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Review Article

Integrative medicine considerations for convalescence from mild-to-moderate COVID-19 disease

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ABSTRACT

The majority of individuals infected with SARS-CoV-2 have mild-to-moderate COVID-19 disease. Convalescence from mild-to-moderate (MtoM) COVID-19 disease may be supported by integrative medicine strategies. Integrative Medicine (IM) is defined as healing-oriented medicine that takes account of the whole person, including all aspects of lifestyle. Integrative medicine strategies that may support recovery from MtoM COVID-19 are proposed given their clinically studied effects in related conditions. Adoption of an anti-inflammatory diet, supplementation with vitamin D, glutathione, melatonin, Cordyceps, Astragalus and garlic have potential utility. Osteopathic manipulation, Qigong, breathing exercises and aerobic exercise may support pulmonary recovery. Stress reduction, environmental optimization, creative expression and aromatherapy can provide healing support and minimize enduring trauma. These modalities would benefit from clinical trials in people recovering from COVID-19 infection.

Introduction

The majority of individuals infected with SARS-CoV-2 have mild-to-moderate COVID-19 disease. Despite the non-severe nature of mild-to-moderate (MtoM) COVID-19, these infections are, nonetheless, accompanied by pathophysiological changes, acute and enduring symptoms. Convalescence from MtoM COVID-19 disease is largely overlooked and represents a prime opportunity to support health resilience and to potentially lessen enduring and late-onset sequelae with evidence-informed integrative medicine strategies. Integrative medicine (IM) approaches typically recommend a combination of practices including dietary change, breathing exercises, physical activity, supplements, etc. These authors, all IM subject matter experts, offer plausible integrative strategies to support convalescence from MtoM COVID-19. Whether this multipronged approach has synergistic advantages in COVID-19 recovery deserves further study.

Brief overview of COVID-19

Coronavirus disease of 2019 (COVID-19), the disease caused by the Novel SARS-coronavirus-2 (SARS-CoV-2), was first described in Wuhan, China in December 2019. SARS-CoV-2 is a large RNA virus of the coronavirus family. Its route of infection mimics other members of the Coronaviridae family, which are responsible for many common upper respiratory infections. The virus is enveloped, with a prominent spike protein ("S protein") on its surface; this protein is responsible for virion attachment.[1] The virus enters the body via common mucosal portals and attaches to the cellular ACE2 receptor.[2] The ACE2 receptor is found on diverse cell types, including endothelial and epithelial cells of the lungs, heart, blood vessels, kidneys, and gastrointestinal tract.[3–5] This broad tissue distribution of ACE2 may explain the pleiotropic effects of viral replication in different hosts.

The SARS-CoV-2 virus has demonstrated marked heterogeneity in both host symptomology and target organ pathogenicity. Viral infection of mucosal epithelial cells occurs and may be followed by aggressive replication that spreads the virus down the respiratory tree to the upper and lower lungs. Coronavirus infects both type I and II pneumocytes, which leads to a loss of surfactant and can lead to an

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acute respiratory distress syndrome (ARDS)-like pathology, with respiratory failure and sepsis. Compounding this issue, a concomitant immune response commonly described as a "cytokine storm" can occur. Activation of macrophages, monocytes, and lymphocytes in response to the virus leads to massive release of cytokines.[6] These cytokines contribute to overwhelming and uncontrolled inflammation, leading to septic shock and death in some patients.[7] Acute treatment of these COVID-19 patients becomes a balancing act between maintaining innate antiviral immune responses and suppressing the robust and unregulated cytokine release.

Convalescence appears to be a lengthy process relative to the initial infection. For instance, complications of macro- and microthromboses are relatively common, and may require prolonged anticoagulation.[8,9] Recovery from ARDS is a slow rehabilitative process, and supplemental oxygen is often required. Even individuals with MtoM disease – the majority of infected patients – may experience sequelae of this respiratory viral infection with few supportive conventional therapeutic options. This article will provide additional options for these patients. We will focus on integrative lifestyle-based and dietary supplement strategies. While not all-inclusive of potentially useful strategies, the recommendations outlined here reflect the expertise and experience of these authors. Additionally, while other whole systems of healing such as Asian traditional medicine[10] and Ayurvedic medicine[11] have much to offer in recovery from COVID-19 infection, inclusion is beyond the scope of this paper.

Goals of convalescence from mild-to-moderate COVID-19 disease

The natural course of COVID-19 recovery is variable and influenced by divergent factors including age, the baseline health of the individual, the presence of comorbid conditions, the nature and severity of infection, and socioeconomic circumstances. This variability, coupled with our incomplete understanding of this illness, presents a challenge to the development of a standard convalescence protocol.

Up to 50% of asymptomatic COVID-19 patients have atypical chest CT findings, specifically ground-glass opacities,[12] indicative of pulmonary inflammation and possibly fibrosis. Unresolved post-viral fibrosis can lead to altered lung elasticity and decreased pulmonary function as has been seen in other coronavirus infections.[13] In a cohort of patients over age 65 hospitalized for various types of infectious pneumonia, the risk of cardiovascular disease events increased 4-fold in the first year compared to age-matched controls and remained elevated for 10 years after the pneumonia.[14] Whether this will be seen with COVID-19 is not yet known but is a concern. Liver impairment is also a concern; for instance, out of 926 patients with non-severe COVID-19 in China, elevated AST was seen in 18.2% and elevated ALT was seen in 19.8% of these patients.[15] Another complication is inflammatory activation of the coagulation cascade, evidenced by thrombocytopenia and elevated D-dimer. Although more common in severe infection, over 1/3 of all patients with COVID-19 develop these coagulation abnormalities which may impede patient recovery.[16, 17] Immune dysregulation can occur, especially in individuals over the age of 50 years, characterized by decreased lymphocytes, especially CD8+ *T* lymphocyte counts and impaired adaptive immunity.[18] Inflammation and other ongoing sequelae may lead to lingering fatigue. Additionally, inflammatory cytokines, such as IL-6 and TNF-alpha, which are characteristically elevated in SARS-CoV-2 infection, are implicated in mood disorders especially depression.[19]

Convalescence from MtoM COVID-19 infection is not the primary concern of conventional medicine, whose resources are appropriately directed to life-saving interventions in those with severe infection. However, supporting convalescence is directly within the scope of integrative medicine. Drawing from the deep repository of research and experience in lifestyle-based strategies that optimize recovery and wellbeing after infections, there are a multitude of integrative strategies that can be employed for individuals recovering from MtoM COVID-19 illness. The strategies highlighted here are curated from the expertise of the authors as plausible integrative strategies to support convalescence from MtoM COVID-19.

Overview of integrative medicine

Integrative medicine is defined as healing-oriented medicine that takes account of the whole person, including all aspects of lifestyle. It emphasizes the therapeutic relationship between practitioner and patient, is informed by evidence, and makes use of all appropriate therapies.[20] To be explicit, IM is a larger paradigm that includes conventional approaches. As more effective conventional treatments for COVID-19 become available, and as primary prevention with a vaccine is developed, integrative approaches are likely to remain critically important in re-establishing well-being.

A focus on restoring homeostasis plays a key role in IM. Even when diseases do not have clear treatment, practitioners can use the principles of IM to facilitate recovery.[21] Below are summaries of the evidence for selected IM approaches that can be used to combat inflammation, repair lung injury or dysfunction, replete nutritional deficiencies, reduce chronic stress, and mitigate fatigue.

In addition, IM may empower the patient to aid their recovery. This is important in chronic diseases such as diabetes and cancer to enhance individual control of the disease as well as to reduce the cost of care.[22,23] Many of the evidence-based recommendations that follow are interventions that people can do for themselves. Incorporating these behaviors moves the locus control from external ("the doctor must prescribe medicine or treat me") to internal ("I can take actions to restore my own health.")

Diet

A low-glycemic, low-saturated fat diet can be used to modulate inflammation generally.[24] An anti-inflammatory diet combines traditional Mediterranean and Asian eating patterns and is characterized by high consumption of vegetables, fruit, legumes, fish, lean protein, whole grains, spices, nuts and seeds and low consumption of both refined grains and processed foods. Various nutrient components of an anti-inflammatory diet, such as monosaturated and polyunsaturated fatty acids[25] and plant-derived flavonoids[26] are associated with decreased activation of the NLRP3 inflammasome. The NLRP3 inflammasome is a critical cytosolic protein complex responsible for both acute and chronic inflammation in response to various pathogens,[27] including SARS-CoV-2.[28,29] Anti-inflammatory diets are associated with improved pulmonary function in non-asthmatic Hispanic adults[30] and improved lung function and lower mortality in individuals with COPD.[31] Anti-inflammatory diets emphasize the inclusion of herbs and spices which have known antioxidant and anti-inflammatory effects and may slow the progression of COPD in which NLRP3 inflammasome activation plays a critical pathogenic role.[32,33] With any prolonged illness, COVID-19 included, mental health can be compromised. In a period as short as 10 days, a Mediterranean style diet may result in improved mood and cognition.[34]

Infection is a catabolic process which leads to transient nutrient deficiencies, particularly of protein, B vitamins, vitamin C, copper, zinc, and iron.[35] Individuals with prolonged infections, as well as those who are undernourished prior to infection, are at greatest risk for these nutrient depletions. Thus far, it has been observed that individuals with patients with COVID-19 are likely to have nutrient deficiencies, with one study reporting 76% of hospitalized patients with COVID-19 deficient in vitamin D, 42% deficient in selenium.[36] Further, among patients with respiratory distress, 91.7% were deficient in at least one nutrient while 78.9% without respiratory distress had a deficiency of at least one nutrient. With appropriate dietary support during convalescence, nutrient repletion can be expected, although it is

estimated that it takes up to 3 times as long to replete nutrients than it took to become depleted.[37]

Dietary intake of meat, poultry, fish, eggs, dairy, legumes, beans, nuts and seeds supply amino acids such as alanine, glutamate and glutamine which provide the substrates for nitrogenous compounds. Branched chain amino acids (namely leucine, isoleucine, and valine) improve intestinal permeability, regulate glucose metabolism, enhance endogenous protein synthesis, and fuel immune cells resulting in increased phagocytosis, NK cell activity and immunoglobulin production.[38] The global consensus for protein intake needed by healthy individuals is 0.8 g/kg body weight/day.[39] Older individuals have greater protein needs associated with acute inflammatory and catabolic conditions and PROT-AGE evidence-based recommendations advise the consumption of 1.2 – 1.5 g protein/kg body weight/day.[40]

In addition to protein, consumption of foods rich in vitamins and minerals, and avoidance of foods which may further deplete these nutrients, will support nutritional convalescence. Fruits and vegetables are the main dietary sources of vitamins and minerals and also provide anti-inflammatory and antioxidant phytochemicals. Not surprisingly, consuming fruit and vegetables is associated with improved respiratory function, specifically reduced airway inflammation and oxidative stress,[41] reduced TNFα, reduced C-reactive protein and increased T-cell activation.[42] The USDA-recognizes produce subgroups as follows: dark green vegetables, red/orange vegetables, legumes, starchy vegetables, other vegetables (such as iceberg lettuce, onions, green beans), and fruit.[43] Eating produce from all subgroups is important in order to ingest a full-spectrum of these phytochemicals. The USDA MyPlate guidelines recommend that half of each meal is fruit and vegetables.[44]

Dietary supplements

While dietary supplements are now being studied in acute COVID-19 infections, there are no clinical trials demonstrating the efficacy of dietary supplementation to support convalescence. The therapeutic goals of adjunctive support are prioritized differently between these phases, notably, during active infection, anti-viral support is key, while during convalescence, the primary goal is downregulation of inflammation. There are a number of supplements which may support recovery and minimize post-infectious complications; several of which are highlighted here.

Vitamin D: Vitamin D has anti-viral, anti-inflammatory, and immune enhancing actions in the lungs.[45] Among 43 consecutive older patients hospitalized for treatment of COVID-19, 17.6% of those who received oral 1000iu vitamin D3, 150 mg magnesium and 500mcg vitamin B12 throughout their hospitalization required oxygen therapy compared to 61.5% of patients who did not receive the supplements.[46] Serum vitamin D levels are positively correlated with improved pulmonary function in children and adults with asthma.[47] Vitamin D deficiency is associated with reduced risk of respiratory tract infections,[48] decreased lung function, as well as increased susceptibility to, and delayed recovery from, infections and inflammatory conditions.[49] Not surprisingly, vitamin D deficiency is associated with greater COVID-19 disease severity, and vitamin D deficiency is more prevalent among severe cases compared to mild cases.[50] Vitamin D_3 supplementation is ideally based on serum 25OH vitamin D levels to achieve sufficiency and is typically recommended at a dose of 300 - 4,000IU daily.[51] Those with very low levels of vitamin D, older adults, people with darkly pigmented skin, and obese patients may require higher doses.

Glutathione: Glutathione is the body's primary endogenous antioxidant and is the most abundant antioxidant in the lung epithelium. Glutathione exerts non-specific anti-viral actions, has anti-inflammatory actions, and upregulates vitamin D synthesis and vitamin D receptor activity.[52] A published report of two patients with COVID-19 pneumonia reported relief of respiratory distress using 2 g of either oral or IV glutathione at the peak of their illness.[53] Various studies of patients with acute respiratory distress syndrome have shown that the intake or administration of a number of glutathione-generating compounds, including selenium,[54] n-acetyl cysteine,[55] and ginger,[56] are associated with increased pulmonary glutathione, improved pulmonary function and reduced inflammation. Contrary to popular belief, oral glutathione increases systemic tissue levels of glutathione and natural killer cell cytotoxicity in a dose and time dependent manner.[57] Glutathione supplementation ranges from 250 mg to 1000 mg daily to achieve tissue increases and immune changes.[58]

Melatonin: Melatonin is a potent endogenous antioxidant, anti-inflammatory and immunomodulatory molecule.[59] The natural decline in melatonin production over the lifespan[60] is one theoretical postulation for the increased susceptibility to COVID-19 infection and sequelae among the elderly. Melatonin has been shown to reduce symptoms of other viral infections.[61] Importantly, exogenous melatonin has been found to reduce inflammation, specifically IL – 1β, in the face of acute systemic inflammation.[62] Given the integral role of inflammation in the symptoms of COVID-19 and its post-infection sequelae, there is compelling rationale for the use of melatonin in the convalescent population. Long term melatonin supplementation has been clinically studied at dosages ranging from 2 mg to 20 mg nightly.[63]

Cordyceps sinensis: Cordyceps is a medicinal mushroom with a long tradition of use due to its antioxidant, antitumor, anti-inflammatory, and antimicrobial actions.[64] Cordyceps has been shown to increase Natural Killer (NK) cell activity in randomized clinical trials of healthy adults.[65,66] Cordyceps has also been shown to increase exercise performance – both metabolic and ventilatory capacity - in adults ages 50–75 after 12 weeks of supplementation.[67] A randomized controlled trial of adult patients with moderate chronic asthma found that Cordyceps supplementation for 2 months resulted in reduced serum markers of airway inflammation, including lower IgE, sICAM-1, IL-4 and MMP-9.[68] Long term cordyceps has been most commonly studied in doses between 1.5 g – 3 g daily.[69]

Astragalus membranaceus: The root of Astragalus membranaceus, or milkvetch, has a long tradition of use in Asian medicine (*Huang-Chi*) and has increasingly been incorporated into Western herbal medicine. The root extract contains polysaccharides which have been found to increase innate and T-cell adaptive immunity, to exert anti-oxidant and anti-proliferative effects, and to modulate inflammation.[70] The anti-inflammatory effects of intravenous astragalus have been documented in a DBRCT of 23 patients with metastatic cancers of various types[71] Astragalus resulted in significant quality of life improvements (reduced pain, nausea, fatigue, improved appetite and sleep) which was attributed to reduced inflammatory cytokines, notably IL – 1β and IL-6. In another clinical trial of 82 patients with acute exacerbation of COPD, the addition of 15 mg of astragalus granules twice daily for two weeks to conventional bronchodilator therapy resulted in significant reductions in TNFα, IL – 8, IL – 1β and IL-32.[72] Furthermore, the astragalus group experienced improved measures of adaptive and innate immunity and improved pulmonary function tests. Astragalus root extracts standardized to 40% polysaccharides or 3% astragalosides can be dosed at 320 mg – 500 mg daily and astragalus granules dosed between 4 g – 60 g daily.[73]

Garlic: Garlic, or Allium sativa, can be a component of the diet and also supplemented. Garlic is a source of organosulfur compounds which downregulate nuclear factor-kappa B (NFkB), thereby reducing the expression of many inflammatory cytokines.[74] Several clinical trials have demonstrated immune enhancing and anti-inflammatory effects using aged garlic extract. A DBRCT 3-month study of 120 individuals found that aged garlic extract reduced the severity and duration of cold and flu symptoms.[75] The garlic extract also improved T-cell and NK cell activity. A subsequent trial found similar results with reduced cold and flu severity as a result of aged garlic extract.[76] Garlic supplementation is also associated with reduced inflammation. In a DBRCT of 51 healthy obese adults, 3.6 g of aged garlic extract resulted in significantly lower IL-6 and TNFα after 6 weeks of supplementation.[77] The effective dose of garlic varies according to the formulation studied and the indication.

Clinically studied daily dosages of garlic supplements range from 600 to 900 mg dried garlic powder tablet, standardized to 1.3% alliin or 0.6% allicin) or 7.2 g of aged garlic extract.[78]

Osteopathic manipulation techniques

One historical narrative of the 1918 great influenza reports that people treated by an osteopathic physician had death rates of 10% compared to the 30% overall estimated death rate.[79] While there is no published data confirming this supposition about the 1918 flu, the wisdom that therapies such as Osteopathic Manipulation Techniques (OMT) may be of assistance in respiratory illness is long standing.[80]

Noll et al. examined osteopathic manipulation as an adjunct treatment for hospitalized patients with pneumonia in a DBRCT study of hospitalized patients over age >50 with pneumonia. The researchers found significant reductions in length of stay, respiratory failure and duration of antibiotics in the conventional care plus OMT group.[81] Yao et al. performed a systematic review of the literature examining OMT in patients diagnosed with pneumonia. [82] This review examined 6 RCTs of good quality and summarized their findings as 5 effective techniques that address lung function: inhalation and exhalation dysfunction, diaphragmatic and rib cage mobility, and thoracic lymphatic flow (i.e. thoracic pump). All techniques are illustrated in this review. While this review examined bacterial pneumonia, these OMT techniques address underlying issues also seen in viral pneumonia and ARDS. Based on an extensive literature review and clinical experience, Wang et al. conclude that the best OMT techniques for COVID-19 recovery are modified segmental breathing, lymphatic drainage and rib cage mobility.[83]

OMT may also assist with development of immunity. Jackson et al. examined the effect of OMT techniques (lymphatic pump and splenic pump) during hepatitis B vaccination.[84] In this pilot study (N = 20), participants received the 3 OMT sessions per week for 2 weeks after each vaccination. By week 6, the OMT intervention group had significantly higher antibody titers and this improvement continued throughout the course of the study. The authors posit that lymphatic and splenic pump techniques improved the immunologic response through the movement of lymphatic fluid.

Qigong

Qigong, an ancient practice of meditation, breathing and slow movements, has been shown to improve pulmonary function and may be of benefit in COVID-19.[85] Lim et al. performed a small study (N = 20) examining the effect of Qigong (20 min per day for 10 days) in normal volunteers.[86] Participants had a significant increase in ventilatory efficiency for oxygen use and carbon dioxide production ($p<0.05$); the authors posit that this represented a 20% increase in ventilatory efficiency, and that Qigong is an effective technique for increasing lung capacity and efficiency. Sakata et al. studied the effect of a 12-week Qigong and aerobic exercise program on 72 healthy Japanese women aged 60–86 years of age.[87] The intervention consisted of 90 min of supervised Qigong and 25 min of aerobic exercise once a week, with an additional 20 min of home-based Qigong per day. Physical function improved, and lung capacity increased significantly in participants aged 60–69, although not in those older than 69.

Feng et al. completed an extensive literature search for Qigong to examine its potential in COVID-19 prevention and rehabilitation.[88] They reviewed data for effectiveness in hypertension, asthma, COPD, mood disorders, cognitive impairment, pain relief and muscle strength. They concluded that the efficacy of Qigong is based on 4 mechanisms: management of stress and emotion, strengthening respiratory muscles, reducing inflammation, and enhancing immune function. In respiratory patients, Qigong improved pulmonary function as well as 6-minute walking distance. They specifically recommend three Qigong practices for COVID-19 prevention and rehabilitation - Diaphragmatic breathing, Ba Duan Jin (a series of 8 slow movements and stretching), and Liu Zi Jue (diaphragmatic breathing with pursed lip breathing, toning and mild- body movements.

Wayne et al. did a systematic review of 22 studies on Tai Chi and Qigong with cancer related symptoms and found significant improvement in fatigue, sleep, depression, and overall quality of life.[89] Chan et al. reviewed data on Qigong in two studies of chronic fatigue patients, both trials lasted between 5 and 8 weeks, with a minimum practice of 30 min 3 times per week.[90] They found significant decrease in depressive symptoms, fatigue, and an improvement in sleep.

Home based Qigong may also be very effective for COVID-19. A small feasibility study in China offered a 12-minute Qigong routine twice a day to COVID-19 patients while convalescing.[91] Patients kept a journal of their experiences. This pilot found 100% adherence; the authors conclude that home Qigong is a feasible at home rehabilitation program for COVID-19 recovery. Qigong can be learned through classes (including on-line); the feasibility of doing Qigong at home is promising.

Breathing exercises

Expert opinion in the recent COVID-19 literature stresses the use of breathing exercises in COVID rehabilitation, with the caveat that it must not be introduced too early; patients should be off supplemental oxygen.[92,93] Hanada et al. published a systematic review of 14 studies examining the effect of specific types of pulmonary rehabilitation (PR) on hypoxia and pulmonary function in patients with idiopathic pulmonary fibrosis (IPF).[94] The authors report that aerobic exercise plus either diaphragmatic breathing exercises or inspiratory muscle training (IMT) significantly increased 6-minute walk distance, leading the authors to conclude that breath work added to aerobic exercise may be an important addition to the treatment of pulmonary fibrosis.[95] Borge et al. did a systematic review of breathing exercises including diaphragmatic breathing (DB), pursed-lip breathing (PLB), yoga breathing relaxation techniques (RT), and body position exercises (BPEs) in COPD patients.[96] The strongest evidence was for PBL, with an improvement of dyspnea found to be at 40%.

Wang et al. also included breathing exercises in their recommendations for MtoM COVD-19 rehabilitation.[97] They recommend starting 10 min per session, 2–3 times per day, with a progression up to a total of 60 min per day. The techniques they suggest include DB, PLB, pranayama (a yogic breathing practice), tai chi breath work, or singing.[98] As patients are able to do this before aerobic exercise, breathing exercises are one of the first elements that can be started for COVID-19 rehabilitation.[99] Breathing techniques can be instructed virtually and may be easily added early in recovery and effective for COVID-19 rehabilitation.

Exercise and pulmonary rehabilitation

Moderate exercise appears to be key for immune support and improved recovery. Many observational studies correlate exercise fitness prior to viral infection with lowering the severity of illness; interventional studies also support this finding.[100] Moderate exercise improves cytotoxic immunity[101] and reduces pulmonary fibrosis[102] in animal studies.

A single blinded randomized controlled study by Lau et al. of 133 SARS survivors examined a 6-week exercise training and demonstrated a significant improvement in the 6-minute walk test (77.4 m vs 20.1 m, $p<0.001$) and VO2max (3.6 ml/kg/min vs 1 ml/kg/min, $p = 0.04$).[103] This study found that the type of training (self-trained versus supervised training) was not significant although all the participants' regimens were overseen by a physical therapist during the course of the study. This suggests that virtual oversight could be utilized.

The Stanford Hall consensus statement for post COVID-19, created as an evidence-based set of UK guidelines, states that rehabilitation should be started after it is clear there are no cardiac complications

and within 30 days in the post-acute phase.[104] For asymptomatic, mildly symptomatic and symptomatic patients not requiring hospitalization, they recommend exercise training as the core of the rehabilitation, graded to the patient's ability. For patients who were asymptomatic, they do not suggest exercise restrictions. For those with MtoM COVID-19 symptoms, once recovering, they suggest 1 week of low-level stretching, and light muscle strengthening, before returning to moderate cardiovascular exercise. They stress that high intensity training is avoided until fully recovered.[105]

Wang et al. structure their COVID-19 rehabilitation recommendations according to the severity of dyspnea with the Borg dyspnea score.[106] For MtoM COVID-19, they recommend initially starting with aerobic exercise (i.e. walking or biking) for 10–15 min, 1–2 times per day on 3–4 days each week with an intensity that keeps the Borg dyspnea score ≤ 3. Next they recommend incremental increases in intensity every 2–3 sessions to reach a Borg dyspnea score of 4–6, and to increase the duration incrementally to a maximum of 30–45 min per session.

Stress management

Mindfulness

Extensive literature shows that chronic stress, termed allostatic load,[107] impacts immune system function and, largely through the anti-inflammatory effects of glucocorticoids,[108,109] leads to more frequent and severe viral infections,[110,111] reduced vaccine take-rate,[112] prolonged wound healing,[113] and speeding of chromosomal aging.[114] Mind-body interventions, such as mindfulness meditation, or those combining mindfulness with gentle exercise, such as yoga and Tai Chi, lower the brain's stress response, and also trigger the brain's relaxation response.[115] The latter, via enhancing the parasympathetic nervous system and vagus nerve release of acetylcholine, provide a brake to the stress response and boost the anti-inflammatory components of the immune response.[116] All mind-body practices, including, but not limited to meditation, yoga, Tai Chi, and guided imagery, incorporate deep breathing. Deep breathing initiates the vagal parasympathetic response, as measured by heart rate variability (HRV),[117] lowers the stress response and impacts the immune response.[118,119] In addition, these, and other, mind-body practices boost brain dopamine reward and endogenous opioid anti-pain pathways.[120]

Creativity

Studies have demonstrated measurable health benefits associated with creative expression in healthy individuals as well as in those with medical conditions. Improvements in mood, psychological well-being and immune system functioning have been noted.[121,122] There have been more than 400 studies assessing the impact of expressive writing on various health conditions.[123] Although studies on the benefits of expressive writing have mixed or marginal results, expressive writing is associated with some conditions with relevance to COVID-10 convalescence. Expressive writing is associated with improvements in lung function in adults with asthma,[124] improvement in chronic pain,[125] and improvement in mental health.[126] One well-studied form of creativity is expressive writing, or journaling. A small randomized trial was conducted in which individuals with active HIV infections were assigned to one of two groups over a 4-day period.[127] One group wrote about an emotional topic, while the control group wrote about non-emotional events. The emotional writing group was noted to have decreased viral load and an associated increase in CD4 counts compared to the control writing group. Although causality is not established here, there is a suggestion that this expressive writing exercise could potentially be beneficial.

Creative writing may provide individuals with an opportunity to express their experiences without interruption by a listener, without the need to filter entries to make them acceptable to others, and without the need for special equipment or supplies. However, there may be need for caution in using this technique with those unaccustomed to any emotional expression.[128]

Aromatherapy

Aromatherapy is the aerosolization of plant-derived essential oils. The volatile essential oils found in plants carry aromatic qualities, interact with the mucus membranes of the respiratory tract and affect the limbic system. There are certain clinical applications of aromatherapy which may be of benefit in the setting of convalescence from COVID-19 infection. Lavender essential oil has potential therapeutic value in convalescence due to its stress-reducing and anxiolytic effects. Lavender aromatherapy has been found, in a variety of clinical contexts, to exert anxiolytic effects and to improve sleep quality.[129,130,131] Reduction in anxiety correlates with self-perceived wellness, improves adherence to healthy behaviors and improves sleep – all essential to convalescence from viral infections. In another application of aromatherapy in light of the shared underlying pathophysiology between asthma, COPD and COVID-19 pulmonary disease, namely NLRP3 inflammasome activation, oxidative stress, hypoxia and mitochondrial dysfunction,[132] it is proposed that essential oils beneficial in asthma and COPD may also be beneficial in COVID-19 disease. Specifically, oral administration of 1,8-cineole, a main constituent of eucalyptus oil, at 200 mg three times daily, improves pulmonary function in asthmatics.[133] 1,8-Cineole improves lung function via mucolytic, anti-inflammatory, bronchodilatory, antioxidant and antimicrobial effects. However, in healthy volunteers, nebulized essential oils of peppermint, eucalyptus or rosemary did not affect spirometry readings.[134]

Sleep

Good sleep quality is essential for health, and the physical environment plays an important role in supporting healthy sleep. Exposure to full spectrum circadian sunlight from 8am to 12 noon reduces sleep latency (time to fall asleep), improves sleep quality and improves mood.[135] In the absence of sunlight, full spectrum light boxes can also be effective in sleep support and in reducing depressive symptoms.[136]

Environment

The physical environment can similarly play a role in either triggering the stress response and contributing to chronic stress, or in triggering the relaxation response. There are many features of the physical environment that increase stress: noise; light; foul odors; extremes of temperature and humidity; crowding; and mazes. Cumulative exposure to stressful environments can thus contribute to allostatic load and impair immune system function. Conversely elements of the physical environment that relax and counter these effects of stress include soothing nature sounds; diffuse light and full spectrum sunlight in the morning; natural fragrances from essential oils, such as lavender; social support and positive social interactions[137]; and labyrinths, which unlike mazes, can induce a state of walking meditation. Human preference for green spaces, termed biophilia, whether views of nature, being in nature, or even images of nature, reduce stress, and has even been shown to speed post-surgical recovery[138] and improve quality of life in bone marrow transplant patients.[139]

Sound can also stress or calm. Spaces that are too noisy or too quiet can increase the stress response,[140] and sound abating features can help to mitigate these effects (carpets, ceiling tiles). A study in Sweden showed that changing the ceiling tiles in intensive care units reduced stress in staff and led to a better night's sleep.[141] Nature sounds, such as running water or forest sounds have also been shown

to reduce stress and bring on better sleep quality.[142] Similarly calming music improves moods, reduces stress and activates dopamine reward pathways.[143,144]

Finally, relative humidity (RH) outside the 30–60% range increases stress, as measured by HRV by up to 25%, while RH in the 45% +/- 5% range is optimal for reducing the stress response.[145] RH in the discomfort range (less than 30% or greater than 60%) is also associated with poorer sleep quality, due to increased stress. Relative humidity lower than 30% also increases susceptibility to viral infection, likely due to drying of mucus membranes.[146]

Summary

The recommendations outlined in this review are summarized in Table 1. below.

Table 1
Summary of IM Considerations in Convalescence from MtoM COVID-19.

Integrative Intervention	Rationale	Clinical Considerations	Citations
Anti-inflammatory diet	Improved pulmonary function; reduced NLRP3 inflammasome activation; antioxidant; improves mood and cognition	Daily dietary pattern	Ralston(2017)[25] Lim(2018)[26] Han(2020)[30] Biswas(2013)[32] Nachmias(2019)[33] Lee(2015)[34]
Increase dietary protein intake	Repletion post-infection; increases phagocytosis, improves NK cell activity, increases immunoglobulin production	1.2–1.5 g/kg body weight/ day Bauer(2013)[40]	Nie(2018)[38]
Increase fruit and vegetable intake	Vitamin and mineral repletion post-infection; reduces airway inflammation; increases T-cell activation	$^1/_2$ the plate each meal Chang(2017)[44]	Hosseini(2017)[41] Hosseini(2018)[42]
Vitamin D3	Anti-viral; anti-inflammatory; vit D sufficiency is associated with improved COVID-19 related morbidity and mortality	Oral: 300–4000IU/day Martineau(2017)[48]	Gorman(2017)[45] Herr(2011)[49] Pereira(2020)[50]
Glutathione	Anti-viral; upregulates vit D receptors, decreases respiratory distress; increases NK cell cytotoxicity	Oral: 250mg- 1000 mg/day Richie(2015)[57]	Polonikov(2020)[52] Horowitz(2020)[53] Richie(2015)[57]
Melatonin	Anti-inflammatory by reducing IL – 1β; antioxidant; decreases symptoms of viral infections	Oral: 2 mg – 20 mg/night Therapeutics Research Center Natural Medicines(Accessed 2020)[63]	Reiter(2020)[59] Reiter(2020)[61] Alamili(2014)[62]
Cordyceps	Improved NK cell cytotoxicity; improves ventilatory capacity; reduces airway inflammation	Oral: 1.5 g – 3 g/day Therapeutics Research Center Natural Medicines(Accessed 2020)[69]	Jung(2019)[65] Kang(2015)[66] Chen(2010)[67] Wang(2007)[68]
Astragalus	Reduces inflammation, specifically IL – 1β and IL-6, TNFα, IL-8 and IL-32; improves pulmonary function	Oral: 400 mg – 2000 mg of standardized extract/day Therapeutics Research Center Natural Medicines(Accessed 2020)[73]	Huang(2019)[71] Jiang(2015)[72]
Aged garlic extract	Anti-inflammatory with down-regulation of NFkB; reduces inflammation with decreased IL-6 and TNF; improves T-cell and NK cell activity	Oral: 2.4 g – 3.2 g/day Tattelman(2005)[78]	Ruhee(2020)[74] Nantz(2012)[75] Xu(2018)[77]
Osteopathic manipulation	Increases pulmonary function, diaphragmatic and rib cage mobility, and thoracic lymphatic flow; increases immune response	3 OMT sessions per week of: modified segmental breathing, lymphatic drainage, rib cage motility Jackson(1998)[84]	Noll(2010)[81] Yao(2014)[82] Wang(2020)[83]
Qigong	Increases ventilatory efficiency, increases lung capacity, improves physical function	20–90 min/day Lim(1993)[86] Sakata(2008)[87]	Lim(1993)[86] Sakata(2008)[87]
Breathing exercises (pursed lip breathing, diaphragmatic breathing, pranayama, tai chi breath work, singing)	Added to exercise, reduces risk of pulmonary fibrosis; improves dyspnea	Start after supplemental oxygen treatment is concluded; 10 min/session, 2–3 times/day and progress up to 60 min/day Wang(2020)[83]	Hanada(2020)[94] Borge(2014)[93] Wang(2020)[83]
Aerobic exercise	Increases ventilatory capacity, decrease pulmonary fibrosis	10–15 min of moderate exercise 1–2 x/day on 3–4 days/week Wang(2020)[83]	Lau(2005)[103] Barker-Davies(2020)[104] Wang(2020)[83]
Stress reduction	Anti-inflammatory, initiates parasympathetic response, activates endogenous opioid anti-pain pathways	Meditation, yoga, Tai Chi, guided imagery	Tracey(2007)[116] Thayer(2006)[118] Williams(2019)[119] Bhasin(2013)[120]
Creative expression	Improves mood and psychological well-being; enhances immunity; improves lung function; improves chronic pain	Visual art, music, expressive writing	Stuckey(2010)[121] Baikie(2005)[122] Smith(2015)[124] Trompetter(2015)[125]
Aromatherapy	Improved pulmonary function, decreased stress and improves sleep quality	Oral: 1,8-cineole 200 g three times daily; Diffused or topical lavender essential oil Juergens(2020)[133]	Ozkaraman(2018)[129] Senturk(2018)[130] Lillehei(2015)[131] Juergens(2020)[133]
Environment optimization	Stress reduction, improved mood, enhanced immunity, better sleep	Full spectrum Circadian light exposure; time in Nature; calming music or sounds; indoor relative humidity 30–60%	Cohen(1997)[111] Ulrich(1984)[138] Levitin(2006)[143] Ellis(2010)[144] Razjouyan(2020)[145] Taylor(2016)[146]

Value of integrative medicine in convalescence from mild-moderate COVID-19 illness

Integrative Medicine focuses on the human organism's innate capacity for healing. Convalescence from disease, like recovery from injury, places great demands on the body's mechanisms of healing. In this article, we have given specific advice based on current evidence about diet, supplements, physical activity, stress management, and other helpful therapeutic modalities. This advice will continue to evolve as we care for patients recovering from MtoM COVID-19. Ideally, a randomized a trial would confirm the value of these therapies as well as any additive, negative, or synergistic effects. Until that time, the high safety profile of these recommendations align with the first principle of medicine *primum non nocere*.

The most important contribution of IM is the assurance that the body's healing system is fully capable of restoring wellness. Depending on age, state of health at the onset of illness, and the severity of your illness, the process may take longer for some. Nonetheless, it is imperative to trust in the wisdom of the body and the healing power of nature.

Declaration of Competing Interest

None.

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