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Purpose:

This document strives to provide the accrual of data to date regarding post-COVID-19 conditions. While management strategies and etiologies remain relatively unknown, the following is a general guide to management of these patients.

Section 1: Definition

- Currently no accepted case definition.[1]
- Currently known also as 'long COVID,' 'post-COVID-19 syndrome,' 'post-acute sequelae of COVID-19,' 'chronic COVID syndrome' and 'long-haul COVID.'
- Centers for Disease Control and Prevention (CDC) recently proposed defining late sequelae as sequelae that extend beyond 4 weeks after initial infection.[2]

Section 2: Epidemiology

- **General**
    - Cohort study of 1,733 patients with laboratory confirmed COVID-19 who were discharged from Jin Yin-tan Hospital in Wuhan, China demonstrated that at 6 months, 76% of all patients had at least one of the listed symptoms, which range from fatigue/muscle weakness (63%), difficulty sleeping (26%), hair loss (22%), difficulty with smell and taste (11 and 9%), anxiety/depression (23%) and trouble with mobility (7%).[3]
    - Dyspnea is the most common persistent symptom beyond acute COVID-19, ranging from 42–66% prevalence at 60 to 100-day follow-up.[4]
    - The severity of illness during acute COVID-19 has been significantly associated with the presence or persistence of symptoms, reduction in health-related quality of life scores, pulmonary function abnormalities and radiographic abnormalities in the post-acute COVID-19 setting.[5]
    - There are potential associations of dyspnea at 4-8 week follow up with pre-existing respiratory disease, higher body mass index, older age and Black, Asian and other minority groups.[6]

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[1] *CMAPhysicians. (2021, April 13). Virtual Grand Rounds: Post-acute COVID syndrome - in it for the long haul? Retrieved April 15, 2021, from https://www.youtube.com/watch?v=iFFJGmDa6uY*
[2] *Clinical spectrum. (n.d.). Retrieved March 04, 2021, from https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/#:~:text=Common%20persistent%20symptoms%20include%20fatigue,and%20worsened%20quality%20of%20life.*
[3] *Huang C;Huang L;Wang Y;Li X;Ren L;Gu X;Kang L;Guo L;Liu M;Zhou X;Luo J;Huang Z;Tu S;Zhao Y;Chen L;Xu D;Li Y;Li C;Peng L;Li Y;Xie W;Cui D;Shang L;Fan G;Xu J;Wang G;Wang Y;Zhong J;Wang C;Wang J;Zhang D;Cao B;. (n.d.). 6-Month consequences of COVID-19 in patients discharged FROM hospital: A cohort study. Retrieved March 04, 2021, from https://pubmed.ncbi.nlm.nih.gov/33428867/*
[4] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*
[5] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*
[6] *Halpin, S. J. et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. J. Med. Virol. 93, 1013–1022 (2021).*

- Prolonged symptoms and disabilities after COVID-19 have also been reported in patients with milder illness, including outpatients,[7] as well as younger COVID-19 survivors including those physically fit prior to illness.[8]
- Malnutrition has been noted in 26–45% of patients with COVID-19, as evaluated by the Malnutrition Universal Screening Tool in an Italian study.[9,10]
- No known prognostic markers for developing post-COVID-19 syndrome.

- **Pulmonary epidemiology**[11,12,13]
  - The need for supplemental oxygen due to persistent hypoxemia, or new requirement for continuous positive airway pressure or other breathing support while sleeping, was reported in 6.6 and 6.9% of patients, respectively, at 60-day follow-up in the post-acute COVID-19 US study.[14]
  - Approximately 50% of 349 patients who underwent high-resolution computed tomography of the chest at 6 months had at least one abnormal pattern, the majority of which were ground-glass opacities.[15]
  - A longitudinal study of 97 SARS survivors found persistent radiographic abnormalities and diffusion capacity impairments in 28% and 24% of patients, respectively, at 1 year.[16]
  - Prevalence estimates of post-acute COVID-19 sequelae from these studies suggest that patients with greater severity of acute COVID-19 (especially those requiring a high-flow nasal cannula and non-invasive or invasive mechanical ventilation) are at the highest risk for long-term pulmonary complications, including persistent diffusion impairment and radiographic pulmonary abnormalities.[17,18,19]
- **Hematologic epidemiology**
  - Retrospective data, although limited by small sample size, variability in outcome ascertainment and inadequate systematic follow-up, suggest the rate of venous thromboembolism (VTE) in the post-acute COVID-19 setting to be <5%.[20]
  - In one study, there was a 3.7% cumulative incidence of bleeding at 30-day post-discharge, mostly related to mechanical falls.[21]

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[7] Clinical spectrum. (n.d.). Retrieved March 04, 2021, from https://www.covid19treatmentguidelines.nih.gov/overview/clinical spectrum/#:~:text=Common%20persistent%20symptoms%20include%20fatigue,and%20worsened%20quality%20of%20life.
[8] Late sequelae of covid-19. (n.d.). Retrieved March 04, 2021, from https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/late-sequelae.html
[9] Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z
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[11] Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z
[12] Mo X, Jian W, Su Z, et al. Abnormal pulmonary function in COVID19 patients at time of hospital discharge. Eur Respir J. 2020;55(6): 2001217.
[13] Cosgriff R. Ahern S. Bell S.C. et al. A multinational report to characterise SARS-CoV-2 infection in people with cystic fibrosis. J Cyst Fibros. 2020; 19: 355-358.
[14] Chopra, V., Flanders, S. A. & O'Malley, M. Sixty-day outcomes among patients hospitalized with COVID-19. Ann. Intern. Med. https://doi.org/ 10.7326/M20-5661 (2020).
[15] Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 397, 220–232 (2021).
[16] Hui D.S.Wong K.T.Ko F.W.et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. Chest. 2005; 128: 2247-2261.
[17] Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z
[18] Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 397, 220–232 (2021).
[19] Arnold, D. T. et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. Thorax https://doi.org/10.1136/thoraxjnl-2020-216086 (2020).
[20] Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z
[21] Patell, R. et al. Post-discharge thrombosis and hemorrhage in patients with COVID-19. Blood 136, 1342–1346 (2020).

- **Cardiovascular epidemiology**[22,23,24]
    - Chest pain was reported in up to ~20% of COVID-19 survivors at 60-day follow-up, while ongoing palpitations and chest pain were reported in 9% and 5%, respectively, at 6 months follow-up in the post-acute COVID-19 Chinese study.[25]
    - In a study of 26 competitive college athletes with mild or asymptomatic SARS-CoV-2 infection, cardiac MRI revealed features diagnostic of myocarditis in 15% of participants, and previous myocardial injury in 30.8% of participants. There were no diagnostic ST/T wave changes on electrocardiogram. No athlete had elevated serum levels of troponin I.[26,27]
- **Neuropsychiatric epidemiology**[28]
    - In a follow-up study of 100 patients, approximately 38% had ongoing headaches after 6 weeks.[29] Loss of taste and smell may also persist after resolution of other symptoms in approximately one-tenth of patients at up to 6 months follow-up.[30,31]
    - One study of 62,354 COVID-19 survivors from 54 healthcare organizations in the United States estimated the incidence of first and recurrent psychiatric illness between 14 and 90 day of diagnosis to be 18.1%. It reported the estimated overall probability of diagnosis of a new psychiatric illness within 90 days after COVID-19 diagnosis to be 5.8% (anxiety disorder = 4.7%; mood disorder = 2%; insomnia = 1.9%; dementia [among those ≥65 years old] = 1.6%) among a subset of 44,759 patients with no known previous psychiatric illness. These values were higher than matched cohorts of patients diagnosed with influenza.[32]
    - Cognitive impairment has been noted with or without fluctuations, including brain fog, which may manifest as difficulties with concentration, memory, receptive language and/or executive function.[33]
- **Nephrology epidemiology**[34]
    - Decreased eGFR; defined as <90 ml min−1 per 1.73 m2 was reported in 35% of patients at 6 months in the post-acute COVID-19 Chinese study.[35]
    - The extent of the recovery of renal function remains to be seen.[36]

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[22] Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z

[23] Brito D;Meester S;Yanamala N;Patel HB;Balcik BJ;Casaclang-Verzosa G;Seetharam K;Riveros D;Beto RJ;Balla S;Monseau AJ;Sengupta PP;. (n.d.). High prevalence of Pericardial involvement in college student Athletes recovering FROM COVID-19. Retrieved March 04, 2021, from https://pubmed.ncbi.nlm.nih.gov/33223496/

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[25] Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 397, 220–232 (2021).

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[27] Clinical spectrum. (n.d.). Retrieved March 04, 2021, from https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/#:~:text=Common%20persistent%20symptoms%20include%20fatigue,and%20worsened%20quality%20of%20life.

[28] Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z

[29] Pozo-Rosich, P. Headache & COVID-19: a short-term challenge with long-term insights. In Proc. AHSAM 2020 Virtual Annual Scientific Meeting (Infomedica, 2020); https://www.ahshighlights.com/ summaries-podcasts/article/ headache-covid-19-a-short- term-challenge-with- long-term-insights

[30] Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z

[31] Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 397, 220–232 (2021).

[32] Taquet, M., Luciano, S., Geddes, J. R. & Harrison, P. J. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry 8, 130–140 (2021).

[33] Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z

[34] Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z

[35] Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 397, 220–232 (2021).

[36] Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z

- **Endocrine epidemiology**[37]
    - Diabetic ketoacidosis has been observed in patients without known diabetes mellitus weeks to months after resolution of COVID-19 symptoms.[38]
    - Similarly, subacute thyroiditis with clinical thyrotoxicosis has been reported weeks after the resolution of respiratory symptoms.[39]
- **Gastrointestinal and hepatobiliary epidemiology**[40]
    - Significant gastrointestinal and hepatobiliary sequelae have not been reported in COVID-19 survivors.
    - COVID-19 has the potential to alter the gut microbiome, including enrichment of opportunistic infectious organisms and depletion of beneficial commensals.[41]
- **Dermatologic epidemiology**[42]
    - Only 3% of patients noted a skin rash at 6 months follow-up in the post-acute COVID-19 Chinese study. The predominant dermatologic complaint was hair loss, which was noted in approximately 20% of patients.[43]
- **Multisystem inflammatory syndrome in children (MIS-C) epidemiology**[44]
    - Patients with MIS-C are typically >7 years old, encompass a broader age range and are of African, Afro-Caribbean or Hispanic origin.[45]
    - A comparable incidence of coronary artery aneurysm and dilation has been noted among MIS-C and Kawasaki disease (20 and 25%, respectively).[46]
    - A pooled meta-analysis of MIS-C studies reported recovery in 91.1% and death in 3.5% of patients.[47]

Section 3: Acute complications of COVID-19 (including but not limited to):[48]

- **Pulmonary**
    - Pneumonia
    - Hypoxemic respiratory failure, ARDS
- **Hematologic/vascular**

[37] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*

[38] *Suwanwongse, K. & Shabarek, N. Newly diagnosed diabetes mellitus, DKA, and COVID-19: causality or coincidence? A report of three cases. J. Med. Virol. https://doi.org/10.1002/jmv.26339 (2020).*

[39] *Ruggeri, R. M., Campenni, A., Siracusa, M., Frazzetto, G. & Gullo, D.Subacute thyroiditis in a patient infected with SARS-COV-2: an endocrine complication linked to the COVID-19 pandemic. Hormones (Athens) 20, 219–221 (2021).*

[40] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*

[41] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*

[42] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*

[43] *Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 397, 220–232 (2021*

[44] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*

[45] *Henderson, L. A. et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 1. Arthritis Rheumatol. 72, 1791–1805 (2020).*

[46] *Henderson, L. A. et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 1. Arthritis Rheumatol. 72, 1791–1805 (2020).*

[47] *Jiang, L. et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect. Dis. 20, e276–e288 (2020).*

[48] *Lutchmansingh DD;Knauert MP;Antin-Ozerkis DE;Chupp G;Cohn L;Dela Cruz CS;Ferrante LE;Herzog EL;Koff J;Rochester CL;Ryu C;Singh I;Tickoo M;Winks V;Gulati M;Possick JD;. (n.d.). A clinic blueprint FOR post-coronavirus DISEASE 2019 Recovery: Learning from the past, looking to the future. Retrieved March 04, 2021, from https://pubmed.ncbi.nlm.nih.gov/33159907/*

  - Coagulopathy
  - Thrombotic events
- **Cardiovascular**
  - Arrythmia
  - Myocarditis
- **Neuropsychiatric**
  - Cerebrovascular accident
  - Large vessel disease
  - Encephalopathy, delirium
  - Anosmia, Ageusia
- **Nephrology**
  - Acute kidney injury
- **Gastrointestinal/hepatobiliary**
  - Diarrhea
  - Gastrointestinal complications
  - Acute liver injury
- **Musculoskeletal**
  - Rhabdomyolysis
- **Dermatologic**
  - Livedo reticularis
  - Maculopapular or urticarial rash

Section 4: Signs & symptoms of Post-COVID-19 (including but not limited to):[49]

- **General**
  - Fever
  - Myalgias and arthralgias
  - Fatigue
  - Post exertional malaise
- **Pulmonary**
  - Dyspnea
  - Decreased exercise capacity
  - Hypoxia
  - Cough
  - Wheezing
  - Sputum production
  - Pulmonary emboli
  - Residual lung disease

[49] *Lutchmansingh DD;Knauert MP;Antin-Ozerkis DE;Chupp G;Cohn L;Dela Cruz CS;Ferrante LE;Herzog EL;Koff J;Rochester CL;Ryu C;Singh I;Tickoo M;Winks V;Gulati M;Possick JD;. (n.d.). A clinic blueprint FOR post-coronavirus DISEASE 2019 Recovery: Learning from the past, looking to the future. Retrieved March 04, 2021, from https://pubmed.ncbi.nlm.nih.gov/33159907/*

  - Pulmonary effusions
  - Hemidiaphragm paralysis
  - Obstructive Sleep apnea
  - Hyperventilation syndrome
  - Pulmonary fibrosis
  - Interstitial lung disease
- **Hematologic**
  - Thrombosis
- **Cardiac**
  - Chest pain
  - Chest wall pain
  - Palpitations
  - Arrythmias, paroxysms of tachycardia
  - Pericarditis
  - Myocarditis
  - Coronary artery disease
  - Postural orthostatic tachycardia syndrome (POTS)
  - Dysautonomia
  - Dilated cardiomyopathy
  - Ventricular dysfunction
  - Costochondritis
  - Myocardial fibrosis or scarring
- **Neurology**
  - Cognitive impairment 'brain fog'
    - Confusion, loss of concentration or memory issues
  - Headaches
    - Often constant, frontal, pressure like, and fluctuating in severity
  - Peripheral neuropathy symptoms
    - Focal, diffuse, alternating in locations
  - Cerebrovascular events and sequelae
    - Small vessel/lacunar infarct or large vessel occlusion
    - Multiple vascular territories
    - Can occur in older patients with stroke risk factors or young patients with no risk factors
  - Anosmia, ageusia
  - Myalgic encephalomyelitis/chronic fatigue syndrome like process?
  - Sleep disturbance
  - Dizziness
  - Delirium
  - Fatigue
  - Seizures and encephalitis and cranial neuropathy seem to be rare[50]

[50] *Varatharaj A, Thomas N, Ellul MA, et al., CoroNerve Study Group. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry2020;S2215-0366(20)30287-X. doi:10.1016/S2215-0366(20)30287-X pmid:32593341*

- **Psychiatric**
  - Anxiety
  - Depression
  - PTSD
  - Insomnia
- **Gastrointestinal and hepatobiliary**
  - Reflux
  - Diarrhea
  - Abdominal pain
  - Nausea
  - Anorexia and reduced appetite
- **Nephrology**[51]
  - Reduced eGFR
- **Endocrinology**[52]
  - New or worsening control of existing diabetes mellitus
  - Subacute thyroiditis
  - Bone demineralization
  - Menstrual cycle irregularities
- **Dermatology**
  - Skin rashes
  - Hair loss
- **Multisystem Inflammatory Syndrome in Children (MIS-C)**[53]
  - Diagnostic criteria: <21 years old with fever, elevated inflammatory markers, multiple organ dysfunction, current or recent SARS-CoV-2 infection and exclusion of other plausible diagnoses
  - Typically affects children >7 years old and disproportionately of African, Afro-Caribbean or Hispanic origin
  - Cardiovascular (coronary artery aneurysm) and neurologic complications (headache, encephalopathy, stroke and seizure) can occur
- **Ear, Nose & Throat (ENT)**
  - Upper airway edema
  - Sore throat
  - Congestion
  - Tinnitus
  - Ear pain

[51] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*

[52] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*

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Section 5: Possible Pathophysiology of Post-COVID-19[54,55]

- **General Theories:**
  - Potential direct viral toxicity, i.e. invasion of alveolar epithelial/endothelial cells.
  - Sequelae of endothelial and cellular damage; and microvascular and organ injury from acute infection period.
  - Immune system dysregulation, autoimmunity and manifestations of long-term hyperinflammatory state (duration of hyperinflammatory state induced by infection is unknown).
  - Sequelae of maladaptation of angiotensin-converting enzyme 2 (ACE2) pathway.
  - Physical or psychological sequelae following long or difficult disease course.
  - Sequelae of hypercoagulability from acute illness.
  - Overlapping symptoms with post-intensive care syndrome (PICS).
- **Pulmonary pathophysiology**[56]
  - Viral-dependent mechanisms (including invasion of alveolar epithelial and endothelial cells by SARS-CoV-2) and viral-independent mechanisms (such as immunological damage, including perivascular inflammation) contribute to the breakdown of the endothelial–epithelial barrier with invasion of monocytes and neutrophils and extravasation of a protein-rich exudate into the alveolar space, consistent with other forms of ARDS.[57,58]
  - Have seen organizing and focal fibroproliferative diffuse alveolar damage later in the disease course. This fibrotic state may be provoked by cytokines such as IL-6 and transforming growth factor-β, which have been implicated in the development of pulmonary fibrosis.[59,60,61,62]
  - The severity of endothelial injury and widespread thrombosis with microangiopathy seen on lung autopsy is greater than that seen in ARDS from influenza.[63]
- **Hematology pathophysiology**[64]
  - Unlike the consumptive coagulopathy characteristic of disseminated intravascular coagulation, COVID-19-associated coagulopathy is consistent with a hyperinflammatory and hypercoagulable state, which may explain the

[54] *Long COVID and the road to Recovery (Feb. 13, 2021). (n.d.). Retrieved March 18, 2021, from https://www.idsociety.org/multimedia/podcasts/long-covid-and-the-road-to-recovery-feb-13-2021/*
[55] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*
[56] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*
[57] *Huppert, L. A., Matthay, M. A. & Ware, L. B. Pathogenesis of acute respiratory distress syndrome. Semin. Respir. Crit. Care Med. 40, 31–39 (2019).*
[58] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*
[59] *McElvaney, O. J. et al. Characterization of the inflammatory response to severe COVID-19 Illness. Am. J. Respir. Crit. Care Med. 202, 812–821 (2020).*
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[61] *Le, T. T. et al. Blockade of IL-6 trans signaling attenuates pulmonary fibrosis. J. Immunol. 193, 3755–3768 (2014).*
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[63] *Ackermann, M. et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. N. Engl. J. Med. 383, 120–128 (2020).*
[64] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*

disproportionately high rates (20–30%) of thrombotic complications rather than bleeding complications in acute COVID-19.[65,66]

- **Cardiovascular pathophysiology**[67]
    - Mechanisms perpetuating cardiovascular sequelae in post-acute COVID-19 include direct viral invasion, downregulation of ACE2, inflammation and the immunologic response affecting the structural integrity of the myocardium, pericardium and conduction system. The subsequent inflammatory response may lead to cardiomyocyte death and fibro-fatty displacement of desmosomal proteins important for cell-to-cell adherence.[68,69,70]
    - Autopsy studies in 39 cases of COVID-19 detected virus in the heart tissue of 62.5% of patients.[71]
    - Myocardial fibrosis or scarring, resultant cardiomyopathy from viral infection, and heightened catecholaminergic state can lead to arrhythmias.[72]
    - Autonomic dysfunction after viral illness, resulting in postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia, has previously been reported as a result of adrenergic modulation.[73,74]
- **Neuropsychiatric pathophysiology**[75]
    - There is not yet compelling evidence of SARS-CoV-2 infecting neurons. However, autopsy series have shown that SARS-CoV-2 may cause changes in brain parenchyma and vessels, possibly by effects on blood–brain and blood–cerebrospinal fluid barriers, which drive inflammation in neurons, supportive cells and brain vasculature.[76,77]
    - Other proposed mechanisms include dysfunctional lymphatic drainage from circumventricular organs, as well as viral invasion in the extracellular spaces of olfactory epithelium, and passive diffusion and axonal transport through the olfactory complex.[78,79]
    - Post-COVID brain fog in critically ill patients with COVID- 19 may evolve from mechanisms such as deconditioning or PTSD, or dysautonomia.[80]
- **Nephrology pathophysiology**[81]

[65] *Pavoni, V. et al. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. J. Thromb. Thrombolysis 50, 281–286 (2020).*
[66] *Connors, J. M. & Levy, J. H. COVID-19 and its implications for thrombosis and anticoagulation. Blood 135, 2033–2040 (2020).*
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[76] *Romero-Sánchez, C. M. et al. Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. Neurology 95, e1060–e1070 (2020).*
[77] *Reichard, R. R. et al. Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. Acta Neuropathol. 140, 1–6 (2020).*
[78] *Perrin, R. et al. Into the looking glass: post-viral syndrome post COVID-19. Med. Hypotheses 144, 110055 (2020).*
[79] *Morbini, P. et al. Ultrastructural evidence of direct viral damage to the olfactory complex in patients testing positive for SARS-CoV-2. JAMA Otolaryngol. Head Neck Surg. https://doi.org/10.1001/jamaoto.2020.2366 (2020).*
[80] *Kaseda, E. T. & Levine, A. J. Post-traumatic stress disorder: a differential diagnostic consideration for COVID-19 survivors. Clin. Neuropsychol. 34, 1498–1514 (2020).*
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- SARS-CoV-2 has been isolated from renal tissue, and acute tubular necrosis is the primary finding noted.[82]
- COVID-19-associated nephropathy (COVAN) is characterized by the collapsing variant of focal segmental glomerulosclerosis, with involution of the glomerular tuft in addition to acute tubular injury, and is thought to develop in response to interferon and chemokine activation.[83,84]
- Thrombi in the renal microcirculation may also potentially contribute to the development of renal injury.[85]

- **Endocrine pathophysiology**[86]
  - There is no concrete evidence of lasting damage to pancreatic β cells. Primary deficit in insulin production is probably mediated by factors such as inflammation or the infection stress response, along with peripheral insulin resistance.[87]
- **Gastrointestinal and hepatobiliary pathophysiology**[88]
  - Significant gastrointestinal and hepatobiliary sequelae have not been reported in COVID-19 survivors, although there is prolonged viral fecal shedding.[89]
- **Dermatologic pathophysiology**[90]
  - Hair loss can possibly be attributed to telogen effluvium resulting from viral infection or a resultant stress response.[91]
- **Multisystem inflammatory syndrome in children (MIS-C)**[92]
  - The timing of the emergence of MIS-C (which was lagging approximately 1 month behind peak COVID-19) and the finding that most patients are negative for acute infection but are antibody positive suggest that MIS-C may result from an aberrant acquired immune response rather than acute viral infection.[93]
  - Insights into the pathophysiology of MIS-C may be derived in part from Kawasaki disease and toxic shock syndrome, with possible mechanisms of injury related to immune complexes, complement activation, autoantibody formation through viral host mimicry, and massive cytokine release related to superantigen stimulation of T cells.[94,95]

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Section 6: Post-COVID-19 Diagnostics

- **General**
  - Confirm prior diagnosis of COVID-19
  - Keep differential broad while evaluating
  - Measure vitals including pulse oximetry
  - Baseline characteristics:
    - i.e. Race, Smoking status, Comorbidities (HTN, DM, Asthma, COPD, Malignancy, CKD, Weight)
  - Subjective symptom data: i.e., Dyspnea–12 score for dyspnea, STOP-BANG for obstructive sleep apnea, HRQoL-14 for Healthy Days measure,[96] Patient-Reported Outcomes Measurement Information System (PROMIS) (e.g., Cognitive Function 4a), Post-Covid-19 Functional Status Scale (PCFS), EuroQol-5D (EQ-5D), Modified Medical Research Council Dyspnea Scale (mMRC)[97]
  - Subjective measure of physical function: i.e., 6 Minute Walk Test (6MWT), Activity Measure for Post-Acute Care (AMPAC)
  - Subjective measure of pain: i.e., McGill Pain Questionnaire
  - Consider obtaining: CBC with differential, BMP, hepatic function panel, LDH, Ferritin, ESR, CRP, creatine kinase, BNP, ferritin, D-dimer, TSH, vit B12, folate level, vitamin D level, RPR, HIV serology
  - Unclear utility outside of academic research:
    - Ammonia, uric acid, troponin, procalcitonin
  - Utility of COVID serology unclear
    - Antibody tests are not standardized
    - Oftentimes serology levels wane after infection and a negative test does not rule out prior history of COVID-19
- **Pulmonary**
  - Consider pulmonary function assessment with a physical therapist
  - Spirometry with bronchodilator, Pulmonary Function Test (PFT)
  - Imaging if indicated with Chest Xray, CT thorax, V/Q scan
    - Can demonstrate reduced diffusion capacity, restricted pulmonary physiology, ground-glass opacities and fibrotic changes on imaging
  - Sputum culture if indicated
- **Hematology**
  - If patient had thrombotic complications or a cerebrovascular accident consider: anti-phospholipid antibodies, lupus anticoagulant, anticardiolipin IgA antibodies as well as anti-B^2 glycoprotein I IgA and IgG antibodies
- **Cardiology**

[96] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*

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- Orthostatic vital signs if indicated
- 3-minute active stand test, or 10 minutes if you suspect postural tachycardia syndrome, or other forms of autonomic dysfunction[98]
- 6-minute walk test
- 10 Meter Walk Test (10MWT)
- Consider:
  - Stress testing
  - Perfusion testing
  - Electrocardiogram
  - Echocardiography
  - Cardiovascular magnetic resonance imaging (or cardiac MRI)
    - Look for abnormalities such as left ventricular dysfunction (i.e. myocarditis), right ventricular strain from acute hypoxia, pericardial disease
  - Tilt table testing (if concerned for POTS)
  - Cardiac event monitoring, such as Holter or Ziopatch monitor

- **Neurology**
  - Consider following subjective scales
    - MMSE for cognitive impairment
    - MoCA-BLIND for cognitive impairment
    - Compass31 (for dysautonomia)
    - Neurobehavioral Symptom Inventory
    - Insomnia Severity Index for sleep disturbances
    - Neurocognitive screening
  - Consider following tests
    - BERG Balance Scale
    - Tinetti Gait and Balance Assessment Tool
  - Depending on symptoms, consider obtaining HbA1c, TSH, immunofixation, serum protein electrophoresis, vitamin B12 level, folate level, RPR, thiamine level
  - Consider (especially if had severe COVID, >50 years of age, impact on ADLs, focal symptoms [although new focal neurological symptoms may be an emergency depending on clinical presentation]):[99]
    - CT brain
    - MRI brain (usually normal)
    - EEG (often normal)
    - EMG
    - Lumbar puncture (no major inflammatory/infectious changes generally noted)

[98] *Overview: COVID-19 rapid GUIDELINE: Managing the long-term effects of COVID-19: GUIDANCE. (n.d.). Retrieved March 04, 2021, from https://www.nice.org.uk/guidance/NG188*

[99] *Webinar January 28, 2021 - treating Long covid: Clinician experience with post-acute COVID-19 Care. (2020, September 04). Retrieved March 04, 2021, from https://emergency.cdc.gov/coca/calls/2021/callinfo_012821.as*

        - Skin biopsy for small fiber neurology (could confirm diagnosis but wouldn't change management)
- **Psychiatry**
    - Consider following subjective scales
        - GAD 7 questionnaire for anxiety
        - PCL5 questionnaire for depression
        - PTDS Symptom Scale (PSS)
        - Screen for Posttraumatic Stress Symptoms (SPTSS)
        - HADS questionnaire for anxiety and depression
        - Impact of Event Scale (IESR) questionnaire
        - EQ-5D questionnaire for health status
        - Hospital Anxiety and Depression Scale (HADS)
- **Nephrology**
    - Consider obtaining a urinalysis
- **Endocrinology**[100]
    - Serologic testing for type 1 diabetes associated autoantibodies and repeat post-prandial C-peptide measurements should be obtained at follow-up in patients with newly diagnosed diabetes mellitus in the absence of traditional risk factors for type 2 diabetes.[101]

Section 7: Post-COVID-19 Treatment[102]

- **General**
    - Most post-COVID conditions can be diagnosed and managed by primary care providers, and a patient-centered medical home model could be helpful, with coordinated comprehensive care and open communication among a core group of specialty care providers and support services (e.g., occupational therapy, physical therapy, social work) to maximize functional improvement and rehabilitation efforts.[103]
    - Multidisciplinary team: Specialist referral by primary care provider may be indicated based on clinical and diagnostic findings:
        - Primary care
        - Pulmonary medicine
        - Cardiology
        - Infectious diseases

[100] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*
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[103] Centers for Disease Control and Prevention. (n.d.). *General clinical considerations| evaluating and caring for patients with post-covid conditions*. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-clinical-eval.html.

        - Nephrology
        - Physiatry
        - Physical and occupational therapy
        - Pulmonary rehabilitation
        - Radiology
        - Neurology
        - Psychiatry
        - Psychology
        - Nutrition consultant
        - Home health services
        - Social workers
        - Case management
        - Pharmacists
    - Symptom assessment through in-person/virtual follow-up at ~4-6 weeks and 12 weeks post discharge.
    - Patient education about pathophysiology, epidemiology, treatments and prognosis. Healthcare professionals should advise patients that post-COVID conditions are not yet well understood, and assure them that support will continue to be provided as new information emerges. Symptoms not explained by, or out of proportion to, objective findings are not uncommon after COVID-19 and should not be dismissed even if there is not yet a full understanding of their etiology or their expected duration.[104]
    - Providing holistic patient-centered management approaches to improve patient quality of life and function and partnering with patients to identify achievable health goals.[105]
    - Set treatment goals. Patients tend to slowly improve.
    - Creating a comprehensive rehabilitation plan may be helpful for some patients and might include physical and occupational therapy, speech and language therapy, vocational therapy, as well as neurologic rehabilitation for cognitive symptoms.[106]
    - Listening and empathy.
    - Address pain concerns.
    - Address any care barriers i.e., financial assistance, health inequities due to disability, racial disparities, etc.[107]
    - Provide patient with ER precautions (i.e., significant shortness of breath, chest pain, confusion, focal weakness).[108]

[104] Centers for Disease Control and Prevention. (n.d.). *General clinical considerations| evaluating and caring for patients with post-covid conditions*. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-clinical-eval.html.
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[108] *Greenhalgh, T., Knight, M., A'Court, C., Buxton, M., & Husain, L. (2020, August 11). Management of post-acute covid-19 in primary care. Retrieved March 04, 2021, from https://www.bmj.com/content/370/bmj.m3026*

- Sleep hygiene: assess for sleep apnea. Consider sleep aids such as melatonin, mirtazapine, gabapentin or amitriptyline (consider if paresthesia and headaches also present).[109]
- Attention to general health (diet, sleep, quitting smoking, limiting alcohol and caffeine intake) and management of comorbidities.[110]
- Avoid over medicalization, and consider iatrogenic effects of current medications.[111]
- Patient diaries and calendars might be useful to document changes in health conditions and symptom severity, especially in relation to potential triggers such as exertion (physical and cognitive), foods, menstruation, and treatments or medications.[112]
- Rest and relaxation. Self-pacing and gradual increase in exercise, as tolerated.[113] Do not push to recondition quickly.
    - i.e., See Graduated return to play guidance following COVID-19 infection[114]
- Connect with peer support groups, mental health support service, community services[115]
    - Some Peer Advocacy groups include: COVID Advocacy Exchange (https://www.covidadvocacyexchange.com), the National Patient Advocate Foundation COVID Care Resource Center (https://www.patientadvocate.org/covidcare), long-haul COVID fighters Facebook groups, the Body Politic COVID-19 Support Group (https://www.wearebodypolitic. com/covid19), Survivor Corps (https://www.survivorcorps.com/) and Patient-Led Research for COVID-19 (patientresearchcovid19.com). Surveys conducted by these groups have helped to identify persistent symptoms such as brain fog, fatigue and body aches as important components of post-acute COVID-19.[116]

- **Infectious Disease**
    - Patient education
    - Consider enrollment in clinical research trials
    - Monitor for secondary infection
- **Pulmonary**[117]

[109] *Webinar January 28, 2021 - treating Long covid: Clinician experience with post-acute COVID-19 Care. (2020, September 04). Retrieved March 04, 2021, from https://emergency.cdc.gov/coca/calls/2021/callinfo_012821.asp*
[110] *CMAPhysicians. (2021, April 13). Virtual Grand Rounds: Post-acute COVID syndrome - in it for the long haul? Retrieved April 15, 2021, from https://www.youtube.com/watch?v=iFFJGmDa6uY*
[111] *CMAPhysicians. (2021, April 13). Virtual Grand Rounds: Post-acute COVID syndrome - in it for the long haul? Retrieved April 15, 2021, from https://www.youtube.com/watch?v=iFFJGmDa6uY*
[112] Centers for Disease Control and Prevention. (n.d.). *General clinical considerations| evaluating and caring for patients with post-covid conditions*. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-clinical-eval.html.
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[114] *Elliott N;Martin R;Heron N;Elliott J;Grimstead D;Biswas A;. (n.d.). Infographic. graduated return to play guidance FOLLOWING COVID-19 infection. Retrieved April 22, 2021, from https://pubmed.ncbi.nlm.nih.gov/32571796/*
[115] *Greenhalgh, T., Knight, M., A'Court, C., Buxton, M., & Husain, L. (2020, August 11). Management of post-acute covid-19 in primary care. Retrieved March 04, 2021, from https://www.bmj.com/content/370/bmj.m3026*
[116] *Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z*
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- Consider daily pulse oximetry if dyspneic or otherwise indicated[118]
- Consider serial evaluation using questionnaires such as 6MWT
- SpO2 ≤92% may require supplementary oxygen
- Differentiate from other possible etiologies, i.e. COPD and asthma
- The decision to institute corticosteroids for presumed secondary organizing pneumonia and/or other post-COVID inflammatory lung disease or defining the length of therapy for those already receiving corticosteroids remains uncharted territory.[119] Steroid use during acute COVID-19 was not associated with diffusion impairment and radiographic abnormalities at 6 months follow-up in the post-acute COVID-19 Chinese study.[120]
- For the subset of patients with evidence of fibrosis, it is unclear if this will persist or progress; as such, the role of antifibrotic therapy remains speculative.[121] Clinical trials of antifibrotic therapies to prevent pulmonary fibrosis after COVID-19 are underway.[122]
- There is unclear utility in repeating imaging at certain intervals.

- **Pulmonary Rehabilitation**
  - After 6 weeks of respiratory rehabilitation in the intervention group, there were significant differences in FEV1(L), FVC(L), FEV1/FVC%, DLCO% and 6-min walk test.[123]
- **Hematology/Oncology**[124]
  - Although conclusive evidence is not yet available, extended post-hospital discharge (up to 6 weeks) and prolonged primary thromboprophylaxis (up to 45 days) in those managed as outpatients may have a more favorable risk–benefit ratio in COVID-19 given the noted increase in thrombotic complications during the acute phase. This is an area of active investigation (NCT04508439, COVID-PREVENT (NCT04416048), ACTIV4 (NCT04498273) and PREVENT-HD (NCT04508023)).[125,126]
  - Direct oral anticoagulants and low-molecular-weight heparin for extended thromboprophylaxis may be considered after risk–benefit discussion in patients with predisposing risk factors such as cancer and immobility, or persistently elevated d-dimer levels (greater than twice the upper limit of normal) and other high-risk comorbidities such as cancer.[127]
  - The role of antiplatelet agents such as aspirin as an alternative (or in conjunction with anticoagulation agents) for thromboprophylaxis in COVID-19 has not yet

[118] *Greenhalgh, T., Knight, M., A'Court, C., Buxton, M., & Husain, L. (2020, August 11). Management of post-acute covid-19 in primary care. Retrieved March 04, 2021, from https://www.bmj.com/content/370/bmj.m3026*
[119] *Lutchmansingh DD;Knauert MP;Antin-Ozerkis DE;Chupp G;Cohn L;Dela Cruz CS;Ferrante LE;Herzog EL;Koff J;Rochester CL;Ryu C;Singh I;Tickoo M;Winks V;Gulati M;Possick JD;. (n.d.). A clinic blueprint FOR post-coronavirus DISEASE 2019 Recovery: Learning from the past, looking to the future. Retrieved March 04, 2021, from https://pubmed.ncbi.nlm.nih.gov/33159907/*
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been defined and is currently being investigated as a prolonged primary thromboprophylaxis strategy in those managed as outpatients (ACTIV4 (NCT04498273)).[128]
    - Physical activity and ambulation should be recommended to all patients when appropriate.
- **Cardiology**[129]
    - For patients with ventricular dysfunction, guideline-directed medical therapy should be initiated and optimized.[130]
    - Cedars Sinai has a Post-COVID-19 Cardiology Program.
    - Unclear utility in serial clinical and imaging evaluation with echocardiography or electrocardiography, but current evidence does not support routine use of advanced cardiac imaging.[131,132]
    - Recommendations for competitive athletes with cardiovascular complications related to COVID-19 include abstinence from competitive sports or aerobic activity for 3–6 months until resolution of myocardial inflammation by cardiac MRI or troponin normalization.[133,134]
    - Renin-Angiotensin-Aldosterone System inhibitors have been shown to be safe and should be continued in those with stable cardiovascular disease, and abrupt cessation has been shown to be potentially harmful.[135,136,137]
    - Dysautonomia: appropriate fluid intake, salt intake, proper sleep, exercise and rehab, compression stocking, recommend consultation with cardiology and guideline-directed medical therapy.
    - Myo-pericarditis: recommend consultation with cardiology and guideline-directed medical therapy.
    - POTS: recommend consultation with cardiology and guideline-directed medical therapy.[138]
- **Neurology**
    - Consider neurorehabilitation:
        - University of California San Francisco has a Neuro-recovery clinic, University of California Los Angeles has a Neurocognitive team
    - Management of headaches per current practice guidelines
    - Brain fog: No specific therapy for brain fog. Evaluate for other possible etiologies.[139]

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  - Small fiber neuropathy: evaluate for other possible etiologies.[140]
  - Anosmia/ageusia: No proven therapies, some theoretical therapies include:
    - deliberate sniffing of rose, lemon, clove, and eucalyptus for 20 seconds each, twice a day

- **Nephrology**[141]
  - COVID-19 survivors with persistent impaired renal function in the post-acute infectious phase may benefit from early and close follow-up.
- **Endocrinology**[142]
  - Management of new onset diabetes, and thyroid syndromes based on guidelines
  - Hyperthyroidism due to SARS-CoV-2-related destructive thyroiditis should be managed using guideline-directed medical therapy, but new-onset Graves' disease should also be ruled out.[143,144]
- **Multisystem inflammatory syndrome in children (MIS-C)**[145]
  - Current recommendations include immunomodulatory therapy with intravenous immunoglobulin, adjunctive glucocorticoids and low-dose aspirin until coronary arteries are confirmed normal at least 4 weeks after diagnosis.[146,147]
  - Therapeutic anticoagulation with enoxaparin or warfarin and low-dose aspirin is recommended in those with a coronary artery z score ≥ 10, documented thrombosis or an ejection fraction < 35%.[148]
  - Studies such as the Best Available Treatment Study for Inflammatory Conditions Associated with COVID-19 (ISRCTN69546370) are evaluating the optimal choice of immunomodulatory agents for treatment.[149]
  - Serial echocardiographic assessment is recommended at intervals of 1–2 and 4–6 weeks after presentation.[150]
  - Cardiac MRI may be indicated 2–6 months after diagnosis in those presenting with significant transient left ventricular dysfunction (ejection fraction < 50%) in the acute phase or persistent dysfunction to assess for fibrosis and inflammation. Serial electrocardiograms and consideration of an ambulatory

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cardiac monitor are recommended at follow-up visits in patients with conduction abnormalities at diagnosis.[151,152]

- **Nutrition and rehabilitation considerations**[153]
  - Severe COVID-19, similar to other critical illnesses, causes catabolic muscle wasting, feeding difficulties and frailty, each of which is associated with an increased likelihood of poor outcome.[154]
  - Swallowing function evaluation, nutritional status and measures of functional independence should be assessed.[155]
  - There are protocols in development, including "Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol."[156]
- **Physiatry and Physical and Occupational Therapy**
  - Consider early rehabilitation
  - Virtual rehabilitation resources exist
  - Set realistic goals

Section 8: Public Health Recommendations[157]

- People with post-COVID conditions should continue to follow CDC's recommended COVID-19 prevention measures,[158] including wearing a mask when and where indicated, maintaining the appropriate physical distance from people who are not from their household, avoiding crowds and poorly ventilated indoor spaces, washing hands, and when vaccinated following the general recommendations for vaccinated people.[159]
- COVID19 vaccination should be offered to all eligible people, regardless of their history of SARS-CoV-2 infection. Although anecdotal reports indicate that some patients with post-COVID conditions have experienced improvements in their symptoms after COVID-19 vaccination, research is ongoing to establish the extent of this effect, if verified.[160]

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Section 9: Great resources

- IDSA: https://www.idsociety.org/covid-19-real-time-learning-network/disease-manifestations--complications/post-covid-syndrome/
- CDC: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/late-sequelae.html
- NIH: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/#:~:text=Common%20persistent%20symptoms%20include%20fatigue,and%20worsened%20quality%20of%20life.
- Excellent Article: Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., . . . Wan, E. (2021, March 22). Post-acute COVID-19 SYNDROME. Retrieved March 25, 2021, from https://www.nature.com/articles/s41591-021-01283-z