

COVID-19 Update 2021

The New Normal

EXECUTIVE SUMMARY



MARCH 2021



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Adjusting to the New Normal

For most of us, there has never been a time where infections have taken precedence at the forefront of our minds. At the time of writing, 8th March 2021, it is almost one year since the World Health Organization declared a global pandemic. Fortunately, for those within Australia and New Zealand, the virus SARS-CoV-2 and the disease it causes, COVID-19, has been well contained. Even so, the ramifications of COVID-19 have changed the way we live. By necessity, we are more vigilant of even the mildest sniffle, staying home, isolating and testing. For many this creates fear, and for some, lost income that they can't afford to lose. Now, more than ever, natural medicine Practitioners have an opportunity to support patients' immune resilience.

The Key to Prevention Lies With Nutrition

For all patients, it is essential to ensure optimal status of the nutrients vitamin C, vitamin D and zinc, which are all required for appropriate immune response. This safe and effective strategy can help build a robust defense against infection. For instance, a systematic review and meta-analysis investigating vitamin D supplementation (between 800 IU and 2,000 IU for periods spanning months to years) demonstrated a reduced risk of all acute respiratory tract infections.¹ Interestingly, while vitamin D supplementation was particularly effective in those whose baseline levels were below 25 nmol/L, those with higher levels still experienced some benefit.² Similarly, a Cochrane review recognised that zinc supplementation, when taken for at least five months, reduced the incidence of colds.³ Here, prevention is truly key, and it seems this is especially true when it comes to COVID-19. While studies using vitamin D and zinc in patients already suffering from COVID-19 symptoms have not been consistently successful, those with lower levels of these important immune nutrients appear to be at greater risk of infection, and associated complications. For instance, a significant negative correlation between vitamin D levels and COVID-19 cases was established in European countries.⁴ COVID-19 patients with zinc deficiency had higher rates of complications, including acute respiratory distress syndrome and mortality.⁵ Ensuring our patients are replete with essential immune supporting nutrients by supplementing with *Vitamin D* and *High Bioavailability Zinc with Vitamin C* or *High Bioavailability Zinc with P5P* is key to preventing infections, and reducing infection severity.

Microbiome Support Protects Those Prone to Infection

When it comes to supporting our patient's immune health, it would be remiss to forget about the microbiome, especially in those who experience frequent infections. In a clinical trial, 898 participants who were frequently sick with colds were allocated to receive either 500 million CFU/d each of *Lactobacillus plantarum* HEAL9 and *Lactobacillus paracasei* 8700:2 or a placebo for 12 weeks throughout winter. Compared to the placebo, the probiotic group experienced significantly fewer colds overall, as well as a 30% reduction in the incidence of repeated colds.⁶

The Immune Tide

Of course, even in the best of health, we can succumb to the occasional cold or flu. When this happens, Practitioners can utilise ingredients that optimise immune function to speed up recovery and reduce severity. These strategies apply to the common cold and influenza, as well as coronaviruses such as SARS-CoV-2. In the early stages of infection our innate immune defence is quickly activated, resulting in antigen presentation and the recruitment of our adaptive immune response. Proliferation of T and B cells follows, accompanied by a strong, acute spike in inflammation (depicted in red in Figure 1).⁷ A healthy phenomenon which is essential for threat elimination, this wave of inflammation retreats when the threat (depicted in blue in Figure 1) is resolved.^{8,9} This process is known as the tide of immunity, and it describes the natural ebb and flow of immune activity that should occur during infection, whether that's a cold, the flu or the majority of COVID-19 cases (green panel in Figure 1). However, some individuals infected with SARS-CoV-2 will go on to develop a much more critical presentation, developing acute respiratory distress syndrome (ARDS), pneumonia and multiple organ dysfunction (pink panel in Figure 1).¹⁰ When this occurs the tide of immune activity looks quite different and is marked by concurrent immune dysfunction and unchecked inflammation.¹¹ The inflammatory cytokine interferon, plays a key role in kicking off innate immune activity in response to viral infections, and is a crucial part of the body's antiviral defence. Interestingly, SARS-CoV-2 can inhibit interferon production.¹² Furthermore, in those with severe COVID-19, impaired interferon production is even more pronounced.¹³ The stealthy nature of SARS-CoV-2, coupled with a dysfunctional immune system in those at risk, allows for fast viral replication and inefficient viral clearance. This heralds a second wave of inflammation known as a cytokine storm, as rapid viral replication causes capillary leakage and cytokine release, as well as a process called pyroptosis, which involves inflammasome assembly and proinflammatory cell death.¹⁴

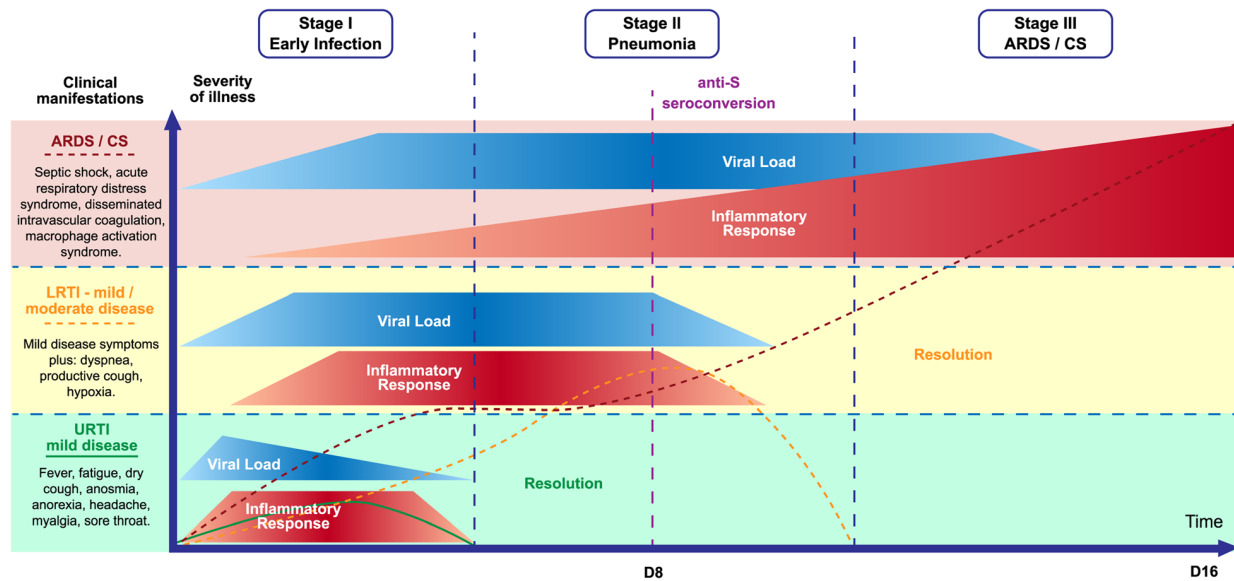


Figure 1: The immune tides of COVID-19, from mild disease, to severe acute respiratory distress syndrome and cytokine storm.¹⁵
ARDS: Acute respiratory distress syndrome; CS: Cytokine storm; LRTI: Lower respiratory tract infection;
URTI: Upper respiratory tract infection; D8: Day 8; D16: Day 16

T Cell Exhaustion May Underpin Severe COVID-19

The presence of exhausted T cells, which often initially appear in adequate quantity, but lack the ability to mount a cytotoxic response, is a key feature in chronic infection (Figure 2).¹⁶ Essentially, when this occurs, the immune system isn't able to mount an effective adaptive response and fails to eradicate the pathogen. Compared to effector T cells, exhausted T cells display increased levels of inhibitory receptors, such as PD-1, which leads to apoptosis upon activation, eventually resulting in a decline in T cell numbers.¹⁷

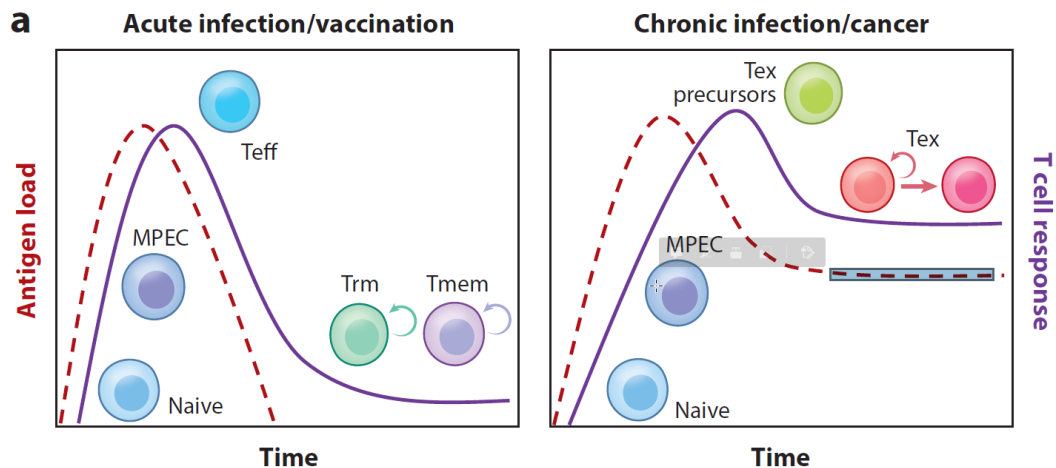


Figure 2: Left - eradication of an acute infection as illustrated by the receding tide of T cell function. Right - chronic infection is linked to persistent T cells who have changed to an exhausted phenotype with substantially diminished cytotoxic capacity.¹⁸
MPEC: Memory precursor T cell; Teff: Effector T cell; Tex: Exhausted T cell; Tmem: Memory T cell; Trm: Resident memory T cell

Interestingly, T cell exhaustion also seems to be a hallmark of severe COVID-19,¹⁹ with up to 85% of patients in this category presenting with lymphopenia.²⁰ This is in direct contrast to patients with mild presentations of COVID-19, who display a robust adaptive response complete with T cell expansion.²¹ Because T cell activity is essential for viral clearance, and the subsequent inhibition of the innate immune system's inflammatory state, T cell exhaustion (along with an impaired interferon response) also underpins the COVID-19 cytokine storm.²²



Supporting Patients Whatever the Ill

Fortunately for those of us in Australia and New Zealand, at the time of writing, the chances of supporting a patient who has contracted SARS-CoV-2 is very low compared to other countries. However, in our current state of vigilance, in addition to prompt COVID-19 testing, it is important to have the tools to combat infections that we may encounter as soon as they arise, even if that infection is as mild as the common cold. *NK Cell Regulation* contains *Andrographis paniculata*,²³ *Camellia sinensis* (green tea), zinc,²⁴ and vitamins C²⁵ and D,²⁶ and is formulated for effectively lowering symptom severity and duration of acute respiratory tract infections, via immune modulation, inflammatory regulation, and viral control. A meta-analysis concluded that andrographis significantly reduced cold and influenza symptoms and shortened illness by up to three days.²⁷ Of note, andrographis has been approved by Thailand Health Ministry for the treatment of mild to moderate COVID-19, as preliminary investigations confirmed that commencing with 180 mg extract daily (with unspecified andrographolides content) within 72 hours of a positive test result supported symptom improvement within three days without complications.²⁸ Furthermore, zinc and green tea play an important role in supporting our antiviral defence, and both have been suggested as ingredients of note for targeting SARS-CoV-2 pathology. Not only is zinc deficiency associated with inflammasome activation and the expression of inflammatory cytokines,²⁹ zinc is also integral for interferon production,³⁰ both key targets for COVID-19. Furthermore, epigallocatechin-gallate (EGCG) from green tea has been shown to improve the intracellular uptake of zinc, through the formation of zinc ionophores.³¹

If a patient does receive a positive COVID-19 test, stepping up immune support maybe beneficial. Polysaccharides from medicinal mushrooms such as *Cordyceps sinensis* (cordyceps), *Lentinula edodes* (shiitake), *Ganoderma lucidum* (reishi), and *Trametes versicolor* (coriolus) can act as food associated molecular patterns (FAMPs) to stimulate toll like receptors on antigen presenting cells, activating adaptive immunity and therefore T cell response.^{32,33,34,35} To read more on *NK Cell Regulation*, or the combination *Cordyceps, Coriolus and Reishi for Immune Stimulation*, including safety information, please refer to the technical data on Metagenics Institute.

What Can We Do for Those at Risk?

The immune dysfunction, characterised by T cell exhaustion and the hyperinflammatory state present in severe COVID-19, is exacerbated by the existence of conditions marked by inflammation and immune impairment.³⁶ A history of cancer, as well as conditions that affect the lungs, such as pneumonia, chronic obstructive pulmonary disease and smoking, are important risk factors, especially in older patients.³⁷ Importantly, while metabolic syndrome and obesity do increase risk, age is by far the biggest predictor of mortality.³⁸ This is likely due to immunosenescence, the progressive deterioration of the immune system which is associated with ageing, hallmarked by alterations in T cell function, higher proinflammatory cytokine production, and an impaired interferon driven antiviral response.³⁹ For patients at risk of more severe presentations of COVID-19, or other infections such as influenza, consider active hexose correlated compound (AHCC™). This extract from shiitake, is supported by a large body of evidence for its immune enhancing effects in cases of immunosuppression.^{40,41,42,43,44,45,46,47,48,49,50} Specifically, AHCC™ supplementation has been shown to improve T cell release of interferon,^{51,52} and improve viral clearance in humans,⁵³ and animal models.^{54,55} Not surprisingly, AHCC™ has been identified as a possible therapeutic strategy to combat COVID-19.^{56,57}

Whether the goal is to prevent infections, treat a patient at the first signs of symptoms, or support at-risk patients, Practitioners can use ingredients to build a robust and resilient immune response (Table 1). While COVID-19 is known for the being a respiratory virus, patients can experience systemic dysfunction. For example, functional changes in the microbiome, as well as the presence of opportunistic pathogens have been identified in COVID-19 patients, with, up to 10% presenting with gastrointestinal symptoms.⁵⁸ For more information about how to support patients with COVID-19, please see the **COVID-19 Protocol** on Metagenics Institute.

Table 1: Considerations for supporting patient's immune response.

PREVENT	STIMULATE		
Key immune ingredients	At first sign of any symptoms	Recurrent infections	Chronic infections
	Positive COVID-19 test		At risk population
Vitamin D3 High Bioavailability Zinc with Vitamin C High Bioavailability Zinc with P5P	<i>Lactobacillus plantarum</i> HEAL9, <i>Lactobacillus paracasei</i> 8700:2 and <i>Lactobacillus rhamnosus</i> (LGG®) to Boost Immunity		
	NK Cell Regulation	Cordyceps, Coriolus and Reishi for Immune Stimulation	AHCC™ and Ginger



Long COVID

Whilst the focus has been heavily on managing the severity of COVID-19 and lowering mortality, many patients continue to experience symptoms months post-SARS-CoV-2 infection. Feeling ignored and unsupported by the medical community, with some experiencing medical gaslighting, those impacted by the lingering effects of this virus called themselves COVID long haulers.⁵⁹ Long COVID presents with a variety of symptoms, which can wax and wane over an extended period, with the most prominent being fatigue, shortness of breath, body aches and pains and cognitive deficits.^{60,61,62}

Strangely, the development of long COVID is not influenced by initial disease severity, pre-existing health condition or age, with children displaying similar symptoms to adults post infection.^{63,64} In fact, in Australia 20 to 39 year olds make up 40% of long COVID cases,⁶⁵ a starkly different demographic to patients who typically develop severe COVID-19. So what is behind this mysterious presentation?

Like other post viral conditions, long COVID is poorly understood, and similarities have been drawn between this and chronic fatigue syndrome/myalgic encephalomyelitis.⁶⁶ However, key observations of patients with this condition offer suggestions of how Practitioners can offer support. Ongoing neuroinflammation, resulting in central nervous system damage and neurological changes, have been observed in long COVID patients, and seems to be caused by unchecked proinflammatory cytokine activity, rather than directly by the virus itself.⁶⁷ This can lead to mitochondrial and neuroendocrine dysfunction, explaining the presence of chronic fatigue and postural orthostatic tachycardia (POTS), experienced by many patients with long COVID.⁶⁸ Comparisons have also been made between long COVID and mast cell activation syndrome (MCAS), and it's been suggested that patients should be screened for this condition.⁶⁹

With this in mind, strategies to combat neuroinflammation and to encourage inflammatory resolution are recommended, including *BCM-95™ Turmeric and Saffron for Depression and Specialised Pro-Resolving Mediators*. Furthermore, mitochondrial support with *Mental and Physical Energy Powder*, *Vitamins B5, B6 and C for Stress and Adrenal Health*, and *Enhanced Bioavailability Coenzyme Q10 or Enhanced Bioavailability Ubiquinol for Energy and Cardiovascular Health* may also be beneficial. To access patience for the presence of MCAS, the **Metagenics MCAS Screening Questionnaire** is available on Metagenics Institute, along with the **MCAS Protocol**. For more information about how to support patients with long COVID, including the importance of pacing to address post-exertional malaise, and resources for patient support, please see the **COVID-19 Protocol** on Metagenics Institute.

Hope on the Horizon

Never in our history have we seen the focused distillation of technology and resources into the rapid development of, not one, but multiple vaccinations, as we have in this pandemic. The global response has been unmatched, and as a result many have started entertaining hope of a life resembling pre-2020. Large clinical trials have been reporting success, with the Oxford-AstraZeneca vaccine showing up to 90% efficacy in reducing symptomatic COVID-19.⁷⁰ Furthermore, promising results continue to emerge, with early success being reported from Israel, where new COVID-19 infections and moderate to severe presentations have plummeted. Analysis of data from Israel suggest that the Pfizer vaccine is up to 90% effective by day 21.⁷¹ At the same time, this effort has not been without resistance, with concerns about the safety echoing online. Fortunately, reports on safety have been positive. For instance, in the aforementioned Oxford-AstraZeneca trial, there were more adverse events reported in the placebo group than in the group receiving the vaccine.⁷² In a trial on almost 44,000 participants who received the Pfizer vaccine or placebo, a total of six participants passed away; four from the placebo group and two from the vaccine group. Of those in the vaccine group, cause of death was determined to be unrelated to the treatment, being due to cardiac arrest and arteriosclerosis.⁷³ While side effects are common with any vaccination, the majority of these are mild, transient, and an expected result of immune activation, including injection site pain, fatigue, headache and myalgia, with serious side effects being extremely rare.^{74,75} In any case, receiving the COVID-19 vaccine will remain voluntary. For those who chose to receive the vaccine, there are tools Practitioners can use to optimise efficacy and reduce the risk of side effects. To learn more about how to support patients receiving vaccinations, please see the **Vaccination Protocol** on Metagenics Institute.

Practitioners Stand in a Unique Position

Hopefully Practitioners won't need to support patients through a positive COVID-19 result. However, it's important to understand how to do so, even if this is so we are a place of reassurance and sound information. Furthermore, being able to prevent and treat infections like colds and flu, has never been more important. Natural Healthcare Practitioners stand in a unique position, having the tools to help build immune resilience and tackle the underlying dysfunction driving ongoing symptoms.



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