Long-Covid Syndrome

SARS-CoV-2 Infection COVID-19 is a major pandemic that is worldwide and causing significant mortality and morbidity. About 80 percent have mild to moderate disease. However, among the 20 percent with severe disease, five percent develop a critical illness. There is a subset of patients, however, who will have lingering, persistent or prolonged symptoms for weeks or month afterwards, which we termed "Long COVID-19" or Long Haulers, or Post-Covid Syndrome. This has extended the significant morbidity worldwide from this pandemic presently. It is estimated that about 10% of patients who tested positive for SARS-CoV-T will remain ill beyond three weeks and a smaller proportion for months. This is a subset that constitutes the chronic Covid syndrome. Globally, there are estimated over 200 million confirmed cases of COVID-19. Although the majority of infected individuals recover, we still do not know the exact percentage that will continue to experience symptoms or complications after the acute phase of the illness is over. While it is estimated that 10 percent will develop a chronic syndrome, or symptoms that are persistent, this statistic may actually increase in time as we do not know the long-term sequelae of someone who has recovered from acute COVID, since this is a new illness. Not just the quality of life, but the mental health and employment issues become paramount when the acute phase of COVID the subacute and the chronic phases occur. In our experience, approximately 20 percent of people will exhibit symptoms for up to five weeks and 10 percent will have symptoms for more than 5 weeks.

COVID-19 was reported in Wuhan, China in December 2019. It is caused by a small novel coronavirus. The acute phase of COVID-19 infected patients has been well described and may a have varying number of symptoms and intensity. The majority of patients have fever, sore throat, cough, shortness of breath, and chest pain. Although, multiorgan involvement can become extensive. Covid symptoms can be identified in six clusters (Sudre C, Leek, and Lochlainn, Symptom Clusters in COVID-19, A potential clinical prediction tool from the COVID Symptom Study APP Sci Adv. 2021 Mar 19; 7(12). These include:

1 ('flu-like' with no fever, which consist of headache, loss of smell, cough, muscle pains, sore throat, chest pains with no fever.

2 ('flu-like' with fever, which consists of headache, loss of smell, cough, sore throat, hoarseness, fever, loss of appetite.

3 (gastrointestinal, which consists of headache, loss of smell, loss of appetite, diarrhea, sore throat, chest pain, but no cough.

4 (severe level one, (fatigue), which consists of headache, loss of smell, cough, fever, hoarseness, chest pain and fatigue.

5 (severe level two, which consists of (confusion), headache, loss of smell, loss of appetite, cough and fever, hoarseness, sore throat, chest pain, fatigue, confusion and muscle pain.

6 (severe level three, which is (abdominal and respiratory), and this consists of headache, loss of smell, loss of appetite, cough, fever, hoarseness, chest pain, fatigue, sore throat, confusion, muscle pain, diarrhea, shortness of breath and abdominal pain.

The recovery from COVID-19 usually occurs at seven to ten days after the onset of symptoms in mild disease but could take up to six weeks in severe or critical illness. It is for this reason that mild cases are usually quarantined for between 7-10 days, and severe illnesses are for a more extended period of time. However, it is believed that even when one is ill for 3-6 weeks, they are probably not actively contagious. Some studies have shown that active coughing is indicative of continuing contagiousness although this has not been clarified completely. Studies have shown that household cases support the highest incidences of contagiousness and that rational for mass appears to be most beneficial with close contacts for prevention.

The most common feature of acute illness is interstitial pneumonia, which can in some cases be complicated by the serious acute respiratory distress syndrome where individuals require high does of oxygen, and this has a high mortality particularly in elderly people who have comorbidities. The cough is usually dry. Laboratory abnormalities can be present and include low lymphocyte counts, elevated inflammatory markers, such as sed rate, C-reactive protein, ferritin, tumor necrosis factor, interleukin 1 and 6 abnormalities, and others, which will be discussed later. Coagulation system abnormalities (also to be discussed later) can occur, and clots can form in the acute phase and even in the subacute phase.

To complicate matters, not only do the long-term effects of those infected by the virus remain largely unknown, but there are also reports that highlight that sustained transmission and emergent variants continue to cause challenges throughout the world to healthcare providers and therefore we do not know when the pandemic, if ever, will cease.

The chronic COVID syndrome is also known as Post-Acute Sequelae of SARS-CoV-2 infection. It is colloquially also termed the" Long-COVID" Syndrome or just simply the Post-Acute COVID-19 Syndrome. Other colloquial terms include the term "Long Haulers COVID-19". This prolonged phase with morbidity and ongoing symptoms creates significant morbidity to the patient and burden to the healthcare system and is not completely understood.

What exactly is Post-COVID Syndrome? There are many definitions that have been offered. Basically, there are individuals who do not completely recover over a period of weeks, usually 2-3 weeks. Since COVID-19 is a novel disease, there is still no consensus of the definition of Post-COVID-19 symptoms. In a study by Salamanna and coworkers (Front Med (Lausanne) 2021, Vol 8 (653-516 20% of reports of long-term COVID symptoms were abnormal lung function, 24% of neurological complaints and dysfunction, and 55% on specific widespread symptoms, mainly chronic fatigue and pain. The WHO developed a clinical case definition of Post-COVID-19 by Delphi methodology that included 12 domains. However, the understanding of this definition has been going through changes as new evidence emerges and we are gaining a better understanding of the consequences of COVID-19 as it evolves. Usually, three or more months past the COVID-19 infection symptoms that last for at least two months and cannot be explained by alternate diagnoses can fit this definition. These symptoms include fatigue, shortness of breath, cognitive dysfunction, and symptoms that affect the functional capacity of individuals with daily living. Symptoms may fluctuate, flare up or relapse over time. Long-COVID or Post-COVID-19 is an umbrella term that refers to symptoms persisting past the initial phase. In addition, Post-COVID-19 can adversely affect multiple organ systems, which include the kidneys, lungs, pancreas and heart. Unfortunately, the lack of a standardized definition for Long-COVID Syndrome presents obstacles for researchers in studying the condition with controlled studies and arriving at a precise diagnosis, algorithms and treatment algorithms. In addition, many patients with Long Covid Syndrome require rehospitalization especially those with comorbidities, such as cardiovascular disease, diabetes mellitus, obesity, cancer and kidney disease.

There is data to suggest that the evolution of Post-COVID Syndrome is driven by chemicals produced in the body from inflammation called cytokines. Research is ongoing regarding pathogenesis that will be discussed later in this communication. Post-infection factory dysfunction occurs in over 60% of those with SARS-CoV-2 infection, even in asymptomatic infection, and this represents an important frequent symptom of Post-COVID-Syndrome. Also, loss of taste has been seen. Many patients are not diagnosed with Post-COVID-Syndrome, when in reality their taste or smelling remains impaired as the only symptom.

Meta-analysis have shown the prevalence of post-COVID manifestations show that fatigue and muscle weakness are by far the major symptoms followed by dyspnea and then pain and discomfort. Then there is anxiety and depression and impaired concentration. Also, and the little lower frequency is insomnia and sleep disorders. Interestingly, alopecia has been described as occurring. Chronic cough can persist and arthralgias and myalgias may be present. Chest pain, cognitive impairment, dizziness and headache are also symptoms but less common than the ones above. Persistent sore throat, palpitations, lack of smell, diarrhea, vomiting, fever, blurry vision, lack of

taste, nasal congestion, anorexia, nausea, ringing in the ears and rash are a much lower prevalence of symptoms with Long Covid Syndromes. Interestingly, autonomic clusters in the Post-COVID-Syndrome (by COMPASS 31, which is a questionnaire for autonomic symptoms) have identified two clusters. Impaired visual activity and blurry vision were more frequently registered during the acute phase in patients, while depression, chills, weakness, diarrhea, musculoskeletal, palpitations, tachycardia, dryness, cognitive dysfunction, headache, dizziness and tinnitus were more frequently observed in the Post-COVID second cluster. Levels of antibodies to the SARS virus were not different between two clusters. This has given us some insight into one of the main mechanisms of Long Covid Syndrome, mainly autonomic dysfunction, which is an imbalance between the parasympathetic and sympathetic nervous system. It is believed that a chronic inflammatory process, or autoimmune, or even a hormonal imbalance as a consequence of alterations in the hypothalamus-pituitary- adrenal axis may also be operative in conjunction with this acquired dysautonomia, or autonomic dysfunction with constitutional symptoms as described above.

The term Long-COVID syndrome was first used by Perego and social media to describe symptoms weeks or months after the initial SARS-CoV2 infection.

The term "long haulers" was used by Watson and by Yong (Perego, Twitter, May 20, 2020, Edwards NBC News July 31, 2020 and Yong Theatlantic.com July 31, 2020). There can be persistence of one or more symptoms of acute COVID or appearance of new symptoms and they can be relapsing and remitting; therefore showing the variable presentation of Post-COVID-Syndrome. Interestingly, the majority of people with Post-COVID-Syndrome are PCR negative including any microbiological recovery. It is interesting how many people continue to see infectious disease doctors and seek out other alternative infection diagnoses when serology is continuously negative. Garg, Arora, Kumar, and Wig in the Post-COVID Syndrome: How deep is the Damage? JMed Virology 2010 August, have stated that Post-COVID-Syndrome is the time lag between the microbiologic recovery and clinical recovery. In fact, the majority of those with Long Covid Syndromes have biochemical and radiological recovery. It has been postulated that there are two stages of Post-COVID-Syndrome. One, which symptoms that extend beyond three weeks but less than 12 weeks, which is more of a subacute phase, and one where chronic COVID symptoms extend beyond 12 weeks. An interesting diagram and timeline can be found in the article by Raveedran and coworkers published online May-June 2021, Vol 15, #3, 869-875 which shows that Short-COVID will generally last less than three weeks from onset of symptoms. Post-acute COVID, or subacute COVID will last from onset of symptoms approximately up to 10-12 weeks and chronic COVID will last from onset of symptoms beyond 12 weeks. It would make sense to group the Post-Acute or Subacute COVID, which lasts from up to 10-12 weeks and then chronic COVID, which lasts more than 12 weeks as long COVID

Syndromes. In this review, however, we are more concerned with those symptoms that last more than 12 weeks, the true long or prolonged COVID Syndrome.

Sometimes individuals are fairly asymptomatic, and by the time they develop Long-Covid symptoms, we do not know when the initial infection occurred nor are we certain. They did not undergo any test to confirm SARS-CoV2. When these individuals develop multiple symptoms consistent with a Long-Covid Syndrome, we oftentimes consider them as probable, or possible Long Covid Syndrome, since we cannot confirm that they indeed did have COVID exposure since they were asymptomatic. With individuals who were symptomatic but not tested it is more likely that this is a Post-COVID-Syndrome. The problem is not only in those who have persistent symptoms who have never checked positive for COVID, but similarly in individuals who had upper respiratory tract infections and had a negative COVID test and then developed long prolonged symptoms, one has to ask did they have a false-negative test performed too early or too late in the disease course. Antibodies are unreliable as up to 1/5 patients do not seroconvert, and antibody levels decrease over time and by three months oftentimes are not measurable. Not only is the morbidly important with Post-COVID-Syndrome, but the economic cost to society, as 1/3 people in one survey did not return to their job for up to three weeks after being COVID-positive, and this is more common in older people. Not returning to work is often associated with obesity and psychiatric disease in addition.

Of all the risk factors for individuals that develop the Long Covid Syndrome, it is noted that the risk of COVID is twice as common in women as it is in men. Increasing age is also a risk factor for development of Post-Covid Syndrome. Studies show that individuals who develop Long Covid Syndrome are four years older than those who did not (Nabavi, Nikki, Long COVID, British Medical Journal 2021, 370). If one has five or more symptoms in the acute phase of illness, they have a higher likelihood of developing a Long Covid Syndrome. We have empirically found that obesity and increased body mass index is an extremely important risk factor as is female sex. Symptoms that various studies report to be predictors of Post-COVID-Syndrome include diarrhea, anosmia, dyspnea, pleurisy, skin sensitivity, and A blood type (Cirulli ET et.al. Long-term COVID-19 symptoms in a large, unselected population, medRxiv. 2020). One study showed that a lower SARS-CoV2 IgG titer at the beginning of the observation period was associated with a higher frequency of Post-COVID-Syndrome (Augstin and coworkers, Lancet Reg Health EUR 2021, Vol 6 100-122). Also, the severity of acute COVID-19 suggests that the recovering critically ill patient commonly experiences long-lasting mental health issues that include depression, anxiety, post-traumatic stress, memory disorders, attention deficit disorders, and ongoing brain fog. This is controversial as others have shown that acute disease was not associated with Post-COVID-Syndrome. All of this negative speaks to a heterogenous presentation of Post-

COVID-Syndrome with risk factors and its time-line. Even if the virus is cleared, there were high neutralized antibody titers that suggest that the immune system could continue to be overactive and induce this syndrome. Therefore, the question of autoimmunity is raised. This is especially true since viral shedding has shown that persistent fragments of viral genes and body secretions can cause hyperimmune responses, and this may explain some of the persistent symptoms in Post-COVID-Syndrome.

Meta-analysis of prolonged COVID-19 looking at age, sex, comorbidities, ethnicity and severity of acute disease confirm that female gender and long-COVID risk are associated. In addition, increasing age, minority/ethnicity was also associated with Long Covid Syndrome. However, some of these results have been inconsistent (Michelen et.al. BMJ Global Health Vol 6, issue 9, pages 1-29). Studies have shown that Long-Covid Syndrome effects with previously hospitalized and non-hospitalized patients. Perhaps, the best known study from the Office for National Statistics (ONS), a study including controlled participants reports that the most common symptoms persisting for 12 or more weeks include fatigue (8.3%), headaches (7.2%), cough (7%) , and myalgias (5.6%), (May 3, 2021, ONS. Prevalence of ongoing symptoms following coronavirus infection 19 in the United Kingdom, Office for National Statistics, 2021).

A lack of case-controlled studies presents a direct attribution of symptoms that are solely related to COVID-19, however. We need larger perspective studies with match controlled groups. Similarly, many of the studies on Long Covid Syndrome and statistics are based on Long-COVID cohorts produced in Western Europe on patients recently discharged from the hospital, and there was not enough information on Post-COVID-19 patients in low-to middle income countries and people who were not hospitalized. And, certainly, there are no large studies that identify on children specifically. This is despite the fact that young children are affected and can be affected by Long-COVID.

POST-COVID-SYNDROME:

Organ Involvement: Post-COVID-Syndrome involves a hyperinflammatory and hypercoagulable state that affects all organ systems. It reflects a maladaption of the angiotensin converting enzyme ACE 2 pathway. Therefore, it is understandable that many organ systems are susceptible to involvement from direct viral infection and inflammation based on the fact that angiotensin converting enzyme receptors are present in virtually every organ system. The Post-COVID-Syndrome is a complex condition with prolonged heterogenous symptoms that are related to multiple organ involvement. As previously mentioned, pending on duration of symptoms, Post-COVID or Long-COVID Syndrome can be divided into two stages post-acute COVID, or

symptoms extending beyond three weeks but less than 12 weeks, and chronic COVID where symptoms extend beyond the 12 weeks (Greenhalgh- BMJ 2020, 370 Vol 10).

Multiple organ sequelae and abnormalities of COVID-19 that may go beyond the acute phase of infection are increasingly being noted as data is being experienced. Assessment of key clinicals and serological imaging features are important to understand the natural history of this disease as it progresses beyond the acute viral infection phase. Workup consists of considering pulmonary function tests, chest x-ray, six minute walk test, pulmonary embolism workup when needed, echocardiograms, even serially, and at times high resolution CT scans to assess for a fibrosis. This will be discussed under the Pulmonary section. With hematological assessment one needs to consider extending thromboprophylaxis against clots and high-risk survivors. A neuropsychiatric screening for anxiety, posttraumatic stress, sleep disorders, depression, cognitive impairment, memory abnormalities and other factors associated with brain fog, including full autonomic dysfunction testing especially in patients with orthostatic intolerance symptoms and chronic fatigue syndromes is important in addition. If there are renal function abnormalities, Nephrology followup and creatinine clearance determination may need to be necessarily along with urinalysis evaluation. These can be performed in person or on virtual clinical visits. We will now discuss some of the various organ systems and how they are affected.

I. PULMONARY SYSTEM:

The pulmonary system is the most commonly involved. Chronic complications, such as chronic cough, fibrotic lung changes also known as Post-COVID fibrosis or post-ARDS fibrosis, bronchiectasis and pulmonary vascular disease can occur (Fraser, Emily, Long-term respiratory complications of COVID-19, BMJ, 2023 70, M300). Even if a person is asymptomatic, they can have CT scan abnormalities that are seen many months after infection has resolved. If COVID-19 leads to pulmonary fibrosis it can result in shortness of breath and the need for supplemental oxygen. On one study, approximately 50% of 349 patients who underwent high resolution computer tomography of the chest at six months had at least one abnormality pattern in a post-acute COVID-19 Chinese study (Huang et.al, 6-month consequences of COVID-19 in patients discharged from hospital: Lancet 397, 220-232, 2021). These changes involved the appearance of ground-glass opacities. There are also long-term risks of pulmonary embolisms and chronic pulmonary hypertension, but at this point it is unknown and further research is being conducted. It is thought that patients with a greater severity of acute COVID, especially those on high-flow nasal cannula and noninvasive or invasive ventilation are at the highest risk for long-term severe pulmonary complications that include even pulmonary function test abnormalities such as persistent diffusion impairment. Pulmonary vascular

micro-clotting or microthrombosis has been observed in 20% to 30% of patients with COVID-19 (Cui-S et. al. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia: Journal of Thrombosis and Haemostasis, 1814, 21-1424, 2020, Klok - Thrombotic complications of critically ill ICU patients with COVID-19, Thrombotic Research, 191, 145-147, 2020).

Persistent lung symptoms are to be expected in many patients with Long-COVID Syndrome because the lungs appear to be one of the main organs affected by the virus. This can result in diffuse damage to the alveoli, the lining of the small sacs in the lungs, desquamation of alveolar epithelial type 2 cells, Hyaline membranes, scattered interstitial inflammation, monocytes and macrophages (Hall J. et.al. Thorax: 2021, 10.1136).

Up to six months after hospitalization, pulmonary function abnormalities or structural changes can occur. In severe COVID-19 patients in a study by Han, up to 35% of patients at six months can show fibrotic-like changes after infection (Han X, Radiology 2021, Vol 299, 203153). Abnormal airway function can occur up to 11 months in severe COVID-19 infections (Zhum M,, ??? European Journal of Clinical microbiology and infectious disease, 2021). Persistent diffusion lung carbon monoxide impairment also described the noncritical COVID patients who present with shortness of breath up to four months after infection (Bellanm and coworkers, JAMA Netw Open: 2021, 4e2036142).

Other abnormalities beside abnormal DLco include abnormalities in total lung capacity, poor expiratory Vol at 1 second, forced vital capacity and FEV1 to FVC ratio and small airway function abnormalities (Ref 31: Salamann and Paper, on Tiers of Medicine, 2021 paper).

Mild cases usually can have persistent chronic cough, which can be do to fibrosis, bronchiectasis and pulmonary vascular disease.

One study showed that at three-months post infection, chronic dyspnea is noted in approximately half of the patients who have recovered from COVID, again associated with lower DLco in a reduced functional capacity. They also have oxygen desaturation during exertion compared to individuals who have no symptoms of shortness of breath post-COVID (Ref Cortes-Tellesa at.al. Pulmonary function and functional capacity in COVID-19 survivors in persistent dyspnea: Respiratory Physiology/Neurobiology 2021: Vol 288, 103-644).

II: CARDIAC INVOLVEMENT:

Common cardiac problems can occur with labile heart rate and blood pressure response to activity. Myocarditis and pericarditis can occur chronically. In the acute stages, myocardial infarction, cardiac failure, life-threatening arrhythmias and sudden cardiac death have been described. The incidents of arrhythmias in Post-COVID-Syndrome is unknown, but many individuals have palpitations and studies using ambulatory monitoring need to be further conducted. Sequelae from acute COVID, such as coronary artery aneurysm, aortic aneurysm, atherosclerosis, venous and arterial thrombolic disease including life-threatening pulmonary embolism can occur (Ref Kerrc, Becker, ??? 2019 coronavirus as an infarct attack on heart: Journal of Thrombosis and Thrombolysis, 2020, 10.1007, 11239). These structural abnormalities can manifest itself in Long-COVID Syndrome long after recovery of acute illness and predisposed to arrhythmias, breathlessness, and acute coronary events, such as heart attacks and chest pain syndromes.

Myocardial injury is the most common abnormality detected with acute COVID infection. It is usually detected even when patients are asymptomatic with no cardiac symptoms with elevated cardiac troponin levels, which can be evident in a high percentage of patients with COVID-19 (Sandoval Y and Coworkers: Cardiac Troponin for Assessment of Myocardial Injury in COVID-19. JACC Review: Topic of the Week, Journal of the American College of Cardiology, 2020: Vol 76, #10, 1244-1258). Further research is ongoing as to wether this myocardial injury pattern, even when subclinical, can lead to increased arrhythmias and heart failure in the long-term.

Echocardiographic studies have shown abnormalities with COVID, including right ventricular dysfunction 26.3%, left ventricular dysfunction 18.4%, diastolic dysfunction 13.2% and pericardial perfusion 7.2%. To what extent this is reversible in patients who go on to Post-COVID-Syndrome is not known (Ref Giustino G et.al. Characterization of Myocardial Injury in Patients with COVID-19. Journal of the American College of Cardiology: 2021, Vol 76, #18, 2043-2055). In addition, sleep abnormalities and difficulties that reduce quality of life have been noted in Post-COVID-19 Syndrome patients may also adversely effect cardiac function, provoke arrhythmias, elevate blood pressure and exacerbate or cause hypertensive states.

Chest pain and palpitations are status post the acute phase of COVID. In a Chinese study, palpitations were reported in 9% and chest pain in 5% of patients six months after followup (Huang C et.al. 6-month Consequence of COVID-19 in patients discharged from hospital: A cohort study. Lancet 397, 220-232, 2021). To track heart inflammation, one of the most effective and sensitive tests is cardiac magnetic resonance imaging (MRI), and these rates may be as high as 60% more than two months after a diagnosis of COVID, although this is a very difficult test to obtain in many centers that do not have it

readily available (Putnam V.O. et.al. JAMA Cardiology: 2019, Vol 5, s 1265-1273). Another study showed that Long-COVID Syndrome patients may be present with chest pain in 17% of patients, palpitations in 20% of patients, and dyspnea on exertion 30% of patients (Putnam VO. et.al. JAMA Cardiology: 2019, Vol 5, 1265-1273).

The question of myocarditis is always raised especially in children, but adults are also known to have myocarditis and this may be smoldering. One study showed that in healthy collage athletes the mild symptoms were asymptomatic up to 15%, and they have evidence of MRI findings consistent with myocarditis on a screening study (Rajpal S et.al. Cardiovascular Resonance findings in competitive athletes recovering from COVID-19 infection. JAMA Cardiology. Vol 6, 116-118: 2021). More importantly, many of the chest pains and palpitations, which appear to be cardiology in etiology, are actually due to autonomic dysfunction and then a postural orthostatic tachycardia state. Therefore, the importance of not only doing cardiac imaging, ambulatory monitoring, stress testing, six-minute walk test, echocardiography and other noninvasive cardiac workup but also autonomic testing, such as HRV interval testing, beat-to-beat blood pressure with tilt testing and sudomotor testing may be useful in diagnosing autonomic nervous dysfunction.

Arrhythmias are noted post-COVID but attention to the use of anti-arrhythmic drugs, for example - amiodarone, must be used carefully in patients who have fibrotic pulmonary changes after COVID-19 (Kociol - Circulation 141-e69-e92, 2020).

III: NEUROLOGICAL:

Encephalitis, seizures, and other conditions including prolonged brain fog can occur for several months after acute COVID infection (Zubair. Neuropathogenesis and Neurological Manifestations of Coronavirus Disease: 2019, A Review JAMA Neurology 2020, Vol 77, 1018-1027). Three months after followup MRI abnormalities can be demonstrated (Lu Y Cerebral Vascular Micro-Structural Changes in COVID-19 Patients, an MRI-Based Study 3 Months After: EClinical Medicine 2020, Vol 25, 100484). Neuropsychiatric sequelae are often common and reported with many post-viral symptoms, such as chronic tiredness, myalgias, depressive symptoms, non-restorative sleep (Fauci, International AIDS Conference: YouTube 2020 and Nordvigas: Potential Neurological Manifestations of COVID-19: Neurology Clinical Practice 2020). Migraine headaches often refractory to treatment and late-onset headaches have been presumed to be due to high cytokine levels have been noted (Belvis R - Headaches during COVID-19: Vol 64, 1422-1426). In a followup study of 100 patients, 38% had ongoing headaches after six weeks (Pozi-Rosich: Virtual Annual Scientific Meetings 2020). Loss of taste and smell also can persist for up to six months and longer on followup of patients.

Brain fog, cognitive impairment, concentration, memory difficulties, receptive language, executive function abnormalities also can persist over a long period of time. This may be related to autonomic dysfunction and other factors (Henek A. Alzheimer's Research Therapeutics Vol 1269, 2020. Ritchie K Brain Communications 269, 2020. Kaseda ET. and Levine AJ. Posttraumatic Stress Disorder Post-COVID-19 survivors: Clinical and Neuropsychology: Vol 35, 1498-1514, 2020). Psychiatric manifestations are also common in COVID-19 survivors more than one month. In an Italian study, approximately 15% have at least some evidence of depression and post-traumatic stress, anxiety, insomnia and obsessive compulsive behavior (Mazza. Brain Behavior Immunology: Vol 89, 594-600,2020. Some studies have shown up to 30-40% of patients with COVID-19 have depression and anxiety for prolonged periods of time (Nalbandian A. March 2021: Nature Medicine).

After ischemic or hemorrhagic strokes, hypoxic and reversible encephalopathy syndrome and acute disseminated myelitis, neurological defects can also require extensive rehabilitation and their sequelae linger. Also, acute critical illness, myopathy and neuropathies resulting during acute COVID-19 can leave residual symptoms week to months later (Nalbandian A. et.al. Tankisi Clinical Illness, Myopathy and Consequences of COVID-19 Infection: Clinical Neuropsychology Vol 131, 1931-1932).

More should be said about post-COVID brain fog. This may involve mechanisms of deconditioning, post-traumatic stress or dysautonomia. And long-term cognitive defects can be seen occurring in up to 20%-40% of patients (Novac E. Neurologicals Vol 21, 100-276, 2021. Migalis MG: Clinical Microbiology Infection, 2020: Sakusic A & Rabinstein A.A. Cognitive Outcomes after Critical Illness, Current Opinion in Critical Care: Vol 25, 410-414, 2018).

In addition, muscle wasting and fragility are often seen prolonged. This is because COVID-19 when it is severe may cause catabolic muscle weakness and feeding difficulties (Hosi E.Y. Survivorship after COVID-19 ICU Stay. NAT. REV. DIS. PRIM. 6-60, 2020).

Autonomic dysfunction also has been noted to be significant. Patients with orthostatic tachycardia and inappropriate sinus tachycardia can benefit from heart rate management including beta-blockers (Arjs R. Propanolol Decrease in tachycardia improved symptoms in postural orthostatic tachycardia; less is more. Circulation 120, 725-734, 2009).

Neurophysiatric manifestations of COVID-19 have been documented in a British study including stroke and altered mental status. Multiple physiatric symptoms emanating

from encephalopathy and encephalitis and primary psychiatric diagnoses were noted in young adults (Ref Varathar AJA & Thomas et.al. Lancet Psychiatry: 2020, October 1, Vol 7, #10, 1016). Prolonged effects on patients who have had prone ventilation and COVID can cause focal and multifocal peripheral nerve damage (Malik G.R. medRxiv Vol 20, preprint, 2020:July 06. PubMed).

Symptoms consistent with orthostatic hypotension syndrome and painful small fiber neuropathy were reported in as short as three weeks and as long as three months by two case reports and several small series (Dani. Clinical Medicine, 2020, Vol 21, 63-67. Hellmeth J. Journal of Neurovirology: 2021, Vol 2,s 1-5. Novac: ENeurological Science: 2020. Rahimi M.M. British Medical Journal and Case Report, 2021: Vol 14e,240178).

The most frequent neurological long-term symptoms in patients were myalgias, arthralgias, sleeping troubles and headaches (Salamanna Francesca. May 4, 2021:FrontMed (Lausane) 2021, Vol 8, 653-516).

Autonomic dysfunction findings resulting from analysis of Compass-31 Questionnaires demonstrates significant symptomatology (Ref: Compass-31). Based on autonomic symptoms by Compass-31, two clusters were obtained with differential characteristics. Cluster 2 exhibited high scores of Compass-31. This accounted for 31% of all patients included. Median Compass-31 score of 22 suggesting that one third of patients with PCS may yield higher scores when compared with the general population (Ref 64. Rodriguez Y. Rojas M. et.al. Clinical Autonomic Research: 2018, Vol 20, 211-214). Patients with higher scores exhibited more clinical manifestations and depression. These clusters have therapeutic implications and clinicians should be aware of particular manifestations during the follow-up and all social intervention may reduce the burden of PCS (Ref: Anaya et.al. Autoimmune Review 2021, Nov 20, #11, 102947).

Orthostatic intolerance has been described by Dani and Coworkers (Dani M. et.al. Clinical Medicine: London, 2021, Jan. 63-67) with the patients having orthostatic intolerance. They presented a series of patients that had orthostatic intolerance of either resting or postural hypotension and/or tachycardia. Although the series was small, or awareness to the fact that orthostatic intolerance symptoms, such as orthostatic hypotension, vasovagal syncope, postural orthostatic tachycardia syndrome that all occur and last for a prolonged period of time after COVID viral infection. These are often associated with palpitations, breathlessness and chest pain, which are common symptoms seen in Long-COVID patients. It is postulated that high catecholamine levels can lead to paradoxical vasal dilatation and increased activation of the vagus nerve that can result even in syncope and also sympathetic activity withdraw (Freeman R. Orthostatic Hypotension, JACC State of the Art Review: 2018, Vol 72, 1294-

309). Jardine. Pathophysiology of vasovagal syncope: Heart Rhythm 2018, Vol 15, 921 to 9?). Hypovolemia can also exacerbate or worsen these symptoms. The relationship between COVID-19 infection and how it affects the autonomic nervous system is not completely understood, but it is believed to be due to inflammatory cytokine release and a cytokine storm, which results from the initial sympathetic activation produced by a pro-inflammatory cytokine release (Konig M.F. Journal of Clinical Investigation: 2020, Jul 1. 130, Vol 7, 3345-3347). However, vagal stimulation can also result in anti-inflammatory responses (Fudi M.M. Journal of Cardiovascular Translational Research: 2020, Dec 13; Vol 6, 894-899). Also, the COVID-19 related to autonomic dysfunction may be related by viral infection itself and immuno-mediated neurological syndromes have been described. (Immuno-mediated neurological symptoms of SARS COVID infected patients, Guilmot A et.al. Journal of Neurology: 2021, Mar. 266 751-757). It is well known that some forms of orthostatic hypotension and POTS are associated with autoantibodies perhaps caused by other viruses in the past, and this can also be the case with COVID; for example, antibodies against Alpha and Beta receptors and muscarinic. Treatment of these autonomic nervous systems disorders involves exercise with both aerobic and resistant elements in a graded fashion that oftentimes begin with recumbent, fluid and salt repletion, avoiding exacerbating factors, such as prolonged sitting and warm environments, some counter maneuvers and isometric exercises, compression garments especially up to the waist or abdominal binders and pharmacological treatment that can involve many different pharmacologic regimens. Volume expanders such as Fludrocortisone or desmopressin may be used along with vasoactivation such as midodrine or pyridostigmine. If there are prominent hyperadrenergic symptoms, Propranolol, Clonidine, methyldopa or other beta-blockers may be considered especially if there is a postural orthostatic tachycardia response.

Again, the questionnaires that address autonomic symptoms that is the Composite Autonomic Symptom Scale-31 (Compass-31) can be used to validate dysautonomic symptoms post COVID. In a study of 180 participants (70% males) by Stella and Coworkers (Journal of Neurology 2021, Aug 12, 1-10) orthostatic hypotension was found in 13.8% of the subjects. The mean Compass-31 score was 17.6 with the most affected domains being orthostatic intolerance, sudomotor, gastrointestinal, and pupillomotor dysfunction. Higher Compass-31 scores were found in those with neurological symptoms due to more severe orthostatic intolerance symptoms. Although, interestingly, gastrointestinal, urinary and pupillomotor domains were more represented than non-neurological symptom groups. Therefore, this study concluded that it is important to monitor autonomic nervous system symptoms as a complication of COVID-19 disease that may persist in a post-acute period. The authors in this study stated that about half of post COVID individuals have reported secretomotor and

sweating abnormalities. Also, thermoregulatory alterations were also frequently reported.

In regard to the urinary tract and bladder incontinence, urinary symptoms may occur with inflammation and demyelinization of the pudendal nerve as a feature of COVID-19, and this has been reported in other viral infections (Coronavirus and demyelinization of neuropath ways triggers neurogenic bladder overactivity in a mouse model in multiple sclerosis: McMillan and Coworkers: American Journal of Physiology and Renal Physiology, 2014-Sep 1, 307, 612-622). Bladder and Bowel Incontinence in COVID-19: Pourfridone M. and Coworkers (Journal of Med Virol. 2021-May, Vol 93(5), 2609-2610). Up to a quarter to a half of patients may have urinary dysfunction in individuals who have had post-COVID syndrome (Stella article). It is also suggested that sexual impairment such as erectile dysfunction is possible after COVID infections which may affect both endothelial and autonomic components. However, the psychiatric component due to stress and anxiety cannot also be separated (Sansone - Journal of Endocrinology Investigation: 2021 - Feb, Vol 44, 223-231. Preliminary evidence of association between erectile dysfunction and COVID-19: Sansone - Andrology 2021, Jul 9. 1053-1059).

Gastrointestinal symptoms after COVID may occur along with a combination of other symptoms. This is because in the GI tract there is a significant amount of angiotensin coenzyme ACE-2 receptors present. These include abnormal appetite, nausea and diarrhea that are also seen in the Compass-31 score (Ref: Evidence of gastrointestinal infection of SARS-CoV2 (XIAO et.al. Gastroenterology 2020 May, 158, Vol 6, 1831-1833).

Vision disturbances also may occur in post COVID syndromes including sore eyes and light sensitivity (Dominguez-Varel IA - Infectious disease: London 2021 Jun. Vol 53 (6) 399-403). Also, in acute conjunctivitis, an abnormal pupil response may be noted (Karahn in the Graefes Arch Clin Exp neuro Ophthalmology: 2021 Sep. 259, Vol 9, 2821-2826). Light sensitivity is often a common complaint. In a study by Stella and Coworkers, nearly 50% of patients complained of ocular abnormalities. Therefore, multiple organ systems can manifest symptoms in post-COVID syndrome which may be attributed to the autonomic dysfunction, and this need not necessarily just be orthostatic intolerance symptoms ???(Goodman, BP Front. Neurol. 13 Apr 2021) As noted, GI, ocular, urological, sudomotor, and endocrine organs ban be affected.

In an article by N. Barizien published on July 7, 2021 - Open Access article entitled Clinical characteristics of dysautonomia and Long-COVID-19 syndromes, they emphasize the anosmia, hypogeusia, headaches and hypoxia components of the chronic COVID syndrome. In that study, they hypothesize that dysautonomia occurs secondary to

COVID-19 infection and demonstrated dysregulation of HRV testing that is reflected by what they termed an abnormal NOL index that refers to an abnormal parasympathetic-sympathetic balance. The NOL algorithm with a multiparameter non-linear combination of heart rate, HRV, amplitude of the finger, photoplethysmograph, skin conduction level and there time derivatives were obtained using a noninvasive finger probe and quantitated.

A recent study from the Mayo Clinic reported autonomic dysfunction in up to 63% of patients presenting with specific symptoms having survived a corona infection between March 2020 and January 2021. Diagnoses were revealed by recording and evaluating beat-to-beat blood pressure and heart rate during head-up tilt (Shouman K. et.al. Autonomic dysfunction following COVID-19 infection: an early experience. Clinical Autonomic Research 2021 Apr 16, 1-10).

A recent study reported that at six to eight months after recovery from COVID-19, patients still suffer residual autonomic symptoms and 60% are unable to return to work and only 50% have completely recovered (Blitshteyn S. & Whitelaw S. Postural orthostatic tachycardia and other autonomic disorders after COVID-19 infection in a case series of 20 patients. Immunol Res 2021).

Chronic fatigue syndrome, also known as post-infective syndrome, has been commonly recognized in the Long-COVID Syndrome. In a study by Liam Townsend and Coworkers, Aug 25, 2021, (Open-Access), 20 fatigued and 20 non-fatigued post-COVID patients with a mean age 44.5 (90% female) were followed up for 166 days. A scale known as a Chalder fatigue scale was used. They underwent a Ewing autonomic function test battery including deep breathing, active standing, Valsalva and cold-pressure testing with continuous electrocardiogram and blood pressure monitoring and also cerebral oxygenation. A 24-hour ambulatory blood pressure monitoring was conducted. They concluded that there were no differences between the fatigued and non-fatigued patients in autonomic testing and that increased anxiety was strongly associated with chronic fatigue syndrome. This, however, is in contradistinction to other studies which have shown autonomic dysfunction with post-COVID syndrome and chronic fatigue.

Post infectious myalgic encephalomyelitis, which is also synonymous with chronic fatigue syndrome, has been recognized along with sleep disturbances, neurocognitive changes, orthostatic intolerance and post-exertional malaise (Poenanj S. Therapeutic Advance of Infectious Disease: 2021 - Apr 20. Vol 8. Sandler C.X and Coworkers: Systematic review of fatigue after COVID-19 and scanned articles published from Jan 2020-Jan 2021. PubMed). They concluded that fatigue at 6 weeks post symptoms that can occur in 13-33% of patients. There are many factors responsible which include sleep

disturbances, autonomic dysfunction with sympathetic predominance, endocrine disturbances, abnormalities of the hypothalamic-pituitary-adrenal axis, reactive mood disorders, depression, and anxiety. Findings therefore concluded that chronic fatigue post Long-COVID Syndrome is multifactorial. More testing is required to see the association of autonomic disturbances with the emergence of a chronic fatigue syndrome. This has been demonstrated with other viral infections. In fact, in cohort at our autonomic clinic we have found significant disturbances in cardiorespiratory and HRV testing in patients with chronic fatigue with Post-COVID-Syndrome with abnormal of sympathetic withdraw and vagal excess with stand present. Whether they have drops in blood pressure, postural rise in heart rate or none of the above changes.

It has been widely reported that autonomic dysfunction and various viral infections including HIV, Herpes virus, enterovirus 71, flavivirus, Human-T lymphotrophic virus, etc may result in loss of heart rate variability, hypersalivation, photophobia, and dyspnea. Epstein-Barr virus may lead to dysautonomia through alterations of cerebral autoregulation by high nitric oxide release with subsequent autonomic nervous system dysfunction (Steinberg - 2012). It has been postulated that the coronavirus shares a common feature of neuroinvasion (Khatoon et.al. 2020). SARS-CoV-2 can also reach the autonomic nervous system by employing the retrograde axonal transport by the olfactory nerve (Li. et. al. 2020), ACE 2 and brain stem (Baig et.al. 2020), systemic blood circulation (Baig et.al. 2020) immune injury (Wu & Yang 2020) and neuronal pathways (McGovern & Kang 2011). While the virus may indirectly invade the ANS nervous system by the enteric nervous system (ENS) and its sympathetic afferent neurons by infecting the GI tract (Toljan, 2020). This is all well reviewed in a review article by Al-Kuraishy and Coworkers entitled COVID-19-induced dysautonomia: A menace of sympathetic storm Nov 20, 2021 in ASN Neuro). In a study of 50 patients showed that 26% of patients had sweat dysfunction as measured by SUDOSCAN test with motor, sensory and autonomic dysfunction (Hinde JA et.al 2021). Abnormalities of heart rate variability is more common in COVID-19 patients who develop fatigue (Barizien et.al. 2021; Becker 2021). The findings proposed that Long-COVID-19 is associated with persistent symptoms, such as hypoxia and fatigue due to development of dysautonomia (Crook et.al. 2021). It is initially believed that SARS-COVID-19 causes sympathetic nervous system activation with catecholamine excess of activation in a sympathetic storm which activates the renin angiotensin system. Simultaneously, there is inhibition of the parasympathetic nervous system, which is anti-inflammatory and that leads to a decrease in neuro-vagal anti-inflammatory effects and enhances the cytokine storm. This all leads to cardiopulmonary complications and COVID-19-induced dysautonomia (Al-Kuraishy et.al. Nov 10, 2021, ASN Neuro).

Post-COVID-Syndrome is associated with brain fog, and this may be resulted to autonomic dysfunction with sympathetic withdraw, a decreased cerebral perfusion (Stefano et.al. 2021).

IV. GASTROINTESTINAL SYMPTOMS ASSOCIATED WITH LONG-COVID SYNDROME.

COVID-19 can cause intestinal dysfunction due to changes in intestinal microbes and an increase in inflammatory cytokine. Multiple organ systems can evolve acutely and can even produce septic shock. Increasing diarrhea may be an early manifestation that can continue in the chronic phase. Patients can have persistent anorexia, vomiting, abdominal pain along with diarrhea. It appears gastrointestinal symptoms are accompanied by inflammation or intestinal damage. Coronavirus has also been found in the stool (Sonia Villapol: Gastrointestinal symptoms associated with COVID-19 impact on the gut microbiome. Transl Res Dec; 2021; Dec, 226: 57-69). A gastrointestinal manifestation of COVID-19; a review of what we know. Journal of Summer 2021, Vol 21; (2) 177-118). Acute hepatocellular injury was also identifies with elevated liver enzymes, and we often postulate that fecal oral transmission of COVID-19 may be suspected because of the presence of COVID-19 RNA in stool samples of COVID-19-positive patients. In an article by Weng J. Gastrointestinal sequelae 90-days after discharge of COVID-19, at least 76% of patients had one symptom persisting six months after disease onset. Only 13% of patients recorded GI symptoms on admission and 49% during hospitalization. After discharge, GI symptoms were present in 44% of patients. The most common gastrointestinal sequelae were loss of appetite at 24%, nausea 18%, acid reflux 18%, and diarrhea 15%. Less common symptoms were abdominal distention 14%, belching 10%, vomiting 9%, abdominal pain 7% and bloody stools 2%. Patients who had GI symptoms going beyond 90 days more often had shortness of breath and myalgia as coexisting presenting symptoms in the acute phase. Interestingly, patients with gastrointestinal sequelae were less frequently severely ill than those without gastrointestinal sequelae 17 versus 37%. These patients with gastrointestinal sequelae appeared to have a lower frequency of supplemental needs in the long-term also. Also, patients with GI sequelae at 90 days were treated more often with proton-pump inhibitor and corticosteroids and were less frequently treated with enteral nutrition. This suggests that there are different mechanisms in Post-COVID Long syndrome for GI abnormalities versus pulmonary or cardiac. Potential Long coronavirus disease; 2019. Gastrointestinal symptoms six-months after coronavirus by Blackett; published under Gastrointestinal online Oct 20 2021, showed that 29% of 220 patients reported GI symptoms six months after COVID-19; 9.6% had diarrhea, 11% had constipation, 9.4% abdominal pain, 7.1% nausea and vomiting and 16% with heartburn. A GI symptom was the most bothersome recurrent symptoms in 83 patients, 11%. Many symptoms resembled irritable bowel syndrome. There were 39% who met criteria for the Rome IV

Criteria for irritable bowel syndrome, and women were much more likely to report this than men. These symptoms were not trivial as almost 10% of patients reported this as their most significant symptom.

Studies are currently evaluating the long-term consequences of COVID-19 on the gastrointestinal system including postinfectious, irritable bowel syndrome, and dyspepsia.

V. MISCELLANEOUS:

Brain fog, amnesia, which is memory loss, sore throat, hoarseness, runny nose, hair loss, hearing loss and tremors have been reported at low incidences in Long-COVID Syndrome (Alyebbusi OL and Coworkers; Journal of the Royal Medical Society of Medicine. Jul 15, 2021).

VI. HEMATOLOGICAL SEQUELAE OF LONG-COVID SYNDROME.

Post-COVID venous thromboembolism has been estimated to be less than 5%. A single center report of 163 patient in the United States without postdischarge thrombotic prophylaxis suggested a 2.5% index of thrombosis at 30 days following discharge to include segmental pulmonary embolism, intracardiac thrombus, thrombosed AV fistulas and ischemic stroke (Patell R. et.al. Postdischarge thrombosis and a hemorrhage in patients with COVID-19 blood; 126, 1242-1346, 2020).

Late onset hematological complications post-COVID-19 has become an emerging medical problem for the hematologists. These include coagulopathy disorders, immunothrombotic states, and hemorrhagic events. Late onset thrombocytopenia related to immune system dysregulation has also been reported as a rare complication of COVID-19 (Korompoki 23 October 2021; American Journal of Hematology).

VII: KIDNEY DISEASE:

Patients that are extremely frail and have chronic comorbidities are at an increased risk for kidney disease and progression of kidney failure after infection of SARS-CoV-2. The kidney function gradually declines over time even in the absences of the virus infection (Silver SA. et.al The prevalence of Acute Kidney Injury in Patients Hospitalized with COVID-19 Infection; a systemic review and meta-analysis; KidneyMed. Vol 3, 83-98. 2021). Initially, approximately 28% of patients hospitalized with COVID are diagnosed with acute kidney injury and up to 9% have shown a received kidney replacement therapy, according to an article (Silver SA. et.al The prevalence of Acute Kidney Injury in

Patients Hospitalized with COVID-19 Infection; a systemic review and meta-analysis; KidneyMed. Vol 3, 83-98. 2021).

An article by Manami and Coworkers (Manami T. OpenAcess 2020; Dec BMC) 26 autopsy patients who died from COVID-19 were reported in China. Particles were noted in epithelial cells and diffuse proximal tubal injury was demonstrated. The study found that older-aged diabetes, cardiovascular disease, black race, hypertension, and need for ventilation vasopressor medications are at risk for acute kidney injury in COVID-19 (Hirsch J.S. Kidney Int. 2021, Jul 9; Vol 98 (1); 209-218)).

VIII: OlFACTORY and GUSTATORY ABNORMALITIES:

Recovery of the olfactory and Gustatory system may last more than one month after the onset of smell and taste loss (Addison AB, Journal of the Allergy Clinical Immunology; 2021 Vol 10- 1016 and Le Bon SD. European Archives of Otorhinolaryngology 2020, Vol 278; 101-108)___???. Loss of olfactory receptor neurons may be the mechanism in some of these cases. Long-lasting effects on taste and smell are uncommon but have been noted in isolated cases.

PATHOPHYSIOLOGY OF LONG COVID-19:

The mechanism beyond the causation of Long-COVID Syndrome may be multifactorial. As mentioned earlier, immune response, antibody generations, direct effects of the virus, complications of the critical illness, psychosocial factors and post-intensive care syndrome, post-traumatic stress and oxidative stress may be operative mechanism. Deconditioning may also be a factor (Raveedran AV: Long COVID An Overview: metabolic syndrome 2021 May-June; Vol 15 869-875). The mechanism of heart failure as another organ system involved pro-inflammatory cytokines with interleukin 1 and interleukin 6 tumor necrosis factors, and these can cause prolonged effects (Adeghate EA. Heart Fail Rev. 2021 Mar; Vol 26 (2); 363-369). Redox imbalance linking COVID-19 and chronic fatigue syndromes and systemic inflammation and neuroinflammation have also been postulated (Paul B. Process National Academy of Scientific USA: 2021-Aug 24; Vol 118 (34)).

Oxidative phosphorylation may be operative in a hyperinflammatory state with altered cardiorespiratory function. It is thought that a shift in energy system contribution from ATP recent____??? and other viral infections (Sandler LE. The Mitochondrial respiratory change and metabolic etc. Mitochondria 2018, 41; 28-36). An increased rate of oxidative phosphorylation is seen (Burtscher J. et.al. Mitochondria: In Cross Fire of SARS-CoV-2: Science 2020 Vol 23 (10) 101-631). Oxidative stress has been implicated in many

acquired myocardial disorders and can lead to significant autonomic dysfunction (DePace & Columbo publishers).

TREATMENT IN LONG-COVID SYNDROME:

For the most part, supportive therapy for post-COVID symptoms is a keystone and there is treatment for autonomic dysfunction that can be demonstrated objectively in a laboratory. As mentioned earlier, volume expanders and vasodilators in addition to fluids, electrolytes, compression garments, and various exercise techniques have been prescribed for orthostatic intolerance symptoms. Omega-3 fatty acid and dietary supplementation have been investigated (Weil P. Biochimie 2020, Dec, 179; 275-280). It is believed that omega-3 may help resolve inflammatory imbalance. L-arginine has also been proposed as a treatment modality (Adebay and Coworkers: Nutrients 2021- Nov-5, Vol 13 (11)). It is believed that L-arginine on endothelial cells to a nitric oxide pathway and immune system may be beneficial especially in chronic fatigue states. Various antioxidants and zinc have also been used empirically but there are no controlled studies to confirm their utility. Vaccination has been suggested as possibly a factor that can ease symptoms of Long-COVID. In one large survey, 57% of responders reported an overall improvement in their symptoms following vaccination and around 19% reported an overall deterioration (Medical News Today). Mental health conditions can be treated with various psychological aides, such as cognitive behavioral therapy as well as antidepressants and tricyclics. Treatment of liver function abnormalities irritable bowel syndrome, dyspepsia and other GI symptoms are very challenging. Renal dysfunction should be followed serially, nephrotoxins avoided and proper hydration maintained.

POST-COVID:

INSERT: Cardiopulmonary testing for unexplained dyspnea post COVID-19 was reported in a study by Mancini DM and Co-workers in the Journal of the American College of Cardiology Dec 3, 2021. Patients with symptoms consistent with chronic fatigue had an abnormal pattern of oxygen uptake on cardiopulmonary testing consistent with what is seen with chronic fatigue syndrome. Circulatory impairment, abnormal ventilatory pattern and chronic fatigue syndrome may be common in patients with post-acute sequelae of post-concussive syndrome, and this accounts for the mechanism of dyspnea in many patients who do not have pulmonary disease from post-COVID.