

Autoimmune Flare Protocol Application Guide

Clinical Context

Patients with autoimmune diseases or autoimmune processes going on can experience flares of their disease process. **It's important to understand the immunology and it's useful to give people a standing set of instructions, a "flare protocol,"** that they can put into action if/when they start to get symptoms of an autoimmune flare starting up. If they know what to do and can apply their flare protocol quickly, they can shorten the flare. This diminishes tissue damage and reduces the likelihood of epitope spreading, a mechanism by which their autoimmune baseline is made worse for the long term. If you need more information about epitope spreading, watch Module 5 Video 3 and Module 6 Videos 7 and 8. If you need more information about autoimmune disease, watch the Introduction Module and watch Modules 5 and 6. This application guide is about flares of existing autoimmune disease, which is different from the development of new autoimmune disease. Here are key contributors to flare activation in patients with autoimmune disease.

Inflammation (NFkB) – Autoimmune (STAT3) Co-Activation

NFkB, a primary signaling element in the inflammatory process, co-activates with STAT3, the gene expression factor that drives naïve T cells to become Th17 cells. Th17 cells are the T cells that drive tissue destruction in the autoimmune process. **Anything that increases inflammation has the potential to increase the NFkB-STAT3 co-activation, which increases Th17 cell numbers and activity, thereby increasing autoimmune flare activation.** So, a key step in the management of autoimmunity is to use a functional medicine inventory to identify all the factors in the patient's case that contribute to inflammation. This could be dysbiosis, sleep dysfunction, stress, dysglycemia, infection, dietary factors, environmental exposures, or other factors. When a flare occurs, attention should be placed on the knowledge that you've gained in working with the patient, **to see if any of the factors you've already addressed is re-emerging as a driver of inflammation.**

To downregulate NFkB-STAT3 co-activation during a flare, consider the following:

Balanced Immune (Pure Encapsulations) – 2 or 3 as often as QID if necessary during flares, to downregulate NFkB and STAT3. Or you can use the components of Balanced Immune: curcumin, trans-resveratrol, black ginger, sulforaphane, and quercetin.

Chinese Skullcap aka Baicalin – 300-450mg BID. To downregulate interleukin-8 (IL-8) which is a neutrophil chemotaxis promoter. Note that **Th1 Support** contains Baicalin, so if you've got this installed as part of your approach to balancing T cell polarization, this base is covered.

Boswellia (Pure) – 2 or 3 BID. To downregulate human leukocyte elastase (HLE), a tissue destructive lysosomal enzyme released by neutrophils to kill pathogens. HLE is often central to ongoing tissue destruction in neutrophilic inflammation.

EPA/DHA Essentials (Pure) – 2 BID. In some patients, a higher dose on the order of four grams of fish oil taken for three months before reducing to 2 BID may be suitable. If CNS inflammation is a concern, emphasize DHA, as with **DHA Ultimate**. It can take three months for this to shift the patient's biology. Don't expect a person to say they felt better in a week.

Vitamin D – Dose depends on the patient’s baseline dose needed to bring blood levels into the top 25% of the normal range. If the patient’s D level is already there, additional D may not be needed.

Within the category of inflammation in the topic of **autoinflammatory mechanisms, driven by inflammasomes**. Autoimmune diseases often have a percentage contribution from autoinflammatory mechanisms. In susceptible individuals, the inflammatory activation can be a significant contributor to the overall picture of autoimmune flare activation. For more information on the NLRP3 inflammasome and autoinflammatory disorders, see Module 7 Videos 7 and 8.

The following substances are worthy of consideration, to downregulate inflammasome activation:

Balanced Immune (Pure) – 2 or 3, as often as QID if necessary to bring down the inflammation.

The ingredients have the following relevance: Curcumin and black ginger inhibit NFκB, which is required for the first step of inflammasome activation (Signal 1), so inhibition of NFκB inhibits inflammasome formation. Resveratrol promotes SIRT2, which inhibits inflammasome activation. Quercetin prolongs the effectiveness of resveratrol. Sulforaphane reduces ROS that promote inflammasome formation.

Potassium – only give if needed. The goal is to get the patient’s blood level to or above 4 mmol/L. Low cellular potassium allows NLRP3 inflammasome assembly, leading to increased inflammation. NAD or caloric restriction – NAD dosing can be on the order of 400mg BID. NAD is also increased by caloric restriction. NAD promotes SIRT2, blocking NLRP3 inflammasome assembly.

Uric Acid Formula (Pure) – 2 BID. To lower uric acid. Hyperuricemia drives inflammasome assembly.

Inflammasome assembly is also driven by low pH, hyperglycemia, hypercholesterolemia, and elevated ROS. It may thus be necessary to change diet to increase pH (more vegetables, less meat, etc.), and to address the other factors appropriately.

Antibody Glycation

Under the influence of interleukin-22 (IL-22), antibodies become more glycosylated. **This makes the antibodies more sticky, so they bind more aggressively to their targets**. If the target is self-tissue, the autoimmune attack against the autoreactive target is increased. IL-22 is made by both Th17 cells and by Th22 cells. Th17 response is downregulated by inhibiting STAT3, as we’ve discussed, and by promoting adequate Th1 response, which we’ll talk about next. Th22 cells are generated through signaling from TNFα and IL-6. These cytokines are both part of the inflammatory process. IL-6 drives naïve T cells to become Th17 cells. IL-6 is also generated by Th17 cell activity, via IL-17 activation on macrophages and other cells. So, when the patient is Th17 dominant, there will likely be IL-6 around. At that point, if the patient gets inflamed, the addition of TNFα driven by the inflammation will combine with the IL-6 and drive a likelihood that the patient will make Th22 cells that make IL-22. If this happens and the IL-22 drives antibody glycation, flare activation may follow. To address antibody glycation, reduce inflammation. You would also place a particular emphasis on the use of **Chinese Skullcap aka Baicalin**, as it downregulates IL-6.

Th1 Support (Pure) – 2 or 3 at breakfast and lunch. Contains substantial amounts of **Baicalin**.

Balanced Immune (Pure Encapsulations) – 2 or 3 BID or TID, to reduce TNFα.

As with everything you learn in Cogence Immunology, your use of this information should be guided by your expertise, in the context of your training and your license to practice. These approaches are in addition to, rather than instead of, conventional approaches to care. Interactions between supplements and medications, as well as the effect of patient improvement on their responses to current doses of medications, need to be considered by the clinician. Cogence, LLC member terms of use apply to this document.

The other important thing to understand about antibody glycation is that **glycation can drive the patient into a flare without any elevation in total antibody level.** The same number of antibodies, if more glycated, will yield a greater extent of attack against self-tissue targets. This means that you can test antibody levels on a patient who is having an autoimmune flare and find no increase in antibody levels. In a patient with Hashimoto's disease, for example, the TPO level may be 90 routinely, after you've gotten the level down from 12,000. They have a flare, and you retest TPO, expecting it to be higher during the flare. If it's not higher, that tells you there's a likelihood that antibody glycation is playing a role.

Loss of Th1 Response

Interferon gamma (IFN γ) made by Th1 cells and natural killer (NK) cells inhibits the ability of Th17 cells to make their effector cytokines. When the patient's Th1 response declines, they lose the inhibition of Th17 that the Th1 system of cells was providing. Decline of Th1 can occur directly, like when stress chemistry induces apoptosis of Th1 cells, or when glutathione levels decline due to elevations in ROS or other factors. Or escalation of the Th2 response can yield inhibition of Th1. Th2 response is promoted by dysbiosis or inflammation in other hollow spaces like lungs or sinuses. Th2 response is also escalated by things like mold reactions, candida, or aspergillus, or by NLRP3 inflammasome activation, or poor sleep. For more information on Th2 dominance, see the Introduction Module and Module 4.

To support adequate Th1 response and downregulate excessive Th2 response, consider the following:

Th1 Support (Pure) – 2 or 3 at breakfast and lunch. Supports adequate Th1 response. Note: Because berberine increases AMPK, it can give the patient more energy. That's useful, but also means taking it late in the day might need to be avoided in some patients.

Innate Immune Support (Pure) – 1 or 2 BID. Upregulates natural killer cell activity as part of Th1 system activation. This helps restore adequate Th1 response.

Th2 Modulator (Pure) – 2 or 3 BID. Downregulates IL-4 and GATA3, reduces mast cell degranulation, breaks down excess mucous, supports glutathione production.

Perilla Extract (Pure) – 2 or 3 BID. Downregulates IL-4. May need dose escalation early in entrenched cases.

Epi-Integrity (Pure) – 1 or 2 scoops BID. Downregulates IL-4 and GATA3, repairs leaky epithelial barriers, supports Th1 response. Useful when epithelial dysfunction is present, as is common for example with dysbiosis, sinusitis, or respiratory issues.

Diminished Vagal Motor Activity

The motor output of the vagus nerve inhibits Kupfer cell IL-6 production and TNF α production by macrophages in the intestine and spleen. Diminished vagal motor outflow yields increases in IL-6 and TNF. The combination of IL-6 and TNF drives Th22 cell production, resulting in increased production of IL-22 and increased antibody glycation, driving autoimmune flare activation. It's important to consider using transcutaneous vagal nerve stimulation (tVNS) to help patients

improve vagal motor outflow. Click on the TOOLS tab to find a description of tVNS. It may also be important to support acetylcholine neurotransmitter production, since synapses of the vagus nerve to target organs are cholinergic. This means that for some patients, it may be useful to give **phosphatidylcholine or other choline sources**. This is particularly important if the patient carries PEMT or MTHFD1 gene polymorphisms.

Excessive Exercise

With heavy exercise, muscles make abundant IL-6. Autoimmune patients should avoid excessively intense exercise. They can also bracket their exercise with **Baicalin** to inhibit IL-6 and **Balanced Immune** to downregulate the NFkB/TNF α loop activation. 2 each an hour before and right after exercise. If they take these supplements already, just move their daily doses to these times.

Fungal Infection in the GI Tract

Fungal infection in hollow spaces like the GI tract, lung, or sinus are cleared by the body using Th17 cells. In normal circumstances, if a fungal infection occurs, the body generates a Th17 response acutely and the infection is cleared. But if a fungal infection lingers, it can drive a chronic but futile Th17 response that persists through time but fails to clear the infection. In a patient with an autoimmune disease, the persistent Th17 can drive a worsening of autoimmune reactivity. This makes it especially important to address any kind of fungal infection, including candida albicans, aspergillus, or other molds or fungi.

Remember also that inflamed epithelia in hollow spaces generate Th2-promoting cytokines. Thus the patient may present with co-dominance of Th17 and Th2. Refer to the section on T cell polarization above for supplements to consider. Also consider the following:

AC Formula II (Pure) – 2 BID away from food. To address fungal dysbiosis.

Caprylic Acid (Pure) – 2 BID away from food. To address candida dysbiosis.

Microdefense (Pure) – 2 BID away from food. To address fungal dysbiosis.

Stevia, Garlic or other biofilm disruptor. Garlic's biofilm disrupting ingredients don't survive first pass clearance in the liver, so it's only useful to address biofilms in the GI tract.

Charcoal or other substances used to adsorb debris of killed pathogens.

The broad picture of anti-fungal treatment may include more elements, including other natural elements or anti-fungal medications. These decisions rest with the clinician.

Making a Flare Protocol

With all this in mind, your task is to make a flare protocol for each patient that is tailored to their unique pattern of dysfunction. It will likely include something like additional **Balanced Immune**, to downregulate inflammation. It may also include items appropriate to addressing their T cell polarization issues, and/or something to push harder on the pattern of dysfunction that is particularly entrenched in their case, like additional **Glucofunction** for dysglycemia, **Melatonin** for sleep disruption, or an adaptogen for high stress. A patient's flare protocol may or may not include supplements the patient isn't already taking. In some cases, a patient's flare protocol may simply involve escalation of the doses of supplements that are already core components of their baseline protocol. In other cases, a few added items, with dose escalation of core items, works best.