Protocol—Immune Response

Assessment			
Health history	Chronic stress		
	History of autoimmune disease		
	History of immunodeficiency		
Symptoms	Chronic/reoccurring infections	🗖 Joint pain	
	□ Allergies	🗖 Myalgia	
	Pruritis	□ Sleep disturbances	
	🗖 Fatigue	Difficulty concentrating/brain fog	
Physical signs	□ Allergic shiners		
	🗆 Pallor		
	🗖 Rash, urticaria		
	🗖 Edema		
	Delayed wound healing		
Labs	□ hs-CRP	□ 4pt cortisol	
	🗖 Cytokines: e.g., IL-6, TNF-a, IL-1β, IL-10	Assess for leaky gut:	
	Lipid mediators: e.g., PGE2	Lipopolysaccharide (LPS) and anti-	
	🗖 MMP-9, TGFβ	LPS levels; Zonulin	
	CBC—WBC populations and relationship e.g.,	saturation saturation	
	Antibodies: IgM, IgG, IgA and/or IgE tests	🗖 Ferritin	
	ANA (antinuclear antibodies)	🗖 Omega-3 index (fatty acid [FA]	
	Erythrocyte sedimentation rate (ESR)	status [i.e., EPA and DHA])	
	\square Serum vitamin B ₁₂	Oxidative stress:	
	🗖 RBC magnesium	Urinary F2-isoprostanes, serum	
	□ 25-Hydroxyvitamin D		
	□ Organic acid test (OAT)		
	□ Thyroid panel (TSH, anti-TPO, FT4, FT3, rT3)		

> Protocols

Assessment cont.			
Rx/OTC directions	□ Antihistamines		
	□ Antibiotics		
	□ Immunosuppressant medications		
	□ Anti-inflammatories		
	🗖 Immunoglobulin therapy		
	□ Interferon-gamma therapy		
	Growth factors		
Other considerations	Increased risk for/associated with:		
	□ Gl concerns/dysbiosis/leaky gut		
	□ Opportunistic infections		
	Chronic fatigue syndrome		
	□ Autoimmune conditions		
Additional	Review medications; certain medications may interfere with immune response.		
Notes:			

Recommendations				
Focus	Nutritional & Lifestyle Recommendations	Notes		
Nutrition	 Nutrient-dense, high-protein food plan Anti-inflammatory food plan 			
Lifestyle	Gress management			
	Restorative movement			
Foundational nutrients and nutritional bioactives	 Allicin¹⁻³ Andrographis paniculata^{4,5} Boswellia serrata^{6,7} Curcumin⁸⁻¹³ Echinacea purpurea^{14,15} EPA and DHA^{17,18} Hemp extract (<i>Cannabis sativa</i>)^{19,20} Lactoferrin²¹⁻²³ Magnesium²⁴⁻²⁷ Multivitamin/mineral^{28,29} Medicinal mushrooms including: Reishi (<i>Ganoderma lucidum</i>), Shiitake (<i>Lentinus edodes</i>)³⁰⁻³² Probiotics (<i>Saccharomyces boulardii, Lactobacillus paracasei</i> 8700:2, <i>Lactobacillus</i> 			

Recommendations				
Focus	Nutritional & Lifestyle Recommendations	Notes		
Foundational nutrients and nutritional bioactives	Quercetin ³⁷⁻³⁹ □ Specialized pro-resolving mediators (SPM) ⁴⁰⁻⁴⁴ □ Vitamin A ⁴⁵ □ Vitamin C ⁴⁶⁻⁴⁸ □ Vitamin D ₃ ⁴⁹⁻⁵³ □ Whey protein concentrate ^{54,55} □ Xanthohumol ⁵⁶⁻⁵⁸ □ Zinc ⁵⁹ □ Zinc ⁵⁹			
	\Box Zingiber officinale ^{60,61}			

References

- 1. Patya M et al. Allicin stimulates lymphocytes and elicits an antitumor effect: a possible role of p21ras. *Int Immunol*. 2004;16(2):275-281.
- Bakri IM et al. Inhibitory effect of garlic extract on oral bacteria. Arch Oral Biol. 2015;50(7):645– 651.
- Josling P. Preventing the common cold with a garlic supplement: A double-blind, placebocontrolled survey. Adv Ther. 2001;18(4):189–193.
- Caceres DD et al. Use of visual analogue scale measurements (VAS) to assess the effectiveness
 of standardized Andrographis paniculata extract SHA-10 in reducing the symptoms of
 common cold. A randomized double blind-placebo study. *Phytomedicine*. 1999;6(4):217-223.
- Saxena RC et al. A randomized double blind placebo controlled clinical evaluation of extract of Andrographis paniculata in patients with uncomplicated upper respiratory tract infection. *Phytomedicine*. 2010;17(3-4):178-185.
- Kimmatkara N et al. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee – A randomized double blind placebo controlled trial. *Phytomedicine*. 2003;10(1):3-7.
- 7. Sontakke S et al. Open, randomized, controlled clinical trial of Boswellia serrata extract as compared to valdecoxib in osteoarthritis of knee. *Ind Jour Pharm*. 2007;39(1):27-29.
- 8. Hanai H et al. Curcumin maintenance therapy for ulcerative colitis: randomized, multi-center, double-blind, placebo-controlled trial. *Clin Gastro Hepatol.* 2006;4(12):1502-1506.
- 9. Chandran B et al. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phyto Resear*. 2012;26(11):1719-1725.
- Belcaro G et al. Efficacy and safety of Meriva®, a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. Altern Med Rev. 2010;15(4):337-344.
- 11. Usharani P et al. Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus: a randomized, parallel-group, placebo-controlled, 8-week study. *Drugs R D*. 2008;9(4):243-250.
- 12. Khajehdehi P et al. Oral supplementation of turmeric decreases proteinuria, hematuria, and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis: a randomized and placebo-controlled study. *Ren Nutr.* 2012;22(1):50-57.
- Panahi Y et al. Effects of curcumin on serum cytokine concentrations in subjects with metabolic syndrome: A post-hoc analysis of a randomized controlled trial. *Biomed Pharmacother*. 2016;82:578-582.
- 14. Ross SM. Echinacea purpurea: A proprietary extract of echinacea purpurea is shown to be safe and effective in the prevention of the common cold. *Holist Nurs Pract*. 2016;30(1):54-57.
- 15. Rondanelli M et al. Self-care for common colds: the pivotal role of vitamin D, vitamin C, zinc, and echinacea in three main immune interactive clusters (physical barriers, innate and adaptive immunity) involved during an episode of common colds-practical advice on dosages and on the time to take these nutrients/botanicals in order to prevent or treat common colds. *Evid Based Complement Alternat Med.* 2018;2018;5813095.
- Miles E et al. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. Br J Nutr. 2012;107 Suppl 2:S171-S184.

- 17. Rangel-Huerta OD et al. Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomarkers: a systematic review of randomised clinical trials. *Br J Nutr.* 2012;107 Suppl 2:S159-S170.
- Nordgren TM et al. Omega-3 fatty acid supplementation, pro-resolving mediators, and clinical outcomes in maternal-infant pairs. *Nutrients*. 2019;11(1):E98.
- 19. Barrie N et al. The endocannabinoid system in pain and inflammation: Its relevance to rheumatic disease. *Eur J Rheumatol*. 2017;4(3):210-218.
- 20. Russo EB. Clinical endocannabinoid deficiency reconsidered: current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. *Cannabis Cannabinoid Res.* 2016;1(1):154-165.
- 21. Dix C et al. Bioavailability of a novel form of microencapsulated bovine lactoferrin and its effect on inflammatory markers and the gut microbiome: A pilot study. *Nutrients*. 2018;10(8):1115.
- 22. Mulder AM et al. Bovine lactoferrin supplementation supports immune and antioxidant status in healthy human males. *Nutr Res.* 2008;28(9):583-9.
- Vitetta L et al. The clinical efficacy of bovine lactoferrin/whey protein Ig-rich fraction (Lf/IgF) for the common cold: a double blind randomized study. *Complement Ther Med.* 2013;21(3):164-171.
- 24. Guerrero-Romero F et al. Severe hypomagnesemia and low-grade inflammation in metabolic syndrome. *Magnes Res.* 2011;24(2):45-53.
- 25. Rodríguez-Morán M et al. Serum magnesium and C-reactive protein levels. Arch Dis Child. 2018;93(8):676-680.
- Guerrero-Romero F et al. Hypomagnesemia, oxidative stress, inflammation, and metabolic syndrome. *Diabetes Metab Res Rev.* 2006;22(6):471-476.
- Simental-Mendía LE et al. Oral magnesium supplementation decreases C-reactive protein levels in subjects with prediabetes and hypomagnesemia: A clinical randomized double-blind placebo-controlled trial. Arch Med Res. 2014;45(4):325-330.
- Chandra RK. Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. *Lancet*. 1992;340(8828):1124-1127.
- Girodon F et al. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: A randomized controlled trial. Arch Intern Med. 1999;159(7):748-754.
- 30. Jan RH et al. Immuno-modulatory activity of Ganoderma lucidum-derived polysaccharide on human monocytoid dendritic cells pulsed with Der p 1 allergen. *BMC Immunol*. 2011;12:31.
- 31. Chen X et al. Monitoring of immune responses to a herbal immuno-modulator in patients with advanced colorectal cancer. *Int Immunopharmacol.* 2006;6(3):499-508.
- 32. Zhang M et al. Mushroom polysaccharide lentinan for treating different types of cancers: A review of 12 years clinical studies in China. *Prog Mol Biol Transl Sci.* 2019;163:297-328.
- Berggren A et al. Randomised, double-blind and placebo-controlled study using new probiotic lactobacilli for strengthening the body immune defence against viral infections. *Eur J Nutr.* 2011;50(3):203-210.

References

- Saini R et al. Probiotic nutrition for gastrointestinal health modulations in inflammatory bowel disease: A placebo-controlled clinical study (P20-021-19). *Curr Dev Nutr.* 2019;3(Suppl 1):nzz040.P20-021-19.
- 35. Saavedra JM et al. Human studies with probiotics and prebiotics: clinical implications. *Br J Nutr.* 2002;87 (2):5241-246.
- 36. Mousa HA et al. Prevention and treatment of influenza, influenza-like illness, and common cold by herbal, complementary, and natural therapies. J Evid Based Complementary Altern Med. 2017;22(1):166-174.
- 37. Ou Q et al. Impact of quercetin on systemic levels of inflammation: a meta-analysis of randomised controlled human trials. *Int J Food Sci Nutr.* 2019:1-12.
- Mohammadi-Sartang M1 et al. Effects of supplementation with quercetin on plasma C-reactive protein concentrations: a systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Nutr.* 2017;71(9):1033-1039.
- Weng Z et al. Quercetin is more effective than cromolyn in blocking human mast cell cytokine release and inhibits contact dermatitis and photosensitivity in humans. *PLoS One*. 2012;7(3):e33805.
- 40. Duvall MG et al. Non-type 2 inflammation in severe asthma is propelled by neutrophil cytoplasts and maintained by defective resolution. *Allergol Int.* 2019;68(2):143-149.
- 41. Gottfried S et al. The role of specialized pro-resolving mediators (SPMs) in inflammation & cellular resilience: A new paradigm on the resolution of inflammation. www. metagenicsinstitute.com. https://www.metagenicsinstitute.com/blogs/spms-inflammationresilience/. Accessed June 28, 2019.
- Barden ME et al. Specialised pro-resolving mediators of inflammation in inflammatory arthritis. Prostaglandins Leukot Essent Fatty Acids. 2016;107:24-29.
- Chiang N et al. Identification of resolvin D2 receptor mediating resolution of infections and organ protection. J Exp Med. 2015;212(8):1203-17.
- 44. Dalli J et al. Identification and structure elucidation of the pro-resolving mediators provides novel leads for resolution pharmacology. *Br J Pharmacol*. 2019;176(8):1024–1037.
- 45. Lisulo MM et al. Adjuvant potential of low dose all-trans retinoic acid during oral typhoid vaccination in Zambian men. *Clin Exp Immunol.* 2014;175(3):468–475.
- Hunt C et al. The clinical effects of vitamin C supplementation in elderly hospitalised patients with acute respiratory infections. *Int J Vitam Nutr Res.* 1994;64(3):212–219.
- Hemilä H et al. Vitamin C for preventing and treating pneumonia. Cochrane Database Syst. Rev. 2013;8:CD005532.

- Hemilä H. The effect of vitamin C on bronchoconstriction and respiratory symptoms caused by exercise: A review and statistical analysis. *Allergy Asthma Clin Immunol.* 2014;10:58.
- 49. Mayte M et al. Vitamin D: Effect on haematopoiesis and immune system and clinical applications. Int J Mol Sci. 2018;19(9):2663.
- Pincikova T et al. Vitamin D treatment modulates immune activation in cystic fibrosis. Clin Exp Immunol. 2017;189(3):359–371.
- Petri M et al. Vitamin D in SLE: Modest association with disease activity and urine protein/ creatinine ratio. Arthritis Rheum. 2013;65(7):1865–1871.
- 52. Margherita T et al. Vitamin D and 1,25(OH)2D regulation of T cells. Nutrients. 2015;7(4):3011–3021.
- 53. Jung HC et al. Vitamin D₃ supplementation reduces the symptoms of upper respiratory tract infection during winter training in vitamin D-insufficient Taekwondo athletes: A randomized controlled trial. *Int J Environ Res Public Health*. 2018;15(9):2003.
- 54. Zavorsky GS et al. An open-label dose-response study of lymphocyte glutathione levels in healthy men and women receiving pressurized whey protein isolate supplements. *Int J Food Sci Nutr.* 2007;58(6):429-436.
- 55. Grey V et al. Improved glutathione status in young adult patients with cystic fibrosis supplemented with whey protein. *J Cyst Fibros*. 2003;2(4):195-198.
- 56. Gao X et al. Immunomodulatory activity of xanthohumol: inhibition of T cell proliferation, cell-mediated cytotoxicity and Th1 cytokine production through suppression of NF-kappaB. Immunopharmacol Immunotoxicol. 2009;31(3):477-484.
- 57. Ferk F et al. Impact of xanthohumol (a prenylated flavonoid from hops) on DNA stability and other health-related biochemical parameters: Results of human intervention trials. *Mol Nutr Food Res.* 2016:60(4):773-786.
- Pichler C et al. Xanthohumol prevents DNA damage by dietary carcinogens: Results of a human intervention trial. *Cancer Prev Res (Phila)*. 2017;10(2):153-160.
- 59. Wang L et al. Efficacy of zinc given as an adjunct to the treatment of severe pneumonia: A meta-analysis of randomized, double-blind and placebo-controlled trials. *Clin Respir J.* 2018;12(3):857-864.
- 60. Phan PV et al. Ginger extract components suppress induction of chemokine expression in human synoviocytes. J Altern Complement Med. 2005;11(1):149-154.
- 61. Grzanna R et al. Ginger—An herbal medicinal product with broad anti-inflammatory actions. *J Med Food*. 2005;8(2):125-132.

This template protocol is for your informational and educational purposes only. It does not constitute medical advice. As a health care practitioner, you may use this protocol as you deem appropriate in your independent professional judgment and should make any and all changes that you believe are appropriate, or disregard this protocol in its entirety. Neither Metagenics Institute nor its affiliates shall be responsible for any course of action that is selected for any patient or individual based on your or another individual's use of this protocol.

