previous steps, so that it can palliate any resulting immunopathology while the 25-D levels are decreasing. Patients should keep several weeks' supply of olmesartan in reserve to use in case it is needed to treat intolerable immunopathology.

6. **Wait for patient to stabilize on olmesartan** – It usually takes a month or two to stabilize symptoms on olmesartan alone. Some patients may need more time. Depending on the patient's bacterial load and a host of other factors, some patients initially feel better on olmesartan, some worse, and some don't experience any change. All three reactions are normal. A partial list of typical immunopathology symptoms includes: depression, irritability, mania, paranoia, fatigue, muscle weakness, rash, headache, photosensitivity, pain anywhere, numbness, nausea, diarrhea, constipation, ringing in the ears, toothache, sinus congestion, nasal stuffiness, fever/chills, flu-like body ache,

cough, sleep disturbances and “brain fog.”

7. **There may be benefit from olmesartan every four hours** - the immunostimulative and palliative effects of olmesartan are believed to be maximal at four-hourly dosing. Once the patient has stabilized, the frequency should be gradually increased to every four hours, over several weeks, or in accordance with the patient's ability to tolerate any increases in immunopathology that may result. (Some patients will actually feel better at the higher frequency.)

8. **Optionally begin minocycline** – Once the patient has become fully stable on olmesartan, too low a level of immunopathology optionally may be remedied by prescribing the first MP antibiotic, brand name or generic minocycline, at 25 mg every 48 hours. Do not use less or any substitute such as doxycycline. As with the other MP antibiotics, patients may need to divide the contents by opening a capsule or using a pill cutter. While using minocycline and olmesartan, patients should begin to learn the nature of their immunopathology, and how, in conjunction with their physician, they can adjust their olmesartan and/or antibiotic dosing to elicit tolerable immunopathology. *Sudden increases in immunopathological reactions may occur at any time as the immune response strengthens.* Patients should familiarize themselves with the managing immunopathology article to manage symptoms. The response may even necessitate reducing or temporarily stopping some or all of the antibiotics for an extended period of time This is not uncommon and should not be regarded as a setback, but rather as a sign of progress as it usually signals a more robust immune response. Note that olmesartan alone may generate adequate immunopathology in some patients: there is no requirement to use antibiotics during the MP, although many patients find them helpful at some stages.

9. **Optionally increase dosage of minocycline** – When patients using minocycline feel able to increase the strength of their immunopathological reaction, they typically increase their dosage of minocycline, in increments of 25 mg (q48h), until they reach 100mg. It is strongly recommended that patients should stay at each dosage for at least a week and should not

increase the antibiotic until their immunopathology at a particular dosage has declined to a low level.

10. **Optionally add a second or third antibiotic** – There is no requirement for patients to take more or higher doses of antibiotics if symptoms become uncomfortable. Nor should patients feel reluctant to reduce their doses of antibiotics if they find immunopathology at their current doses excessively troublesome. *Olmesartan plays the most critical role in the recovery process.*

Adding a second antibiotic

Patients who are still experiencing significant immunopathology from 100mg of minocycline alone are not yet ready to add a second antibiotic because a two antibiotic combination is much stronger than minocycline alone. As previously discussed, olmesartan is the most important factor in strengthening the innate immune system. In fact, it is possible patients may be able to recover on olmesartan. However, provided immunopathology is kept at a reasonable level, the antibiotics can accelerate the process.

It should be noted that if the level of 25-hydroxyvitamin-D in a patient's bloodwork is above the 12 ng/ml therapeutic target, the patient may experience a sudden increase in immunopathology as their level of 25-D falls, and extreme care should be taken not to increase the antibiotics too quickly.

If additional immunopathology is desired, patients should be prescribed a second antibiotic in conjunction with their minocycline (which should continue at 100mg q48h). Historically, that second antibiotic has been azithromycin – but this drug has been difficult to dose, and very difficult to wean, so many patients, and their physicians, now choose to use clindamycin or Bactrim.

When to use clindamycin as a second antibiotic – Clindamycin is especially effective at increasing neurological and psychological immunopathology including symptoms of depression, anxiety, intrusive thoughts, paranoia or obsessive

compulsive behavior. Compared to azithromycin, clindamycin is easier to dose at a level which will control immunopathology, as it is dosed at a 48 hour interval and doesn't linger in the tissues. Clindamycin has proven to be the most generally applicable second antibiotic.

When to use Bactrim as a second antibiotic – For many patients, Bactrim is the least aggressive second antibiotic, and may be used as a primary antibiotic, replacing minocycline, if immunopathology from minocycline becomes too aggressive. Patients who have reported sensitivities to sulfa drugs in the past often find that this sensitivity decreases as they progress on the MP. Like clindamycin, Bactrim does not linger for long periods in the tissues, is dosed 48-hourly, and is generally relatively easy to dose at levels generating acceptable immunopathology. However, a small subset of patients exhibits unusually high sensitivity to Bactrim and may be unable to tolerate it.

When to use azithromycin as a second antibiotic – **Azithromycin is no longer recommended for use while on the MP.** *Also, patients with cardiac dysfunction should avoid azithromycin.*

A special consideration for patients with levels of 25-D higher than 12 ng/ml – The bloodstream levels of 25-hydroxyvitamin-D of some patients can remain elevated for months, or years, even when they are abstaining from further vitamin D consumption, and limiting exposure to outdoor radiation. Patients who are severely ill and have a 25-D exceeding 12 ng/ml should not be administered azithromycin. When a second antibiotic is needed any of the other faster decaying antibiotics such as clindamycin are preferred.

Optional supplementary antibiotics

Brand (generic)	Dose	Frequency	Molecular activity	Effective half-life
Minocycline (Minocin)	25-100mg	every 2 days	antibiotic – may bind to the 30S ribosomal subunit; binds to the PXR nuclear receptor	11-22 hours
Zithromax (azithromycin) ***no longer recommended***	12-125mg	every 8-10 days	antibiotic – binds to the 50S subunit of the bacterial ribosome	reportedly 68 hours, but some studies[19,20] and ARF patient reports suggest it remains in tissues for up to 45 days
Cindamycin	18mg-150mg	every 2 days	antibiotic – binds to the 50S subunit of the bacterial ribosome	more than 12 hours [21]
Bactrim DS (co-trimoxazole)	125-1000mg	every 2 days	antibiotic – inhibits bacteria's ability to synthesize folate	10 hours
Declomycin (demeclocycline)	18-150mg	every 2 days	antibiotic – binds to the 50S and 30S subunit of the bacterial ribosome	10-17 hours

For a more detailed discussion on the MP antibiotics including combination strategies, examples of progression through the MP, and general tips, please read the Knowledge Base article, Dosage and administration of Marshall Protocol antibiotics.

Additional antibiotics for later stages of recovery

During Stage 4 of recovery, patients with low levels of immunopathology *may* seek to add a third antibiotic, or rotate amongst antibiotic combinations.

Combinations which have proven useful include:

BCD – Bactrim DS + clindamycin + demeclocycline
BCM – Bactrim DS + clindamycin + minocycline
BDM – Bactrim DS + demeclocycline + minocycline
CDM – clindamycin + demeclocycline + minocycline

Managing immunopathology

Patients' goal during the MP should be to maintain tolerable immunopathology as they get well. In cases where IP is becoming intolerable, certain strategies are available including:

- **Take no antibiotics**. In the presence of noticeable immunopathology, discontinuing antibiotics is acceptable and can make the task of adjusting MP medications to achieve tolerable immunopathology significantly simpler.

- **Adjust olmesartan (Benicar)** - Depending on which of olmesartan's two main properties a patient experiences most strongly during a particular period of treatment, increasing *or* decreasing the dose may help manage immunopathology. For some, taking olmesartan sublingually (under the tongue) can provide immediate relief.

- **Take lower doses of antibiotics** – Typically, reducing or stopping one or more antibiotics is the most effective way to manage immunopathology. Many patients find that as their nuclear receptor function stabilizes, their immune response becomes more active and their immunopathology may increase. At this point, they may need to reduce or stop antibiotics while staying on olmesartan alone. This occurs as a result of improved immune function and is not a sign that a patient is ”getting worse.” Note that in stopping minocycline (or other antibiotics for that matter), some patients report more symptoms, not less.

- **More frequent minocycline** – If minocycline is not pulsed and taken more frequently such as every 12-24 hours, it may help reduce symptoms of immunopathology.

Take palliative medications – A range of symptom-specific palliative medications can be relied upon in the case of intolerable immunopathology.

Note that three forms of IP are particularly life-threatening and should be handled with an *abundance of caution*: cardiac immunopathology, neurological immunopathology, and respiratory immunopathology. Patients who are concerned about any of these or other symptoms should not hesitate to call their physician.

In case of emergency

ARF has prepared a Notice for emergency medical personnel treating a Marshall Protocol patient. Important points from that document include the following:

Do not withdraw Olmesartan – In a critical care situation, it is essential to continue oral olmesartan, even in the presence of hypotension, as abrupt withdrawal can be life-threatening. Along with routine lifesaving procedures, it is essential to continue oral olmesartan 40mg dosing every four hours, with 20mg SL p.r.n., until symptoms subside - even if an NG tube is necessary. If B/P is extremely low (mean arterial pressure <55), continue olmesartan as above and increase fluid volume with 0.9 NS or packed red cells.

Antibiotics – We strongly recommend patients not be treated with MP antibiotics for an acute infection. Unless patients have reached a late stage of the treatment these antibiotics may greatly increase immunopathology as they leave a patient's system. Flouroquinolone antibiotics are generally well tolerated although instances of tendon damage have been reported; the patient should be advised of the FDA black-box warnings. Cephalosporins, Claforin, and the macrolide Biaxin are usually tolerated.

Corticosteroids – Do not give corticosteroids in any form or by any route (injected, inhaled, oral or IV) as they will lead tmetabolic instability. Do not give **nimesulide** (Aulin / Mesulid / Nimed). It could cause bleeding.

Epinephrine or Norepinephrine – Adverse reactions may occur if epinephrine or norepinephrine is used to raise B/P or treat anaphylaxis. Use epinephrine and norepinephrine only for cardiac arrest. Local anesthetics containing epinephrine may cause adverse events (tachycardia, psychosis), and the epinephrine may hinder anesthesia.

For the details of these recommendations, please consult the Notice for emergency medical personnel. In an emergency, physicians may call Trevor Marshall at 1-805-492-3693.

Length of the Protocol

The exact duration of the Marshall Protocol (MP) depends on any number of factors, including degree of illness, amount of fibrosis, subclinical inflammation, the health of the kidneys, and personal preference to remain on the MP.

While someone who is very ill might expect the MP to take five or more years, there is no way to know for sure how long the treatment will take. Due to the nature of immunopathology, feelings of well-being and blood markers of disease tend to be variable in the short-term and improve over the long-term. Also owing to the nature of infection, different symptoms will improve at different rates.

So long as one is responding to olmesartan or olmesartan plus antibiotics with symptoms that wax and wane, there are still bacteria to be killed.

Note that there is no requirement that patients reach the maximum dosages for all antibiotics or do all antibiotic combinations in order to complete the Protocol. In many cases, patients can make considerable progress on olmesatan (Benicar) alone as the drug increases expression of the body's own antimicrobial peptides. However, it is considered ideal for patients to stay on the Protocol until they no longer experience immunopathology from any antibiotic combination.

Endpoints of the Protocol

To a large extent, patients who have completed the Marshall Protocol can return to a normal life with the following modifications:

- **Consumption of vitamin D** – MP patients are free to enjoy foods such as fish that naturally contain vitamin D. Even so, patients are encouraged not to consume any food products that are fortified with extra vitamin D.

- **Light** – Although suntanning is not an option, veterans of the MP may choose to expose their eyes and skin to increasing amounts of light. A word of caution: some patients in later stages of treatment may experience a Stage Five reaction when exposed to too much light. To limit the possibility of a severe immunopathological reaction, always increase light exposure (and exercise) gradually. Also, be aware that sometimes an increase in symptoms from light may begin one or two days after exposure and last for several days or even longer.

- **Antibiotics** – In later stages of the MP, the immune system is self-sustaining and can eradicate bacteria without antibiotics. However, there is no harm in using a couple weeks' worth of MP antibiotics as an annual checkup in order to see if they can generate immunopathology.

- **Olmesartan (Benicar)** – In later stages of the MP, the Vitamin D Receptor, which controls key components of innate immunity, is properly working again and is activated even in the absence of olmesartan. However, olmesartan is still essential to palliate symptoms and protect organs from systemic immunopathology.

- **Laboratory Tests** – Various tests are expected to come in range: return of ACE, CRP, triglycerides, ALP to low end of normal increase in % lymphocytes, back into the normal range 1,25-D at 25-35pg/ml measured over a six-month interval signs of inflammation resolution on CT and MRI imaging

Stopping the Protocol

Stopping antibiotics only

The length of time it takes for antibiotics to no longer increase immunopathology is variable. Determining factors include how long the antibiotics stay in one's system. Due to its unusually long half-life, Zithromax can remain in the tissues for a month or more. In addition, the self-sufficiency of the immune system is an important factor. Some patients may find their immune response is relatively self-sustaining due to the body's own increased antimicrobial peptide production, and thus it will take longer for the immunopathology to wane. If the patient is stopping antibiotics for the purpose of minimizing immunopathology, in some cases it may be preferable to stay on either 100 mg minocycline every other day or take it daily for its palliative effects (many of which are the result of its effect on the PXR nuclear Receptor, see *Bioessay*,[22] Figure 1).

Stopping antibiotics and Olmesartan

To discontinue both antibiotics and olmesartan, patients should first discontinue their antibiotics following the above instructions. If necessary, olmesartan should be weaned gradually, only after the antibiotics have been discontinued and over the course of several weeks. Note that the immune response may remain activated for a period of time even after discontinuing olmesartan.

An alternative to discontinuing olmesartan alone is to wean the patient across to another ARB, valsartan (Diovan), 80mg every 6 hrs (80 mg is one quarter of a 320mg Diovan tablet). The patient reduces the olmesartan dosage (e.g., from 40 mg to 30mg to 20mg to 10mg to 0) while simultaneously ramping the valsartan (e.g. 0 to 20mg to 40mg to 60mg to 80mg). The length of time the organ protection from the valsartan will be needed depends on how long it takes the immune system to slow. This ARB does not activate the immune system, but does protect organs and provide a little palliation. The patient can be weaned across in 2 to 3 days.

Patients who stop olmesartan are terminating their recovery.

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