Inflammation Application Guide

Clinical Context

Many of the problems patients present with in a functional medicine practice can drive inflammatory activation, including stress, sleep dysregulation, dysbiosis, food antibody reactions, environmental factors, etc. So, you know you'll have to consider those as part of your clinical process. This is discussed in the Introduction Module and throughout the course. And because the NFkB of the inflammatory process co-activates with the STAT3 that drives Th17 cell activation, there is a co-activation between inflammation and autoimmunity. So, when a person becomes more inflamed, they move closer to the threshold of expression of autoimmune flares.

In the Introduction Module Application Guide, we talked about a three-step process, where Step 1 addresses T cell polarization, Step 2 addresses the inflammation/autoimmune axis and Step 3 focuses on individualizing the process to whatever else is required in the case. This Inflammation Application Guide is best applied in the context of that way of thinking about staging, where you start by introducing influences on T cell polarization for a week or two before you introduce treatment elements aimed at reducing inflammation. Here are the key factors to consider when you're thinking about the inflammatory component of the case.

The "Inflamed and Infected" Conundrum

The majority of patients with chronic illness that you'll encounter in a functional medicine setting have a combination of chronic inflammation and increased pathogen burden. Inflammatory cytokine signaling is a normal part of the pathogen-killing immune response. So, if these patients are inflamed, shouldn't that help them kill pathogens? Shouldn't the more inflamed patient have fewer pathogens? It turns out not to work that way. The problem is that the chronic inflammation is too generalized, like the difference between a smoldering forest fire (inflammation everywhere) versus a blow torch (immune elements effectively targeting pathogens only right where the pathogens are, then turning off the blow torch when it's time for the resolution phase of inflammation). **You want the blow torch, not the forest fire.**

You want to reduce the generalized inflammation. This will make room for the normal housekeeping functions that help to kill pathogens, which is the Th1 system of cells: Th1 cells, natural killer (NK) cells, M1 macrophages, and CD8+ cytotoxic T lymphocytes (CTLs). When the overall level of inflammation is low enough, the routine and well-targeted increments of in inflammation associated with pathogen killing are fine and don't create an inflamed patient.

Indeed, one of the problems with a lack of Th1 and NK cell mediated pathogen killing is that higher levels of pathogen are associated with higher levels of inflammation. And this is what we see clinically; the patient has a high background pathogen burden, with elevated viral burdens, bacterial burdens, and/or fungal burdens. And they're too inflamed.

Key Questions / Components of Chronic Inflammation

What is the inflammation responding to?

- PAMPs (Pathogen Associated Molecular Patterns): viral, bacterial, fungal?
- DAMPs (Damage Associated Molecular Patterns): All kinds of immune cells have receptors that sense the presence of DAMPs. Tissue damage, whether caused by a pathogen or simply by tissue injury or breakdown with wear and tear, yields DAMPs. The normal response to DAMPs is inflammatory activation. That's normal up to a point, but beyond that point, you get smoldering upregulation of persistent inflammation, which creates more damage and therefore more DAMPs. That needs to be shut down.
- HAMP (Homeostasis Altering Molecular Process) effect: This is the mechanism by which, in susceptible individuals, changes in homeostasis, even useful changes, induce inflammatory activation.

Is there a failure of the resolution phase?

Inflammation doesn't just fade away. Normal inflammatory response involves distinct activation, sustaining, and resolution phases. Each of these phases involves distinct signaling patterns. The "finishing" of the inflammatory process is an actively signaled process, called the resolution phase. Is this resolution signaling impaired? Genetically under-functioning? Normally, omega 3 fatty acids turn into specialized pro-resolving lipid mediators (SPMs aka PRMs), which inhibit neutrophil chemotaxis into tissue and instead promote monocyte chemotaxis. Monocytes turn into macrophages, which phagocytize apoptotic neutrophils and clear them from tissue, yielding resolution. This clearance of apoptotic neutrophils by macrophage phagocytosis is referred to as efferocytosis. When macrophages phagocytize apoptotic neutrophils, the macrophages also produce PGE2, IL-10, and TGFβ, which signal for tolerance and resolution.

But in the context of vigorous inflammation, omega 3 fatty acid conversion to SPMs is inhibited via NLRP3 inflammasome activation. In such cases, there can be resolution failure. It's appropriate to give SPMs directly in these cases, at least until the inflammation is quiet enough that omega 3's can convert to SPMs, at which point regular EPA/DHA supplements can be given. And some patients are simply genetically not robust in their formation of SPMs. They may need persistent use of SPMs as their routine form of fatty acid support.

In such cases, it becomes important to consider sources of NLRP3 inflammasome activation. See "Markers related to NLRP3 inflammasome activation" in the "Labs" section and see "Inflammation" under "Order of Operation" below.

Remember that gene expression of the NLRP3 protein in naïve T cells upregulates Th2 transcriptional expression, independent of whether multiple NLRP3s have assembled into the multi-NLRP3 inflammasome ring structure. In other words, NLRP3 expression, separate from inflammasome assembly, pushes the T cell toward Th2 polarization. If the patient is substantially inflamed, it's likely that gene expression of NLRP3 is occurring as part of that process.

Is there a loop-reinforcement of inflammatory activation?

- Neutrophilic inflammation is most common, since DAMPs and PAMPs evoke TNFα and interleukin 1β (IL-1β) production by tissue resident macrophages (TRMs). These inflammatory cytokines function as chemokines (chemotactic attracting cytokines) that attract neutrophils to migrate from the circulation into the tissue where the DAMPs or PAMPs are present. This is the tissue-specific difference between the forest fire and the blow torch. As long as the inflammation is local ***and*** the resolution phase works, the patient is likely to stay out of trouble. But if there is a failure of the resolution phase, or if the neutrophil influx is simply too strong for too long, eliciting too much tissue damage, production of more DAMPs and therefore more neutrophil influx, there will be persistent inflammation.
- Eosinophilic inflammation. This may be driven by excessive Th2 dominance signaling, particularly from IL-5, typically in response to epithelial inflammation, often with participation from mast cell degranulation that creates more epithelial damage.
  Mast cell mediated histaminic damage, typically mediated by IL-4 and often involving excessive Th2 dominance.
- Stress-induced macrophage activation of TNFα in GI or spleen macs, or IL-6 in Kupfer cells (liver macs). Remember that sympathetic nervous system activation drives these mechanisms of inflammatory activation. Vagal motor outflow inhibits them. And high insulin inhibits vagal motor outflow. Body inflammation drives CNS inflammation, which activates hypothalamic CRH production, driving sympathetic ns activation, driving the inflammatory cytokine production in macs.

Is the patient's metabolism dysregulated?

Metabolic dysregulation drives inflammation in several essential ways, including the following:

- Poor TCA cycle function diminishes the effect of cortisol. This means that people with metabolic impairments will have a less effective anti-inflammatory effect of their cortisol.
- Insulin inhibits vagal motor nucleus activity. Patients with higher insulin output will have less vagus nerve motor activity, so they'll lose the vagal inhibition of GI and spleen macrophage TNFα production and liver Kupfer cell IL-6 production.
- Fat stores make TNFα and NFkB, so fat has an endocrine function, driving inflammation.

Is the patient simply too good at a particular type of response?

This is a question that should get you thinking about 1) dosing questions, and 2) persistent need for supplementation. A patient may have greater capacity to generate IL-6, due to genomic upregulation of IL-6 production or IL-6 receptor expression. Or they could be efficient at generating IL-4, IL-17, etc. These increase the efficiency of systems that persistently skew the patient's immunology toward activation of the efficient function. In these cases, higher doses of substances used to inhibit these functions may be needed.

What is the status of the patient's Th1/Th2 balance?

The Th1/Th2 balance is only one part of the picture of T cell polarization. But it's an important pivot point, because the Th2 dominant patient often is more inflamed for several reasons, including these and others:

1. Th1/NK cell responses are inhibited, so Th17-mediated neutrophilic inflammation can increase.
2. Loss of Th1/NK cell response allows pathogen burdens to expand, driving inflammation.
3. Dysbiosis is more likely, driving GI epithelial cells to express NFkB, driving systemic inflammation.
4. Greater mast cell expression drives microglial inflammation, yielding CNS inflammation.

It can be useful to have the patient fill out the *Cogence Brief Immunological Assessment*. You'll find it at the tools tab. The left side will quantify how much support for the Th1 system the patient needs. If this score is high, the patient needs more than the usual amount of Th1 support. The right side of the questionnaire indicates how Th2 dominant the patient is, with higher scores indicating more need to modulate (downregulate) the over-active Th2 response. Remember that NLRP3 activation will tend to drive Th2. This means your very inflamed patients are even more likely to be Th2 dominant. It also means your anti-inflammatory efforts are important in addressing polarization..

Is the TGFβ Level Elevated?

Inflammation can drive immature myeloid cells to become myeloid-derived suppressor cells (MDSCs). MDSCs make excessive amounts of TGFβ. TGFβ drives ROS activation, which loops back to drive TGFβ production. The ROS also contribute to inflammation. The TGFβ drives a tolerogenic signaling program that helps quiet down inflammation, which can also be useful for quieting down autoimmunity. But too much immune suppression yields more pathogen burden expansion, yielding more generalized inflammation. This will ultimately worsen autoimmunity, through the NFkB-STAT3 coactivation that drives Th17-mediated autoimmune tissue destruction.

And, because TGFβ drives ROS formation, you need to consider whether persistent or cyclical elevation of ROS is depleting GSH. GSH is required for Th1 response, so your efforts to increase the patient's Th1 activity toward normal levels may be hampered if the GSH level is not adequate. Also GSH is essential for the support of barrier integrity. If GSH levels are low, the GI, lung, sinus, and BBB barriers are less likely to be healthy.

Also, keep in mind that when immature myeloid cells mature as MDSCs, they're not maturing as neutrophils, macs, and dendritic cells. This can be useful as part of how the immune system is helped to quiet down in the context of inflammation, by taking some of the steam out of the innate immune response. But in the chronically ill patient, you'll see high TGFβ, suggesting MDSC formation, but the patient will still be inflamed. This is part of the picture of the inflamed but infected patient that we see so often.

Labs

All of biology is connected, so it's not possible to make an exhaustive list of the things that could increase inflammation or contribute to resolution failure. A more detailed discussion can be found in Module 22. Here is a starting point for consideration.

CBD with differential wbc count – This is the cheapest and one of the best ways to track inflammatory process. Keep in mind that the majority of chronically ill patients will have low or low normal wbc counts, so it's unlikely that the absolute level of any components of the differential will be elevated. The percentages will tell you which cell types are expanded, which is a clue about immunological shifts related to inflammation. However, when looking at percentages, use the absolute levels as perspective on why the percentages have shifted. For example, high neutrophil percentage could occur with the absolute neutrophil level moving up into the top of the normal range or with the absolute lymphocyte level moving down toward the bottom of the range. Those are different pictures. Normal percentages are 60/30/9/1/0. A few patterns to look for:

- Neutrophil percent elevation suggests neutrophilic inflammation, driven by infection, by resolution failure, or by Th17-mediated neutrophilic inflammation, with IL-17 driving up neutrophil numbers and activity.
- Eosinophil percentage elevation suggests eosinophilic inflammation, driven by IL-5, a component of the Th2 response. Basophil elevation should be interpreted similarly.
- Lowering of the neutrophil/lymphocyte ratio suggests activation of the adaptive immune response or loss of neutrophil numbers. The most common cause of this shift is GI dysregulation, with T and B cell numbers increasing in response to dysbiosis. Attention to the GI tract commonly moves the ratio back to approximately 2:1.

hsCRP & GlycA are inflammatory markers that are important to measure and track. High sensitivity CRP (aka hsCRP or cardiac CRP) is useful, especially as a measure of IL-6. You want the value to be <1. But plenty of obviously inflamed patients have normal hsCRP, so it's not a grand referendum on whether or not the patient is inflamed. GlycA is a more modern version of hsCRP. You want the value to be <350, though 400 is the top of the range. And again, it's not completely sensitive. When they're elevated at baseline, tracking these markers will tell you if you're making progress. "Regular" CRP is rarely elevated. hsCRP is a zoom in on the lower end of the CRP range, where you'll see meaningful variation from patient to patient, or in one patient across time. SED rate is virtually useless in the chronically ill patient population. If the patient's SED rate is high, they are very inflamed, as it takes very vigorous inflammation to raise it.

Omegacheck or another fatty acid profile can be indispensable in understanding the patient's fatty acid balance. The eicosanoid system has a huge effect on the patient's inflammatory status.

VEGF – as a marker reflecting tissue hypoxia, though other things can drive up VEGF. See "Other Factors" at the end of the document for what to do with VEGF results.

Markers related to NLRP3 inflammasome activation:

With more intense inflammation, there is a likelihood of NLRP3 inflammasome activation as a component of the process. And patients with gout or other autoinflammatory disease processes will have a baseline tendency toward NLRP3 inflammasome upregulation. These markers give information about factors known to favor inflammasome intracellular assembly, through inhibition of SIRT2. SIRT2 inhibits inflammasome assembly, so more SIRT2 equals less inflammasome-mediated inflammation.

- Uric acid – some patients need uric acid levels to be below 5.
- Potassium – should be at least 4.
- Cholesterol – high cholesterol inhibits SIRT2, but statin use may be problematic for some patients.
- HA1c and Glycomark – to assess glycemic status. A CGM may be required to smoke out cases in which glycemic control is poor, but lab markers do not reveal the problem.
- oxLDL, glutathione, TGFβ – to characterize oxidative stress levels.

It's very useful to measure TGFβ levels and to track them temporally, perhaps monthly. You'll often see elevated TGFβ in chronically ill patients. If you're measuring TGFβ with Quest, you can use their normal range. If you're using Labcorp ELISA (changed in 2023), you can think of 12,000 as the high end of the functional range. It's also useful to track oxLDL as a marker of oxidation and MPO as an indicator of neutrophilic oxidative stress. Neither is completely sensitive, but movement from the top quintile of the normal range down to the middle of the range can be instructive.

Note also, however, that TGFβ is made by macrophages when they phagocytize apoptotic neutrophils. You will occasionally see a patient with low TGFβ, suggesting inadequate mac clearance of apoptotic neutrophils. However, most commonly, the overabundant production of TGFβ by MDSCs in the context of chronic inflammation will overshadow this diminished mac TGFβ production, so you won't be able to discern this reduction.

Putting the Picture Together

At this point, you're considering/evaluating the following:

1. Inflammatory drivers: PAMPs, DAMPs, HAMP effects
2. Failure of resolution
3. Loop reinforcement mechanisms
4. Metabolic Dysregulation
5. Baked-in efficiencies, likely based on genomic uniqueness
6. T cell polarization patterns
7. TGFβ/ROS/MDSC issues

Your task is to size the variables, decide which ones to attend to first, plan the order of operation, and then see how it goes as you start to roll out the strategy. As always, you'll learn a lot about the patient by seeing how they respond to the first few cycles of work. As the 19th century German military strategist Helmuth von Moltke is purported to have said, "No battle plan survives contact with the enemy." So, you'll always need to see how it goes. In particular, the patient may be highly efficient at producing a cytokine that drives a problematic mechanism. You may need higher doses of the supplement(s) you're using to downregulate that cytokine or functional mechanism.

Treatment Strategies

The order of operation is key here. Different cases will need to be unfolded in different ways. Here are some ideas that will help you succeed, including keeping the patient out of the troubles you're likely to see. The immunology of these cases is a big equation that can go lots of different ways. You won't encounter these problems in the majority of patients. But you're trying to avoid a practice that has 20% of the patients doing worse rather than better, so it's good to avoid these problems.

Staying out of trouble

Trouble Type 1: Going after inflammation first

The main issue with trying to reduce inflammation is that if you go after the inflammation itself first, you can get into trouble in two main ways. First, creating more immunological tolerance will allow pathogen burdens to expand more, driving more inflammation, tissue destruction, and autoimmune upregulation. Second, more immunological tolerance means more regulatory T cells (Tregs), which make more TGFβ. If the patient is Th2 dominant, they'll have a lot of IL-4, which will combine with the TGFβ, yielding Th9 cells. These will drive more inflammation.

Trouble Type 2: Going after the pathogens first

On the other hand, if you go after the pathogens first, you're likely to make inflammation markedly worse, because killing pathogens creates a field of pathogen debris, which can vigorously drive the PAMP response.

Option 3

The safer bet is to address T cell polarization, using substances that also have anti-inflammatory effects. This will support the body's own ability to inhibit pathogen burdens, while also keeping a lid on excessive inflammatory responses. Here is the order of operation that typically yields the best results. Here are a few examples of dual anti-inflammatory and pathogen killing activity:

- Glutathione increases Th1 activity and reduces macrophage inflammatory action.
- Vitamin D is anti-inflammatory and required for macrophage lysosomal enzyme production.
- Berberine promotes Th1 and AMPK. AMPK promotes SIRT2, inhibiting inflammasome activation.
- Baicalin inhibits IL-6, repairs barriers, and also promotes Th1.
- Vitamin C reduces ROS and also promotes NK cells that kill viruses.

Order of Operation

These steps can be done in stages, cumulatively, continuing the first steps while layering in the later steps. This is typically done in one or two week steps, depending upon the patient. Some steps, like steps 1 and 2, can be done at the same time.

1. Subtractions

Subtractions means changing the inflammatory equation in the body by getting rid of sources of inflammation. The big advantage of subtractions is that they typically have a very low side effect profile. Patients don't typically have adverse responses to the not-eating of something, unless they run into hypoglycemia or problems with something new they substitute in.

- Address sleep, stress, over-training, and other lifestyle issues.
- Get rid of inflammatory foods.
    - Foods to which patients have antibodies.
    - Foods that are deep fried, highly processed, or other junk foods.
    - Foods that are glycemically problematic.
    - Foods that drive dysbiosis or other problematic processes (eg, fructose drives uric acid production, which drives inflammasome activation).

2. T Cell Polarization

You can refer to the T cell polarization application guide for details here. The key pieces will typically be as follows:

Th1 Support (Pure) – 2 or 3 at breakfast and lunch. Support 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. AMPK also promotes SIRT2.

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

Th2 Modulator (Pure Encapsulations) – 2 or 3 BID. Downregulate IL-4 and GATA3, reduce mast cell degranulation, breakdown excess mucous, support glutathione production.

Perilla Extract (Pure) – 2 or 3 BID. Downregulate IL-4. May need dose escalation early in entrenched cases. Note that perilla also inhibits candida from shifting to its hyphal form.

If the patient has GI, lung, or sinus based inflammation, you can add:

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

2b. TGFβ/ROS/GSH

If the patient's TGFβ level is high, and/or if their GSH blood level is inadequate, step 2 is also a good time to introduce some glutathione into the process. If the patient has dysautonomia (POTS), and the GSH level is normal, the ROS and TGFβ levels can be driven down with alpha lipoic acid instead. This is also a good time to introduce vitamin D.

Liposomal Glutathione (Pure) – 2 or 3 BID. Find the dose that drives down TGFβ. Labcorp GSH should typically be at least 240.
Alpha Lipoic Acid (Pure) – 400mg BID.
Vitamin D – Dose should be tailored to blood level of 25-hydroxy vitamin D, with the goal of bringing the blood level to the top quintile of the normal range without going out the top of the range. If the blood level is below 50 (assuming 30-100 range), consider giving 20,000iu QD for a week or two, then dropping to 10,000iu QD. It's typically suitable to test blood levels every month or two, until you've identified the steady dose that yields a steady blood level. This typically involves the patient taking 5,000 iu or in some cases 10,000 iu of D per day. Note that the difference between "just below the top of the range" versus "just above the top of the range" is not equal to "normal" versus "toxic." In other words, if the person goes slightly above the top of the range, do not imagine that they have vitamin D toxicity. Simply tell them to skip taking D for a week, then in an ongoing way, skip taking vitamin D on the weekends, so their blood level nudges down below the top of the range. Be sure to match D with adequate K. I give them separately, so that the doses don't have to be locked together.

Giving glutathione will help the process of shifting T cell polarization toward adequacy of the Th1/NK cell system, so that the body can start to kill pathogens more effectively. TGFβ is tolerance promoting, which is great up to a point, but if the level gets too high, effector T cells will be inhibited, and pathogen burdens will expand. In addition, the ROS can deplete GSH, without which Th1 response is diminished. So, enough GSH really helps your T cell polarization efforts here. The vitamin D also helps with pathogen killing, since D is necessary for macs to make lysosomal enzymes.

3. Inflammation

a. DAMPs & Resolution Failure

These go together since the resolution phase of the inflammatory process involves more efficient macrophage clearance of apoptotic neutrophils and more efficient clearance of DAMPs. This all depends on the SPMs described above. Increase SPMs with:

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 of particular concern, a fish oil supplement emphasizing DHA, such as **DHA Ultimate**, may be suitable. 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.

The D & E series resolvins are the specialized pro-resolving lipid mediators (SPM's) that signal for the resolution phase of the inflammatory process. These come from EPA and DHA. In patients with more aggressive inflammation, NLRP3 inflammasome biology will block conversion of EPA and DHA to the SPM's, so the reduction of inflammation won't take place. In these patients, it can be of particular importance to use a form of fish oil that includes the SPM's already in it.

Pro-Resolve Omega (Pure) – 2 or 3 BID or TID. Source of SPM's. In the most affected patients, NLRP3 inflammasome activation will block conversion of EPA and DHA to the E and D series resolvins (SPMs). This means that at the start of a case, it may be quite important to use a source of SPMs (aka PRMs), so that the resolution signaling can go forward. This may be suitable for a month or two, with dose depending upon patient response and also depending upon the results of their fatty acid lab profile. Once the inflammation has been reduced, the blocking effect of the NLRP3 may be reduced enough to shift to a "regular" fish oil supplement.

Low arachidonic acid? PGE2 is generated by macs when they phagocytize apoptotic neutrophils. But the substrate for PGE2 is arachidonic acid. You will sometimes see low arachidonic acid on a patient's fatty acid profile. These patients tend to do better when they eat more sources of arachidonic acid, like chicken. Vegetarian sources would be eggs and dariy. Vegan is seaweed. Or you can supplement linoleic acid, which converts to arachidonic acid via delta-5-desaturase (D5D). D5D is inhibited by sesamin from sesame, so vegetarians who eat a lot of humus may not have much conversion. Insulin promotes D5D.

Trans fat consumption? Omega 3 and 6 fats are required for normal eicosanoid balance. Their conversion to anti-inflammatory PGE1 and PGE3 requires delta-6-desaturase (D6D). Trans fats are D6D inhibitors. All patients, all humans, need to eliminate trans fats. If that is not installed, failure of the case is much more likely, no matter what else you do.

Inflammasome Inhibition can be a key mechanism for downregulating inflammatory process. Promoting SIRT2 and eliminating SIRT2 inhibitors will drive SIRT2-mediated inhibition of inflammasome assembly. Detailed inflammasome information is in Module 8, Videos 7 and 8.
SIRT2 promotion:
Th1 Support (Pure) – 2 or 3 at breakfast and lunch. Berberine increases AMPK, promoting SIRT2.
Balanced Immune (Pure) – 2 or 3 BID or TID. Curcumin and resveratrol are SIRT2 activators.

Addressing SIRT2 inhibitors:
SIRT2 is inhibited by ROS, uric acid, cholesterol, high glucose, low pH, low potassium, high inflammatory fatty acid levels.

- If glycemic control is poor, address it.
- If the fatty acid profile is abnormal, addressing fatty acid balance will also create the advantage of reducing SIRT2 inhibition.
- If the patient eats a lot of meat, they may benefit from drinking some baking soda away from food, to try to lower systemic pH.
- If cholesterol is high, bring it down, though doing so with statin can increase risk of diabetes or cognitive decline.
- If potassium is below 4, consider giving potassium, but this must be monitored in labs.
- If oxLDL is high, or if glutathione is low, or if TGFβ is high, consider giving **Glutathione 500mg** BID or **Alpha Lipoic Acid** 400mg BID, or at dose sufficient to move the markers. If uric acid is high, consider:

Uric Acid Formula (Pure) – 2 or 3 BID. Consider also that uric acid reuptake is inhibited by vitamin C and by EGCG, so these may also be useful and can be titrated to patient response. White mulberry can also be of significant value here.

Inhibiting Neutrophil Chemotaxis is a key component of quieting down the DAMP production that drives persistent neutrophilic inflammation. This is the core of the DAMP issue, as well as the failure of resolution and the neutrophilic inflammation loop, all of which are ways of describing the same phenomenon. TNFα and IL-1β drive inflammation by signaling for neutrophils to migrate into tissue. TNFα and IL-1β are in a loop activation with NFkB. Downregulating NFkB can help take the steam out of the process.

Balanced Immune (Pure) – 2 or 3 BID or TID. It may be necessary to give a higher dose at first, to bring down the inflammation from a high level. Once there is less inflammation, a lower dose may be enough to keep it down.
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 in Step 1 as part of the 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.

Part of DAMP clearance includes promoting efficient degradation of phagocytized cells and cellular debris. Niacinamide can be helpful in this regard.
Niacinamide – 300mg to 1 gram per day. To support oxidative burst of the neutrophil. Methylation support as needed, per the patient's genetics and related factors.

Improving lymph clearance can also be important, if required by the case.
Quercetin (Pure) – 1 or 2 BID or TID. To promote eNOS, for lymphatic endothelial relaxation.
Vinpocetine (Pure) – 1 or 2 BID. To downregulate excess nitric oxide production by iNOS.

b. Metabolic Dysregulation

This is a topic too broad to cover in an application document that isn't entirely focused on metabolic dysregulation. Broadly speaking, there are reinforcing loops between inflammation, metabolic dysregulation, mitochondrial dysfunction, and failure of autophagy. Restarting autophagy involves adequate Th1 activity to drive autophagosome formation, reduction of ROS, adequate thyroid function, and reduction of inflammation. When mitochondria work well, metabolic integrity improves. Reducing caloric intake to avoid mitochondrial over-fueling is also essential.

c. Efficiencies

Genomically-mediated efficiencies persistently skew the patient's immunology toward activation of the efficient function. In these cases, higher doses of substances used to inhibit these functions may be needed. Here are examples:

Efficiency	Inhibition Tactics
IL-6 and/or IL-6R (IL-6 receptor)	**PE Th1 Support** (baicalin)
TNFα / IL-1β / NFkB / STAT3	**PE Balanced Immune** (curcumin, trans-resveratrol, black ginger, sulforaphane.)
IL-4 / Th2 Dominance	**PE Perilla Extract, Th2 Modulator, Epi-Integrity** (if GI)

d. Loops

The most important loop activation that drives inflammation is **the loop between stress chemistry and inflammation,** described above. Inhibition of this loop involves the following steps:

a. Downregulate NFkB. Balanced Immune (Pure) noted above can be used here as well.
b. Reduce the extent to which the patient makes stress chemistry when they're stressed. This is typically done with adaptogens, especially **Siberian Ginseng.**
c. Increase vagus nerve-mediated inhibition of macrophage production of inflammatory cytokines. Use the Search function and Topic Index to find course materials that discuss vagus nerve function.
d. Improve TCA cycle function. The loop activation between inflammation and stress depends on NFkB-induced hypothalamic production of corticotrophin releasing hormone (CRH). CRH drives the sympathetic nervous system. But CRH also drives cortisol production. With chronic stress, or with TCA cycle dysfunction, the anti-inflammatory effect of the patient's own cortisol can be diminished, allowing inflammation to go forward. Restoration of robust TCA cycle function can help restore the anti-inflammatory effect of the patient's cortisol. Address the need for metabolic repair according to the needs of each patient. Remember that the berberine in **Th1 Support** has been shown to have significant reparative impacts on metabolism.

The next most important and common loop is the **neutrophilic inflammatory loop,** typically driven by resolution failure, though it can also be driven by persistent infection or by Th17 polarization, where high IL-17 levels drive excessive neutrophil activation. These issues should already be addressed by addressing the DAMP/Resolution failure step and addressing T cell polarization.

Eosinophilic and mast cell activation loops are addressed as follows:
Perilla Extract (Pure) – 2 or 3 BID. Downregulate IL-4. May need dose escalation early in entrenched cases.

Epi-Integrity (Pure) – 1 or 2 scoops BID. Downregulate IL-4 and GATA3, repair leaky epithelial barriers, support Th1 response. Useful when epithelial dysfunction is present, as is common for example with dysbiosis, sinusitis, or respiratory issues.
Hist Reset (Pure) – 2 BID or TID, to inhibit mast cell histamine release, promote histamine breakdown, clear inflammatory mast cell mitochondrial DNA fragments released by mast cells. Depending upon how efficient the mast cell activation is, higher doses may be needed.
Vitamin D – dose to raise patient blood levels to the top quintile of the normal range. Vitamin D inhibits IL-5, which is a main driver of eosinophil numbers and function.

4. PAMPs & Pathogen Burdens

At this point, it's suitable to consider addressing pathogen burdens directly. The patient's inflammatory baseline should be low enough that they'll be able to tolerate the pro-inflammatory effect of the PAMP debris that will be generated by killing pathogens. You will already have supported the body's own pathogen killing mechanisms, by supporting the Th1 / NK cell activation process.

Depending upon your style of treatment, you can address pathogens with natural substances and/or pharmaceuticals. The first step is to use lab work to identify the particular pathogens. Then you can decide how you want to eradicate them. It can be especially important to identify and eliminate pathogens with known Th2-promoting evasion strategies, such as candida. Pathogens promoting Th2 shift T cell polarization away from Th1, reducing anti-viral surveillance.
AC Formula II (Pure) – 2 BID away from food by an hour. Or **Caprylic Acid** (Pure) – 2 BID away from food by an hour. Addressing candida is a broad topic, so there's often more to do here.

Other Factors

- If the patient has circulatory or respiratory concerns, or if they have anemia, it's suitable to be concerned about whether there is any incremental uptick of tissue hypoxia. A common mistake in this thought process is to think that normal pO2 means the patient isn't hypoxic. If the patient is anemic, 1005 of their hemoglobin can be saturated with oxygen, but there still isn't enough hemoglobin. If they have perfusion issues, oxygenated blood may not be getting to a specific site, Either of these yields hypoxia, despite normal pO2. Hypoxia drives activation of hypoxia-inducible factor 1α (HIF1α), which drives activation of NFkB.
  Berberine – 500-750mg BID. To downregulate HIF1α. **Th1 Support** contains berberine, so if you've got Th1 Support installed in Step 1 as part of the approach to balancing T cell polarization, this base is covered.
- Consider avoiding chronic NSAID use, as this can interfere with resolution phase chemistry. NSAIDS are described in the literature as "resolution toxic."
- Identify sources of toxins, haptens, or other factors that could promote neutrophil necrosis.