T Cell Polarization – Application Guide

Clinical Context

Use this Application Guide in conjunction with the materials in the Introduction and T Cell Polarization Modules (especially Modules 4 & 5). The comments presented here are basics followed by useful tips for what to watch out for, rather than an attempt to teach the subject overall. For an understanding of T cell polarization, watch the videos in Modules 4 & 5). And remember that T cell polarization is a dynamic process, in which the clinical goal is to influence the tissue signaling environment in favor of the polarization pattern that would favor a useful outcome.

Th2: Epithelial Dysfunction, Allergy, Food Reactions, Histamine, Mast cell issues, Asthma, Atopy

The items listed above are all indications that the patient is Th2 dominant. Consider the inventory of factors that drive patients into Th2 dominance: GI, lung, or sinus epithelial inflammation, sleep dysfunction, stress chemistry, pathogens like c albicans, aspergillus or other molds, older age, pesticide or other endocrine disrupting chemical exposure, genetics, etc.

The ubiquitous nature of this list of factors in chronically ill patients makes it common for patients arriving in a functional medicine practice to present with Th2 dominance. Th2 dominance also inhibits the Th1 system. Inadequate Th1 response can yield a greater than normal background viral burden, increasing inflammation and increasing the likelihood of virally induced autoimmune disease development. It's common in these patients that Th1 system activation and Th2 dominance inhibition are both useful.

To inhibit naïve T cells from polarizing into Th2 cells, it's useful to inhibit IL-4 and GATA3, restore barrier integrity, remove irritants to epithelia (problematic foods, pollen, etc.) and address the inventory of Th2 polarizing factors. Here are useful options:

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.
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. Inhibit mast cell histamine release, promote histamine breakdown, clear inflammatory mast cell mitochondrial DNA fragments released by mast cells.

The Th1 System: Anti-Pathogen Support & Autophagy/Mitophagy Support

Inadequate activation of the Th1 system (Th1 cells, NK cells, CD8+ CTL's, M1 macrophages) can occur with or without Th2 dominance, thought Th2 dominance is extremely common for the reasons mentioned above. Chronically elevated stress levels, pesticide exposure, genetics, and other factors can directly yield inadequate Th1 response.

The Th1 system drives anti-viral and anti-bacterial immunity, suppresses Th17-mediated autoimmunity, and provides anti-cancer surveillance. Th1 cytokines are also necessary for autophagy. Autophagy (and the special case of autophagy of mitochondria called mitophagy) is required for bone marrow stem cell recycling, macrophage and neutrophil phagocytosis and digestion of pathogens, and for repair of neurons. Patients with ineffective autophagy can have low wbc counts, poor anti-pathogenic immune surveillance, poor neuronal repair (both CNS and PNS), and poor mitochondrial function, among other problems.

Loss of adequate Th1 response can yield a greater background viral burden, since the Th1 system drives anti-viral surveillance. A greater background viral burden drives inflammation. Research shows that CVD risk is more than doubled in patients with greater pathogen burden, for example, reflecting this increased inflammatory activation. In these patients, it's often necessary to support adequate Th1 system function, modulate (downregulate) Th2, and also downregulate inflammation.

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.
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.
Vitamin D – Dose to bring 25-OH D blood level into top 20% of range. Repeat D lab testing is required, to establish the dose that consistently maintains the proper blood level. Macrophages take up vitamin D and use it to make lysosomal enzymes (beta defensin and cathelicidin). Without D, viral burdens can increase. And, viruses like EBV are known to down-regulate vitamin D receptor (VDR) function. This yields reduced functionality of the D / VDR system, effectively blunting vitamin D function. This again advantages the virus populations. So, keep vitamin D levels in the upper portion of the normal range, to try to overcome the possibility of VDR downregulation.

Autoimmunity – Th17 & Tregs

Autoimmune tissue damage is driven by Th17 cells. Th17 cell differentiation requires STAT3, which is driven by NFkB, IL-6 and other Th17 differentiation cytokines. Th17 expression is inhibited by promoting regulatory T cells (Tregs), by inhibiting the NFkB-STAT3 axis, by downregulating IL-6, and by supporting interferon gamma (IFNɣ) production by Th1 cells and NK cells.

The order of operation is important. If you start by promoting Tregs in a patient who is Th2 dominant, the TGFβ made by the Tregs may combine with the patient's abundant IL-4, driving production of Th9 cells (see below for Th9). So, start by downregulating (inhibiting) Th2 and supporting the Th1 system. Then promote Tregs. If the patient is in significant inflammatory trouble, you can address T cell polarization and address inflammation at the same time.

If they're not in significant inflammatory trouble, **it's better to start with 1 or 2 weeks Th1 system support first, combined with downregulation of Th2 dominance described above.**

1. Support for Th1 and downregulation of Th2 dominance (see above). Note that the baicalin in Th1 support downregulates IL-6, reducing Th17 activation directly. Likewise, the sulforaphane is a STAT3 inhibitor. So Th1 Support provides some direct Th17 inhibition, as well as the inhibition provided by activation of Th1.

2. Inhibition of NFkB-STAT3 axis and promotion of Tregs.
   Balanced Immune (Pure) – 2 or 3 BID or TID. Higher doses may be needed at first, to capture adequate inhibition of the NFkB-STAT3 co-activation axis. Doses can be reduced, once the inflammation is better controlled (including by subtraction of instigators of inflammation – see the Inflammation Application Guide).
   EPA/DHA Essentials (Pure) – 2 BID. Downregulate NFkB, promote Tregs.
   Vitamin D – Dose to bring 25-OH D blood level into top 20% of range.

Note that a fasting mimicking diet has also been shown to substantially increase Tregs.

Remember also that viruses can often instigate the development of new autoimmune disease expression. When you're doing a workup on a new patient who has an autoimmune disease, measure EBV and other virus antibodies and address as needed. In the setting of chronic illness, it's common to see a patient with inadequate Th1 response, so they can't adequately inhibit viral burdens. This is part of why it's so important to promote adequate Th1 and inhibit Th2 in autoimmunity.

Candida or other yeast/fungal pathogens – chronicity driving chronic Th17 activation

Th17 cell activation is the normal immune response to fungal pathogens. But if a fungal pathogen is persistently present, the Th17 response will be persistently upregulated, driving autoimmune mediated tissue damage in those who have autoimmune disease. So it's important to address fungal pathogens in these patients. Candida, aspergillus and others are known to drive the host into Th2.

AC Formula II (Pure) – 2 BID away from food.
Caprylic Acid (Pure) – 2 BID away from food.
Stevia, Garlic or other biofilm disruptor. Note that garlic's function as a biofilm disruptor is restricted to the GI tract, as the molecules that provide its biofilm degrading characteristics don't survive first pass clearance in the liver.
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.

Th22: Antibody glycation worsening autoimmune expression

TNFα and IL-6 in combination drive naïve T cells to polarize into Th22 cells. Th22 cells make interleukin-22 (IL-22). IL-22 drives antibody glycation, which makes antibodies more aggressive in their attack against their targets. When auto-reactive antibodies are more glycated, they have

higher affinity for their self-tissue targets and the patient moves closer to the threshold of autoimmune flare activation. Th17 cells make both IL-21 and IL-22, both of which drive antibody glycation. So, in the autoimmune patient, downregulation of Th17 is a primary goal. In addition, it's important to watch for Th22 cell activation and production of additional IL-22 that can push the patient deeper into disease manifestation.

Since TNFα and IL-6 are the drivers of Th22 cell polarization, it's important to consider common ways that these cytokines can be increased. Vagus nerve motor signals inhibit production of TNFα in the intestines and spleen. Any inflammatory activation drives up TNFα. Vagal motor outflow also inhibits Kupfer cells from making IL-6. So again, attention to vagal motor outflow, perhaps using tVNS, might be suitable.

IL-6 is made during muscle contraction (the IL-6 myokine effect), so overtraining generates a lot of IL-6 and can be a significant problem. The worst version of this is when a woman who has just given birth, and has a lot of prolactin in her system (a known autoimmunity instigator) decides to lose weight by training hard. The combination of IL-6 (driving both Th17 and Th22) and prolactin (driving autoimmune disease expression) can promote new autoimmune disease expression.

It's also useful to assess whether the patient has gain of function gene defects for TNFα and/or IL-6. Their presence can alert you to a greater likelihood of a concern about Th22 polarization. A genetic basis for increased TNFα and/or IL-6 levels would also suggest that measures taken to downregulate their levels might have to be installed long term, or that if lowering doses was successful later in the case, the patient would need to be prepared to raise doses again at the first sign of trouble. Similarly, the patient's attention to maintaining healthy vagal motor outflow would need to be sustained. Here are options for downregulating Th22 cell polarization:

Balanced Immune (Pure Encapsulation) – 2 or 3 BID or TID. Downregulate the NFkB – **TNFα**/IL-1β loop activation. 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 IL-6. (Baicalin also downregulates IL-8). 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.

Excessive Mucous Accompanied by Inflammation – Th9 Cell Polarization

When you start working with a new patient, it's tempting to think that the best first move is to downregulate inflammation with things like curcuminoids, fish oil, and vitamin D. That's not unreasonable. But occasionally the patient does badly. This can be because the patient is Th2 dominant at the start of the case, so they have high levels of IL-4 in affected tissues. When you add curcuminoids and fish oil, you're downregulating the NFkB-STAT3 axis, which is great, and the patient is shifted away from Th17, which is typically also great. But the effect is also that regulatory T cell (Treg) numbers and function increase. This increases TGFβ. The problem is that IL-4 plus TGFβ yields naïve T cell polarization into Th9 cells. **Th9 cells increase inflammation and mucous production.**

It's noteworthy that Th2 dominance can, just by itself, push the patient into Th9 cell production. This can occur when there is enough IL-13 (another Th2 cytokine) to drive up the numbers and function of myeloid derived suppressor cells (MDSC's), which make TGFβ. At that point, you've got IL-4 and TGFβ being generated by the patient's Th2 dominance. With one key addition, the approach is similar to addressing Th2 dominance. And the key is that **this needs to be done before applying measures to reduce inflammation, so that you don't inadvertently push the Th2 dominant patient into Th9.**

The key additional factor is that TGFβ increases reactive oxygen species (ROS) and ROS drive up TGFβ, creating a loop. If you drive down ROS, you take the steam out of the loop. It's best to use non-polyphenol anti-oxidants for this, for reasons discussed in the course videos. Here are useful options:

Liposomal Glutathione (Pure) – 2 or 3 BID. Downregulate TGFβ. Use if TGFβ blood levels are high and/or glutathione blood levels are low or toward the low end of normal. Find the blood glutathione level that adequately suppresses excessive TGFβ production.
Alpha Lipoic Acid (Pure) – 400mg BID. Another non-polyphenol antioxidant that can be used to downregulate TGFβ. If dysautonomia is part of the picture, this can be an especially useful choice.

When you're working with a Th2 dominant patient, trying to prevent them from shifting into Th9, it's essential to downregulate both the TGFβ and IL-4 components of the picture. While you're using glutathione and/or alpha lipoic acid to downregulate TGFβ, it's essential to sustain the work of downregulating the Th2-mediated production of IL-4 and to address the underlying Th2 dominance. These are useful options (from the Th2 dominance discussion) when working to downregulate Th2 dominance:

Th2 Modulator (Pure) – 2 or 3 BID. Downregulate IL-4, downregulation of GATA3, to interfere with the IL-4 / TGFβ combination that drives Th9.
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.
Hist Reset (Pure) – 2 BID or TID. Inhibit mast cell histamine release, promote histamine breakdown, clear inflammatory mast cell mitochondrial DNA fragments released by mast cells.

Keep in mind that inhibiting Th2 will also reduce the extent to which IL-13 (another Th2 cytokine) will drive MDSC production of TGFβ, so your focus on downregulating Th2 will also give the patient advantages against excessive TGFβ.